PSYCHO-ENDOCRINOLOGY

by

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INTRODUCTION.

In recent years and especially since the advent of corticotrophin and cortisone, more and more attention and research have been made in to the endocrine system and in particular in to new techniques of biochemical investigation and control. This new field of knowledge is now being explored in regard to its psychiatric applications in several hospitals and centres in this country. Even if only a fraction of one percent of psychiatric conditions could be helped by endocrine therapy, it would be a major step forward in making more accurate the diagnosis of mental disorders which at present are made on a descriptive rather than an etiological basis.

It is the purpose of this paper to give a review of the published work relating to disturbed hormone equilibrium as a factor causing mental imbalance and secondly to describe published material concerning psychiatric cases in which hormonal upsets were held to be involved. The author's work comprises firstly a case of manic-depressive psychosis whose adrenal function was followed over a long period and who was subjected to corrective hormonal treatment; and secondly, a classified analysis of the neutral 17-ketosteroids of 100 consecutive admissions to a mental hospital. Those patients whose figures showed variations outside the accepted normal range were treated with the appropriate hormone and a description of the clinical state, type of hormone disturbance and response to treatment is given. The results of estimating the serum cholesterol levels in 200 consecutive admissions is presented along with the assessment and results of treatment in those patients showing abnormal values. A case of Cushing's syndrome successfully treated by surgery with relief of the

co-existing mental disorder is also described. Finally, a discussion is attempted of the value and place of such investigations and treatments in psychiatric practice.

Too often in the past, various hormone treatments have been advocated for certain psychiatric clinical conditions and have been so extensively used and in such a scientifically uncontrolled fashion that they have quickly fallen in to disrepute: such events can be expected to recur until the whole subject has been put on a similar basis as insulin in the treatment of diabetes mellitus, where the disturbance of metabolism has been scientifically assessed and replacement or corrective therapy scientifically prescribed.

The author has been the Deputy Medical Superintendent of The Retreat, York for the past five years whence the clinical material described in this thesis has been collected and he has had access to all such cases and was responsible for their management.

Disturbed Hormone Equilibrium and its Psychiatric Implications.

One of the major difficulties in investigating psycho-endocrinology is that the relationship is never a static one and that it involves more than two variables even when the function of a single target gland is being scrutinised and assessed. A primary thyroid under-function may cause cerebral and emotional retardation which in turn influences the hypo-thalamic-anterior pituitary axis to an over- or under-production of thyrotrophic, gonadotrophic and adrenotrophic hormones: this may occur in addition to the peripheral interaction of the separate hormones, such as the antagonism which exists between thyroxin and the adrenal corticosteroids.

Reiss (1950) points out that no matter whether the primary disturbance has arisen in the brain or in the endocrine system, the end result is a widening and spreading of the disturbance throughout the systems and the establishment of a vicious circle: any treatment, physical, endocrine or psychological, acts by breaking in to this circle but at different points on the circumference.

In recent years, the adrenal gland has assumed an importance hardly less than that occupied by the thyroid and the pituitary in former years and an examination of its function in relation to mental changes seems relevant.

The Adrenal Cortex.

The cortex of the gland originates as a series of buds from the coelomic cells at the root of the mesentery; later in development these

buds become separated from the coelomic epithelium and form a suprarenal ridge in to which at the eighth week of foetal life sympathochromaffin tissue migrates to form the adrenal medulla.

The adrenal cortex, histologically speaking, consists of a connective tissue network containing glandular epithelium much of the latter possessing abundant lipoid material. Traditionally, there are three main zones described.

1. The outer or zona glomerulosa in which the cells are arranged in rounded groups.

2. The middle or zona fasciculata in which the cells are arranged in radially directed columns.

3. The inner or zona reticulata where the glandular cells are arranged in cylindrical columns.

Two other less well defined zones are described one being a transition zone which inconstantly lies between the outer and middle zones and the other an "androgenic" zone situated between the inner zone and the medulla or which may even replace the inner zone.

Cholesterol and ascorbic acid are both found in the cortex and cholesterol is considered to be the substance from which the steroid hormones are synthesised. Most of the lipoid globules are found in the middle and outer zones and there is still doubt as to the precise significance and purpose of the different zones. The steroid hormones are probably secreted from the deeper layers of the middle zone and from the inner zone after being synthesised in the outer layers of the middle zone. The zona glomerulosa appears to react differently from the rest of the

cortex; administration of corticotrophin (ACTH) is followed by a reduction of lipoid material in all three zones but while the two inner zones hypertrophy under such stimulation, the outer zone diminishes in size. The administration of cortisone which functionally depresses cortical activity leads to a decrease in size of the two inner layers but a hypertrophy of the outer zone.

The transition area between the glomerulosa and fasciculata zones seems only to be present when the gland is in a low state of activity and it has been suggested that the cells are then being kept in reserve able to migrate either to the outer or middle zones when demand for secretion arises. Functioning cortical tissue is essential for life and there is no known neural control of the secretory activity of the adrenal cortex.

Hormones of the Adrenal Cortex.

The adrenal cortex hormones are known as corticoids and are steroids based on the phenanthrene ring structure: more than 60 such steroids have been isolated from extracts but the vast majority are probably intermediate or artificially produced substances possessing little or no physiological activity.

Two main groups of substances derived from extracts of cortex can be described.

1.The amorphous fraction possessing physiological activity but whose composition is largely unknown; this fraction restores function when administered to an adrenalectomised animal.

2. Crystalline compounds of which the majority possess no activity. These comprise three functionally distinct groups although

overlapping of function occurs to quite an extent.

a). The Sex Hormones include androgens such as androsterone and adrenosterone, progesterone and oestrogens; the androgens in addition have a protein anabolic effect and those with a ketone grouping at C17 can be isolated and measured in the urine as neutral 17-ketosteroids.

b). The 11-Desoxycorticosteroids also known as the mineralo-corticoids (Selye) are concerned in maintaining electrolyte balance in the organism. Desoxycortisone (Compound F) and desoxycorticosterone acetate (DOCA) are examples. These steroids exert no effect on general metabolism but act on the renal tubular epithelium favouring reabsorption of sodium and chloride ions and decreasing the tendency to retain potassium ions; they have no effect on peripheral eosinophil levels.

c). The 11-Oxycorticosteroids with a ketone or hydroxyl grouping in the C11 position are also known as glucocorticoids but in addition to an effect on carbohydrate metabolism also influence protein and fat metabolism. Cortisone (Compound E) and hydrocortisone (Compound F) and corticosterone are examples of this group: they produce a depression of the circulating eosinophil levels.

Administration of these cortisone like steroids exerts an anti-anabolic action on protein metabolism with the production of a negative nitrogen balance and increased excretion of creatine and uric acid in the urine: creatinine excretion is unchanged and the changes in the ratios of the former substances compared with the creatinine excretion serves as an index of protein movement. The increased breakdown of protein releases amino acids which are converted in to glucose: in addition, the cortisone

like substances diminish the utilisation of glucose by the tissues leading to increased deposition of liver glycogen and an increased demand for insulin: glycosuria may be found. The effects on body fluid and ionic equilibrium resemble the actions of the DOCA like steroids.

Administration of corticotrophin causes increased secretion of all three groups of steroids.

Clinically, the physiological effects which are seen on prolonged ACTH, hydrocortisone or cortisone administration even in moderate dosage or on short term suppressive dosage with cortisone and hydrocortisone are the development of a Cushing type syndrome. Body weight increases, the "moon-facies" appears and there is deposition of fat in the cervico-dorsal and supraclavicular regions, retention of sodium and chlorine ions and fluid, increased excretion of potassium and the appearance of glycosuria; androgenic effects such as mild hirsutism and an acneiform rash may be observed and amenorrhoea occurs in women.

Tests of Adrenal Function and Responsivity.

1. Blood Eosinophil Count. The significance of the levels of circulating eosinophils in relation to adrenal cortical activity is now well established (Prunty 1950, Sayers 1950). The fluctuations from hour to hour in the eosinophil count are comparatively slight in any one individual (Thorn et al. 1950) although there is a tendency for the count to rise from midday onwards.

Corticotrophin, extracts of adrenal cortex and in particular cortisone and hydrocortisone produce falls in the eosinophil count

maximal four hours after administration of the particular hormone and a reduction of more than 50% from the control count in the case when ACTH has been employed is held to indicate evidence of corticoid secretion: corticotrophin will only produce this effect however in the presence of an intact adrenal cortex. This is the basis of the Thorn test (Thorn et al. 1948) in which 25mg. of ACTH is given intramuscularly, eosinophil levels being counted immediately before and four hours after the injection: in adrenal cortex insufficiency the response is nil or less than 50%.

The injection of adrenalin also brings about a fall in circulating eosinophils formerly considered to be due to stimulation of the hypothalamus and subsequent secretion of ACTH. There is now some doubt whether corticoid secretion is affected at all by adrenalin in man (Hunter et al. 1955), although the authors believe that if the eosinophil count is lowered by more than 50% following the injection of adrenalin, adrenocortical function is probably intact.

By studying serial eosinophil counts, it was found that many different stresses, surgical, traumatic and psychological as well as disease processes produce depression of the count. The actual fate of the eosinophils when the levels fall, as to whether they are stored, destroyed or their production in the marrow inhibited, has not yet been convincingly determined.

2. Neutral 17-Ketosteroid Urinary Output. The adrenal cortical androgens are excreted in the urine as 17-ketosteroids that is steroids with a ketone grouping at C17: certain corticosteroids in which the side chain has been oxidised and the 17-hydroxylated substituent

oxidised to a 17-ketone grouping also appear as 17-ketosteroids. In the male certain testicular hormones are also excreted as 17-ketosteroids, estimated as one third of the total output.

The method most commonly used in this determination is that of Callow et al.(1938) improving on the method devised by Zimmerman (1936). Several modifications of the former's technique have been made.

Butt and his colleagues (1950) give the range for men as 11-21 mg. per 24 hours and for women as 4.5 to 19.5 mg. Forbes et al.(1947) give an average of 12.5mg. for young men and 8.2mg. for young women. Callow's own figures are a range of 11.4-18.4mg. in young men aged 20-40 years, 8.2-13.2mg. in women of the same age group and in men aged 60-90 years the figures were 2.0-8.5mg. and in older women 0.9-7.5mg.

Fractionation of the total neutral 17-ketosteroids by digitonin precipitation enables the 3beta-hydroxy-17-ketosteroid excretion to be estimated. This largely consists of dehydroisoandrosterone considered to be derived solely from adrenal cortex.

Dingemanse and his co-workers (1946) worked out and have since elaborated a method using chromatographic analysis after performing the Zimmerman-Callow technique which enables them to identify more accurately and in more detail the various 17-ketosteroid constituents. He describes 8 peaks in the chromatogram, the more important of which are peak ii consisting of i-androstanolone, peak iii containing the beta ketosteroids, peak iv consisting of androsterone and peak v of aetiocholanolone. If dehydroisoandrosterone is administered to normal subjects it is converted mainly in to androsterone and aetiocholanolone. Dingemanse strongly

suspects that dehydroisoandrosterone is not a natural constituent of urinary 17-ketosteroid excretion, but an artefact produced by the initial acid hydrolysis necessary to prepare the urine for performing a Zimmerman reaction; the large amounts of dehydroisoandrosterone apparently found in the urine of patients suffering from adrenal cortical tumour, in her opinion actually consist of i-androstanolone.

Clinical conditions in which decreased excretion of 17-ketosteroids are found are thyrotoxicosis, female hypogonadism, diabetes mellitus, hypertension, eunuchoidism, Addison's disease, panhypopituitarism, myxoedema or any debilitating disease.

Increased excretion is found in interstitial tumour of the testis, adrenal hyperplasia, adenoma of the adrenal cortex, Cushing's syndrome, adrenal cancer and pregnancy.

3. Urinary Adrenal Corticoids. Evidence has accumulated in recent years that 17-hydroxycorticosteroid (Kendall's Compound F) is the principal cortical steroid secreted in to the blood in humans (Nelson and Samuels 1952). Both cortisone and hydrocortisone have been found in the urine of normal subjects. Romanoff et al. (1952) succeeded in isolating 20 steroids from urine, six of which have been identified and fall in the group known as 17-ketogenic steroids: a method for estimating this group of substances has been described by Norymberski et al. (1955) who consider that the results give an index of adrenal cortex activity and in particular that part of the cortex concerned with the production of 17-alpha-hydroxycorticosterone. They calculate that the daily output for men is about 30mg. and for women 20mg. ACTH increased the output

figures irregularly and administration of cortisone of an order greater than 37.5mg. daily could almost completely suppress the endogenous production of 17-ketogenic steroids.

The Control of the Adrenal Cortex.

The activity of the adrenal cortex is regulated by the anterior pituitary by means of its adrenocorticotrophic factor (ACTH, corticotrophin). Hypophysectomy leads to atrophy of the adrenal cortex and subsequent administration of the trophic hormone restores the appearance of the cortex to normal.

Many conditions of stress stimulate adrenocortical activity but only in the presence of an intact pituitary-adrenal axis: Harris (1951) demonstrated that stimulation of the hypothalamus in the posterior region of the tuber cinereum or mamillary body resulted in increased adrenal cortical activity due to secretion of a substance in to the hypophysial portal system. Part of the body's reaction to stress is that the hypothalamus is bombarded by afferent stimuli with the production by the pituitary of ACTH.

One of the first reactions of the tissues to local or general stress is increased utilisation of cortical hormones. This leads to a fall in the levels of circulating hormones and a response by the anterior pituitary in releasing greater amounts of ACTH. This reciprocal arrangement is the basis of Sayers tissue utilisation hypothesis and Harris while believing that the hypothalamus constitutes the major factor in control of ACTH secretion concedes that Sayers mechanism may be responsible for very fine adjustment of ACTH production, except when emergency or

acute stress conditions are operating.

Long (1950) believes that two mechanisms are involved: firstly the relative blood levels of ACTH and corticosteroids and secondly in an emergency, the release of adrenaline which operating through the anterior pituitary produces ACTH. Recent work (Hunter et al. 1955) must tend to minimise the importance of the latter mechanism.

Clinically, the administration of ACTH produces the same physiological response as cortisone but leads to an hypertrophy of the cortex rather than atropy as in the case of cortisone.

The Stress Concept. Many diseases have no single cause, no specific pathogen but are largely due to non specific stress and to pathogenic situations which result from inappropriate responses to such non specific stress (Selye 1952). All stresses which act upon the organism do so with a dual effect:

1. Specific action e.g. an anaesthetic producing anaesthesia.

2. Non specific action manifesting itself in the form of the General Adaptation Syndrome, mediated through humoral and nervous pathways. The former pathway is by means of the anterior pituitary-adrenal cortex axis and produces the "adaptive" hormones, ACTH and the glucocorticoids which inhibit inflammatory responses (anti phlogistic corticoids) and somatotrophic hormone (STH) and the mineralocorticoids which stimulate such responses (prophlogistic corticoids).

The increased output of adrenal cortical hormones in some way assists the tissues to counteract and resist changes in their internal environment.

Stress affects the peripheral target organ not only by

increased corticoid output but also by increasing the tissue sensitivity to the corticoids: this is known as the "conditioning effect".

There are three stages in the process of combating stress:

1. The "alarm reaction" which in the initial phase leads to a loss of lipoid and chromophil material from the adrenals and an increase in the tissue utilisation of corticoid hormones. The adrenal medulla and certain hypothalamic nuclei are also stimulated, ACTH production is stepped up and simultaneously the production of other anterior pituitary hormones is decreased.

2. Subsequently, an hypertrophy of the adrenal cortex occurs, chromophil material appears in increased amounts in the medulla, the thyroid tends to become hyperplastic and the gonads may atrophy.

3. Under prolonged stimulation, an internal resistance is acquired so that the appearance and physiology of the internal environment may return to normal. If however, stimulation is excessive a stage of exhaustion of the adrenal cortex may be reached.

Selye regards these phenomena as initially indicating a condition of relative adrenocortical insufficiency but it has been repeatedly pointed out that a degree of cortical insufficiency is not essential for the production of the alarm reaction (Kendall 1951, Pickering 1950, Meiklejohn 1950).

Psychiatric States occurring during Cortisone and ACTH Therapy.

All authors are agreed that cortisone and ACTH may have an effect on mood. The incidence of altered mental state in those undergoing treatment by these substances is given as 95% by Rome and Braceland (1952), 70% by Cleghorn (1952), 48% by Rees (1953) and 36% by Ragan (1953).

Some increase in alertness, mental outlook and feeling of well being probably occur in all patients, especially at the commencement of the administration (Bishop 1954) and he notes that it is difficult to seperate the reactive element resulting from improvement in a previously chronic disease, from a specific psychic manifestation attributable to the hormones; he states that more severe reactions when they occur almost always do so in patients who have at some previous time shown signs of instability and the particular form of the psychosis whether manic, hallucinatory, paranoid or depressive is determined by the previous personality pattern.

The psychological effects of cortisone and ACTH have been graded by Rome and Braceland (1951) into four general categories. The first two contain relatively mild deviations of affect, the third group adds to these changes involving ideation and behaviour and the fourth shows an intensification of these functions to such a degree as to merit the description psychotic reaction. They consider that the most frequent change is an elevation of mood which coincides with improved general condition and diminution of the disease process: however, when a grade 3 response occurs a different adaptive mechanism operates, the psychological responses being psychoneurotic in character, the reaction now bearing no

relationship to clinical improvement: the underlying disease may be vastly improved although the patient is anxious and depressed. The content of the grade 4 response is symbolic of conflicts of many years standing: the delusions , hallucinations and mood variations involve early psychosexual conflicts as well as referring to recent physical symptoms; it is a primitive form of adaptation.

In a further joint paper (Rome and Braceland 1952) based on the study of more than 100 patients with various medical conditions who had received ACTH or cortisone and also on a series of patients with schizophrenia or involutional depression, the authors classify the types of psychological responses met. Sixty per cent of the group showed the milder grade 1 and 2 reactions, 25-30% of the patients exhibited grade 3 reactions and 10% showed grossly psychotic reactions, these latter subsiding on discontinuation of treatment spontaneously. None of the patients who were suffering from existing mental upset showed any gross change. The authors suggest that cortisone and ACTH have the capacity to modify ego defences; psychological conflicts, formerly asymptomatic can be lighted up with the production of a new train of symptoms. These substances by producing a metabolic shift provoked an internal environmental stress with which the customary psychological defences could not deal. The authors also remark that sudden transformation in to improved physical health in a psychologically unprepared patient may constitute a stress which in turn mobilises responses characteristic of the patient: they feel the psychotic reactions tend to occur in those patients whose adjustments in the past had been marginal and that there was no positive correlation

between the extent of the metabolic changes and the associated psychiatric picture.

A different scheme of classification of psychotic reactions has been suggested by Hoefer and Glaser (1950). They observed two major psychotic patterns with an incidence of 5.5% of the total cases treated.

1. An affective disorder either in the direction of mania or depression.

2. More frequently they observed an organic picture consisting of mental confusion, disturbance of awareness and disorientation associated with paranoid—hallucinatory and/or affective disorders.

Those disorders belonging to group 2 tended to clear up on discontinuation of therapy but the affective reactions if more than mild required electric convulsive therapy (ECT): some of the patients had shown psychotic tendencies prior to treatment.

It is repeatedly remarked by observors that no significant correlation exists between hormone dosage, type of reaction, degree of metabolic upset, duration of treatment before the psychotic reaction develops and the severity of the reaction (Glaser 1953, Rome and Braceland 1953, Clark et al. 1953, Gookler and Schein 1953).

In a series of 22 patients of both sexes suffering from rheumatoid arthritis (McLaughlin et al. 1953), treatment with ACTH produced remission or physical improvement in 50% of the cases and it was in this group that improved mental outlook evidenced by a sense of wellbeing and lessening of mental tension was observed: the group which showed little or no physical improvement was also reported to show

increased tension and irritability and when the dosage of ACTH was increased in 3 cases in an attempt to secure a remission of physical symptoms, agitation anxiety and depression became so marked as to necessitate hospital care in 2 instances.

Gookler and Schein (1953) reported on 80 patients receiving ACTH or cortisone for various physical conditions: 46% showed some degree of psychic disturbance: of this disturbed group, 70% belonged to the category of euphoria or alternating moods: of the entire group, 15% showed psychotic reaction patterns with a mixed clinical picture classified as depressions, paranoid reactions, schizophrenia and toxic syndromes: most of them were transient and self limited. The authors could observe that there were no indications that pre-treatment psychic structure influenced the appearance of the more severe reactions.

Opinions are sharply divided on this question of the significance of the pre-treatment personality in the production of untoward reactions. Most reports emphasise the increased possibility of psychotic breakdown in those with a previous history of a psychotic episode, emotional instability or psychological maladjustment although those who hold this view cannot justify their conclusions on statistical grounds. Clark and his colleagues (1953) could find no such correlation in their series of 23 patients developing severe mental disturbances, patients who had received previous courses of ACTH or cortisone breaking down on subsequent courses. Brody (1952) in an analysis of 8 patients receiving ACTH or cortisone observed initial euphoria in 7 patients: subsequently, persistent euphoria developed in 2 cases, a psychotic

reaction in 2 cases and a depressive reaction in 3 cases: the author observed that the variety of reaction seemed to depend on the personalities of the patients and to reflect an exaggeration of their normal responses. In most cases these patients' defences were normally rigid or liable to break down under the stress of overstimulation or frustration: they showed the dynamic pattern of turning aggression inwards with the production of organic illness to maintain a neurotic equilibrium and hormone therapy was interpreted as a threat to this equilibrium as when the organic focus was denied the aggression became free floating.

Inadequate expression of feeling, remoteness, overdependence and over censorship of erotic and hostile feelings were the predominant features observed in a mixed group of patients suffering from rheumatoid arthritis (McLaughlin et al. 1953). Increased overtly aggressive behaviour was more prominent in patients with remissions or major improvement in physical symptoms. Patients in whom the precipitating stresses had since diminished, showed the most favourable remissions whereas if the stresses had increased, the patient either failed to improve or relapsed when treatment was stopped.

Rome and Braceland (1952) suggest that several physiological and psychological factors may interact in the production of disturbed mental states in patients receiving ACTH or cortisone.

1. The particular response is governed by personality organisation.

2. Psychotic reactions tend to occur in patients with a previous

history of difficulties in adaptation.

3. Sudden or profound changes in the psychological or metabolic fields demanding rapid adaptation at a different level are more disturbing than more gradually developing changes.

The authors have support from Rees (1953) when they stress that one does not obtain a specific psychic reaction on exhibition of ACTH or cortisone and that many factors besides the hormones themselves are involved, in particular the patient's personality, his predisposition to psychiatric illness and his capacity for adjustment to internal and external changes. In his series, Rees describes 40 patients receiving either ACTH or cortisone and notes the absence of severe psychotic reactions even although 6 of the cases were primarily psychiatric. The rate of physiological change as well as the degree to which these changes in the internal environment occurred were considered important in producing psychotic reactions; milder mental changes occurred in 48% of the patients under treatment.

Fleminger (1955) gives an account of mood changes in relation to adrenal function in a case of psoriasis arthropathica treated firstly with cortisone and later with ACTH. He comes to the conclusion that in this case there are indications that cortisone administration tended to produce an elevation of mood and ACTH provoked a depressive reaction, in both cases irrespective of the effect of the hormones on the disease itself. He suggests on the basis of his investigations and findings that the factors influencing mood may be the relative proportions of androgens to other adrenocortical steroids rather than the absolute

levels of these substances.

What evidence there is for a tendency to a specific mood reaction to the two hormones under consideration is scanty and conflicting. Lidz and his colleagues (1952) considered the reverse relationship to that of Fleminger more probable that is that ACTH provoked a euphoric reaction more frequently than cortisone and in the report previously mentioned of Gookler and Schein, they comment that ACTH is "more likely to be associated with psychic phenomena" but place little significance on this finding. Hench and his co-workers (1950) commented that their patients receiving ACTH were less euphoric than those on cortisone therapy.

The electroencephalographic changes under ACTH therapy usually consist of a reduction in amplitude as well as a slowing of alpha activity (Haefer and Glaser 1950) and irregularities appearing as bursts of slow activity: the authors found a positive correlation to mood changes. In Cleghorn's series, it is remarked that EEG changes were absent in those undergoing ACTH therapy. Studies on patients receiving ACTH or cortisone (Glaser 1953) indicated although cerebral function may be altered there is no consistent relationship between these changes and psychotic reactions. He remarks that many of his patients have shown similar changes in the electroencephalogram without significant mental disturbance being present. Rees (1952) noted no changes in EEG recordings during cortisone administration to schizophrenic patients.

On surveying the literature on mood variations occurring during ACTH or cortisone therapy, one notes repeatedly either the conflicting

conclusions of the various authors on the importance of psychological integration and metabolic upset or more usually the comment that the more severe reactions occurred in a quite unpredictable way unrelated either to hormone dosage, duration of treatment or upset in the internal environment. The previous experiences and innate personality type of the individual must largely colour the content and nature of the particular reaction but would seem merely to provide the clinical material rather than be important in a causative sense. The exception to this generalisation is in the case of certain psychosomatic illnesses where the disease either serves a purpose in maintaining psychological stability and/or is the result of repressed and inturned aggression. Here the suppression of the symptom by hormone therapy may loose forces which the particular individual has no satisfactory way of dissipating apart from his own soma and disintegration of the remaining psychological defences results in the appearance of a psychotic reaction. The position may be likened to the removal of a hysterical paralysis by means of hypnosis without dealing with the underlying stresses: such a procedure although technically successful may result in free floating anxiety or the appearance of a fresh hysterical phenomenon, if the need for a neurotic device still exists.

Cleghorn (1952) puts forward the most convincing explanation of such acutely disturbed states when he postulates that in certain circumstances, cortisone becames a toxin and that in some toxic psychoses it may be the actual agent; if so, he comments, it is an example of the derailment of the process of adaptation. This fails to take account of

the minor degrees of mood changes which occur in the vast majority of patients undergoing therapy and which are not related to relief of the particular disease; here it can be postulated that some internal dysharmony of the total endocrine balance reacting on the hypothalamus has occurred rather than the effect being due to a direct action of the administered hormone.

Adrenal Function in Psychiatric Disorders.

As schizophrenia can be theoretically be regarded as a disorder of adaptation with regression to behaviour patterns involving earlier and more primitive psychological mechanisms, it is understandable that in the last decade much research has gone in to the pituitary-adrenal axis in this disease. Much of the controversy which has arisen and the conflicting reports published have been caused for two reasons. Firstly, the term schizophrenia includes many differing clinical pictures: it is a disorder protean in its manifestations varying from the so-called schizophreniform reaction type which frequently remits spontaneously to a malignant unremitting form which procedes to almost complete fragmentation of intellectual and emotional life. Secondly, the effects of long term hospitalisation in a protected and relatively unchanging environment have to be taken in to account as the degree of adaptation necessary after the initial period is at a calculated minimum; the stage in the development of the illness at which the investigations are undertaken is important: in the earlier or acuter phase, the illness with all its symptoms may well be regarded as a fighting attempt to maintain an internal equilibrium which is on the verge of collapse, while later on a more static even if unsatisfactory balance has come in to existence.

In the main, three problems have been posed and investigated by researchers into the adrenal aspects of schizophrenia.

1. Whether the corticosteroids secreted are abnormal qualitatively or are abnormal in their ratios to one another.

2. Whether the responsivity of the adrenal cortex is normal,

hypo-reactive or hyper-reactive.

3. Whether the peripheral utilisation in the target organs is taking place normally.

The relationship between psychosis and hyperadrenalism was first specifically remarked upon by Broster and his team in 1938 when they commented on the appearance of four cases of psychosis occurring in their series of patients suffering from the adrenogenital syndrome.

In 1948, Hemphill and Reiss published their investigations on a group of six chronic catatonic patients who had not responded to recognised treatments: various investigations including fractionated 17-ketosteroids, urinary cortin excretion and other hormones found in urine were studied: although clinically these patients appeared similar, their fractionated ketosteroids varied greatly and in one patient no dehydroandrosterone whatsoever could be found. This latter patient made a moderate clinical response to injections of testosterone, the benefit being maintained for about a year so long as therapy was continued; similar treatment to the other members of the group failed to produce improvement.

The diurnal variations in excretion of 17-ketosteroids met with in normal persons are a measure of the adaptation displayed to the demands of the environment. Excretion is low during the night but rises steeply on waking followed by a gradual decline during the rest of the day (Pincus 1943). The increase on levels shortly after waking compared with sleeping levels in normals is around 60% (Pincus and Hoagland 1943). Again, in normal subjects, the day to day variations in levels of

urinary 17-ketosteroids are remarkably constant: Reiss et al. (1949) illustrated and confirmed these observations and compared them with their findings in chronic schizophrenic patients. They found that the daily fluctuations estimated at intervals for several months showed either constant or widely varying values and they were able to differentiate four distinct abnormal diurnal curves of 17-ketosteroid excretion.

1. An increase in the waking output compared with the night output greater than 60% and sometimes as much as up to 400%, but followed by a normal fall off.

2. A relatively flat picture with only slight variations from day to night.

3. Maximal excretion delayed until later in the day instead of during the period immediately after waking.

4. A second peak in output occurring late in the day in addition to the morning rise.

In an analysis of their findings they observed that those patients whose excretion was constant over months were older schizophrenics who had been in hospital over 10 years: their diurnal curves were of the flat variety (type 2). The types 1.3 and 4 variations consisted of restless and hallucinated patients and the daily total excretion showed wide fluctuations: no definite conclusions could be drawn from the investigations although the authors thought that differentiation of the type of curve might possibly be useful for diagnostic and treatment purposes.

Further observations of adrenocortical activity in relation to

the psychoses (Hoagland 1953) indicated according to the author that schizophrenic patients compared with normals might be deficient in the production of steroids regulating the retention of sodium and that they were certainly deficient in overall corticosteroid output: the precursors of the 17-ketosteroids however were produced in excess by the patient group. Direct measurements of corticoids indicated a mild hypo-adrenalism in the schizophrenic patients, more pronounced in the younger patients and the excessive loss of sodium and water was consistent with this conclusion although the patients tended to lose more potassium than the normal controls. From the ketosteroid findings, one might conclude that the patients are hyper-adrenal in relation to the normals, in contradiction to the evidence obtained from direct corticoid measurements, as the 17-ketosteroid excretion of the younger control group was 75% of that of the younger patients and the older normals 72% of the older patients. The author suggests that this evidence of "hyper-function" is limited to the precursors of the 17-ketosteroids. The low levels of circulating eosinophils which were demonstrated in the patient group do not indicate a continuous overproduction of 11-oxysteroids as judged by the subnormal corticoid production and the author suggests that some unusual eosinophil lowering substance may be present in certain schizophrenic patients. He concludes by interpreting the data as indicating a correlation between psychosis and certain qualitative and quantative differences in adrenocortical steroid metabolism but there is no evidence to indicate that these disturbances actually initiate the psychosis.

In a review of the psychological changes seen in mental disease, Altschule (1953) finds that the adrenal cortex is hyperactive in many patients suffering from manic-depressive, involutional and schizophrenic psychoses. He cites twelve points to support this view, the more important indications being impaired glucose tolerance, eosinopenia, insulin resistance, negative nitrogen balance, creatinuria and relatively high 17-ketosteroid outputs: clinically, the association of hirsutism and acne with the psychoses is also significant: these findings indicating cortical hyperactivity tended only to be found at the commencement of the psychosis and with increased duration of the illness the differences levelled out. The author concludes that if it is not possible to state categorically whether the changes actually represent increased activity of the adrenal cortex or whether changes in the reactivity of enzyme systems in the peripheral tissues controlled by adrenocortical hormones have occurred: the changes seen are probably both the cause and the effect of the psychoses.

In an earlier paper (Altschule et al. 1952), the authors reported on their observations on blood eosinophil levels in 118 treated and 244 untreated cases of mental illness, as compared with a control group of 25 normal subjects. The counts were in or below the low range of normal in the majority of the patients and mood, degree of activity, nutritional state or type of illness bore no realtion to the count: patients who had been ill continuously for more than one year tended to show more normal counts: again, the conclusions were that patients suffering from severe neuroses and the major psychotic disorders showed

an increase in some adrenocortical functions and that when recovery took place the eosinophil count rose indicating a depression of these functions.

The differing conclusions arrived at by the above authors are not quite so opposed and incompatible as first appearances would suggest but are to some degree a difference of interpretation. Hoagland observed that the eosinophil counts in his patient group were only about half that of the comparable control group, the 17-ketosteroid excretion rate was increased and his main evidence in support of hypocorticalism was the decreased output of urinary corticoids which could be accounted for by increased tissue utilisation: another factor against Hoagland's conclusions are that his group of schizophrenics consisted largely of chronic institutionalised patients and the low outputs are what one tends to find in any long term debilitating disease.

A further possible explanation of these opposing views can be inferred from a study by Stevenson et al. (1953) in to 30 male chronic schizophrenics: the authors studied the responses in the levels of eosinophils to the administration of test doses of adrenalin and corticotrophin compared with similar control periods when no treatment was being given. Both adrenalin and corticotrophin caused mean relative decreases greater than those occurring during the control period but not so great as those reported for normal healthy people. The variations in the responses in different patients was so marked that the authors felt that types and stages of the schizophrenic syndrome may be associated with different functional states of the adrenal cortex and of the systems regulating it:

comparing the test results in 11 catatonic patients compared with 12 paranoid patients partially composing the group, the catatonic patients showed relatively normal responses but with decreases greater than normal on the control days while the paranoid group produced significantly smaller responses to adrenalin and corticotrophin but normal eosinophil changes in the control periods. The authors concluded that there was presumptive evidence that the adrenocortical system was hypo-active and hypo-reactive in the paranoid schizophrenic and perhaps hyper-reactive in the catatonic schizophrenic.

Reviewing the investigations of his group in to the adrenal activity and responsiveness of chronic schizophrenics, Pincus (1952) concludes that the defective stress response observed in the schizophrenic patients does not involve inability of the end organs to respond to adrenal steroids but that the impairment is situated in the pituitary-adrenal axis and more particularly in the responsivity of the adrenal cortex itself. Response to various stress tests including the administration of corticotrophin disclosed that approximately 70% of the schizophrenic patients investigated tended to be hypo-adrenal; to measure this responsiveness, he formulates the term Total Response Index (TRI) which is the mean percentage change from pre-test control values in post-stress samples of 17-ketosteroids, sodium, potassium, uric acid, corticoids and lymphocytes. Normal values for the TRI (i.e. TRI values of greater than 20) were obtained in only 30% of schizophrenics where the disease had a duration of more than 2 years: with more recent admissions normal TRI values were found in 50% of those suffering from

schizophrenia. Increasing the stress, as with larger amounts of ACTH led to TRI values closer to normal. Dealing with urinary steroids, the use of improved chromatographic separation techniques allowed him to report that schizophrenic patients excreted lesser amounts of corticosteroids and neutral non-ketonic steroids and that they have a relatively lower stress responsivity of the adrenal cortex to both endogenous and administered ACTH.: he found the beta-steroids abnormally high in his schizophrenic patients quoting the mean percentage of the total ketosteroid excretion as 11.5%, a figure which is within the usually accepted normal range of 5-15%. The author suggests that steroid dysgenesis exists in schizophrenia, corticosteroids being affected both qualitatively and quantitatively.

Further studies on both schizophrenic and depressed patients (Lingjaerde 1953) failed to show any persistently significant differences compared with normal volunteers. The functions under investigation were the determination of 17-ketosteroids in urine, the adrenalin, ACTH and insulin tolerance tests. No individual patient gave a negative reaction to all the tests or to both adrenalin and ACTH.: the ACTH test gave a normal reaction in 94% of schizophrenics and 100% of depressives. The author failed to find any pattern from the results which could be described as characteristic of schizophrenia. Reiss et al. (1951) reported on their results of investigating the adrenal cortex responsivity in over 350 psychiatric patients comprising acute psychoneuroses and acute and chronic cases of psychoses. Adrenal responses were compared in the various psychiatric categories following the injection of 25mg. ACTH

the ingestion of 150 GM of glucose or one electro-convulsive treatment: the observations were that in chronic schizophrenia fewer positive responses to glucose were obtained than in acute schizophrenia and that in males with anxiety a prominent clinical feature, there were no completely positive responses to ACTH., although no response types were characteristic of individual disease groups. The distribution of the responses indicated that different hormonal components are mobilised when the patients were subjected to the three stressful experiences indicating evidence for the existence of a number of different adrenocorticotrophic fractions with separate functions. It also appeared that improved responsivity occurred following clinical improvement either spontaneously or in response to treatment and that the psychiatric improvement had been to some extent dependent on the total hormonal equilibrium of the patient. Some support for this view is given in a report of two females suffering from recurrent schizophrenia (Rowntree and Kay 1952) on whom a number of physical and metabolic investigations were made during four illness episodes. These two patients displayed a dissociation between different adrenocortical steroids, the course of the attack being progressively associated with a relative preponderance of different steroids: briefly, these changes were that during the build up of the schizophrenic episode there was produced a preponderance of androgenic substances and during the process of recovering and while in remission, a preponderance of glucocorticoids.

Cases of manic-depressive psychosis especially of the cyclical type where a regular rhythm of mood changes has been established would

appear to be a fruitful source of investigation. Reiss et al. (1949) described their findings of the relationships between mood changes and adrenocortical activity and these will be considered in a later section. In other cases of depression Reiss finds that either over- or under-function of the adrenal cortex may occur in association with the affective disorder but stressed that investigating the function of one gland only, presented a most imperfect view and that the total state of the hormone equilibrium was the decisive factor: he illustrates this by presenting nine cases of depression, investigated for 17-ketosteroid activity, urinary corticosteroid output and thyroid activity. Many variations of the separate functions under consideration may be present at the height of the illness but as the patient improves either spontaneously or as the result of physical or hormonal treatment, the various indices tend to shift in to their respective normal ranges.

The apparently conflicting reports regarding adrenal cortex activity and responsivity seem to illustrate the theme that in many psychiatric disorders, variations outside the normal range occur with significant frequency; there is no clear indication whether these deviations are primary or secondary as the fact that improvement in clinical condition may be associated with normalising hormonal equilibrium does not prove that the latter has been a primary cause of the former; there is at present no convincing evidence that schizophrenia or manic-depressive psychosis is either a disease of the adrenal cortex or a disorder of the adaptive mechanisms in the purely physiological sense.

Treatment of Psychiatric Disorders by ACTH and Adrenocortical Extracts.

It is an interesting feature of the psychoses, especially schizophrenia that they do not seem to react in the expected way to the administration of hormones; it requires much higher dosages of thyroid to produce signs of overdosage and similarly the insulin resistance encountered in the insulin coma therapy for schizophrenia may even occasionally render the treatment impracticable; dramatic fluctuations in this resistance may occur in the course of therapy especially after the administration of electroplexy which produces 'shock' effects in the pituitary-adrenal system.

The reaction of the psychotic to the administration of ACTH and cortisone follows the above examples in being atypical. When Hench and his colleagues described the characteristic euphoria in mentally normal patients, it was not unnatural to expect that the exploitation of this primary mood change in the treatment of psychiatric illness would follow. Hemphill (1955) comments that the extensive use of these hormones in the Bristol Group of Mental Hospitals has not been followed by the expected reactions comparable to those described in a normal population: euphoria seldom was a noticeable feature.

Published studies of hormone administration to psychotics are again conflicting and for the most part negative. Rees and King (1952) gave a four day course of cortisone to 12 chronic schizophrenics and no significant improvement was observed either by means of clinical appreciation or by psychiatric rating scales; they were thus unable to

confirm the promising results of Cohn and Karnosh (1951) who claimed dramatic improvements in chronic schizophrenia. In 1953, Cohn and others further reported that 6 out of 21 chronic schizophrenic patients had been so improved by cortisone as to enable them to be discharged from hospital: Cohn pointed out that the dosage employed in Rees and King's series was too low and of too short duration and in 1956 the latter reported on a group of 9 schizophrenics with a control group of similar number and matched for age, sex and duration of illness; the treatment group received dosages of cortisone for three weeks to the point of marked side effects. No significant improvement occurred either in the treated or control group: one patient in the former group showed a temporary worsening of his psychiatric condition. Euphoria was noticeably absent.

Pincus and Hoagland presented evidence that the adrenal cortex in the psychoses might be hypo-reactive and so the administration of ACTH might be expected to produce clinical improvement. This has not been confirmed either by the Bristol Group or in the published reports of Hoefer and Glaser (1950), Rome and Braceland (1950), Glaser and Hoch (1951), Hope et al. (1952) and Kobbernagel et al. (1953).

The effects of cortisone on a wide range of psychiatric disorders of recent origin (Chance et al.1954) were studied from the psychological and psychiatric testing view points. Cortisone was given for 30 days, at first in a high suppressive dosage and then dropping to maintenance levels: the authors stated that the standard measurements of

testing i.e. psychiatric rating and psychological testing, were not significantly altered in the group receiving the hormone as compared to the control group receiving placebos.

High dosage cortisone treatment of nine non-deteriorated schizophrenic patients consisting of 500mg. daily for from 4-10 weeks produced a slight and transient improvement in 3 cases, one case was uninfluenced and the remaining 5 were made worse: the cases showing benefit failed to maintain their progress when the drug was stopped (Polatin et al. 1955).

Similar negative results have been reported in depressive and involutional melancholic states. The beneficial results with cortisone administration reported by Hemphill et al. (1942) have not been confirmed by other workers (Cleghorn et al. 1950, Rome and Braceland 1950).

One of the few adrenal steroids which might establish itself in correcting certain psychiatric states is dehydroisoandrosterone ("Diandrone"). The beta fraction of the urinary 17-ketosteroids mainly consists of this substance and animal tests indicate that it has a mild androgenic effect, weight for weight one hundredth the potency of testosterone; as discussed previously there is still considerable doubt whether it is normally present in urine as there is evidence to suggest that it may be an artefact produced in the process of preparation of the urine by acid hydrolysis: it might also be present merely as an overflow in to the urine of an intermediate substance in the biosynthesis of certain adrenocortical hormones.

Strauss et al. (1952) studied the effect of "Diandrone" on a

group of selected cases of schizophrenics and "schizoid psychopaths" who at the same time showed abnormal 17-ketosteroid excretion values. Their case material consisted of 8 males between the ages of 16 and 35 in whom the total 24 hour ketosteroid output and in particular the alpha-beta ratio was found to be abnormal. Some of the patients showed high beta fractions and some abnormally low values and the frequency, length of treatment and dosage varied from case to case. The changes found were chiefly in the direction of increased self-confidence and a slight euphoria: they became less fearful and apprehensive, more energetic and the outside world became more real. Those patients with undifferentiated or homosexual orientation began to show heterosexual interests. The authors could not confirm that the improvements were necessarily reflected in a more normal 17-ketosteroid excretion spectrum but felt that the correlation with psycho-sexual and physical immaturity was highly significant. Two of the patients with aggressive and paranoid tendencies became more so and treatment had to be stopped and the authors noted the necessity for caution in the matter of dosage when aggression was present in the symptom picture.

Working along the same lines Sands et al. (1952) reported on the use of the drug on 13 juvenile cases, average age 13 years, the clinical picture being predominantly that of constitutional and emotional immaturity. They were physically retarded, looking younger than their ages and in two cases the genetalia were undersized and the testes incompletely descended. As a group they were inadequate, timid and occasionally distinctly effeminate. "Diandrone" was administered in

doses ranging from 10-40mg. daily: as with the previous authors the general effects were an increase in confidence and "outwardness", an improvement in social relationships and a swing towards all round adjustment. The results indicated that of the 13 cases, 2 recovered and 8 showed varying degrees of improvement. As some had relapsed at the end of one year the authors considered that prolonged treatment over months was indicated. The estimation of 17-ketosteroids was of little value in selecting patients for treatment, about half the cases showing normal values and the other half being found to have low outputs but the pre-treatment levels in 17-ketosteroids were not prognostically significant. The drug was also administered to 4 juvenile patients with predominantly aggressive character traits but in all cases treatment had to be stopped on account of destructive behaviour and increased tension or aggressiveness. Two years later these general conclusions were confirmed (Sands 1954), although the author did not feel that a primary mood change occurred but rather that "Diandrone" exerted an androgenic effect on weight and secondary sex characteristics. Combined treatment with "Diandrone" and stilboestrol helped certain cases of schizophrenia who had difficulties in sex and social adaptation and in whom the conventional physical treatments had failed.

Further encouraging results with this hormone in the treatment of a group of university students (Lamb 1955) showed that the personality type which was most helped was again the inadequate, timid, frightened person, lacking in confidence and initiative and poorly socially adjusted. The average dose was 25mg. on alternate days and of the 11

subjects treated, eight showed both subjective and objective improvement in the above characteristics. Strauss and Stevenson (1955) reported obtaining good results in their group of 11 patients showing immature and inadequate features with "Diandrone", some improvement occurring in all cases. They stressed that in the first instance dosage should be low and built up gradually in order to avoid precipitating increased anxiety and aggression.

Endocrinological Aspects of the Physical Methods of Psychiatric Treatment.

Electric convulsive therapy (electroplexy, E.C.T.) and insulin coma therapy are at present the two most accepted physical forms of treatment in the psychoses. Insulin coma therapy introduced by Sakel is used mainly in the treatment of schizophrenia although recent controversy in the Lancet (1955) on the subject of the "insulin myth" has led to a re-examination of the results of the treatment. A recent controlled study by Ackner (1957) also casts doubt on the usefulness of the treatment. Best results are usually obtained only in schizophrenia of recent origin, that is the period during which spontaneous remissions would be most likely to occur (Gottlieb and Houston 1943). There is statistical evidence to suggest that in the long term view the results in the treated and untreated groups are similar. However even if this were so, clinical experience seems to justify the continued use of the treatment for the present in that it can at least produce a remission of the disease at an earlier date than that which would occur naturally. The production of hypoglycaemic coma seems to be the essential factor as lesser degrees of hypoglycaemia such as perspiration and sopor are clinically ineffective.

E.C.T. consists of inducing epileptiform fits at intervals by electrical means and has largely superceded the chemical form of induction. Best responses are seen in patients suffering from depressive illnesses such as involutional melancholia, endogenous depression or senile depressive disorders: manic states and paranoid and schizophrenic states are less influenced.

That electroplexy induces an increase in adrenocorticotrophic hormone output has been established for many years and confirmed on frequent occasions subsequently (Hemphill et al. 1942, Hoagland et al. 1946, Parsons et al. 1949 and Early et al. 1951). Electroplexy also influences other anterior pituitary fractions as evidenced by clinical observations on its effect on menstruation: menstruation may be suppressed for several months following treatment or may occur precipately and excessively in a patient who has not menstruated for several months previously. According to Michael (1956), the usual effect produced is that of temporary amenorrhoea: the author noted that while electroplexy usually led to lengthening of the menstrual cycle, in contrast in certain manic-depressive and paranoid schizophrenic patients it led to premature and heavy menstruation. He felt that whether the cycle was lengthened or shortened was related not to the capacity to improve with treatment but to the type of illness and diagnostic category. That electroplexy also affects the release of thyrotrophic factor seems probable from the work of Reiss and his colleagues (1951, 1953). Using a radioactive tracer method to give an index of thyroid activity before and after treatment, they found that in 1000 psychiatric patients about 20% showed values outside the normal range in both directions and when clinical improvement occurred in some cases, the thyroid indices moved in to the normal range.

Pincus, Hoagland, Freeman and Elmadjian (1949) claim to have shown that the effect of one E.C.T. is equivalent to the effect of 100mg. of ACTH, an observation largely confirmed by Early et al. (1951).

It is clear however that the therapeutic effects of electroplexy depend on more than the release of ACTH as clinical improvement cannot usually be brought about in cases which would respond to E.C.T. by the administration of adrenocorticotrophic factor alone.

On a series of 350 psychiatric cases, Reiss et al. (1951) appeared to show that different functions of the adrenal cortex could be aroused in different degrees and in different orders when they compared the effects of E.C.T., ingestion of glucose and the administration of ACTH in these patients.

The first few treatments by either electroplexy or insulin coma therapy seem to stimulate the adrenal cortex as observed by eosinopenia, water retention, increased excretion of uric acid and 17-ketosteroids and by a worsening of the carbohydrate tolerance (Altschule 1953). As further treatments are given, the adrenal response diminishes, this phase coinciding with clinical improvement and Altschule felt that in those patients who do improve, the adrenal activity fell to below pre-treatment levels as represented by a steadily rising eosinophil count. Alexander and Neander (1953) also found evidence of depressed function of the adrenal cortex following physical treatments in 44 out of 56 patients studied as evidenced by serial eosinophil counts only; of these 44 cases, 75% showed clinical improvement while 5 cases who did not benefit showed no response in the resting eosinophil levels after treatment.

Additional evidence of adrenocortical stimulation by E.C.T. and insulin therapies was published by Shattock and Micklem (1952) in a study of changes in eosinophil levels before and after physical treatments.

Eosinophil counts were made before and four hours after electroplexy as this interval was found by experiment to provide the maximal fluctuations. A fall greater than 50% of the original count was taken as a positive response and over two-thirds of the cases gave this type of response. No definite conclusions can be drawn about the clinical significance of a positive response as some patients who gave less than 50% responses derived benefit from the treatment. On the whole however, the positive responders seem to include a higher proportion of patients who recovered. The authors observed that they could not confirm the observations of Altschule that the eosinopenic response after the first E.C.T. is always adequate and that it tends to fail when repeated treatment is given, as some of the authors' cases showed inadequate responses after first second or third treatments.

The effects on eosinophil levels during coma therapy were also investigated by Shattock and Micklem. By experimentation they found that three hours after the injection of insulin the eosinophil count had changed insignificantly but by four hours after the onset of coma (seven hours after the injection of insulin), the maximal fluctuations had taken place. Seven patients given insulin in non-coma dosages showed only insignificant changes in the later counts. A comparison of the two counts in patients who developed comas showed that in every case a fall greater than 50% had occurred, the mean fall being 74% compared with the earlier count. It is interesting that in both E.C.T. and insulin coma therapy, the maximal depression of the count took place four hours after the effective part of the treatment.

Rud (1947) and Sackler et al. (1951) reported on the observation of a tendency to a rising eosinophil count occurring during the course of the administration of electroplexy or insulin coma therapy, the samples being taken at times when treatment would not directly influence them. They regarded this rise in the 'resting' eosinophil levels as being of good prognostic significance. Shattock and Micklem confirmed this tendency in their insulin patients but found in their series that some patients who were clinical failures had also shown this rising 'resting' level during the course of treatment.

To summarise the conclusions, the exact mode of action of electroplexy and insulin coma therapy is unknown but more detailed research of their effects on hormonal balance seems to be the most promising line. That these physical treatments affect the anterior pituitary seems to be proved but the conclusion that the changes so produced have influenced the clinical condition has not yet been determined. Whatever the results may be it seems unlikely that the beneficial effects are mediated solely through the anterior pituitary-adrenal cortex axis but rather that through the various anterior pituitary trophic hormones, the total glandular equilibrium of the body is disturbed or shaken up giving the organism an opportunity to eventually settle down in to a more stable pattern. That this might be so is indicated by the observations that whether the disturbances in the adrenal cortex, thyroid and ovaries are in the direction of hypo- or hyper- activity, coinciding with clinical improvement the various indices of function of these glands tend to return to within the normal range.

It is not too distant to speculate that emotional disturbances might be received and transmitted through the hypothalamus and anterior pituitary eventually producing in susceptible individuals an infinite variety of hormonal disrangements which prevent the individual, by a feed back arrangement, from reaching a psychological equilibrium to his emotional difficulties. However this theory will only be acceptable when it is possible to measure accurately and define the disturbed hormonal pattern and to correct it and relieve the patient's condition by the appropriate glandular treatment.

Psychiatric Abnormalities in Adrenal Disorders.

If the relationship between psychoses and adrenal function is still obscure, it is natural to consider the reverse relationship and to examine the connection between established cases of adrenal disorder and the incidence of psychiatric abnormality. It is difficult to obtain a precise figure for incidence as most authors were primarily concerned with the physical illness and its response to treatment rather than noting psychiatric abnormalities and their relationship to the disease.

Addison's Disease.

In Addison's original treatise on the condition, he noted the presence of delirious states. From time to time during the last century, isolated reports mention mental disorder in passing but it is only in the last 20 years that real interest in this relationship has been the case, especially since the biochemical derangements have been worked out. Rowntree and Snell (1931) dealt more extensively with the psychiatric aspects but did not note the total incidence of such in the cases they reviewed. In 1938, Porot gave an account of a woman aged 38 who suffered from a chronic paranoid psychosis in addition to proved Addison's disease, who was hallucinated and suicidal. She improved temporarily on the administration of salt but later relapsed mentally and eventually died. A further isolated case was published by Larue (1938) of a 33 year old woman who developed an acute confusional state in association with Addison's disease and who improved mentally on salt. Engel and Margolin (1942) found that in a review of 25 cases of Addison's disease, 16 cases showed such striking neuropsychiatric disorders as to deserve comment.

They observed that such deviations were most common before or during metabolic crises and that they included the widest range of abnormalities, so much so that changes in mood or behaviour were often the earliest signs of impending physical collapse. The most characteristic feature was the fluctuating and episodic nature of the mental and neurological signs; of the 16 cases, 7 showed predominantly neurological signs with secondary mental symptoms and of the other 9, 6 cases were predominantly of a depressive nature and with one case each of paranoid psychosis, confusional state and personality change. Five other cases not of Addison's disease but involving a disturbance of carbohydrate metabolism, featuring flat glucose tolerance curves, a tendency to hypoglycaemic reactions and abnormal E.E.G's showed mixed toxic and vitamin deficiency states. The typical E.E.G. findings in both groups were either

1. Spontaneous bursts of slow waves often of high voltage and originating diffusely from all parts of the cerebral cortex.

or 2. Unusual sensivity to the effects of hyperventilation with abnormal persistence of regular high potential slow waves.

These E.E.G. findings were confirmed by Hoffman et al. (1942) in their series of cases and they observed that a rough correlation between the changes and blood sugar levels existed. Both the authors of the last two publications were in agreement on the fact that symptoms of hypoglycaemia developed at much higher levels of blood sugar than in normal persons.

While Engel and Margolin stated that major and minor mental

disturbances in Addison's disease were commonly encountered, Gorman and Wortis (1947) felt that psychoses were rare but described two cases, one a girl of 28 a longstanding sufferer from Addison's disease who was admitted in a mixed confusional paranoid state with memory retention and recall grossly defective and expressing ideas of grandeur and persecution. The other case was a woman of 61 admitted to hospital with a five day history of violent behaviour and paranoid delusions: she also was a known case of Addison's disease. Both these cases showed gross disturbance of electrolyte and sugar levels during the acute psychiatric phase. Although accepting the latter as triggering mechanisms, the authors felt that there was possibly a coincidental linkage between the endocrine disease and psychoses as the latter was so much more frequent in general incidence than the former. Simpson (1952) remarked that he had seen between 80 and 100 cases of Addison's disease and had never encountered a psychosis except in the terminal stages or where the electrolyte balance had been badly thrown out of equilibrium: he had never observed that even when the mineral and metabolic balance had been restored the patients exhibited undue apathy, lack of initiative, irritability or negativism as are classically described as concomitants of the disease.

It would appear that in the production of mental symptoms in Addison's disease, several factors are operative:-

1. Chronic hypoglycaemia involving both deficient supply of glucose to the brain and an inefficient and inadequate utilisation of sugar. These patients show mental symptoms at relatively high blood

sugar levels.

2. Electrolyte imbalance, decreases in blood pressure and blood volume are also concerned and most reports agree that mental symptoms are more florid and severe in such crises. However the psychiatric picture is not always corrected when these factors are brought within normal limits and abnormal patterns in the E.E.G. tend to persist, thus indicating that some other factors which cannot at present be defined, are operative.

3. As Addison's disease is a chronic debilitating disease some disturbance of outlook could be expected.

4. Although it is not possible to say that a characteristic psychotic picture emerges, descriptions are generally those of a depressive disorder with an attempt at psychological compensation with a paranoid mechanism.

Hyperfunction of the Adrenal Cortex.

There is little doubt that in some cases of hypercorticalism as described by Broster et al. (1938) and Allen et al. (1939), where the removal of an adrenal cortex tumour led to an improvement in the mental state, the role played by the increased cortical activity was to a certain extent at least causative in the development of the mental disturbance.

A review of the literature reveals that the incidence of psychiatric disturbance is significantly high, even taking in to account the psychological aspects of altered physical and sexual

configuration which may result and the effects of an illness which may last several years in its untreated form.

Two broad syndromes of hypercorticalism are described:

1. Cushing's Syndrome showing excessive production of cortisone like steroids.

2. Adrenogenital Syndrome showing excessive amounts of the sex steroids either androgens or oestrogens.

Cushing's Syndrome.

Cushing described 8 cases with certain features in common in 1932: the chief clinical features are a wasting and weakness of the skeletal muscles especially of the limbs, the appearance of obesity with a characteristic distribution on the trunk, shoulders and face, sexual disturbances appearing as amenorrhoea in females, hirsutism, acne, the appearance of purple striae, hypertension, glycosuria proceeding to diabetes mellitus, eosinopenia and usually an increase in the excretion of certain urinary steroids.

In later years, it became apparent (Kepler et al. 1948) that a basophil adenoma of the pituitary was not always necessary to produce the clinical syndrome and that an adenoma or carcinoma of the adrenal cortex or hyperplasia or hyperfunction of the cortex could produce a similar picture: it is estimated that 86% of cases are due to pituitary adenomata (Eisenhardt and Thompson 1939).

The excessive production of adrenal cortical steroids produces a characteristic electrolyte disturbance and an anti-insulin effect appearing as glycosuria, hyperglycaemia and a decreased glucose

tolerance. The urinary excretion of 17-ketosteroids shows wide variations from normal values to figures of 74mg. per day (Fraser et al. 1941), the majority showing only slight increases. The excretion of corticosteroids oxygenated at C11 is markedly increased (Talbot et al. 1947, Mason and Sprague 1948). It can thus be seen that several groups of cortical steroids are involved, the protein catabolism and osteoporosis being produced by overproduction of the 11-oxysteroids, hypertension and electrolyte changes by the DOCA-like steroids and less frequently hirsutism and sexual changes by excessive liberation of androgens.

Psychoses in relation to adrenal hyperplasia were remarked on by Broster and his colleagues in 1938 when 4 cases of adrenogenital disorder were noted to be psychotic and earlier by Jonas (1935) when it was reported that there was a 20.5% incidence of varied mental symptoms in a review of 73 cases of Cushing's syndrome and that depression and hallucinations were relatively frequent. Spillane (1951) also reviewed the nervous and mental disorders in Cushing's syndrome and presented 4 cases with one or more of the following signs:- memory defect, paranoid ideas, auditory hallucinations and depression with suicidal tendencies. In 21 out of 25 cases of Cushing's syndrome (Trethowan and Cobb 1952) psychiatric abnormalities were noted: they were classified as 4 cases severely disturbed, 6 cases moderately so, 8 mildly so and 3 patients with minor psychiatric symptoms. After appropriate physical treatment, 7 out of the 10 cases with moderate and severe mental upsets recovered and some of the others showed

improvement. The commenest clinical picture was that of depression often accompanied by retardation or irritability.

Glaser (1953) reviewed 33 cases of Cushing's syndrome: 21% showed severe psychotic reactions and a further 37% showed minor emotional disturbances such as anxiety, tension, emotional lability, insomnia and mild depression. Four cases showed an organic reaction with memory defect, confusion and auditory hallucinations. The author found that the most frequent tendency was towards a paranoid state with depressive features but closer scrutiny of his and other cases with these paranoid traits give the impression more of a fundamental affective disorder in the direction of depression with the psychological defence of projection to produce persecutory ideas. The mental disorder may appear in patients with little or no physical disorder or sexual dysfunction in contra-distinction to patients suffering from adrenogenital syndrome.

Certainly the positive relationship between psychoses and Cushing's syndrome is much higher than can be explained by coincidence or by a purely psychological reaction to the disease: it is interesting to note that the mental reactions have many features in common with those which may occur during cortisone or ACTH therapy with the exception that no cases of euphoria or mania could be found in the the literature in patients with Cushing's syndrome.

Adrenogenital Syndrome.

This is a condition in which there is an increased output from the adrenal cortex of either androgens or oestrogens, resulting in

marked changes in the sexual characteristics with no disturbance of the other functions of the gland.

The clinical effects depend on the age at onset of the condition: occurring in the female foetus it produces the condition of pseudo-hermaphroditism: developing during childhood in girls, it can cause signs of masculinisation with enlargement of the clitoris, accelerated bony growth, early appearance of axillary and pubic hair, hirsutism, excessive muscular development and deepening of the voice. In boys, sexual precocity, accelerated bony growth, muscularity and acne are the main features. Most of the cases occurring in the first decade are caused by adrenal tumour. In adult females a process of defeminisation and virilisation occurs with amenorrhoea, loss of feminine contours, enlargement of the clitoris, hirsutism and acne, deepening of the voice and a change in the direction of the weakened libido. In men, feminisation occurs but is rare and the picture is more of a negative nature with loss of libido and atrophy of the testes although enlargement of the breasts due to excessive secretion of oestrogens is fairly frequent.

In general a distinction may usually be drawn between cases of adrenal hyperplasia and those in which a tumour, benign or malignant is present, when the 17-ketosteroids are estimated. Where a tumour is present the excretions of 17-ketosteroids and the 3-beta fraction are substantially raised, the former often to the order of several hundred milligrams daily. In cortical hyperplasia only moderately elevated values for both are obtained, the beta fraction being of the normal order of 10% of the total excretion.

That the incidence of psychosis is high in such patients is illustrated by the fact that 4 cases out of 37 showed acute mental disturbances (Allen 1952): the author notes that even those who do not show frank psychotic signs show undue irritability and quarrelsomeness and a tendency to depressive reactions so that suicide is a constant risk. Although no characteristic clinical picture emerges, the most frequent grouping of signs and symptoms suggest the psychiatric state of paraphrenia with acutely disturbed behaviour, auditory hallucinations and persecutory ideas. Depressive reactions were also frequent. Allen has described several cases in which removal of the adrenal tumour or adrenalectomy led to a recovery from the mental symptoms.

The psychological effects of the altered bodily state, emotional outlook and hirsutism are profound in the female and it could be argued that the trauma of such changes would account for the depressive and paranoid ideas: this is probably the case in simple hirsutism whether it can be traced to adrenal hyperplasia or not, but at the same time both qualitatively and quantitatively the acute psychotic reaction found in association with this syndrome is of a different order and would indicate that a further mechanism has come in to action. Even admitting that the acute reactions are extreme cases and insignificant in number in comparison to the large number of cases of paranoid psychoses with no gross adrenal abnormality, nevertheless it is something tangible that the mental state improves either after adrenalectomy or suppressive cortisone therapy; it provides a starting point for the elucidation of abnormal hormonal and biochemical factors and psychiatric disturbance.

The facts which do emerge when considering gross derengements of the adrenal cortex are important even if no definite conclusions can be made. Both over and under function of the cortex can produce both minor and major psychiatric disorders but the psychiatric picture can show wide variations in form from depression, through paranoid and hallucinatory illness to organic reaction types and even in the one patient the type of reaction is not constant. There is a tendency for the severity of the psychosis to bear a relation to the degree of hormonal and biochemical disturbance but not in any hard and fast way. An identical clinical condition can be seen in both diseases involving hypo- and hyper- function of the cortex and the impression one gains is that the factor involved is that of an altered balance of secretion rather than being a question of either a deprivation or overproduction syndrome. Bleuler (1954) in his review of psychoendocrinological relationships could find no specific psychiatric picture in relation to specific hormone disorder. This must be so as any disease which tends to threaten or alter the psychological equilibrium is bound to do so on the basis of the strength and direction of the innate instinctive forces modified by acquired behaviour patterns and experiences: thus the person who begins to appreciate the debility of Addison's disease, the psychosexual changes in the adrenogenital syndrome, or the impotence or amenorrhoea in Cushing's syndrome may compensate in several ways. He may develop anxiety and fear which becomes directed on himself or some object in his surroundings, he may become overwhelmed and depressed, he may withdraw himself from contact with others or he may

react to what appears to him bewildering changes by projection, attributing his symptoms to the evil intentions of those around him.

In the section under review, it is not possible to focus on any one function of the adrenal cortex. It can be said that sometimes the triggering mechanism in producing mental disturbance may be chronic hypoglycaemia with consequent altered cerebration, sometimes disordered electrolyte and fluid balance, sometimes a flooding or deprivation of the system by the 11-oxysteroids, sometimes the effects of excessive androgen or oestrogen formation quite apart from considering what effects these abnormalities may have on other endocrine glands and the total hormonal balance.

Thyroid Function and Mentation.

The Thyroid Gland.

The anatomical units consist of spherical vesicles lined by cuboidal epithelium: this layer of cells secrete in to the vesicle a colloid termed thyroglobulin: iodine, in organic form has long been known to be present in the thyroid gland and Gutman and his colleagues reported that 7% of the total iodine was present as inorganic iodine, 25% as thyroxin and 68% as di-iodo-tyrosine. Thyroxin is the most physiologically active fraction of thyroglobulin although some theoretical doubt still exists as to the precise nature of the "natural" hormone.

The activity of the thyroid gland is regulated mainly by the thyrotrophic factor of the anterior pituitary and perhaps to some extent by the level of blood thyroxin. Hypophysectomy causes atrophy of the thyroid gland and the administration of thyrotrophin stimulates a thyroid which is able to respond. Thyrotrophin increases the rate of formation and the release of thyroxin and its administration causes an increased uptake of radioactive iodine (Stanley and Astwood 1949).

Thyroid hormone regulates the oxygen uptake and usage in the tissues stimulating metabolism generally: it has a variety of other actions affecting almost every other tissue in the body and plays a part in growth and maturation, influences the body water and electrolyte equilibrium, the storage of tissue protein and the metabolism of carbohydrate. It has also a profound effect on mentation and there seems little doubt that emotional trauma can in turn influence the secretion of thyrotrophin via the hypothalamus and anterior pituitary.

Tests of Thyroid Function.

Discussing the clinical tests of thyroid function, Fraser (1956) reaches the following conclusions:

1. The estimation of Basal Metabolic Rate (B.M.R.) gives the best index of severity of dysfunction.

2. The various methods involving the use of radioactive iodine (I^{131}) give the best test for suspected thyrotoxicosis.

3. Estimation of the serum protein bound iodine (PBI) is most useful in cases of suspected mild myxoedema.

It is proposed to consider these three tests but also to add a fourth, the determination of the serum cholesterol.

Basal Metabolic Rate. This refers to the heat production of the individual measured in a basal condition and is determined from the volume of oxygen consumed by the subject compared with established normal standards. The estimation of the B.M.R. has been widely used but from a practical point of view, technical difficulties in the apparatus, the attainment of both a physical and mental basal state and the fact that other conditions such as undernutrition obesity and Addison's disease may alter the B.M.R., have all to be borne in mind. Fraser states that in nervous patients preparatory sedation or intravenous barbiturates are necessary and for reliable results the test should always be carried out with the patient sleeping.

Radio-iodine Uptake by the Thyroid. Several variations of this test exist but basically they involve the use of tracer iodine and its accumulation in a measurable way by the thyroid gland. First described

by Hamilton and Soley (1940), the uptake may be measured during and at the end of one hour (Kriss 1951), after 48 hours (Skance 1949) and a good inverse relationship exists between thyroid activity and the appearance of the iodine in the urine.

A radioactive tracer method has been worked out by Reiss and his colleagues for investigation of thyroid disorders in psychiatric illnesses and a thyroid index (I_t) arrived at based on the linear rate of uptake during the first hour after intravenous injection of I131 and the uptake 24 hours later (Haigh and Reiss 1950, Reiss et al. 1952, Haigh et al. 1954). Values for I_t in normal men ranged from 2.4 - 6.1, in clinical hyperthyroidism from 12.7 - 165 and in clinical myxoedema from 0.0 - 1.1: it is also possible to distinguish between primary hypothyrotic and secondary pituitary hypothyrotic cases.

Serum Protein Bound Iodine. The view that the iodine in the circulation which was bound to the protein rather than the total iodine more truly represented the level of circulating thyroxin has now been established (Perkin and Hurxthal 1939, Barker 1948). The normal range is 3.5 - 7ug. per 100 ml. Kydd et al.(1950) found that in 99cases of hypothyroidism the values were all below 3.0ug. per 100 ml., whereas the lowest concentrations in normals was 3.8 micrograms. The corresponding figures for hyperthyroidism showed that 202 out of a total of 206 patients showed values higher than 8.0 micrograms per 100 ml. In a comparison of the above three tests of thyroid function (Jaffe and Ottoman 1950) on 152 patients, the presence of thyroid dysfunction being made on stated clinical grounds, the B.M.R. gave a diagnostic error in

32.9% of cases, the protein bound iodine in 24.1% of cases and the determination of radio-iodine uptake in 9.3% of cases; this latter figure could be further decreased to 5.7% if patients who had received anti-thyroid therapy were excluded.

Serum Cholesterol Levels.

That abnormal levels of blood cholesterol were obtained in thyroid dysfunction was observed by Epstein and Lande in 1922, raised values being found in hypothyroidism and decreased levels in hyperthyroidism. The normal range of values depends to some extent on the technique employed but Foldes and Murphy (1946) give the figure of 193mg. per 100 ml. with a standard deviation of $\pm$ 36: Mason et al. (1930) found that 15 out of 22 patients suffering from myxoedema had values above the upper range of normal but there was no correlation between these figures and the degree of illness or extent of depression of the B.M.R. These findings have been more recently confirmed by Peters and Man (1950). It can be stated that raised blood levels of cholesterol are found in many cases of hypothyroidism but there are a number of other diseases with which high values can be associated. Bartels (1950) has described 4 cases of myxoedema with normal cholesterol levels. Baron (1956) investigating hypothyroidism found raised values in 58 out of 65 cases: again there was no correlation between the extent of the elevation and the depression of the B.M.R.

In hyperthyroidism the concentration of cholesterol is decreased but not to the same degree relatively as the elevation frequently is in myxoedema. Several authors (McGee 1935, Skance 1949,

Peters and Man 1950) come to the same conclusion that although some cases of hyperthyroidism are associated with low levels, the degree of overlapping between normal values and hyperthyroid levels is so great as to render the test valueless in this condition.

In hypothyroidism, the test has some relevance and application but even here is not so reliable as the estimation of the B.M.R. or the use of radio-iodine techniques.

Thyroid Dysfunction as a Factor in Mental Illness.

Established cases of hyperthyroidism are accompanied by emotional and mental changes but only rarely do they come in to the psychiatrist's care even although superficially many anxiety states have features in common with hyperthyroidism such as loss of weight, excessive perspiration, fast pulse, insomnia, tremor and emotional lability. Some anxious and tense patients even have raised basal metabolic rates (Fraser 1956) and with sedation these fall to normal levels. Frank psychoses are uncommon (Hemphill 1955) even associated with thyrotoxicosis but the development of the latter in relation to an acute emotional upset is frequently noted in textbooks and claimed by patients and is an interesting phenomenon in view of recent knowledge of the mediation of emotion through the hypothalamus and anterior pituitary. Mayer-Gross, Slater and Roth (1954) in their textbook state that the pre-illness personality is often that of a chronic anxiety state with easily provoked mood swings and the mental changes involve not so much the appearance of new character traits but the exaggeration of existing ones. They note that psychotic complications are rare but

when they do occur are frequently disorders of mood in the direction of either mania or depression; successful treatment of the hyperthyroidism usually leads to recovery from the mental symptoms.

Hyperthyroidism is usually regarded as a psychosomatic disorder in contra-distinction to myxoedema which might be classified as somato-psychic. Estimates for the incidence of emotional precipitants in hyperthyroidism vary between 60 and 100% (Lidz 1953) and Conrad (1934) in a study of 200 cases claimed a history of emotional trauma in 94% of the cases.

Much more frequently encountered by the ordinary psychiatrist is the patient suffering from myxoedema, where the presenting symptoms are those of mental change. The retardation of thought, dulling of intellect, apathy, physical sluggishness, sapping of initiative and disturbance of recent memory may on superficial acquaintance resemble the involutional depressive or melancholic case, especially so as most of the cases occur in females about the involutional period. Several surveys (Burnstein 1948, Baron 1956) give the sex incidence as 86% women and the age group affected as 40-60 years with a mean at 45 years. It is intended to give in a later section an account of hypothyroidism in relation to a series of patients admitted to a mental hospital. Gregory (1956) reports on two cases of schizophreniform psychoses, one case secondary to myxoedema and the other to hyperthyroidism. Both cases eventually responded to the appropriate corrective treatment with relief of mental symptoms. Means (1948) however states that there is a difference in response to treatment in the two thyroid disorders in that treatment

of myxoedema usually leads to rapid mental improvement whereas in mental disorder secondary to hyperthyroidism, correction of the physical state is often not followed by corresponding psychiatric improvement.

Reiss and his co-workers at Bristol have made extensive investigations in to thyroid function in relation to the neuroses and psychoses during the last 10 years using I131 tracer methods. These researches have been concerned not with cases showing obvious signs of over- or under- production but with the finer deviations from the normal range in thyroid indices and their attempted correlation with the mental state. Reiss and Haigh (1954) state that minor degrees of hypothyroidism are frequently overlooked and even with recent advances in the determination of thyroid function, there exist a considerable group of cases where the significance of intermediate values between the normal range and definitely low values is still undetermined. They found that in a cross section of the mental hospital population over three years approximately 34% of the patients showed thyroid indices above or below normal limits.: by administering thyrotrophin they were able to differentiate primary and secondary hypothyroidism and in a third group of cases they noted that while thyroid action and responsivity were normal, B.M.R. values were definitely low and they postulate that a degree of peripheral insensivity to thyroid hormone exists. They found that a significant correlation existed regardless of the type of treatment given, between improvement in mental state and normalisation of thyroid function in 95 hypothyrotic cases. Patients with a degree of secondary hypothyrosis regardless of their mental

state showed a significant improvement both mentally and in regard to their thyroid function when treated solely by thyrotrophic hormone.

An account of 5 cases of thyroid overactivity in soldiers suffering from acute anxiety states (Robinson et al. 1956) and in whom 17-ketosteroids were also determined, indicated that several variations of hormonal imbalance could occur. In 2 cases peripheral undersensitivity to thyroid hormone was held responsible and the patients responded to nicotinic acid and in the other 3 cases the thyroid overactivity was coupled with adrenal overactivity and a clinical response was obtained with oestrogens to suppress anterior pituitary function, although one patient did require in addition anti-thyroid medication. None of these cases showed any gross clinical signs of endocrine dysfunction.

In a further study, Reiss (1954) reviews the thyroid activity of over 400 psychiatric patients who were investigated before and after different forms of conventional and hormonal physical treatments. A highly significant correlation was obtained between thyroid activity ending up in the normal range following treatment and clinical improvement regardless of the psychiatic disease entity and independent of the treatment applied.

One of the interesting features in the cases described with thyroid dysfunction is that they show no characteristic psychiatric picture. Some cases of hypofunction, far from appearing sluggish and apathetic are tense and anxious and the converse holds true for minor degrees of overfunction. The finding of disturbed peripheral sensitivity to endogenously produced hormone is interesting in that schizophrenic

patients seem to require much higher dosages of dried thyroid before toxic symptoms appear. With regard to minor clinically non-detectable cases of hormonal dysfunction it is not yet proved that they stand in any causal relationship to the development of psychiatric illness but that improvement in the mental state bears some correlation to the correction of the disturbed hormonal imbalance. It is encouraging that even in a relatively few cases it seems possible to correct this imbalance by 'natural' methods.

Psychiatric Aspects of Other Endocrine Disorders.

Pre-Menstrual Tension.

This is a condition first described by Frank (1931) in which a state of mental and physical tension builds up during the latter half of the menstrual cycle. It is also of observation that in the chronically mentally ill more behaviour disturbances arise during this time than at any other. The symptoms occur in about 50% of women to some degree, consisting of irritability, increased aggressiveness and emotional lability as well as physical discomfort. Water retention associated with an abnormal ratio of the oestrogen progesterone balance is felt to account for the symptoms (Rees 1953, Malleson 1953). Podolosky (1955) believes also that some degree of hypoglycaemia may occur at this time causing mental symptoms.

The condition responds fairly well to treatment either by administration of a diuretic such as ammonium chloride or by giving progesterone or ethisterone.

Pregnancy and the Puerperium.

The incidence of psychoses during pregnancy at a time when a greatly altered endocrine balance exists appears to be no greater than in a similar non-pregnant group. Slightly over 50% of cases of psychoses during the puerperium occur in the 14 days after the birth at a time when massive and sudden hormonal and metabolic adjustments are taking place. Three main types of reaction are seen:

1. An organic reaction type with delirium not necessarily associated with infection.

2. An affective reaction usually in the direction of depression.

3. A schizophrenic reaction.

There is often considerable overlapping of these three types so that a firm diagnosis is not possible for some time.

Puberty and the Menopause.

Psychoses while occurring in children are rare before puberty; in the light of the possible relationship in time of the first attack of manic-depressive psychosis or schizophrenia and of a physically and emotionally changing individual, it is tempting to consider that internal factors of a hormonal nature may be involved. Little proof can be offered however and the matter remains one of supposition only in the main and apart from the rather special groups of the 'inadequate psychopath' type previously described, no corrective hormonal treatment is known to influence these illnesses.

As in the case of puberty, so at the menopause, physiological factors

appear to be involved. Many women experience some emotional upset at the menopause such as depression, anxiety, irritability and lability of mood. There is reason to think that women who have previously been subject to mood swings in relation to menstruation, who are less able to adjust to the altered physical and mental outlook and whose previous life has been of an unsatisfying nature are more prone to develop menopausal features (Hemphill 1955). It is believed however that a factor in the development of symptoms is a disturbance of the balance between pituitary gonadotrophins and the levels of circulating ovarian hormones as when the latter are falling off the former temporarily increase in an attempt to boost ovarian function. It is also interesting that females who have experienced a previous artificial menopause may again experience psychological symptoms at the time when pituitary gonadotrophins would naturally be falling off.

For these types of disturbance, treatment with synthetic or natural oestrones is usually sufficient to control the physical symptoms and to ease the emotional lability along with explanation and reassurance.

A similar picture may be observed in men in middle or later life (Spence 1954) but much less regularly and the diagnosis is much more difficult to establish: in these cases treatment with testosterone leads to physical and mental improvement.

Although affecting a similar age group, the classical case of involutional melancholia rarely responds to hormonal therapy although Ingvarsson (1951) reported good results in 23 out of 28 cases when much larger dosages of oestrogens than are normally employed in the

menopausal state, were administered.

Pituitary Disorders.

The main features of anterior pituitary insufficiency are loss of sexual function and desire, loss of pubic and axillary hair, failure of lactation, intolerance of cold, a tendency to hypoglycaemia and the syndrome is commonly accompanied by asthenia, apathy and mental sluggishness (Sheehan and Summers 1949). The mainstay of treatment was formerly testosterone although the simultaneous addition of thyroid might also be beneficial (Wilson et al. 1954). Since the advent of cortisone, a much greater degree of control has been possible and Beck and Montgomery (1957) comparing the response to different substitution regimes, came to the conclusion that cortisone in combination with thyroid is most effective in maintaining health in these cases and in restoring mental efficiency.

CLINICAL SECTION.

Adrenal Cortex Activity in a Case of Manic-Depressive Psychosis.

Interest in this particular case in respect to adrenal function was aroused by the publication of investigations in to a similar type of illness by Reiss et al. (1949b). Their patient was aged 45 years and suffered from manic-depressive illness of a cyclical type, the manic phases varying between one and five weeks and the depressive phases being of six to twenty-four days duration. The interval of normality between these mood changes was never more than a few days. The values recorded during their investigations were for total neutral 17-keto-steroids, the percentage of 3beta-hydroxy-17-ketosteroids, cortin and oestrone in 24 hour collections of urine extending over one year. The onset of depression appeared to be accompanied by a tendency to the excretion of a high proportion of beta steroids and a low cortin excretion while at the transition in to the manic phase, the converse was observed namely a rising cortin excretion and a fall in the proportion of the beta steroids. The antagonism between these two indices of adrenal cortex activity was regularly observed. There was one period extending over three months when although the urinary excretion pattern continued, the psychiatric state remained unchanged.

The first phase in the investigation of the case about to be presented was previously the subject of a published article (Bryson and Martin 1954). The patient is a male, born in 1914 of wealthy parents and good social background who attended a preparatory boarding school

and later a public school but with only moderate academic achievement. There is no history of nervous or mental disorder in the family although it is interesting that the parents were first cousins. He exhibited no neurotic traits in childhood, mixed easily in a social sense and suffered from no serious physical illnesses. There are two elder sisters born 1909 and 1910 who have been personally interviewed; the elder is of robust build and possessed of a well integrated personality and has managed the family affairs since the parents' death. The younger sister is of asthenic build, over anxious, indecisive, easily swayed, emotionally labile and although she has never suffered from frank breakdown, requires supervision and some degree of protection in day to day life; both are unmarried.

The first signs of the patient's illness appear to commence in 1928 at the age of 14½ when at school he appeared morose irritable and solitary; he returned to school but began to show mild excitement and eventually was admitted to a mental hospital in January 1929. In the admission ward there, it was observed that he was unduly talkative and noisy, would sing loudly and behaved in an exciteable and overactive way. This persisted for several weeks when he then passed in to a depressed phase and these alternating mood phases persisted but in a more modified form until his discharge in November 1929. The following year he continued his education under a private coach for one year and then spent one year on a farm. In July 1932, he was readmitted in a condition of mild mania and after he was discharged was given a sheep farm which he managed until 1935 when he was again admitted in May to a

mental hospital in a state of excitement. In 1936 he spent a further five months in hospital having been admitted in mania but it was observed that the alternating mood changes continued during all his stay although the degree of the affective changes became less. On discharge he lived with a clergyman and helped on a farm but had a further admission to hospital for a short time in 1938. In 1940, he left the protected environment of the clergyman's house and went to London where for the next four years he had innumerable jobs ranging from firewatching, hotel porter, refreshment railway car work to simple office work and fair ground attendant. During the upswings in mood, he would obtain employment for a few weeks but in the succeeding depressed phase would lie in bed, refuse to attend work and lose weight rapidly.

During what appears to be a more prolonged depressive phase than usual in 1945, he disappeared for several months and spent the time as a tramp, living in workhouses until he was admitted to a mental hospital in an emaciated state. He recovered spontaneously and went through several mildly manic phases until discharged in January 1946. His mother had died in 1940 and for the next year he stayed at home with his father and sisters until the former died in November 1946. During this period however he disappeared from home when he became exciteable and grandiose on many occasions but usually returned later when he had passed in to a normal or depressed phase. Eventually in one of his manic periods he travelled up North and in March 1947 was admitted to a county mental hospital in a state of acute mania.

Alternating elated and depressed moods persisted during the following eleven months until he was transferred to The Retreat in February 1948 as a certified patient where he has stayed without interruption since.

The mood swings are regular clear cut and their approximate date can be forecasted with reasonable accuracy. In the year before the present investigations were made and he was receiving no treatment apart from sedation during the exciteable noisy periods, the length of a complete cycle from normal back to normal averaged 38 days. During the manic phase which averages 18 days, he is acutely exciteable and noisy, requires to sleep in a strongroom with special clothes due to his destructive tendencies and he will talk incessantly showing such flight of ideas as to often render him incoherent. He is however quite jolly and happy but towards the end of the phase he becomes physically exhausted at the same time developing an acneiform rash of the face. The transition to a normal phase is a gradual one over several days during which time he shows a progressive diminution in psychomotor activity. The normal phase lasts about four days when no specific treatment has been previously administered and during this period he appears completely normal, rational and responsible, shows a great interest in current events, visits places of interest unaccompanied and there is no evidence of dementia nor deterioration.

He then gradually passes in to a deeply depressed state, refuses to go out or help on the ward, spends hours standing in a state of complete preoccupation in his room and expresses depressive delusions regarding his bowel function. He refuses to eat, shows marked

psychomotor retardation and mild negativism and actively shuns all contact with patients or staff: this phase lasts 16 days when without any premonitory signs, he will suddenly pass into mania within the space of a few minutes, back to the beginning of the cycle.

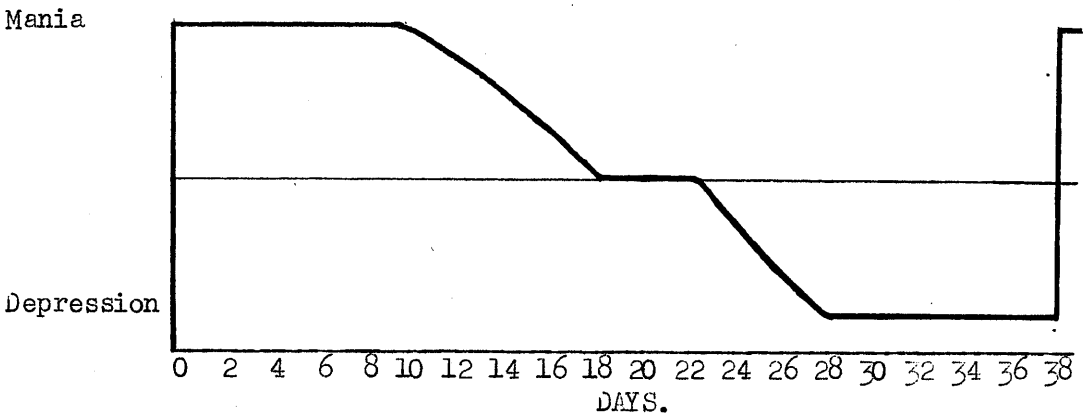


Figure 1. Diagram of an uninfluenced mental cycle.

This regular cycle of events has continued unabated for the nine years he has been in this hospital, five of the years being under the author's observation.

On the charts, the mental state has been plotted on the basis of allotting four points or gradations above and below the "normal". Twenty-four hour collections of urine were made at weekly or shorter intervals and their completeness was checked by estimating the creatinine content; incomplete specimens or those in which the total of creatinine was greatly at variance with the normal, were discarded. The urine collections were then analysed for total neutral 17-keto-steroids and further fractionation was then carried out to obtain the 3beta-hydroxy-17-ketosteroids total. Eosinophil counts were made on alternate mornings at 10a.m. His bodily configuration is asthenic.

Estimation of Ketosteroids. The method used was that of Cook (1952). The alcoholic potassium hydroxide solution was originally prepared by the method of Wilson and Carter (1947) but later the solution procedure of Hamburger (1952) followed by the use of ascorbic acid and nitrogen for stabilisation was adopted. Alcoholic potassium hydroxide is easily prepared by this method and remains useable for at least three months.

Creatinine determinations were made according to the method of King (1951). Eosinophil counts were made by Pilot's method as modified by MacFarlane and Cecil (1951).

Findings. Two separate lines of investigation were carried out consecutively: in both cases two complete mental cycles were charted to establish the fluctuations in ketosteroid excretion and blood eosinophil levels and to serve as a basis for comparison when hormones were later administered.

Figure 2 shows the results of the first line of investigation when after the basic rhythm had been obtained, various hormone preparations were administered. Testosterone propionate 25mg. daily was then injected for one complete mental cycle and this was followed in turn by oral dehydroisoandrosterone ("Diandrone") 30mg. increasing to 50mg. daily for a similar period and finally by oral stilboestrol 5mg. daily for a further mental cycle. The total 17-ketosteroids, the ratio of alpha to beta steroids and the eosinophil levels were charted in relation to the changes in mental state.

During the cycles when no treatment was being given, the

Figure 2.

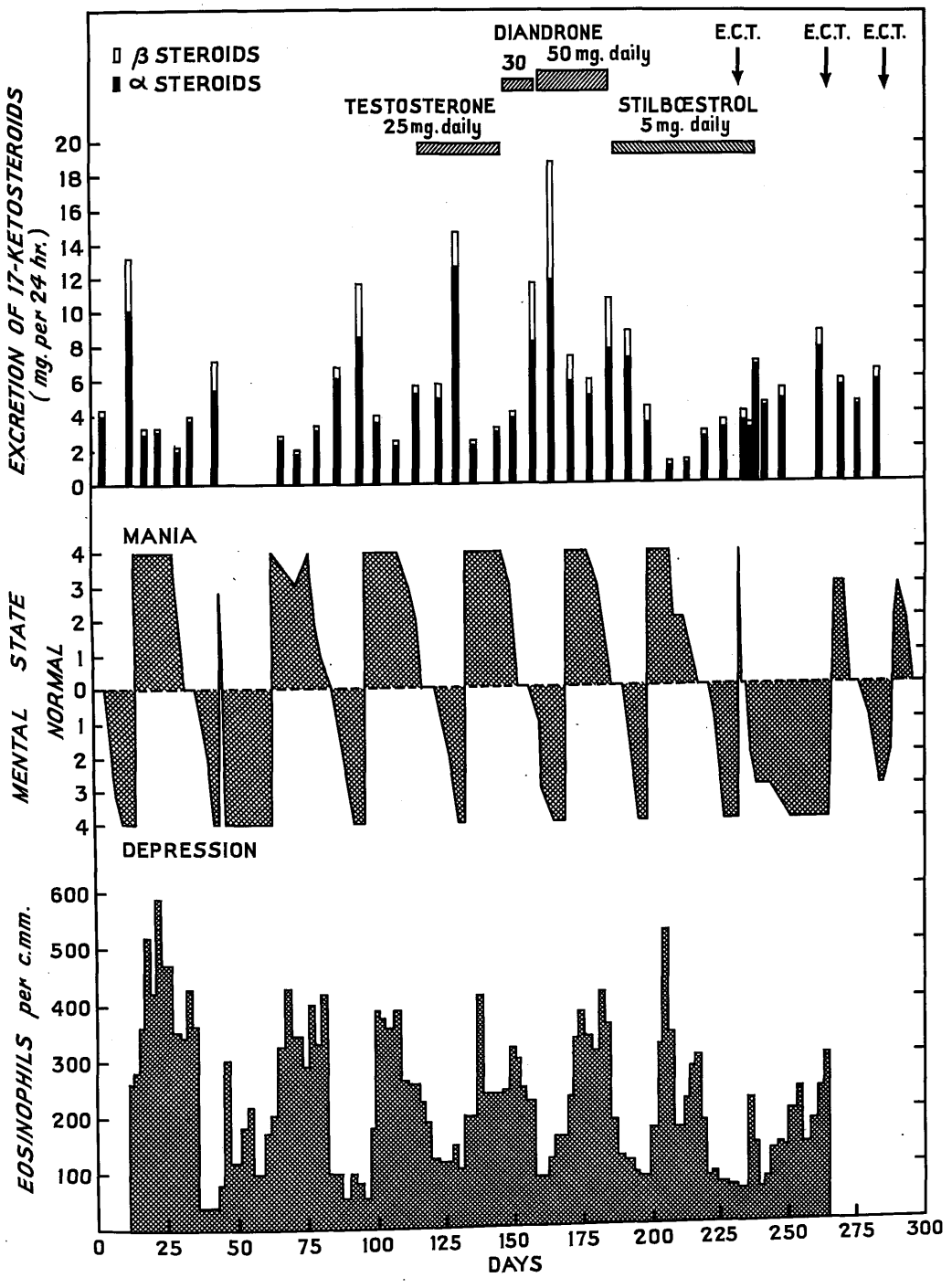
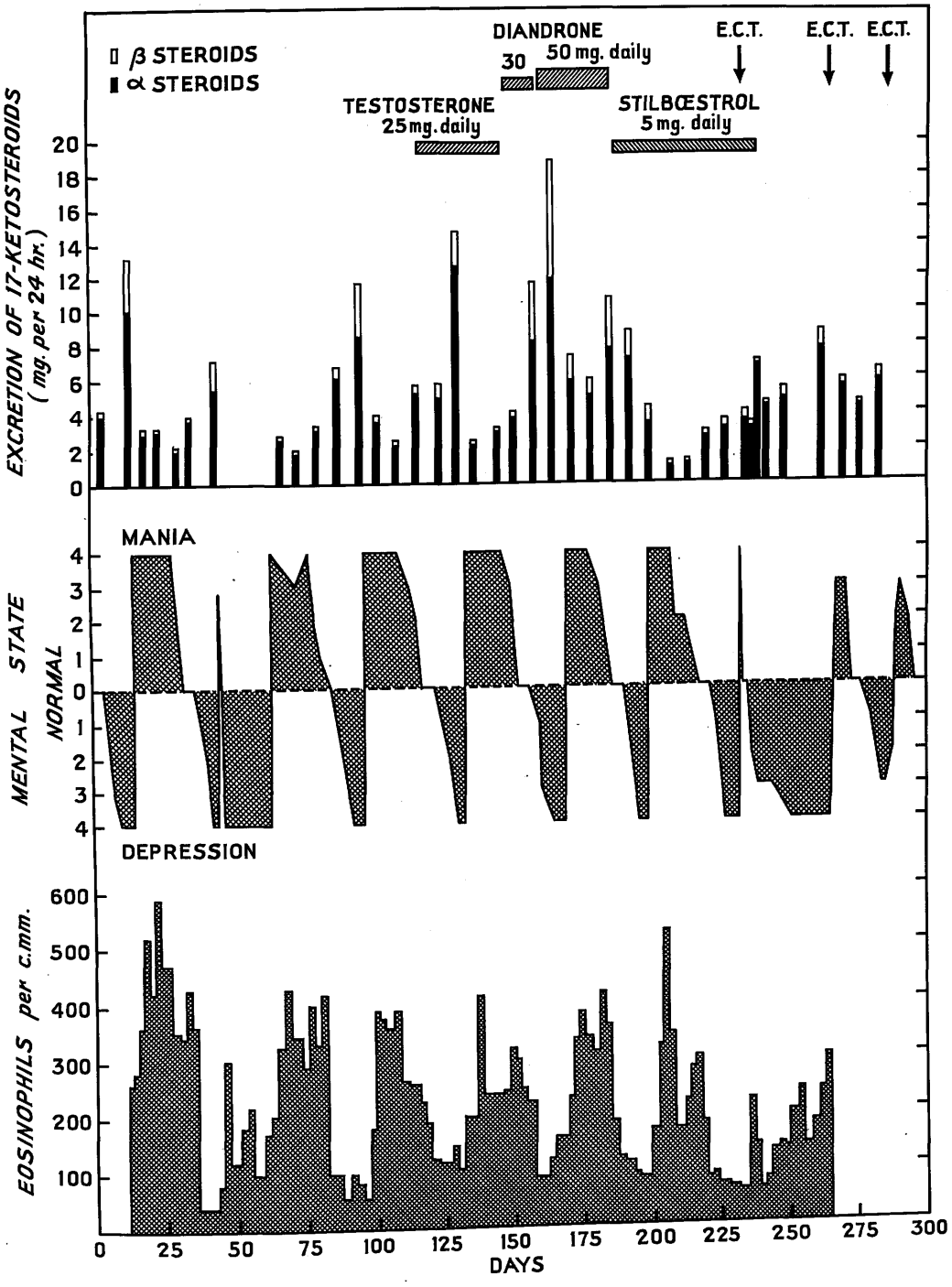

β STEROIDS
α STEROIDS
DIANDRONE
30
50 mg. daily
E.C.T.
E.C.T.
E.C.T.
TESTOSTERONE
25 mg. daily
STILBŒSTROL
5 mg. daily
EXCRETION OF 17-KETOSTEROIDS
(mg. per 24 hr.)
20
18
16
14
12
10
8
6
4
2
0
MANIA
MENTAL STATE
NORMAL
4
3
2
1
0
1
2
3
4
DEPRESSION
EOSINOPHILS per c.mm.
600
500
400
300
200
100
0
25
50
75
100
125
150
175
200
225
250
275
300
DAYS

Figure 2.


β STEROIDS
α STEROIDS
DIANDRONE
30
50 mg. daily
E.C.T.
E.C.T.
E.C.T.
TESTOSTERONE
25 mg. daily
STILBŒSTROL
5 mg. daily
EXCRETION OF 17-KETOSTEROIDS
(mg. per 24 hr.)
20
18
16
14
12
10
8
6
4
2
0
MENTAL STATE
MANIA
NORMAL
DEPRESSION
4
3
2
1
0
1
2
3
4
EOSINOPHILS per c.mm.
600
500
400
300
200
100
0
25
50
75
100
125
150
175
200
225
250
275
300
DAYS

total daily 17-ketosteroid output shows wide fluctuations, the extreme points of the range being 2.0mg. and 13.2mg. The maximum excretion which is quite within the normal range for men of his age is obtained when the patient is in the depressive phase and lowest outputs occur when he is in mania. These features are constant findings in the case of this patient and the correlation between these fluctuations and the changing mental state has been confirmed over many additional months. The fractionated 17-ketosteroids show a similar and almost parallel course although the proportion of beta to alpha steroids rises towards the end of the depressive phase when it then constitutes 15-20% of the total excretion.

Administration of 25mg. of testosterone daily can be seen to raise the peak of 17-ketosteroid excretion in depression by only 4.3mg. This increase occurs in the alpha fraction as the beta steroid excretion actually shows a fall at this point compared with the control period. Administration of "Diandrone" causes the total daily steroid excretion in depression to be raised to 18.8mg. of which 6.9mg.(36.7%) consists of beta steroids. Stilboestrol can be seen to lower the excretion of both the alpha and beta fractions although the fluctuations persist in relation to the mental state but on a reduced scale. At no time during the exhibition of these hormones was it felt that they in any way influenced or modified the mental state. To round off this phase of the investigation, one application of electroplexy was subsequently given at the commencement of three manic phases with considerable improvement in the patient's condition from the purely behavioural point of view.

The steroid excretion continued to show the same relation to the mood changes but on a reduced scale until the suppressing effect of the previously administered stilboestrol on anterior pituitary function had worn off. Electroplexy did not disturb the regularity or rhythm of subsequent cycles.

The eosinophil counts are seen to vary between 46 and 596 per c.mm., the peaks occurring early in the manic phase and the maximal deflections coinciding with the onset of depression.

Figure 3 shows the results of the second part of the investigations during which attempts to modify the mental state by means of ACTH and cortisone were made. As before, two complete cycles were followed to establish the basic rhythm and then immediately after the patient went in to mania, long acting ACTH, 200 units over 5 days was administered. This had a marked effect on his mental state in that within a few hours of the first injection he showed a mixed clinical picture with manic and depressive features either occurring together or alternating rapidly. He would be standing about hesitantly and yet showed marked acceleration of the mental processes but this could not be expressed in his usual press of talk and interference with other patients' conversation. Later on he appeared perplexed and bewildered, at times almost stuporose and yet within a few minutes showing restlessness and overactivity. There was however no evidence of true confusion and his mental condition could best be described as basically manic but the drive and mental acceleration could not be expressed outwardly through the usual somatic and psychic channels. During the following

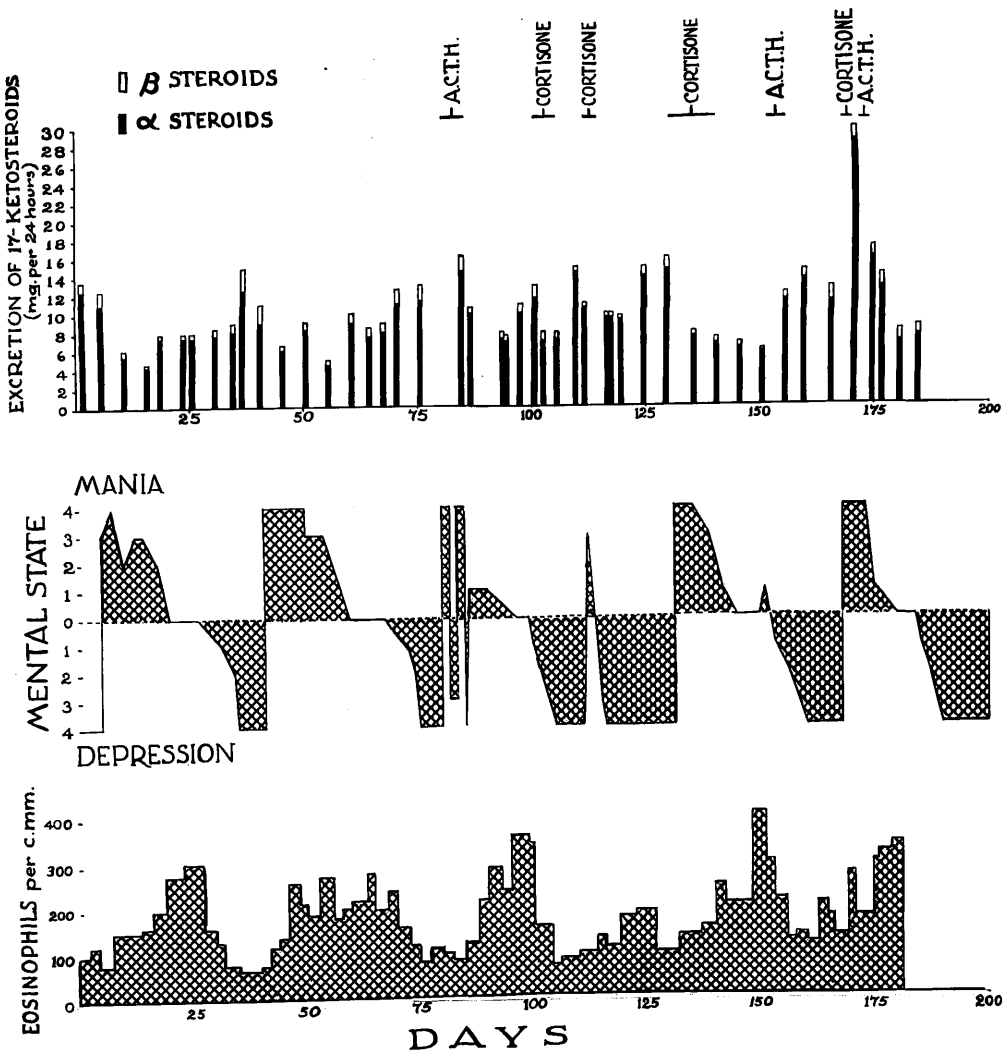

EXCRETION OF 17-KETOSTEROIDS (mg. per 24 hours)
β STEROIDS
α STEROIDS
A.C.T.H.
CORTISONE
CORTISONE
CORTISONE
A.C.T.H.
CORTISONE
A.C.T.H.
MANIA
MENTAL STATE
DEPRESSION
EOSINOPHILS per c.mm.
DAYS

Figure 3.

days of ACTH administration, he continued to alternate between mild mania and depression almost from hour to hour but towards the end of this period he gradually settled in to a state of mild overactivity, such as he usually shows before entering the normal phase. However when the ACTH was discontinued at this point he became more manic, up to point 2 on the scale and this gradually subsided over the next nine days. Thus the total duration of this phase including the treatment period was 15 days.

The effect of ACTH on 17-ketosteroid levels was the expected one of increased output but it was noticeable that after the first two days of ACTH during which normal output was maintained at a time when the values usually drop sharply, the excretion levels did then fall steeply even although ACTH therapy was continuing.

As the next depressive phase was seen to be commencing, cortisone 800mg. over 4 days was administered by injection. This failed to influence the mental state or halt the deepening of the psychomotor retardation: the effect on 17-ketosteroid excretion was to diminish output of both the alpha and beta fractions but when therapy was discontinued the alpha fraction rapidly rose to the normal peak occurring at this time although the beta steroids remained depressed.

At the succeeding manic phase 10 days later, cortisone in high suppressive doses was restarted over 3 days and within a few hours of the first injection, there was a rapid reversal of mood back to deep depression; although cortisone was given for only three days, the patient remained in depression for a further 18 days before suddenly

going in to mania. Thus the mood had been influenced and the total cycle shortened by 14 days. The effect on 17-ketosteroids was to diminish the output of both fractions for seven days when the alpha steroids then rose, the beta fraction remaining depressed.

At the onset of the following manic phase to the above, cortisone was again restarted but administered orally and in smaller dosages of 50mg. daily. On this occasion no change in behaviour or mood could be observed, the length of the phase was uninfluenced and the 17-ketosteroid excretion levels resembled those obtaining in the corresponding control periods.

It was then decided to determine whether the depressive phase could be influenced by ACTH and at the first signs of slowing up in mental and physical activity, long acting ACTH 20 units twice daily was given for four days. This regime failed to raise both the alpha and beta steroids compared with the corresponding control periods and the mental condition progressed steadily in to deep depression.

For the final trial procedure, oral cortisone was given in dosages more or less mid-way between those previously employed (100mg. daily in divided doses for three days), at the onset of mania. As there was no effect on mental state, this was followed immediately by ACTH (40 units twelve hourly) and although his mental state did not show the peculiarities noted when ACTH was previously given in mania, nevertheless the exciteability rapidly subsided in to a mild hypomanic state from which he passed in to his normal phase. The effect on 17-ketosteroid levels on this dosage of cortisone was surprising in

that a 24 hour urine collection showed an excretion of 30.0mg. comprising 95.3% alpha fraction and 4.7% beta steroids. The ACTH which was given immediately afterwards failed to arouse any adrenal response and levels quickly fell to those usually found towards the end of the manic phase.

The fluctuations in eosinophil levels showed no surprising trends compared with the control periods; in the manic phase when eosinophil levels are normally high, both ACTH and cortisone depressed the eosinophil peaks but only for the period of hormone administration.

Figure 4 gives a summary of the effects of ACTH and cortisone on the mental state and adrenal function, in tabular form.

The injection of 25mg. ACTH produces an eosinopenia if measured four hours later of greater than 50% over the control level where the adrenal cortex is normally responsive; it is significant that in this patient a positive response could not be elicited when his mental state was that of depression and in fact the second count on two occasions exceeded the pre-injection count. In mania or in his normal phase, the adrenal was normally responsive. These tests were performed subsequent to the periods reported above when the patient was receiving no hormone therapy.

A liver function test was performed to exclude the possibility of liver damage as the latter could cause disturbance of steroid metabolism. The bromsulphalein dye test was employed and gave a result within the normal limits.

Discussion. The basic pattern of steroid excretion in this patient resembles that of the case described by Reiss and his co-workers

Hormone and Dosage	Affective State	Effect on Mood	Effect on alpha fraction	Effect on beta fraction	Effect on eosinophil levels
ACTH 20 units b.d. for 5 days.	Mania	Alternating state	Increase	Slight increase	Decrease
Injected cortisone 200mg. daily for 4 days.	Depression	None	Temporary decrease	Prolonged decrease	Accentuation of normal fall.
Injected cortisone 200mg. daily for 3 days.	Mania	Prolonged depression	Temporary decrease	Prolonged decrease	Decrease.
Oral cortisone 50mg. daily for 9 days.	Mania	None	None	None	Decrease
ACTH 20 units b.d. for 4 days.	Depression	None	None	None	No accentuation of normal fall
Cortisone 100mg orally daily for 3 days.	Mania	None	500% increase	50% increase	Decrease
ACTH 40 units b.d. for 2 days.		Lessening of mania	None	None	

Figure 4.
Summary of the effect of ACTH and cortisone on mental state and adrenal function.

in that there is a regular fluctuation in 17-ketosteroid excretion with a positive correlation to changing mental state. The excretion rate for both alpha and beta steroids falls sharply when the patient becomes manic, the combined total at this stage being between 2mg. and 5mg. in the 24 hours only rising as the patient's mental condition progresses towards the normal phase at which time total excretion is around 8mg. per day. As he enters the period of depression this rise gradually becomes more marked until when he is at the lowest point of the mood swing, the total excretion of the neutral 17-ketosteroids may be as high as 15.3mg. per day, a figure which is not outside the normal for his age. The eosinophil levels were regularly highest during the manic phase and lowest in depression indicating also that the output of cortins was lowest in mania and highest in depression.

Whereas Reiss et al. in the case they described found an inverse relationship in the excretion of beta steroids and cortin, in the case of the above patient we seem to be dealing with a total response of the adrenal cortex during the uninfluenced cycles. There were great extremes of physical activity during the different phases of the cycle and it is surprising that in the manic state, when adrenalin secretion is likely to be highest, eosinophil levels were at their peak — the opposite to what one would expect if it might be argued that adrenalin production was responsible for the fluctuations in eosinophil levels.

Another unexpected feature of the steroid excretion in this case is the abnormal response to physical and mental stress; if urinary excretion be accepted as an indication of cortical secretion, it is

interesting to note that in mania when psychomotor activity was greatest, adrenocortical activity was lowest and the converse situation prevailed in the depressive phase. The fall in excretion during mania cannot be due to exhaustion of the adrenal cortex as it occurs immediately on entering mania and there is an actual rise in excretion later in the manic phase when exhaustion would be most likely to occur. Taking in to consideration the fact that the adrenal cortex in respect of cortin secretion appeared non-responsive to ACTH in depression, it would appear that a factor in this patient's illness is a faulty adrenal response to internal stress, a failure of the homeostatic mechanisms.

In the first phase of the investigation, endocrine therapy did not alter the mental state although some of the effects on steroid excretion are interesting. The recovery rate for injected testosterone measured as 17-ketosteroids was only 17% of the injected dose whereas West et al. (1951) found that in normal subjects an average of 63% of the injected hormone could be recovered from the urine during the next 24 hours as conjugated 17-ketosteroids. When 50mg. of dehydroisoandrosterone by mouth was given daily, the maximum excretion of beta steroids was only 6.9mg. of which perhaps about 3.0mg. was of endogenous origin. The alpha fraction increased by only 2.2mg. in the 24 hours. In a series of 8 chronic schizophrenics treated with 50mg. of dehydroisoandrosterone by injection, Reiss et al. (1949a) found large increases in the alpha fraction.

Although the effect of stilboestrol was to diminish the

fluctuations of 17-ketosteroid excretion and in fact during the depressive phase values were only about one third of the corresponding figures in the control period, eosinophil levels were not influenced indicating that either one fraction of the adrenocorticotrophic hormone could be quantitatively altered without the others being so affected or that the responsivity of different functions of the adrenal cortex had been affected.

In view of the largely negative results produced by cortisone and ACTH on chronic schizophrenics previously mentioned, it is worthy of note that in this case of manic-depressive psychosis, in certain dosages and combinations of these hormones, definite mood changes could be elicited. The manic state could be influenced by ACTH producing both rapidly alternating changes in mood but also an odd clinical picture where the patient appeared dazed or stunned and where both manic and depressive features could be seen to exist. The state of excitement could also be affected by high cortisone dosage this sending the patient in to a longer than usual depressive phase. Smaller dosages of cortisone produced no clinical change. The effect of cortisone followed by ACTH seemed to be to modify the manic excitement without producing either the violent mood swings nor an "organic" mental picture.

The depressive phase of the illness proved quite refractory to modification by these two hormones. Examination of the results of 17-ketosteroid excretion and of the eosinophil fluctuations during this time would indicate that the adrenal cortex seems to be already making its maximal response and is incapable of being further stimulated.

This theory is strengthened when the negative eosinophil response to injected ACTH during the period of depression is considered. Even in mania, the ability of the cortex to respond to ACTH is faulty and of very short duration.

It is also evident that different functions of the adrenal cortex can be influenced quantitatively to different degrees by means of ACTH and cortisone. In this case however it is unlikely that a hyporeactive or abnormal adrenal cortex is primarily responsible for the illness; it would appear that the abnormal excitation and rhythm is probably generated at a cerebral or hypothalamic level but that subsequent inadequate and inappropriate adrenal responses play a part in influencing the mental state.

Summary. 1. The excretion of both alpha and beta 17-ketosteroids was highest when the patient was in depression and lowest when he was in mania. Eosinophil counts were highest in mania and lowest in depression. This positive relationship between the indices of function and mental state was a regularly occurring feature in the uninfluenced cycles.

2. An inverse relationship between adrenocortical activity and the degree of cerebral excitation was noted.

3. Administration of testosterone, dehydroisoandrosterone and stilboestrol altered the excretion of steroids but did not influence the mental state.

4. Administration of ACTH and of high suppressive dosages of cortisone could alter the manic state but not the depressive phase, and cortisone also altered the periodicity of the cycle.

5. The adrenal cortex appears to be hyporeactive especially when the patient was depressed.

6. ACTH and cortisone affected the various indices of adrenal function in different ways and to different degrees.

7. There is some evidence that in this patient administered hormones were broken down in an abnormal way.

17-Ketosteroid Excretion in Manic Conditions.

It was observed that in the case just presented that the excretion of 17-ketosteroids fell to abnormally low levels during mania. Although the opposite phase of depression is not normally associated with high ketosteroid values, it was felt worthwhile to make estimations on patients in the manic state in order to determine whether abnormally low values were a common feature.

As pure mania either in isolation or as part of manic-depressive illness seems to be increasingly uncommon, it took several months to assemble the following five cases, especially as making 24 hour collections in such patients is often difficult on account of their inability to cooperate.

Case 1.

Mrs W.N.D. aged 63 at the time of the investigations had suffered from recurrent attacks of mania for over 20 years requiring admission to hospital on 5 previous occasions. It was also clear from the history that milder attacks of mania occurred not requiring admission

to hospital. On admission here she was in a state of acute mania, noisy and abusive, running from one end of the ward to the other, showing typical flight of ideas and interfering with the conversation of other patients. The following results were obtained shortly after admission:

Total 17-ketosteroids ..... 2.35mg. per 24 hours.

Alpha steroids ..... 2.31mg.

Beta steroids ..... 0.04mg.

Percentage of beta to total 1.5%

Six months later, shortly before discharge when she had remained quite stable for two months, a repeat urinalysis showed:

Total 17-ketosteroids ..... 7.6mg. per 24 hours.

Alpha steroids ..... 7.43mg.

Beta steroids ..... 0.17mg.

Percentage of beta to total 2.2%

Case 2.

Mr. H.H. aged 66 years. This patient suffered from manic-depressive psychosis for over 12 years before admission to this hospital in 1944. The illness was of a cyclical type but not regular or predictable. In 1947, he had a bilateral pre-frontal leucotomy performed and within a few weeks his condition had become one of chronic hypomania which has persisted. At present he is mildly elated and interfering, shows psychomotor acceleration and bursts of irritability when thwarted. A recent analysis gave the following:

Total 17-ketosteroids ..... 3.28mg per 24 hours.

Alpha steroids ..... 2.91mg.

Beta steroids ..... 0.37mg.

Percentage of beta to total 11.2%

Case 3.

Mr. C.V. aged 52 years. This patient had suffered from manic-depressive psychosis (cyclical type) with short and frequent mood swings but the affective changes followed no regular pattern nor was the sequence true in so far as alternation was concerned. During the hypomanic phase the following results were obtained:

Total 17-ketosteroids ..... 4.68mg. per 24 hours.

Alpha steroids ..... 4.30mg.

Beta steroids ..... 0.38mg.

Percentage of beta to total 8.1%

Unfortunately it was not possible to obtain a further urine collection when he had partially improved as he departed suddenly.

Case 5.

Miss G.P. aged 63 years . This patient was a long standing case of manic-depressive psychosis (cyclical type) with rapidly alternating mild mood swings. During the hypomanic phase the following figures were obtained on separate occasions:

Total 17-ketosteroids	4.6mg.	5.3mg. per 24 hours.
Alpha steroids	4.45mg.	5.06mg.
Beta steroids	0.15mg.	0.24mg.
Percentage of beta to total	3.3%	4.5%

During the depressed phases which on the whole tend to be more severe, the corresponding figures were:

Total 17-ketosteroids	8.42mg.	7.1mg. per 24 hours.
Alpha steroids	7.99mg.	6.63mg.
Beta steroids	0.43mg.	0.47mg.
Percentage of beta to total	5.1%	6.6%

Although no conclusions can be formed from the study of these five cases, it would appear that there is a tendency for manic states to be associated with diminution of 17-ketosteroid excretion. In case 1. when the patient's mental state had stabilised, the 17-ketosteroids had risen to within normal limits. In case 5 with alternating mood swings, there is a tendency to follow the pattern of the case in the previous section with lower steroid excretions in mania than in depression. Similar studies on states of excitement have consistently given excretion figures within the normal range, where the clinical state was usually that of acute schizophrenia. Thus some degree of clinical differentiation may be possible from the use of these estimations in distinguishing manic states from other types of overactivity.

Dehydroisoandrosterone and Testosterone in the Treatment of Psychiatric Disorders.

Sands and Chamberlain (1952) and Strauss et al. (1952) reported encouraging results in the treatment of "inadequate" psychopaths with "Diandrone" but found that the pre-treatment levels of

17-ketosteroids were not significant in relation to the outcome of the treatment. It was observed however that certain types of illness usually depressive in nature occurring in this hospital among women were associated with low total 17-ketosteroids and low or absent beta steroids.

Case 1.

Mrs M.B. aged 51 years. This patient was admitted after persistently taking excess of barbiturates over a period of several months. She had always been a tense anxious person who had found difficulty in managing her house and had undoubtedly been "carried" by her husband for many years. During the six months before admission , she had gradually become more solitary and ineffective, and become more over-dependent on her husband, so that he could not leave her alone in the house. Basically she had always been timid and unassertive, could never take decisions and would easily become depressed if she met difficulties.

The patient was of tall asthenic build, had atrophic breasts, dry inelastic skin and showed a marked arcus senilis. The menopause was 5 years previously. On admission the following figures were obtained:

Total 17-ketosteroids ..... 5.15mg. per 24 hours.

Beta steroids ..... Nil.

After a week when the effects of her self-medication had worn off, she was seen to be quite markedly depressed. She was retarded in thought, indecisive, hesitant in speech and gloomily preoccupied with visceral sensations and ideas of sinfulness.

Testosterone propionate 25mg. intramuscularly was given

three times weekly for three weeks. During the second week, she became progressively more alert and cheerful, actively sought occupation, was able to express herself more fluently and showed more initiative nad drive. By the end of the third week, she was if anything mildly aggressive and tended to be irritable if thwarted. Urine analysis then:

Total 17-ketosteroids ..... 6.53mg. per 24 hours.

Alpha steroids ..... 6.43mg.

Beta steroids ..... 0.10mg.

Percentage of beta to total 1.8%

Her medication was then changed to tablets of methyl testosterone 10mg. twice daily sublingually and three weeks later during which her mental condition continued to improve, the figures were:

Total 17-ketosteroids ..... 6.5mg. per 24 hours.

Alpha steroids ..... 6.46mg.

Beta steroids ..... 0.04mg.

Percentage of beta to total 0.61%

The patient was discharged a week later and continued with therapy. Contact was lost with her after a few months but one year later she was readmitted in an agitated and depressed state but not so severely so as on her first admission. She had discontinued testosterone three months before.

Urine Analysis on re-admission.

Total 17-ketosteroids .....6.1mg. per 24 hours.

Alpha steroids .....6.03mg.

Beta steroids .....0.07mg. (1.21% to total).

No further testosterone was administered but she was placed on "Diandrone" 10mg. three times daily. Her mental outlook improved within ten days but she never became quite so active and "outwards" in her energies as on her first admission. Two weeks after commencing "Diandrone", the urinary excretion figures were:

Total 17-ketosteroids .....21.4mg. per 24 hours.

Alpha steroids .....19.7mg.

Beta steroids ..... 1.7mg.

Percentage of beta to total 7.8%

She was seen one year later and gave the information that she had continued well and was taking the "Diandrone" for nine months after leaving hospital and then discontinued as she "did not wish to keep taking pills for the rest of her life". Three months after this she was admitted to another mental hospital suffering from an agitated depression. I happened to meet her there and she had started electroplexy and was showing improvement in her condition.

Case 2 .

Mrs. K.I. aged 60years. This lady was first admitted to The Retreat in 1947 with the history of recurrent attacks of depression at approximately yearly intervals commencing at the age of 44. She had been in several mental hospitals receiving electroplexy on each occasion with a good temporary result. She was readmitted to this hospital in 1948,1949, 1950, 1951, 1953 and again later in 1953 on which occasion I took over her case.

The pre-illness personality was again of the inadequate type

lacking in aggression and drive and she was unable to maintain the social obligations which her husband's position demanded. The husband stated that for a long time she had shown an "inferiority complex", could never make decisions, hold her own in company and remained for her time of life unhealthily dependent on her aged parents. On several occasions in the past she had been treated conservatively in the hope that the attack would remit spontaneously but this had never occurred.

On admission she was depressed and agitated, wandered in an aimless fashion up and down her room, showed mild psychomotor retardation and voiced ideas of unworthiness.

Urine analysis on admission:

Total 17-ketosteroids ..... 4.38mg. per 24 hours.

Alpha steroids ..... 4.29mg.

Beta steroids ..... 0.09mg.

Percentage of beta to total 2%

The patient was then given "Diandrone" 30mg. daily and an improvement in her condition occurred 10 days later. She became assertive and mildly aggressive, more extravert in her outlook and the morbidly depressive ideas gradually disappeared. Two weeks later, urine analysis gave the following results:

Total 17-ketosteroids ..... 20.2mg. per 24 hours.

Alpha steroids ..... 19.5mg.

Beta steroids ..... 0.7mg.

Percentage of beta to total 3.5%

It is interesting to note that in this patient relatively little of the "Diandrone" was excreted unchanged, the mass of the detectable dehydroisoandrosterone appearing as alpha steroids.

Her mental state continued to improve and stabilise and on discharge she was taking "Diandrone" 15mg. daily. She continued on this dosage in courses of two months followed by one month without therapy and when last heard of, 4 years after her last admission, she remained active and well.

Case 3.

Mrs. E.F. aged 51 years. This patient had a history of recurrent attacks of depression since the age of 30 and had many previous admissions to mental hospitals. She was first admitted to The Retreat in 1945 in a deeply depressed state following a suicidal attempt. Previous attacks without specific treatment lasted 12-18 months before remitting spontaneously. She was readmitted in 1947 and 1952 and on all three occasions had electroplexy with a good immediate result .

In 1953 when the author took over her case, she had been readmitted in a restless and distressed state, voicing ideas of unworthiness and reproaching herself for past indiscretions. She was mildly retarded, grossly indecisive and continually sought reassurance. She had a hypertension (B.P. 180/110) without marked peripheral or retinal arterial changes; her bodily build was pyknic and she looked older than her years.

She was given a four week course of modified insulin treatment at the end of which her condition was quite unchanged. One week later,

the urinary excretion figures were:

Total 17-ketosteroids ..... 10.3mg. per 24 hours.

Alpha steroids ..... 10.6mg.

Beta steroids ..... 0.24mg.

Percentage of beta to total 2.3%

She commenced to take "Diandrone" 30mg. daily, increased after 4 days to 60mg. daily. By the 11th day from the commencement of the treatment her agitation had subsided, she was mildly elated and somewhat over-talkative. At this time, urine analysis showed:

Total 17-ketosteroids ..... 28.2mg. per 24 hours.

Alpha steroids ..... 25.9mg.

Beta steroids ..... 2.3mg.

Percentage of beta to total 8.3%

She was discharged four weeks later, her husband remarking that she seemed more confident and assured than he had ever known her. She continued therapy at home taking "Diandrone" 40mg. daily and remained well for a year, when she suddenly developed a subarachnoid haemorrhage with residual hemiplegia and hemi-anaesthesia. After this she showed well marked signs of dementia and when last heard of was being cared for with some difficulty at home.

Case 4.

Miss J.T. aged 24 years. This patient since her early school days had been a timid shy and self-conscious girl, never able to hold her own in company and never achieved the academic merit which her intelligence indicated to be possible. She had been living a solitary

existence on her parents' farm, for years had been moody and withdrawn and on admission one was struck by her psycho-physical immaturity more appropriate to one ten years younger. She appeared listless, apathetic and never spoke unless questioned, would sit idle for hours unless pressed in to activity and she herself complained of inability to concentrate, crackling noises in the head and loss of feeling. She showed thought blocking and general fragmentation of the personality and the general picture was one of emotional blunting and poverty of ideation occurring in an inadequate personality. She was of asthenic build with poorly developed secondary sex characteristics but her menstruation had been regular since the age of 14 years.

In the first instance she had a 4 week course of modified insulin which apart from a gain in weight produced no mental improvement. She remained passive and withdrawn though quite cooperative. "Diandrone" 30mg. daily was then administered and 14 days later her condition had markedly improved. She conversed spontaneously showed initiative in planning her day, could express herself more easily and remarked "I feel that I really belong to this world now". She stated that she wished to free herself from her dependence on her parents and on her own initiative obtained a resident post in a childrens' home. She continued to take "Diandrone" 30mg. daily for four months after discharge and six months later she was still in her post and maintaining her improvement.

The diagnosis in this case was considered to be schizophrenia of several years duration occurring in a schizoid and inadequate

personality. Although no 17-ketosteroid studies were made of this patient, the length of her illness and her non-response to five weeks of hospital environment in the first instance, would strongly indicate that her improvement was brought about by steroid therapy.

Case 5.

Mrs G.E. aged 57 years. This case is presented as one which resembles both psychologically and in regard to urinary excretion, the type of depression in an inadequate personality which responds to steroid therapy, but in whom in fact it failed to benefit.

On admission the patient was underweight and looked older than her years and took little interest in her surroundings. She was undoubtedly depressed and had in fact been so for just over two years during this time making three suicidal attempts. She complained of lethargy, inability to make decisions, lack of concentration and said that for long periods her mind was a blank. She showed a moderate degree of psychomotor retardation and there was no evidence of dementia. One brother has suffered from a depression in a mental hospital for three years.

Her previous personality was described by her husband as timid and reserved; she had always dreaded meeting strangers and could say little in comapny. Although of average intelligence her husband had had to buy her clothes for years on account of pathological indecision and he had planned her housework for her since marriage as otherwise she flitted from one thing to another in an ineffective way. He said that even before marriage she seemed so pathetic, helpless and

unable to stand on her own feet that he was drawn to her out of sympathy. 17-ketosteroids on admission:

Total 17-ketosteroids ..... 4.12mg. per 24 hours.

Alpha steroids ..... 4.04mg.

Beta steroids ..... 0.08mg.

Percentage of beta to total 1.8%

She then received "Diandrone" 60mg. daily for 18days with no objective or subjective improvement. Excretion figures then were :

Total 17-ketosteroids ..... 34.0mg. per 24 hours.

Alpha steroids ..... 29.05mg.

Beta steroids ..... 4.95mg.

Percentage of beta to total 14.6%

She then received testosterone propionate 25mg. intramuscularly three times weekly for two weeks with no change in any direction. Urinalysis:

Total 17-ketosteroids ..... 48mg. per 24 hours.

Alpha steroids ..... 44.8mg.

Beta steroids ..... 3.2mg.

Percentage of beta to total 6.7%

She then received 10 applications of E.C.T. which made her elated, overactive and grossly confused. One week after the completion of the course, the urinary ketosteroids were:

Total 17-ketosteroids ..... 2.95mg. per 24 hours.

Alpha steroids ..... 2.90mg.

Beta steroids ..... 0.05mg.

Percentage of beta to total 1.6%

Two weeks later when she had stabilised mentally and made a recovery to her previous personality of a rather dependent and clinging outlook and in need of reassurance over the simplest matter, the steroid excretion figures were:

Total 17-ketosteroids .....4.67mg. per 24 hours.

Alpha steroids .....4.56mg.

Beta steroids .....0.11mg.

Percentage of beta to total 2.3%

These figures are more or less identical with those on admission even although the psychotic symptoms of her illness had resolved.

Although no definite conclusions can be drawn from the five representative cases briefly described above, there are indications that psychotic states occurring in the timid, inadequate emotionally overdependent personality can be helped by the administration of androgenic steroids: as will be seen in the following section, depressive states occurring in females are just as frequently found with normal or raised 17-ketosteroid outputs but the combination of the "inadequate personality", low excretion of beta steroids and total 17-ketosteroids and depression make the exhibition of either "Diandrone" or testosterone a worthwhile procedure. It does appear however that therapy has to be continued for long periods after the patient has recovered.

A Review of 17-ketosteroid excretion in 100 consecutive admissions.

Most authors are agreed that in any psychiatric condition , one can obtain high, normal and low values for endocrine indices and taken in isolation thus, little purpose can be served by using as a screening procedure, one particular index; however the purpose of this study was to collect cases who had abnormally low outputs irrespective of their clinical condition and to subject them to corrective therapy. All the collections were not submitted to the fractionation procedure, only those whose total excretion was less than 4.0mg. in the 24 hours or those cases where we had reason to believe that we were dealing with an "inadequate personality".

Reference to Figure 5 shows the distribution of 17-keto-ketosteroids in relation to clinical state and age. Cases of established senile dementia without affective disorder were excluded. No definite trends emerge and all the groups of mental disorder except mania include both high and low figures although there is a tendency for the average figures of each group to be in the lower half of the normal range. There is no significant difference between the average figures for recent and chronic schizophrenia, the latter being defined as schizophrenia existing continuously for a period of over two years before admission. Although only three cases of mania were admitted during the period of this survey, it can be observed that the excretion figures were either at the lower range of normal or below this point .

Three females and one male in the endogenous depressive group had excretion figures below 4.0mg.; the beta fractions were in

Figure 4.

DIAGNOSIS	Age 15-40 years		Age 41-60 years		Age 61+	
	M	F	M	F	M	F
Endogenous depression		4.3	4.5 13.9 4.9 7.3 8.8 10.1 5.9 8.2 (7.9)	8.5 4.3 7.0 6.4 2.9 5.6 7.5 4.9 11.1 5.9 6.4 8.4 7.3 (6.3)	7.3 6.3 5.1 3.7 5.2 (5.5)	4.6 4.7 4.2 3.5 7.9 6.1 7.0 3.9 4.4 6.0 (5.2)
Schizophrenia (recent)	14.9 13.2 13.6 22.1 11.5 (13.1)	12.6 4.3 12.6 5.8 19.7 7.0 13.0 6.6 (10.1)	4.6	2.7 6.3 8.9 (6.0)		
Schizophrenia (chronic)	9.3 10.7 19.2 (13.1)	4.8 9.1		7.1		
Psycho-neuroses	15.4 8.7 6.0 (10.0)	2.5 9.1 3.7 21.0 9.1 6.9 8.4 11.4 (9.0)	5.5 3.7 5.8 10.5 5.6 (6.2)	4.1 7.0 2.3 3.2 5.1 (4.3)		4.2 5.5
Organic states	6.6 10.4				3.4 4.2 5.4	
Psychopathic personality	5.8 3.6 13.3	5.1 9.0 4.8		4.0 5.1	4.5	
Mania			4.7			2.4 2.7

Total 17-ketosteroid excretion rates tabulated in relation to illness age and sex. Figures in parentheses are averages for the group.

the normal range of 5-15% in all cases. In none of them was there clinical or other evidence of glandular disturbance: the three females were given "Diandrone" 30mg. daily for 14 days with no clinical improvement. The man suffered from recurrent endogenous depression and was given "Diandrone" in doses of 60mg. daily and later on, testosterone propionate 25mg. intramuscularly three times weekly again with no benefit resulting. All four cases eventually responded to electroplexy. The three female cases all showed stable and well integrated personalities with no signs of undue dependence, lack of aggression or drive. The man fell more in to the class of longstanding inadequacy and for many years had drifted from job to job and in most spheres of his life lacked any constructive drive.

It would appear that no specific purpose is served in performing 17-ketosteroid estimations as a routine procedure on admission and that selection of cases for "Diandrone" or testosterone therapy is in the first instance on a personality basis although confirmatory indications can often be obtained if the total 17-ketosteroid excretion is low and the percentage of the beta fraction to the total, below 5%.

Serum Cholesterol Levels of 200 Consecutive Admissions.

Very few well established cases of myxoedema are admitted to mental hospitals nowadays as the awareness of the classical signs and symptoms of the disorder has increased. However it was determined t o estimate the total serum cholesterol in 200 consecutive admissions and to pay particular attention to those patients whose blood levels were higher than 300mg. per cent . Unfortunately no further and more precise estimations of thyroid activity were then practicable and once attention had been drawn to a case by a raised figure, diagnosis and treatment were then made on clinical grounds.

The method used was that of Sackett (1925) for the estimation of total serum cholesterol and the normal range is given as 150-240mg. per cent . This figure tends to rise with age and although the blood level is not supposed to be materially altered by a recent meal, all estimations were made in the fasting state. In myxoedema raised figures of up to 700mg.% are obtained and in hyperthyroidism, levels may be down to 80mg%. Small increases may also be found in hypopituitarism and moderate increases in coronary thrombosis and angina pectoris and degenerative disorders of the circulatory system.

Although a certain percentage of cases of myxoedema do not have raised cholesterol levels nevertheless it was felt that the test might have some value as a routine procedure in focussing attention on borderline cases which might be "missed" on ordinary examination.

The average figure obtained for serum cholesterol levels was 225mg.%, the average age of the group being 53 years. The lowest

figure in the range was 114 and the highest 450mg%. The following 15 cases are described whose levels on admission exceeded 300mg.%.

Case 1. Mrs. D.Y. aged 61 years. This patient had suffered from asthma since the age of 18 and was basically an overdependent and hysterical personality who most of her life lived in dread of catching any disease she heard mentioned. Eighteen months before admission, she became tense, agitated and morbidly depressed, made a suicidal gesture and entered a mental hospital where after a course of electroplexy, she made a temporary improvement for four months.

On admission here, she was extremely agitated, miserable and grossly preoccupied with her visceral functions: she picked sores on her skin, made self-disparaging remarks and repeated her symptoms over and over again in an automatic fashion. Blood cholesterol on admission was 438mg.%.

Her weight was 119lbs., her skin dry thickened and scaly and the facies had lost the finer features of expression, becoming coarse and heavy. The hair on the scalp was coarsened and sparse but the eyebrows and other bodily hair were present in normal degree. Her heart was enlarged, the resting pulse was 64/minute and the blood pressure was 165/100mm.Hg. The abdomen was mildly distended and she had severe and obstinate constipation. She kept herself wrapped up in a shawl and several layers of outer clothes and although in a centrally heated atmosphere, constantly complained of the cold.

She commenced dried extract of thyroid gr.1 twice daily and in four weeks her condition had markedly improved: the psychotic

depression had cleared completely, she was active and energetic and her face and bodily movements were lively and expressive. The blood cholesterol had dropped to 245mg.%. She retained most of the features of her chronic neurosis but learned to some degree to be able to live at peace with her difficulties. She remains on a maintenance dose of thyroid gr.2 daily.

Case 2.

Miss D.G. aged 54 years. This patient was first admitted to this hospital at the age of 53 with a history that for many years she had been an oversensitive personality with a tendency to react in a paranoid way to any hint of criticism. For the previous 5 years, she had shown well marked cyclothymic mood swings, the depressive phases being more marked than the elated periods. On her first admission, she was mildly depressed showing itself as a tendency to reproach herself unduly for past decisions and stating that she had let everyone down by her lack of will power and effort. Treatment consisted of intensive psychotherapy for three months during which she improved initially but towards the end of this period became pathologically depressed, hesitant and indecisive. Five applications of E.C.T. were then given and after passing through an elated phase, she became alert, cheerful and confident ceasing to ruminate on past events and was discharged to return to her employment.

She remained well for four months, when without an apparent precipitant, she lapsed quickly in to a deeply depressed condition. She paced up and down the corridors, showed retardation of thought

and inability to express herself, would approach one hesitantly commence to make a remark and break off without completing the sentence and she was once again morbidly self-reproachful.

Her blood cholesterol was noted at this time to be 330mg.%. Her skin was dry and rough, she showed thinning of the hair on her scalp and of the outer third of the eyebrows and complained that the hair on her head was "coming out in handfuls". She showed an undue sensitivity to cold, her face tended to be expressionless and of an ashy gray pallor and folds of skin made her look heavy jowled. Photographs taken ten years previously showed her to have a lively expression with quite finely moulded slim facial features. Her weight was 132lbs., which she claimed to be 14lbs. greater than her usual. The resting pulse was 82/minute and blood pressure 145/85 mm.Hg.

She was started on dried extract of thyroid gr.1 daily, increased after 14 days to gr.1 twice daily. Her mental and physical condition improved from about the third week of therapy and by the sixth week she began to show signs of thyroid overdosage. The dosage was reduced to gr.1 daily and nearly one year later, she continues on this dosage; she is alert, happy and cheerful with no trace of depression, her face has now a good colour and regained its features and she has held down her job with less difficulty than for 7 years.

When she had become stabilised on her maintenance thyroid her blood cholesterol had dropped to 246mg.% and her weight was 120lbs.

Case 3.

Miss R.B. aged 72 years. This lady had a previous admission

at the age of 65 which was diagnosed as an endogenous depression and treated successfully with electroplexy. On the second admission she was in a retarded and depressed state, full of ideas of unworthiness and guilt over past actions and at times refused food. She had intractable insomnia. Her blood cholesterol was 310mg.%. Physical examination disclosed an extremely dry rough skin, thinning of the hair at the temples, loss of hair over the outer eyebrows and a general thickening and infiltration of the skin of the face and body. She was also noticed to have an intolerance of cold to a marked degree. Her weight was 115 lbs. representing little change from normal, her resting pulse was 70/minute and her blood pressure 150/85 mm.Hg. All her movements were slow and laboured and she had severe constipation.

She was started on gr.1 of dried extract of thyroid daily, subsequently increased to gr.2 daily. On this regime she showed considerable improvement in quickening of movements and in mental response. However it was decided to accelerate her progress with one application of E.C.T. at weekly intervals for three weeks. She made a complete recovery and continues on a maintenance dosage of gr.2 thyroid daily without showing toxic signs. Any lessening of this dosage brought about a return of sluggishness and a tendency to depressive symptoms.

Case 4.

Mrs. B.M.B. aged 76 years. This lady had no previous relevant history of physical or mental illness. For six months before admission, she had gradually become more and more unable to look after herself and her house, and gradually shown signs of agitation and a

more obvious depressive state. She appeared perplexed and bewildered, was markedly retarded with regard to her thought processes and expressive powers and expressed ideas of unworthiness. She was of below average intelligence and was normally a timid retiring person but a conscientious one. There were no signs of dementia or disturbance of recent memory out of proportion to her years. On admission she was severely undernourished weighing 87 lbs. and although the skin was inelastic and wrinkled, it was also thick coarse dry and somewhat scaly. She had no axillary hair, the eyebrows were thinned and the scalp hair sparse dry and coarse. Her facial appearance was dull and unexpressive and the thickening of the tissues here gave her a deceptive appearance of plumpness. She complained of feeling cold and would sit on a radiator wearing as many clothes as she could find. The resting pulse was 64/minute and the blood cholesterol was 330mg.%. The blood pressure was 142/90 mm.Hg.

Because of her severe state of malnutrition and her continued refusal to eat, electroplexy was given. One week after the completion of 6 applications of E.C.T., her mental state had markedly improved, she was spontaneous and cheerful and eating well. Her blood cholesterol was now 287mg%. One week later, her mental condition was beginning to deteriorate. She stood around hesitantly, again showed signs of psychic retardation and would apologise unnecessarily. She was started on dried extract of thyroid gr.1 daily and 14 days later she was improving. Her blood cholesterol was now 236mg.%. Ten days later she began to show signs of tremor, restlessness and tension and her thyroid was

reduced to gr.½ daily. The latter symptoms eventually disappeared and her psychiatric condition has remained good. Her weight now that she left hospital is 106 lbs. and she continues on thyroid medication.

Case 5. Mr. N.W. aged 44 years. Serum cholesterol on admission was 370mg.%. He was suffering from chronic alcoholism with advanced cardio-vascular degeneration. No signs of myxoedema. Some months after leaving he developed a coronary thrombosis.

Case 6. Mrs. A.G. aged 85 years. Serum cholesterol on admission was 337mg.%. She was suffering from recurrent endogenous depression and there were no signs of myxoedema. She showed hypertension and marked peripheral arteriosclerosis. She received electroplexy, made a good recovery and shortly before discharge her cholesterol was 314mg.%.

Case 7. Mr L.G. aged 67 years. The diagnosis was endogenous depression and he showed no signs of any endocrine or physical disorder. With electroplexy, he made a good recovery and his serum cholesterol had dropped from 315mg.% on admission to 264mg.% before discharge.

Case 9. Miss M.M.T. aged 50 years. This patient suffered from chronic schizophrenia and remains in hospital. Although of masculine build and facies there were no indications of thyroid or adrenal dysfunction. The excretion of 17-ketosteroids was normal. Cholesterol on admission was 324mg.%.

Case 10. Mrs. S.W. aged 60 years. Serum cholesterol on admission was 450mg.%. This patient was suffering from recurrent depression. She was obese and pyknic in build and was hypertensive with marked arteriosclerosis. She responded to electroplexy and shortly before

discharge her cholesterol remained high at 416mg.%.

Case 11. Mrs M.R. aged 55 years. This lady was suffering from a reactive depression and showed no indications of an endocrine disorder. Shortly before being discharged improved, her serum cholesterol had fallen from 342mg.% to 264mg.%.

Case 13. Mrs E.F. aged 56 years. Serum cholesterol on admission was 300mg.%. There were no signs or symptoms suggestive of thyroid disorder. Three months after discharge her cholesterol had risen to 340mg.% and she was again suffering from an anxiety state with psychosomatic symptoms. Thyroid was given and pushed until signs of overdosage occurred but without relief of her mental condition. She showed no signs of cardio-vascular degeneration.

Case 14. Miss M.R. aged 16 years. This girl was found to be suffering from epilepsy and there was no detectable endocrine disorder. Cholesterol on admission was 322mg.%.

Case 15. Mrs L.A. aged 50 years. Serum cholesterol on admission was 300mg.%. Clinical state was that of reactive depression and she made a good recovery with electroplexy followed by psychotherapy. She showed no signs of physical nor endocrine disorder.

Discussion.

The case material consisted of 12 women with an average age of 58.2 years and 3 men whose ages averaged 46.0 years. Illustrating the remarks in the literature cited when discussing myxoedema the 4 cases in whom thyroid underfunction was diagnosed were all female, post-menopausal and their average was 65.8 years. Although none of these

cases had further confirmatory thyroid studies performed, their response to thyroid medication especially in the 2 cases who had previously relapsed following electroplexy would indicate that the diagnosis had been correct.

The outstanding symptoms were coarsening and loss of hair from the eyebrows and scalp, coarsening of the facial features and intolerance of cold and all four cases had these signs present. Gain in weight was not a feature in these patients and in fact loss of weight due to refusal of food tended to be the rule. The mental symptoms were all in the depressive grouping and all of the cases on superficial acquaintance could easily have been diagnosed as typical endogenous depressions.

It would appear that this test is well justified as a routine admission procedure, not unduly time consuming for indicating cases which might bear further scrutiny for possible thyroid underfunction. Most of the cases described were not fully developed in the sense of classical appearance and could easily have been "missed" if the screening procedure had not drawn attention to them.

If these figures are representative, the incidence of thyroid underfunction in patients admitted to this mental hospital is 2% of new cases, keeping in mind that the methods employed were very crude and afforded only rough indications. It is proposed in the near future to perform screening tests using the protein bound iodine test in conjunction with the serum cholesterol in order to obtain more accurate indices in both directions, but especially in the case of hyper-

thyroidism for which the serum cholesterol is of little value. This project has already commenced and taken in conjunction with 17-keto-steroid estimations, interesting results with therapeutic applications are being obtained. Suitable cases are being referred for iodine tracer techniques to gauge the finer responses of thyroid function.

Case of Hyperthyroidism with Acute Psychosis.

The patient was a married woman of 30 with one child aged $1\frac{1}{2}$ years. The diagnosis of Graves disease was made 8 months previously by a physician who described her condition as "very gross and obvious hyperthyroidism". She was treated with "Neo-mercazole" 0.5mg. daily and steadily improved, putting on weight, showing greater emotional stability and she was considered to be responding satisfactorily.

Three weeks before admission to The Retreat, she became exciteable overactive and morbidly suspicious. She received mysterious and urgent messages and would telephone warnings of impending disaster to friends. After a few days her speech became so accelerated as to be incoherent and she was admitted to an observation unit where her behaviour was described as "aggressive, elated manic and she was in danger of exhaustion". She was treated intensively with E.C.T. and then sent on to The Retreat.

On admission here she was grossly amnesic and confused as a result of the E.C.T. For the most part she gazed around in a terrified fashion and although quite cooperative, little contact could be made

with her. No specific treatment was given for four weeks during which her condition steadily improved. Quite suddenly, she became tense and fearful, stilted and abrupt in manner and showed a typical impairment of thought sequence and expression typical of schizophrenia. Although her behaviour became aggressive and impulsive, it could not be termed truly manic but fell in to the category of catatonic excitement. After 4 applications of E.C.T., she was placed on a course of insulin coma therapy receiving 36 comas in all. She put on over a stone in weight, became tranquil and normal in behaviour and emotional reaction and six months after discharge had maintained her improvement fully returning to her pre-illness personality of a rather strict overconscientious person but not unduly given to worrying.

On admission here her weight was 113 lbs., resting pulse 76/minute, blood pressure 120/76 mm.Hg. and apart from well marked exophthalmos, she showed no signs of hyperthyroidism. She was of athletic build, her skin was moist but she did not perspire unduly. There was a trace of reducing substance in her urine. Anti-thyroid therapy was continued unchanged from the day of admission until her discharge. When seen three months after leaving hospital by the physician who had originally made the diagnosis, he reported that her thyroid condition remained under good control, she continued to gain weight slightly although there had been some increase in the degree of exophthalmos.

In view of her stable and well integrated personality prior to her psychosis, it would appear likely that her hyperthyroidism was

in some way related to her mental disturbance. It is interesting that the mental condition occurred at a time when she was apparently under satisfactory control by anti-thyroid therapy and not 8 months before when she was obviously thyrotoxic.

A Case of Cushing's Syndrome with Psychosis treated by Bilateral Adrenalectomy.

In 1951, Spillane presented 7 cases of Cushing's syndrome, four of whom showed severe nervous and mental symptoms as part of the illness. He also reviewed the literature and presented a list of 50 patients of various authors, all of whom had shown some degree of mental upset, 18 of the cases to such a degree as to be termed psychotic illnesses. He observed that in addition to the reaction which may follow the distressing physical changes found in the syndrome, some cases showed mental changes before the physical changes were severe enough for the diagnosis to be made, indicating that hormonal or biochemical factors could be concerned in producing mental disturbances.

The patient in this case was a married woman aged 35. Her pre-illness personality seemed a stable one and she was described by different friends and relatives as gay, jolly, sociable, actively interested in athletics and riding and also a very good housewife and mother.

The patient first noticed a change in her physical configuration two years before admission and immediately after the birth of her second

child. She had always had a slim figure but now her thighs and hips became very fat and she complained to her family that her face was becoming coarser and fuller. About one year before admission, she began to complain of difficulty in focussing her eyes, on occasion her entire vision would blur and she suffered from frontal headaches and pulsations in the head. Her face continued to become more full and red and she developed a slight excess of facial hair. She was placed on thyroid by her doctor without effect. Four months before admission she had become listless and depressed, wept easily, could not concentrate even on light reading, reacted violently to criticism and spent a lot of time sitting and staring in to space. She was referred to a general hospital where it was noted that she had a polycythaemic appearance, her blood pressure was 170/105 mm.Hg., basal metabolic rate -8%, haemoglobin 117% and P.C.V. 48%. Four to five pints of blood were withdrawn; her weight at that time was 140 lbs.; one month before admission, frontal headaches became severe and continuous, she had periods of confusion and episodes when she could not express herself although she knew what she wanted to say. She had become very depressed, expressed ideas of unworthiness and sinfulness and talked freely in the vein that she had caused so much trouble to her family and so much shame that she wanted to die to free them.

On admission, she was in an acutely disturbed and noisy phase, reciting the Lord's prayer in loud ringing tones, praying for forgiveness for her wickedness and resistive of all nursing attention. For the first few days her condition fluctuated violently. At times

she was cooperative and lucid and could give a reasonably good account of herself while quite suddenly and dramatically she would throw herself on the floor, shouting and screaming, pleading to die and writhing about to such a degree as to cause marked cyanosis and exhaustion. Gradually the disturbed periods became more frequent and her condition was deteriorating so rapidly that intravenous anaesthesia had to be maintained for hours at a time . She also showed marked tonic spasms and clonic movements, becoming alarmingly cyanosed. This acute delirious phase lasted three days and towards the end of this period she developed an extensive purpuric rash.

Thereafter her mental state bore certain resemblances to the condition of catatonic schizophrenia. For the most part she lay in an apparently stuporose state, resisting movement of her body, mute but in intervals of relative normality, she could gave a good account of what transpired during these episodes. From time to time she would have prolonged noisy outbursts fighting and struggling and often ending up in ecstatic religious postures. At no time was there evidence that she was suffering from visual hallucinations although she admitted that she had auditory hallucinations which she interpreted as the voice of God.

Physical Examination. Her face was dusky red in colour with a cyanosed appearance, typically "full moon" and she showed a marked bull neck. There was a moderate kyphosis with an upper thoracic fat pad, her thighs and hips were grossly fat and a few recent purple striae were present on the lateral aspects of the thighs. Hair

distribution was normal as were the genetalia and menstruation had been regular up to admission. Her weight was 120 lbs., blood pressure 160/120 mm.Hg. and retinal examination showed no abnormality.

Laboratory Findings. Examination of cerebro-spinal fluid under anaesthesia disclosed a normal pressure, normal cell count and a total protein of 46mg.%. The haemoglobin was 72%, white cell count 8500 per c.mm. and no eosinophil cells could be seen.

Urine. Two consecutive 24 hour collections were made.

	First day.	Second day.
Total 17-ketosteroids	13.6mg.	13.0mg.
17-Ketogenic steroids (By the modified Norymberski method 1955. Normal range 4-18mg.).	51.2mg.	63.0mg.

Straight X-ray examinations of skull, chest, abdomen, lumbar and thoracic spine showed no abnormality.

A two stage complete bilateral adrenalectomy was performed, the left adrenal gland being removed first and the right gland twelve days later. For 72 hours after the first operation her mental state remained unaltered. She remained semi-stuporose although passively cooperative and quite inaccessible to conversation. From the fourth day, she became cooperative and talkative and the clinical picture was one of profound depression with marked paranoid ideas and ideas of reference and influence. She was suspicious and believed that routine movements about the ward were special tests to trap her. Auditory hallucinations persisted. Blood pressure after the first operation stabilised at 128/86 mm.Hg. and did not change after the second

operation.

The second operation was performed under cover of parenteral cortisone and after one week she was stabilised on oral cortisone 25mg. twice daily. Her mental condition improved only very slowly and she continued to express depressive and paranoid ideas for four weeks. She gradually put on weight in the extremities and the obesity around the hips and the fullness of the face and neck slowly subsided. Within two months after the operation, her mental condition had almost returned to normal and her relatives remarked that the only difference was that she appeared less outward and more passive and somewhat listless. Six months later she was running her own house and had resumed most of her social interests.

Summary and Conclusions.

Harmony in endocrine function is essential to normal mentation. Gross deviations of endocrine function have long been recognised as often being accompanied by psychiatric disorder but little importance has been attached to this until recent years when interest has been intensified in putting psychiatry on a more rational basis. The present system of classification of psychiatric disorders has for long been regarded as unsatisfactory, grouping as it does all patients with a few similar symptoms in to the one category, the position resembling that as if one were satisfied by diagnosing "headache" or "abdominal pain".

The interaction existing between mind and body is no more pronounced than in the endocrine system. The influence of disturbed emotion reacting through the hypothalamus, target glands and the periphery, the latter in turn affecting mentation is now fully accepted and it is important to appreciate that the primary disturbance may be at any level in the circle. An emotional upset or conflict, conscious or unconscious may by this mechanism cause amenorrhoea or hyperthyroidism which in turn may alter the mental state. An unresponsive thyroid or an alteration in peripheral sensivity to hormones may secondarily cause mental symptoms so that it can be seen that by a combination of primary and secondary reactions, a vicious circle can be established which may be interrupted at any level to produce a more stable pattern of body-mind equilibrium. Thus brain surgery may be effective in interrupting the chain of events between the frontal areas and the

thalamus, psychotherapy by helping the individual to increase his ability to deal with or tolerate psychic trauma acts similarly and hormone therapy in addition to its peripheral action can also affect mentation. The use of anterior pituitary trophic hormones while still of limited application is another point at which interference is possible, while the use of hormones from the peripheral glands such as thyroid, testosterone and dehydroisoandrosterone may in certain cases prove therapeutic.

The case material in the clinical section was obtained from a hospital with an annual admission rate of 450, in under two years with the exception of the case of cyclical psychosis thus showing that even with the relatively crude methods of investigating and screening available, that a significant proportion of admissions have some endocrine abnormality. With more exact techniques, every year sees our ability to obtain a finer and a more general picture of endocrine function, a reality. Several points in future research would seem important. A single isolated test will seldom be of any value in a constantly changing internal situation. As under or over production of one gland has widespread repercussions , it would seem essential that not only should indices of function representative of the total hormonal equilibrium be made, but also that serial studies be performed. It is the changing situation internally to which importance must be attached as the elasticity of hormonal response and its ability when bombarded by stimuli to return to a stable pattern must be more significant in assessment than the particular pattern at one specific

time.

The two peripheral glands concerned in mentation are the adrenals and the thyroid. With administered ACTH or cortisone, the incidence of effect on emotions and mentation varies according to the various authors from 5% to 95%. These administered hormones are capable of producing a primary mood change out of keeping with the reality situation and also in a minority of cases to produce a psychotic reaction. This is illustrated by the case of Cushing's syndrome presented where the adrenal hormones produced endogenously to excess precipitated gross mental changes. It would appear that the more gross reactions are not related to total hormone dosage, duration of administration nor to previous personality as administration to psychotics is singularly without effect. In these cases, cortisone seems to act as a toxin but not in the usually accepted clinical form of a toxicosis. It is suggested that in these people, the elasticity of their endocrine system and its ability to minimise internal change is probably innately weak and that even small dosages of administered hormones can derange the total hormonal equilibrium eventually affecting cerebral function.

With regard to adrenal function in psychiatric disorder, there is no evidence for the presence of a qualitative abnormality. In schizophrenia, both hypo- and hyper- function, hypo- and hyper-responsivity of the adrenal cortex have been reported as well as apparently normally functioning glands. Negative as this evidence appears, it is important in illustrating that no specific psychiatric entity is associated with a particular endocrine abnormality but that

dysfunction or disharmony between glands in either direction may be associated with mental disorder. In what are apparently similar mental states, one can obtain an infinite variety or permutations of the various indices of glandular function, indicating quite different approaches in corrective hormonal therapy.

Evidence is presented that abnormal adrenal responsivity was concerned in a case of manic-depressive disorder and that hormone therapy could significantly alter the mental state in the manic phase. Also there are indications that true manic disorders may be associated with a low 17-ketosteroid excretion rate and this may prove to have a diagnostic value.

The use of "Diandrone" would appear to have a place in the treatment of the timid inadequate personality and cases presented in this work show that this type of personality, irrespective of the diagnostic label, often show gross under excretion of dehydroisoandrosterone in the urine along with a low total 17-ketosteroid excretion and respond to the administration of "Diandrone".

Electroplexy and insulin coma therapies may act by disrupting existing unstable patterns of endocrine dysfunction and in successful cases a more stable hormonal equilibrium is established.

The importance of gross thyroid disturbances in patients admitted to mental hospitals would seem indicated from the case material presented and the routine estimation of serum cholesterol levels to focus attention on possible cases of hypothyroidism is simple and well worthwhile. If estimations of the protein bound iodine were

also made even more accurate estimations of thyroid function would be possible. The use of iodine tracer techniques would only seem to be justified in special cases. Similarly routine estimations of 17-keto-steroids are hardly justified but in individual cases taken in conjunction with thyroid studies and the excretion of 17-ketogenic steroids, valuable information of the hormonal balance can be obtained.

The incidence of mental upset at puberty, the menopause and the puerperium indicates the importance of hormonal factors in such conditions acting partly directly and partly indirectly through the stress created by difficult psychological readjustment . However further advancements in psycho-endocrinology will probably occur by elucidating the minor variations in hormonal dysfunction and being able to picture the total hormonal balance as a dynamic constantly changing whole at the same time equating these values with serial studies of the mental state in individual cases.

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