THE DIURNAL VARIATION OF

PLASMA CORTISOL LEVELS IN DEPRESSION

by

David J. McClure, M.D.

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HISTORICAL SURVEY

The association of certain critical periods in life, such as puberty, pregnancy and the menopause, with changes in mental state provoked speculation from the earliest times as to the possible effects of "humors" on the mind. However, the first reported observation associating mental functions with endocrine disease was made by Platter (1602) when he commented on the occurrence of mental deficiency with cretinism. It remained for two centuries to pass and the emergence of the definitive study of the internal secreting glands before a sound connection to mental aberrations became established. In fact, the term endocrinological psychiatry did not appear until 1908 when it was introduced by Laignel-Lavastine (Michael and Gibbons, 1963).

That the adrenals influence the functions of the brain has become increasingly more evident since the clinical manifestations of adrenal cortical insufficiency were described in 1855 by Addison. He reported several cases with psychological symptoms including depression, anxiety, "mind-wandering" and delirium. Delirium was also described by Greenhow in 1875 (quoted by Cleghorn in 1951) and Klippel in 1899, in their cases of Addison's disease. A considerable interval of time elapsed before Engel and Margolin in 1941, reporting on their twenty-five cases, drew attention to the high incidence of psychiatric symptomatology occurring in this condition.

While investigating myxoedema, in 1888, the Committee of the

Clinical Society of London found that insanity often occurred in the advanced cases. The mental disorder took the form of acute or chronic mania, dementia or melancholia and delusions and hallucinations were found in nearly half the cases. Murray, in 1891, used thyroid extract to successfully treat and cure myxoedema and the accompanying mental abnormalities were removed at the same time. This was the first demonstration of the effectiveness of a hormone in the treatment of psychological symptoms.

Dementia praecox was once regarded by Kraepelin (1896) as basically an endocrine disorder. The gonads of schizophrenics were studied by Mott and Prados in 1923, and a regression in the testes was observed. At the Worcester Foundation in Massachusetts, Hoskins used laboratory techniques in his investigations of the schizophrenic illnesses. He published the findings in his Biology of Schizophrenia in 1946. About this time Gjessing demonstrated that periodic catatonia was due to changes in the body's nitrogen balance.

Up until 1921 the primary focus of attention had been the study of psychiatric symptomatology in endocrine disorders. Evidence that the reverse was also true, namely that a change in endocrine function could occur in psychiatric conditions, was demonstrated by Maranon at this time. He showed that a psychological factor was involved in the etiology of hyperthyroidism, and Bleuler, in the English translation of his text book in 1925, described psychosis occurring in hyperthyroidism.

The effects of adrenocortical hyperfunction in producing an

abnormal mental state was first described by Holmes in 1925. He reported a case of virilism in a young woman due to an adrenal tumor; the patient developed mental changes which disappeared when the tumor was removed. This article was followed by others with similar observations; for example, in 1938 Brester stated that the psychosis occurring in the adrenogenital syndrome cleared up following adrenalectomy. Maclay et al. in 1938, felt that the association of Cushing's Syndrome with a psychosis was more than just a coincidental finding.

The psychiatric changes described so far were considered by investigators to be the side effects of the accompanying endocrine disorder. For this reason their importance was minimized or ignored and little effort was made to ascertain their true nature or frequency. This is surprising since Freud, as early as 1905, had referred to endocrinology as the biological nextdoor neighbour of psychoanalysis and observed that certain mental disorders might eventually be treated successfully with hormones.

The revival of interest in the possibility of an endocrine role in the etiology of mental illness occurred in the late 1940's and early 1950's. It was due primarily to two events which occurred almost simultaneously. One was Selye's concept of stress (1946). He postulated that an organism responds to stress by the General Adaptation Syndrome. The second event was the introduction of the adrenocorticotrophic hormone and cortisone into medical treatments (Hench and Kendall, 1949). It was not long before the side effects of these compounds aroused the interest of psychiatrists since they

produced all the psychological manifestations described in the naturally occurring endocrine disorders. The commonest finding was an alteration in mood (Hench, 1950). A mood change occurred in 84 percent of Browne's cases in 1952 and in 80 percent of Goolker's in 1953. The first mood change reported by investigators, and the one most often found, was euphoria (Taylor, 1950; Ebaugh, 1951; Cleghorn, 1952). Depression was found by Pearson (1950), Soffer (1950) and Rome and Braceland (1952) in their cases. Other transient findings were tension, restlessness and excitability. Psychotic symptoms were less common but took the form of delusions, hallucinations, mania, disorientation and catatonia. The clinical picture was therefore often indistinguishable from acute paranoid schizophrenia (Glaser, 1953), or from acute catatonic schizophrenia (Mach, 1951), or from acute organic psychosis (Ritchie, 1956), except that on most occasions the condition was reversible when the hormone therapy ceased.

Over the past fifteen years it is gratifying to note the extent to which interest in these interdisciplinary studies has flourished and grown. It is only partially indicated by the flood of material published about them. Indeed, this material is so extensive that an attempt to review it will not be contemplated in this short survey. Generally, however, it indicates that the two disciplines of psychiatry and endocrinology are being drawn closer together and it is hoped that this convergence will illuminate a number of, as yet, unsolved areas in psychiatry.

NEUROPHYSIOLOGY

(a) Physiology of the Adrenal Cortex

Human adrenal glands are cap-like structures that weigh 5 - 7 grams each. They cover the superior pole of each kidney and lie in the abdominal cavity at the level of the first lumbar vertebra. The complex gland consists of an inner core, the medulla, and an outer shell, the cortex. The cortex forms 80 percent of the organ's total weight and is composed of large lipid-laden epithelial cells which are arranged in three zones. The zona glomerulosa forms the outer layer; lying next to the medulla is the zona reticularis; between these two is the zona fasciculata.

More than fifty different steroids have so far been isolated from the adrenal cortex. The most important biologically are cortisol, cortisone and corticosterone, which collectively influence carbohydrate, protein and fat metabolism. They are called the glucocorticoids and are produced, along with the adrenal androgens, by the cells of the zona fasciculata and zona reticularis. These cells are dependent upon the adrenocorticotrophic hormone of the anterior pituitary gland for their growth and secretory activity (Williams, 1962; Forsham, 1964). The steroids aldosterone and desoxycorticosterone influence the electrolyte functions of the body and are known as the mineralocorticoids. They are formed by the cells in the zona glomerulosa.

These cells are little affected by the adrenocorticotrophic hormone. The remaining steroids are made up of the adrenal androgens, mainly dehydroepiandrosterone, small amounts of estrogens and the progesteroids.

Cortisol represents about 80 percent of the total 17-hydroxycorticosteroids found in the blood. Approximately one half of it circulates as an inactive form conjugated with glucuronic acid, or as a sulphate or phosphate. The biologically active cortisol is bound to an alpha-globulin which is called transcortin (Slaunwhite and Sandberg, 1959) or cortisol-binding globulin (C.B.G.) (Daughaday, 1958). The C.B.G. mechanism makes cortisol readily available to the body tissues, protects it from being inactivated by conjugation in the liver and makes it more soluble. Only a small diffusable fraction of cortisol, not bound to protein, is physiologically active at any given time. The activity of the corticosteroid production by the adrenal cortex is under the control of humoral mechanisms, and the anterior pituitary gland is the site of formation, storage and release of the adrenocorticotrophic hormone (ACTH) or corticotrophin, as it is sometimes called, which activates the adrenal cortex (Rothballer, 1957; Ezrin, 1964). This is in contrast to the medulla which is under sympathetic nervous control.

There are three theories regarding the regulation of corticotrophin secretion (Woodbury, 1958). The cortical hormone titre theory or cortisol servomechanism states that a fall in free

cortisol leads to a rise in corticotrophin secretion, and a rise in the free cortisol prevents corticotrophin release. This mechanism maintains the plasma cortisol at fairly constant levels in the absence of stressful stimuli. The central neural mechanism theory points out the importance of the hypothalamus in regulating the release of ACTH. The median eminence of the hypothalamus contains a network of capillaries which form blood vessels leading down into the anterior lobe of the pituitary gland (Popa and Fielding, 1930, 1933). Nerve fibres from the hypothalamus end on these portal vessels in the median eminence and liberate a neurohumoral agent into them (Harris, 1951, 1952, 1955, 1964). This substance is then carried to the pituitary gland and provokes the release of ACTH and promotes its synthesis (Saffran, 1962). This chemical mediator is called corticotrophin-releasing factor (C.R.F.) (Saffran et al., 1955; Schally et al., 1958). The hypothalamus is activated in this manner by a variety of stimuli which act as stressors. They include chemical agents (food, drugs, metabolites), environmental conditions (heat, cold, sound, light), and psychological phenomena (fear, frustration, anxiety, anger). The epinephrine theory postulates that epinephrine, when released from the adrenal medulla by a stressful stimulus, acts directly on the cells of the adenohypophysis to release ACTH (Gershberg et al., 1950; Long, 1952).

The available evidence suggests that epinephrine plays little part in the secretion of ACTH but that the other two mechanisms

regulate its secretion. In other words, the secretion of the adrenocorticotrophic hormone is under the control of both humoral and neural mechanisms.

(b) The Normal Diurnal Variation of Plasma Cortisol Levels

The existence of a circadian rhythm in the secretion of the adrenal steroids has been established. A diurnal variation in the excretion of the 17-ketosteroids by normal male subjects was originally described by Pincus in 1943, and to him it represented a cyclic variation in adrenal function. Similar studies by other investigators (Romanoff et al., 1949; Sandberg, 1953; Laidlaw et al., 1954) supported these findings. In 1953, Bliss et al. reported a diurnal variation in the levels of plasma 17-hydroxycorticosteroids and other workers (Migeon et al., 1956; Tyler et al., 1954) confirmed his results.

The cycle of the 17-hydroxycorticosteroid levels over a twenty-four hour period in normal subjects and under ordinary conditions shows that the lowest concentration of these steroids is found between 10:00 P.M. and 2:00 A.M. From 2:00 A.M. until 4:00 A.M. there is a gradual elevation which is then followed by a steeper rise reaching maximum values in the region of 6:00 A.M. to 8:00 A.M. After this there is a sharp decline until noon and then a more gradual fall until 10:00 P.M. when the cycle starts anew.

Although it is now accepted that the adrenocortical secretion of cortisol has a diurnal variation pattern, how this comes about is still unclear. Several possible explanations have been suggested,

including the following:

(i) different rates of clearance of cortisol from the plasma at various times of the day,

(ii) differences in the responsiveness of the adrenal cortex to ACTH,

(iii) variations in the secretion rate of ACTH which are dependent on a centrally located mechanism.

Perkoff et al., in 1959, demonstrated that the rate of removal of cortisol from the plasma was the same at various times of the day but that the adrenal production of 17-hydroxycorticosteroids, in response to ACTH stimulation, was less at night than at other times in the twenty-four hour period. They concluded that the diurnal variation in plasma cortisol levels depended upon variations in the rate of secretion of ACTH and that the change in ACTH secretion was probably caused by an, as yet, unidentified centre in the central nervous system. Studying the circadian rhythm of ACTH secretion from the pituitary, Clayton et al. concluded in 1963 that its release in response to stress varied inversely with the levels of plasma cortisol.

The effects of sleep loss on the diurnal rhythm of plasma cortisol were investigated by Murawski and Crabbe in 1960. They showed that in college students deprived of a night's sleep, the normal diurnal curve underwent a change in both shape and amplitude. This was due to the 8:00 A.M. steroid concentration being lower following the nights without sleep than on normal control days, and also because there was a decrease in the expected fall

in levels between 8:00 A.M. and noon. Migeon et al. in 1956, had already observed that in night workers slightly lower levels of plasma corticosteroids occurred at 8:00 A.M. after their night on duty but they did not consider this a significant finding. In 1959 Perkoff et al., found that in normal subjects total reversal of the sleep pattern resulted in a reversal of the diurnal rhythm of plasma 17-hydroxycorticosteroids.

It would appear then that sleep plays an influential part in determining the levels of cortisol in the peripheral blood.

(c) The Effects of Cortisol on the Central Nervous System

The link between the nervous system and the adrenocorticosteroids is demonstrated by the hypothalamico-adenohypophyseal system regulating the secretion of cortisol from the adrenal cortex, and a centre in the diencephalon controlling the secretion of aldosterone (along with other complex mechanisms, of course, such as the blood sodium levels). These steroids in turn, in large quantities, cause changes in brain excitability (Cleghorn, 1963). Cortisol-like steroids increase brain excitability and the desoxycorticosterone-like compounds decrease excitability.

There is a great deal of evidence from animal experiments to show a relationship between the excitability of the central nervous system and an excess of the adrenal steroids. The electroshock seizure threshold in rats was measured by Woodbury after the administration of cortisol and cortisone, and was found to be decreased, that is, there was an increase in brain excitability. These findings were confirmed by De Salva et al. in 1954.

Anti-convulsant drugs such as diphenylhydantoin and phenobarbital were found to protect against this increase in brain excitability produced by cortisone. On withdrawal of the drug, the hyper-excitability again became manifest, demonstrating that the drugs had merely a masking action and did not prevent the increased excitability.

Further evidence for the central excitability effect of cortisone-like steroids is provided by the convulsions which are sometimes produced in experimental animals. Pincus et al. in 1951 described convulsions occurring in rabbits who were given ACTH in high doses. In 1953 Hicks also noted seizures in new-born rats and mice who were administered cortisone for three days. Since only low levels of 17-hydroxycorticosteroids were found in cerebrospinal fluid, the blood-brain barrier was thought to allow only limited quantities of steroids to enter the brain. However, Waterbury and Woodbury in 1957, using radioactive cortisol, demonstrated that cortisol rapidly entered the cerebral cortex and the amount present reflected the degree of brain excitability.

There is abundant clinical data which support the impression that cortisone and ACTH increase the excitability of the brain (Torda and Wolff, 1952; Wayne, 1954). In the early 1950's, when cortisone and ACTH were being used to treat a variety of physical illnesses for the first time, the doses prescribed were far in excess of what was required. Often during the course of treatment patients who had no previous history of seizures developed

generalized convulsions. These reactions diminished as physicians gradually lowered the dosage of these compounds. In Cushing's Syndrome, where the cortisol levels are very high, spontaneous seizures are rare but Starr reported in 1952 that convulsions occurred in 4 percent of his cases.

The neurophysiological changes produced by an excess of adrenal steroids can be detected with the electroencephalograph. Hoefer and Glaser in 1950 found that ACTH and especially cortisone produced a significant amount of slow wave activity and increased sensitivity to hyperventilation. It was suggested by Streifler and Feldman in 1953 that the electroencephalographic changes might be due to the 17-oxysteroids depressing the mesencephalic reticular activating system and enhancing the recruiting response in the diffuse thalamic projection system. Support for this hypothesis was provided by the report of Feldman et al. in 1961.

The adrenocortical hormones also appear to interfere with the normal sleep rhythm. In mice, the sleeping time induced by hexobarbital was shortened by cortisone as was the prolonged sleeping time induced by hexobarbital and diphenylhydramine. Winter and Flataker (1952), who carried out these studies, thought the effect of the steroid was due solely to its antagonistic action to the barbiturate and that the central depressant action of the diphenylhydramine was unaffected. They concluded that cortisone was an analeptic drug but that its central stimulating action differed from that of amphetamine and caffeine.

In a series of articles, Rome and Braceland (1950, 1951, 1952) observed the psychological reactions to the adrenocortical hormones and divided them into four grades of increasing severity. Insomnia, in their classification, was placed in Grade II. An upset in the sleep pattern was reported by other workers. Of fifty-seven patients, aged between eighteen months and eighty- years, who were treated by Mozzicenacci et al. in 1955 with cortisone for various physical ailments, 77.3 percent developed minor psychological disturbances including an upset in sleep rhythm. Levine in 1950 observed wakefulness in premature infants who were getting daily injections of ACTH. In 1953 Fox and Gifford found increasing wakefulness to be one of the principal effects of ACTH and cortisone given to a variety of medical patients.

Whether the effects of these steroids on brain excitability are found under physiological and pathological conditions is still undetermined. Nevertheless, the evidence, according to Engel (1953), is very suggestive that these hormones in excess do have a direct effect on brain function.

(d) The Effects of Aging and Sex on the Levels of Plasma Cortisol

The normal group of subjects and the depressed patients in this investigation consist of persons of both sexes who belong in the older age range, the average age of both groups being sixty years. The effects of aging and sex on the plasma cortisol levels will therefore be considered.

The effects of aging on the secretion of the adrenal cortex was reported on by Pincus in 1960. In his investigations at the

Worcester Foundation for Experimental Biology, he explored the steroid excretion and the adrenocortical responsivity to ACTH by examining the urine of 297 men and 320 women with ages ranging from nineteen to ninety-five years. The data obtained showed that there was no significant age-related change in the basal output of the corticoids. Similar results were obtained by Grad in 1964. He estimated the plasma cortisol levels in a group of 83 normal subjects, made up of 42 men and 41 women, with ages ranging from nineteen to eighty-four years. The findings indicated no significant difference in the plasma cortisol values with regard to age and sex.

We may conclude then that the activity of the adrenal cortex, with regard to the secretion of cortisol, is little affected by the aging process in healthy persons of either sex.

THE INTERACTION BETWEEN THE EMOTIONS AND THE ADRENOCORTICAL SYSTEM

(a) Normal Subjects

The interaction between the emotions and the activity of the hypothalamo-pituitary-adrenocortical system has been investigated in normal subjects and psychiatrically disturbed individuals. The work of Selye (1946) demonstrated that an organism threatened by a stressful stimulus reacted to it by a change in the activity of its adrenal cortex. Under environmental circumstances considered to be stressful, the response of the adrenal cortex was studied in normal persons by a large number of investigators. Bliss (1956) examined the relatives accompanying patients to the emergency room of a general hospital and students just prior to their final examinations. The work of Frankson (1955) and Price (1957), carried out in the Karolinska Hospital and the Walter Reed Hospital respectively, was on patients who were awaiting major surgery. All these investigations involved the estimation of the plasma 17-hydroxycorticosteroids. A number of studies were done on the excretion of urinary corticoids. One of these was conducted by Hill *et al.* (1956) who collected the urine from the Harvard boat crew before and after taking part in a university boat race. Other investigations were carried out by Marchbanks (1958) and Mason (1959) on bomber crews. The common response to all these situations was an increase in the levels of plasma cortisol and in the excretion of urinary corticosteroids.

Similar results were found in the blood and urine of normal subjects who were exposed to experimental stressful situations. Bliss et al. (1956) subjected university students to such stressful procedures as self-revelation before a one-way screen, or exposed them to a situation containing a threat to their future careers. The rise in plasma cortisol levels was greater in spontaneously occurring stressful situations than in those produced under laboratory conditions. This was demonstrated in Mason's study (1959) on a group of soldiers who were admitted to the hospital for sleep deprivation experiments and were found to have raised 17-hydroxycorticosteroid levels in the blood prior to the start of the experiments.

(b) Various Psychiatric Disorders

During the 1950's investigators turned their attention to the endocrine glands in the hope that they would solve some of the etiological problems of mental illness. In a series of articles, Persky et al. (1956, 1957, 1958, 1959, 1962) published the results of their rather extensive investigations on patients whose predominant symptom was anxiety. Their findings showed that the activity of the adrenocortical system in these anxious individuals reacted similarly to that of normal subjects in stressful situations. That is to say, there was an increase in their plasma cortisol levels and an increased excretion of corticosteroids in the urine. They also found that radioactive cortisol had a higher turnover rate in those with anxiety than in

normal persons, indicating that cortisol is produced in larger amounts and metabolised faster in anxious patients. This high output of the adrenal gland was thought to be due to increased secretion of ACTH.

It is not surprising when one considers the complex nature of the schizophrenic illness that conflicting results were obtained by different investigators who were measuring the activity of the adrenal cortex in these psychiatric patients. The findings of Bliss et al. (1955) demonstrated that acute schizophrenics who were emotionally disturbed had elevated plasma 17-hydroxycorticosteroid levels whereas chronic cases with little or no affect had levels comparable to normal emotionally calm subjects. Altschule and Parkhurst (1950) reported the 17-ketosteroid excretion in schizophrenics to be similar to that of normal subjects or a little higher. However, Mittleman et al. (1952) showed that although the total steroid excretion was the same for schizophrenic patients and normal individuals, the 17-ketosteroid excretion in the schizophrenics was much higher. In a more recent study, Geller et al. (1962) indicated that the excretion of 17-ketosteroids was higher in schizophrenic patients who had not regressed than in those who had.

(c) Depressive States

The suitability of depressive illness for the study of adrenocortical activity in relation to emotional stress is apparent, because it is a common psychiatric illness and the

majority of depressed patients recover or improve within a comparatively short time.

Original work on depressed subjects was carried out at the Michael Reese Hospital by Board et al. (1956, 1957). Their findings showed elevation of the 17-hydroxycorticosteroid levels in plasma; the more severe the depression, the higher the corticosteroid levels; and higher cortisol values in the retarded depressions than in the agitated ones. Gibbons and McHugh (1963), in their series of cases, reported a positive correlation between the severity of the depressive illness and the height of the plasma cortisol levels. The majority of their patients showed a decrease in the cortisol levels with recovery or improvement but their retarded and agitated patients had similar corticosteroid values. One cyclothymic subject had high hormone levels with each depressive episode which fell to normal as she became well again. Her phases of elation were accompanied by quite low levels. In a second paper, Gibbons (1964) investigated the secretion rate of cortisol by the isotope dilution method. Relief of depression was accompanied, in most of the cases, by a decrease in the secretion rate and a high correlation was found between the plasma cortisol levels and the cortisol secretion rate.

A group of manic depressive and neurotic depressive patients was investigated by Kurland (1964) who measured the metabolic indices of the corticosteroids in the urine. The excretion of 17-ketogenicsteroids was significantly correlated with the

clinical depressive symptomatology. All the manic depressive and the more severe neurotic depressive cases excreted higher quantities of metabolites than normal persons. The amounts of 17-hydroxycorticosteroids and 17-ketosteroids excreted by all patients were within normal limits. Ferguson et al. (1964), in their investigations, found abnormally high levels of corticosteroids excreted by 5 depressed individuals. A fall to normal levels occurred after treatment. The 11-deoxy-17-oxysteroids, however, had low values before treatment and a rise to normal after it. The urinary excretion of corticosteroids was reported by Gibbons et al. (1960) to be higher in depression with agitation, with a tendency towards lower values in remission. Curtis et al. (1960) considered that the urinary output of corticosteroids was more likely to be raised in patients whose principal symptom was anxiety rather than those who were primarily depressed.

Our knowledge of the adrenocortical response in mania is still small but it is gradually increasing chiefly through the reports of investigators on individual cases. In 1954, Rizzo et al. found low urinary glucocorticoids in a manic depressive female patient during her hyperactive episodes, with the levels returning to normal after clinical recovery. Gibbons and McHugh in 1963 reported a case with high plasma cortisol levels during phases of depression and low levels during phases of mild elation. Psychiatrists in the past have suggested that mania is a defense against the pain of depression (Lewin, 1950). Bunney et al. in

1965 attempted to find biochemical confirmation of this psychological theory. They simultaneously studied the behaviour and the urinary 17-hydroxycorticosteroids in a female patient with regular forty-eight hour manic depressive cycles, over a two year period. The patient's mania was characterized by intense denial of her illness and accompanied by low 17-hydroxycorticosteroid levels. Her days of depression were associated with feelings of suffering and pain and her 17-hydroxycorticosteroid levels were high. Bunney and his associates feel that these findings, as well as agreeing with those of other investigators, also support the concept that the mechanism of denial is associated with low levels of urinary 17-hydroxycorticosteroids. This is an informative and refreshing approach to psychoendocrine problems and further studies along similar lines may help to clarify some of the present difficulties in the field of endocrine psychiatry.

CLINICAL MATERIAL

Selection of Subjects

The investigation was carried out on 14 subjects; half of these were psychiatric patients, 2 male and 5 female, with an average age of sixty years, and the other half were normal controls of comparable age and sex. Each patient was diagnosed as suffering from a depressive psychosis. However, since the classification of the depressive illnesses is a controversial topic and since it is often difficult to decide where to draw the boundary between the psychosis and the neurosis, only those suffering from what is universally described as classical psychotic depression were selected (Mayer-Gross, 1960; Murphy et al., 1964; Hays, 1964). The primary symptoms for the diagnosis were a mood of depression, a diurnal mood change, that is, exacerbation of the depressive mood in the morning, insomnia with early morning awakening and diminution of interest in the social environment. Other symptomatic features were usually present, including fatigue, self-blame, death wishes, loss of appetite, weight and libido, and disturbance in motor activity, either retardation or agitation. No distinction was made between involutional melancholia and the depressive psychosis. Three of the cases had histories of previous depressive breakdowns. Two patients unfortunately could not complete the study; one (number 6)

was found to have diabetes mellitus and was removed to a general hospital for assessment of this condition and the other (number 7) fell and fractured her left leg and was transferred to an orthopaedic unit. The remaining 5 patients completed 28 days' treatment with a selected antidepressant medication.

Clinical Evaluation

The diagnosis of endogenous depression was made by two qualified psychiatrists, independently, one of whom was the author. Added confirmatory data were supplied by the depressive scale of the Minnesota Multiphasic Personality Inventory and Rorschach Test, completed by a member of the psychology staff.

Patients were receiving no medication at the time of admission to the study and had been free from all drugs for a minimum period of 4 weeks prior to it. The difficulty in obtaining such cases is obvious because most patients are placed on medication immediately after being seen by their own physician or by the psychiatrist who carries out the initial interview in order to tide the patient over until he is admitted to hospital. The 7 patients in this study were obtained mostly from the emergency department of the hospital. There, they had been taken by their relatives and had not been seen by an outside doctor. The psychiatrist in the emergency room then referred the case to the study before commencing any form of therapy. All subjects were considered ideal cases for electro-convulsive treatment.

Each suitable candidate for the investigation was placed on placebo three times daily and once at night for the first 48 hours. During this time, bloods were drawn over two consecutive 24 hour periods at intervals which would give most information about the diurnal adrenocortical activity, namely 7:00 A.M., 12 noon and 10:00 P.M. When these were completed the patients were placed on either amitriptyline (Elavil) or imipramine (Tofranil), 150 mgs daily in divided doses and the placebo was continued at bed time. Identical laboratory procedures were repeated after 14 days and again after 28 days of this treatment plan.

Clinical Rating Scale

A clinical assessment of the depression was made by the author on each patient before treatment started and then after 2 weeks and again after 4 weeks of the therapeutic regime. The rating was done on a five point scale as follows:

0 = absence of depression

+ = mildly depressed

++ = moderately depressed

+++ = markedly depressed

++++ = severely depressed

Scoring was of a reasonably high order because each patient was interviewed every day of the investigation and the ward nursing reports were taken into consideration before the final assessment was made in

order that they would be independent of the later chemical estimations.

AIMS OF THESIS

1. To measure the diurnal variation in the levels of plasma cortisol in psychiatric patients suffering from a psychotic depressive illness.

2. To determine whether these levels form a characteristic pattern for the psychotic depressive group as a whole, or whether there is an individual pattern for each patient.

3. To study the effects of two anti-depressant medications on the plasma cortisol levels.

4. To investigate the relationship between the levels of plasma cortisol and the severity of the depressive illness.

5. To contemplate possible etiological factors in the disturbed sleep rhythm and diurnal mood change of the depressive psychosis.

MATERIALS AND METHODS

The plasma cortisol levels were determined by a slight modification of the dialysis method described by Murphy et al. in 1963.

Fifteen ml. of venous blood were drawn at 6:45 A.M., 11:45 A.M. and 10:00 P.M. on two consecutive days into 20 ml. test tubes containing heparin, then centrifuged, and the plasma separated and frozen until assayed.

Materials

Cortisol-4-C^{14} with a specific activity of 45 microcuries per millimole was obtained from the New England Nuclear Corporation. It was stored in ethanol in a concentration of 16,000 cpm/ml. Non-radioactive cortisol, the Merck Co. USP preparation, was diluted in ethanol to give a concentration of 1 µg/ml.

Preparation of Standard Serum

Pooled serum was used as the source of the corticosteroid-binding globulin (C.B.G.). It was kept frozen until a group of samples was to be determined, at which time serum was then diluted to 1:6 by adding physiological saline.

Preparation of the Dialysis Sacs

For each dialysis tube, a dialysis sac was made as follows. Seven-inch lengths of Nojax Visking casing 24/32" were cut and placed in a

beaker of physiological saline, making the casing softer and easier to manipulate. A firm knot was tied in one end of the casing and into the open end was pipetted 5 ml. of the diluted standard serum, then this end was also tied off. The excess ends were trimmed and the sacs were placed in physiological saline until used.

Setting Up a Run

In the first run, there were 90 tubes, two for each of 5 patients taken 0, 2 and 4 weeks after treatment and at three daily times. Each dialysis was carried out in a 50 ml. test tube ("dialysis tube"). The required number of tubes were placed in a test tube rack and numbered. In the second run, there were 84 tubes, six from each of 7 normal and 7 depressed persons. The 6 tubes consisted of duplicate plasma collected at the three daily times.

Standards

The standards were determined in triplicate; 18 tubes (No. 1-18) were required and were prepared as follows. Non-radioactive cortisol in ethanol in the amount of 0.1 μg was pipetted into tubes 4, 5 and 6, 0.2 μg into tubes 7, 8 and 9, 0.3 μg into tubes 10, 11 and 12, 0.5 μg into tubes 13, 14 and 15, and 0.7 μg into tubes 16, 17 and 18. The ethanol was evaporated off by means of a stream of air. To each of the 18 tubes was added 21 ml. physiological saline, 0.5 ml. of cortisol-4-C^{14} in ethanol and a dialysis sac.

Test Samples

One ml. of plasma was pipetted into each dialysis tube; 20 ml. physiological saline plus 0.5 ml. of cortisol-4-C^{14} in ethanol was added to each, except the initial 6:45 A.M. samples, to which 0.5 ml. of plasma and 20.5 ml. of physiological saline were added because high values were suspected. The amount of saline and cortisol-4-C^{14} required for all the tubes containing the samples was calculated and mixed together and dispensed into each dialysis tube using a Calab dispenser with a 20.5 ml. dispenser head. The tubes were then placed in a boiling water bath for 1 minute and allowed to cool. The heating under these conditions destroyed the corticosteroid-binding globulin present so that all the cortisol in the test plasma was in the unbound state.

In the case of the standards, the amount of mixture of saline and cortisol-4-C^{14} required for 18 tubes was measured out and an additional 1 ml. of saline for each tube was added. This material was then dispensed by a Calab dispenser with a 21.5 ml. dispenser head.

The Dialysis

All the tubes (for both standards and test samples) were covered with tinfoil and placed in a 30 rev/min rotator in a refrigerator (4 - 9 degrees Centigrade) for 40 hours. The rotator was a turntable fitted with 2 masonite discs, pierced with holes at regular intervals, and tilted at an angle of 45 degrees.

Preparation of Samples for Counting

At the end of the dialysis, the tubes were taken out and placed in a rack. A duplicate series of tubes was placed in a second rack. Each sac was rolled in gauze to remove excess moisture and then cut so that the contents drained into the corresponding tube. One ml. of the contents was pipetted onto an aluminum planchette, allowed to dry and counted in a Nuclear Chicago D47 gas flow counter with an efficiency of 30% to a minimum of 2,000 counts. The cpm's were then calculated for each.

Estimation of Plasma Corticoids from the Standard Curve

The mean cpm's of the six standards were plotted vs. the amount of unlabelled steroid added to give a standard curve. The corticoids in μg of the test plasma samples were then read from the graph according to the cpm of the samples. This value was multiplied by 100 (or by 200 if 0.5 ml. plasma was used) to express the plasma corticoids in μg/100 ml.

This method measures both cortisol and corticosterone in the plasma but since the amount of corticosterone is only about 1/13 that of cortisol, the results obtained here will be referred to as plasma cortisol (Eik-Nes, 1960).

Statistical Analysis

The material was analysed in the following two ways. In the first analysis, the data of the 5 patients taken three times per day before

treatment, and 14 and 28 days after treatment began, was analysed by an analysis of variance for triple classification (McNemar, 1959). The data were then analysed by means of 7040 I.B.M. computer at McGill University.

The second analysis was between 7 patients and 7 normal subjects of comparable age and sex, the values of the patients being taken before treatment was started. The analysis used in this experiment was that described by Winer for a 2-factor experiment with repeated measures (Winer, 1962). In carrying through this analysis on the raw data, it was found that the parts pooled to form the denominators of the F ratio lacked homogeneity due to the high values obtained from the patients at 7:00 A.M. Therefore, the analysis was conducted on the logarithm to base 10 of the data, and this time the parts pooled to form the denominators of the F ratioes were homogeneous. t tests were conducted on those sources of variation that proved to be significant.

RESULTS

Analysis of Five Patients During Course of Treatment

The raw data of each of the 5 patients taken at 7:00 A.M., 12 noon and 10:00 P.M., before treatment and 14 and 28 days after treatment started, are shown in Table I. The results of the analysis of variance are given in Table II and are as follows.

Differences between patients with regard to their plasma cortisol levels were highly significant ($0.001 > P < 0.0005$). These differences are due to the fact that patient number 5 had very significantly higher values than all the other subjects ($P < 0.001$, Table III). Differences in plasma cortisol levels between the other 4 subjects were not statistically significant ($P > 0.10$, Table III).

Differences between different periods in the course of treatment were also statistically significant. This can be seen from Table IV where the values before treatment started were higher than those taken 14 days after treatment began, and these in turn were higher than those taken after 28 days of treatment. *t* tests, using a standard error based on the variance estimate obtained from the analysis of variance showed that the difference between the before-treatment and 14 day values were highly significant ($P < 0.001$) while differences between the 14 day and 28 day periods were only

of borderline significance ($0.10 > P > 0.05$).

Differences between values obtained at different times of the day were statistically significant ($0.01 > P > 0.005$). Thus, it can be seen from Table V that the values taken early in the morning were higher than those taken around noon, which in turn were higher than those taken in the evening. t tests showed that the differences between the early morning and noon samples were highly significant ($P < 0.001$) while those between noon and 10:00 P.M. were also significant but less so ($0.05 > P > 0.02$).

As for the interactions there was no significant patient x treatment interaction ($0.30 > P > 0.20$, Fig. 1). The meaning of this is that the plasma cortisol levels changed in essentially the same manner in all patients during the course of treatment.

There was however significant patient x time interaction ($0.025 > P > 0.01$, Fig. 2) and treatment x time interaction ($0.025 > P > 0.01$, Fig. 3). The meaning of the significant patient x time interaction is that whereas all the patients showed a decline in the values between 7:00 A.M. and noon, the values fell significantly more in the case of patient number 5 than they did in the remaining 4 patients. The meaning of the treatment x time interaction is that the shape of the diurnal curve changes in the course of treatment, the decline between 7:00 A.M. and noon being more sharp before treatment than it was 14 and 28 days after treatment started.

It should be pointed out that because the patient x treatment interaction was not significant, its sum of squares and degrees of

freedom were incorporated with those of the error term which in this analysis was the patient x treatment x time interaction. This triple interaction was used as the error term to test the patient x time interaction and the treatment x time interaction, the results being significant as indicated above.

Now, because the patient x time and treatment x time interactions were significant, they were used in appropriate places as error terms to test the significance of patients, treatment and time, with the results being as indicated above. It should be noted that in testing for the significance of time or diurnal variation, the error term used was the treatment x time interaction which had the higher variance estimate and the lower number of degrees of freedom than the patient x time interaction. The results by this analysis were nevertheless statistically significant.

	PATIENTS	7:00 A.M.	12 noon	10:00 P.M.
PRE-TREATMENT	1	29.00	20.50	18.75
	2	34.00	18.75	15.50
	3	31.00	19.25	12.50
	4	34.00	16.00	11.75
	5	53.00	32.75	31.25
AFTER 14 DAYS TREATMENT	1	22.25	14.75	11.75
	2	19.75	14.00	9.75
	3	16.50	12.00	6.75
	4	13.00	11.50	8.00
	5	43.50	25.00	16.25
AFTER 28 DAYS TREATMENT	1	16.75	11.25	5.25
	2	16.00	11.25	8.50
	3	15.75	9.50	6.50
	4	11.25	8.50	6.00
	5	32.00	19.75	9.75

TABLE I

Plasma Cortisol Levels (μg/100 ml.) of Each Patient at 7:00 A.M., 12 noon and 10:00 P.M. Before and During Treatment.

SOURCE	SUM OF SQUARES	DEGREES OF FREEDOM	VARIANCE ESTIMATE
PATIENTS (P)	1489.3139	4.	372.3285 ***
TREATMENT (T)	1268.3583	2.	634.1792 **
TIME (t)	1528.0333	2.	764.0167 **
P x T INTERACTION	82.9611	8.	10.3701
P x t INTERACTION	201.2444	8.	25.1556 *
T x t INTERACTION	118.9083	4.	29.7271 *
P x T x t INTER-ACTION	114.9805	16.	7.1863
TOTAL	4803.7999	44.	

TABLE II

The Analysis of Variance for Triple Classification

* Significant at 2.5% level.

** Significant at 1% level.

*** Significant at 0.1% level.

PATIENTS	SEX	AGE IN YEARS	MICROGRAMS PER 100 ml. *
1	F	48	16.7
2	F	62	16.4
3	M	70	14.4
4	M	71	13.3
5	F	56	29.3

* The value shown is the mean of 9 determinations taken during the entire period of investigation.

TABLE III

Plasma Cortisol Levels in the Various Patients

LENGTH OF TREATMENT (DAYS)	MICROGRAMS PER 100 ml. *
0	25.2
14	16.3
28	12.5

* The value shown is the mean of 15 determinations taken during the entire period of investigation.

TABLE IV

Plasma Cortisol Levels Before and During Treatment

TIME OF DAY	MICROGRAMS PER 100 ml. *
7:00 A.M.	25.9
12 noon	16.3
10:00 P.M.	11.9

* The value shown is the mean of 15 determinations taken during the entire period of investigation.

TABLE V

Diurnal Variation of Plasma Cortisol Levels

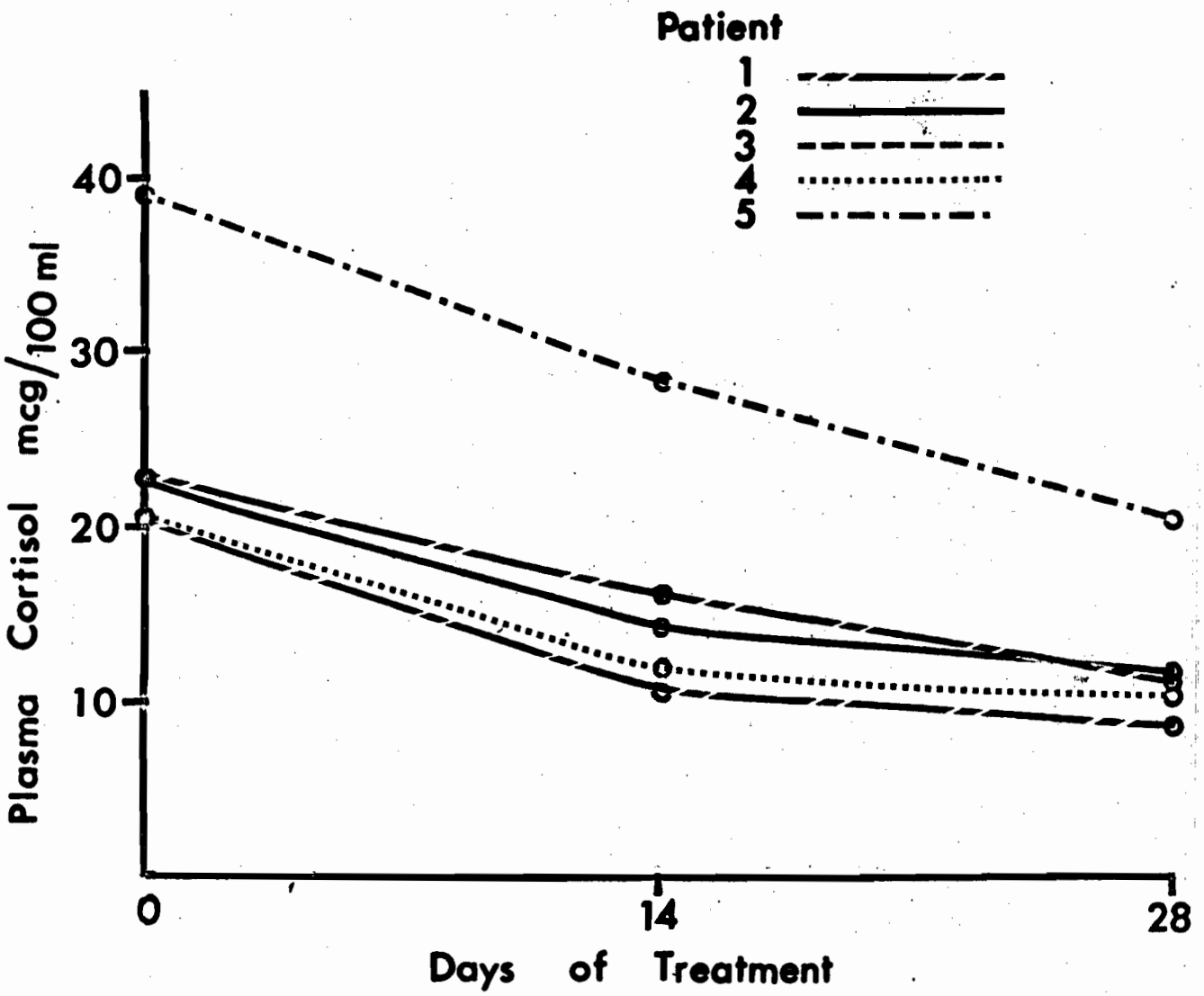

Fig. 1. The graph shows the change in the plasma cortisol levels of each patient during treatment. In the analysis of variance it is represented by the patient X treatment interaction which was not statistically significant ($0.30 > P > 0.20$). The meaning of this is that the change of plasma cortisol during the course of treatment is essentially the same in all patients.

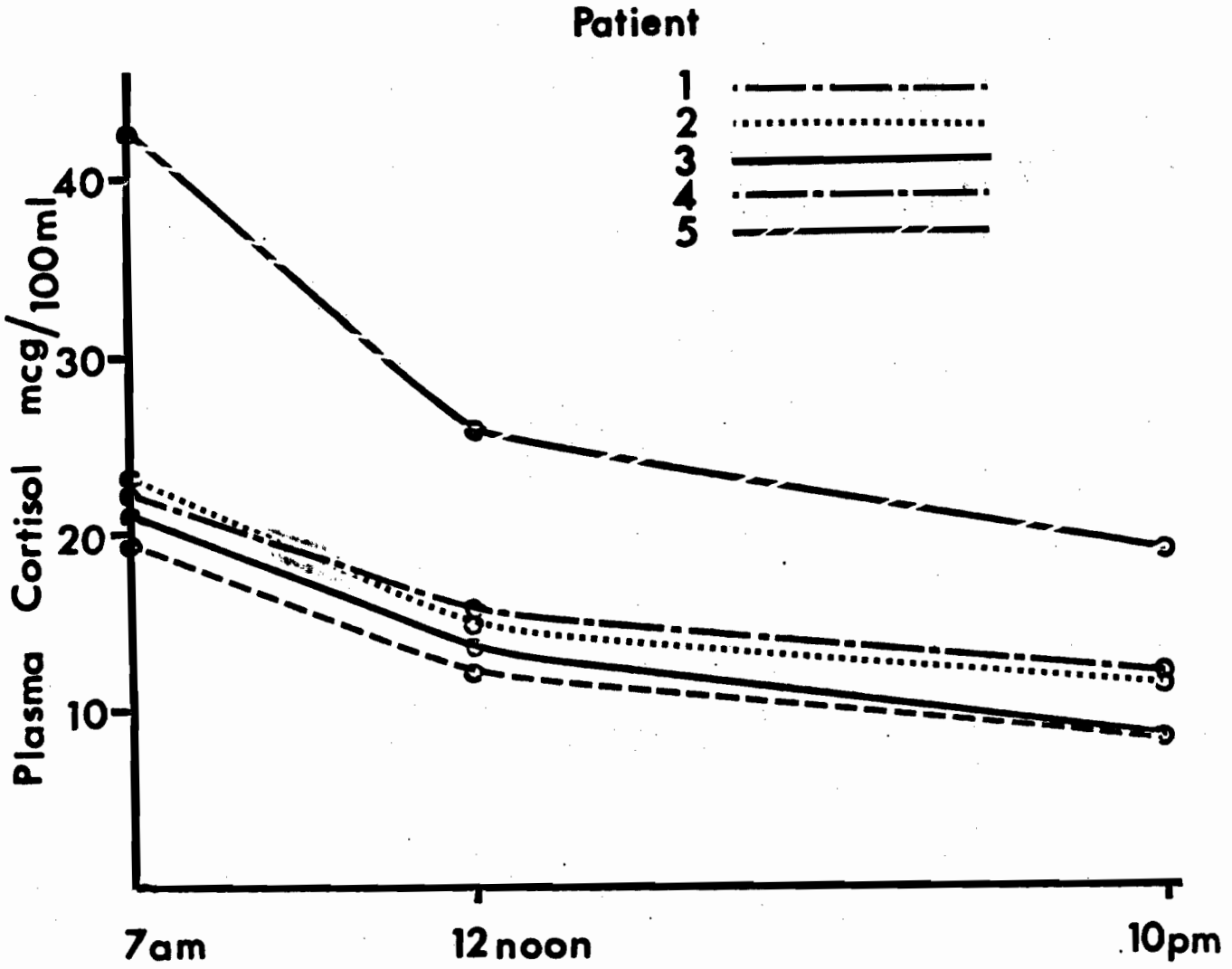

Fig. 2. The graph shows the diurnal variation of the plasma cortisol levels of each patient during the entire period of investigation. This is represented in the analysis of variance by the patient X time interaction which was statistically significant ($0.025 > P > 0.01$). The meaning of this is that while all the patients show a fall in the values between 7 a.m. and noon, the values fall significantly more in the case of patient number 5 than in the remainder.

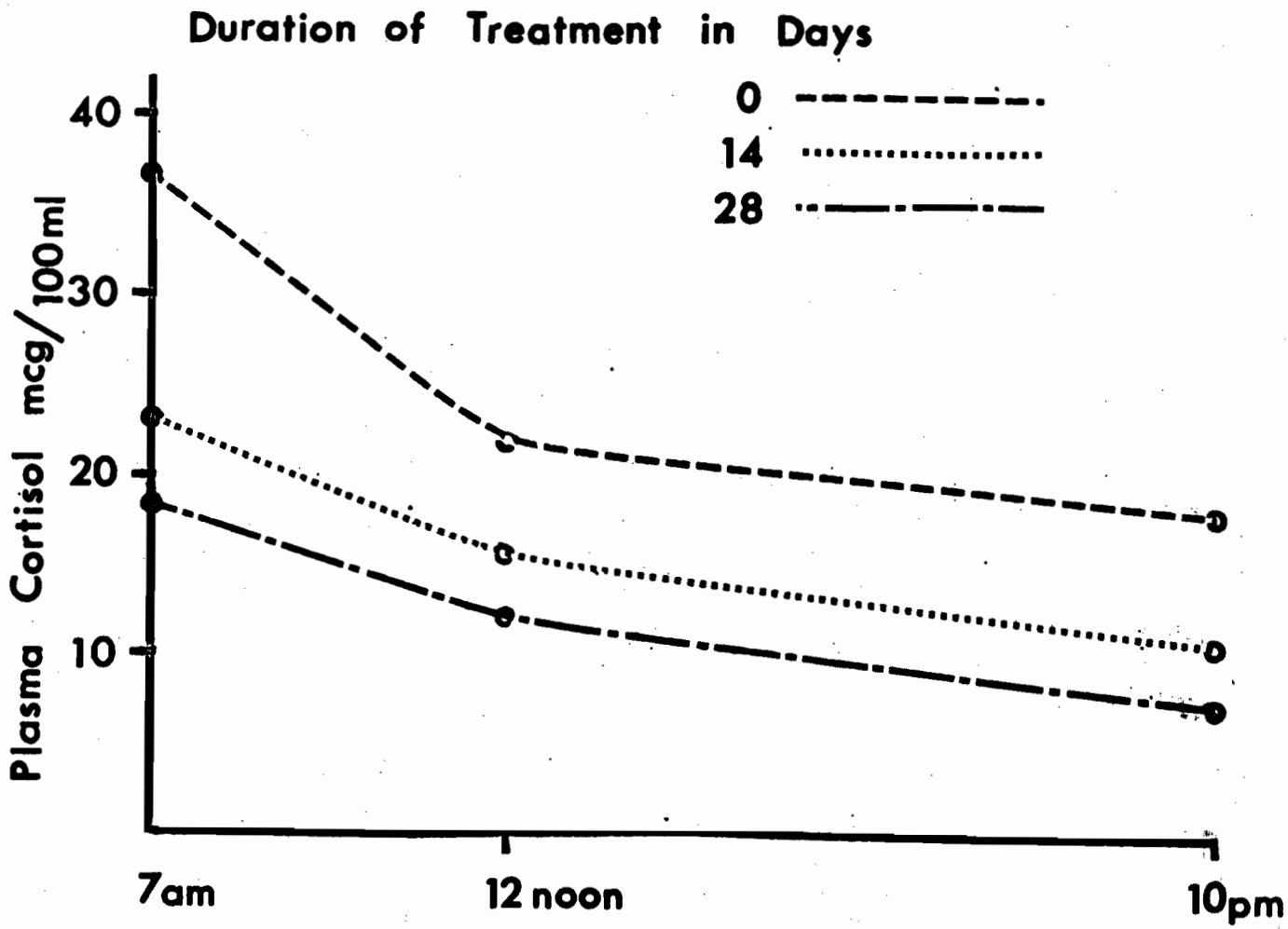

Fig. 3. The graph shows the change in the diurnal variation of the plasma cortisol levels during treatment. This change is represented in the analysis of variance by the treatment X time interaction which is statistically significant ($0.025 > P > 0.01$). The meaning of this is that the shape of the diurnal variation curve changes in the course of treatment; the drop between 7 a.m. and noon being less marked two and four weeks after treatment than before treatment was begun.

Analysis of Seven Depressed Patients and Seven Normal Subjects

The data for the investigation on the 7 depressed patients and the 7 normal subjects are shown on Table VI. The analysis of variance table for this data is given in Table VII. Examination of these results shows that there was a very highly significant difference between the two groups of subjects ($P < 0.0005$, Table VII). The mean and standard error of all twenty-one values for the 7 subjects was 27.8 ± 2.7 μg/100 ml. plasma, while the corresponding values for the normal was 11.8 ± 1.3 μg/100 ml. plasma (Table VIII). Further examination of the data in Table VII shows that there was a very highly significant difference due to diurnal variation in the values ($P < 0.0005$, Table VII). Subsequent t tests showed that there were significant differences between the 7:00 A.M. and noon values ($0.02 > P > 0.01$, Table VIII) and also between the noon and 10:00 P.M. values ($0.01 > P > 0.001$). It will be noted that in examining the data in Table VIII, the differences between the two groups was greater at 7:00 A.M. than at noon or at 10:00 P.M.

The differences between the mean of values obtained from samples taken at 7:00 A.M. and noon (9.9) was higher than those obtained between noon and 10:00 P.M. (6.2). Nevertheless the significance of the difference between noon and 10:00 P.M. values was apparently higher than those obtained between 7:00 A.M. and noon. The reason

for this is that in converting the data to logarithms the larger numbers were reduced much more than were the smaller ones, thus leading to the type of discrepancy just mentioned.

The interaction between the effect of depression and the diurnal variation was statistically significant ($0.025 > P > 0.01$, Table VII). This level of significance was reached when one used the diurnal variation x subjects within groups error which in this analysis is less than the subjects within groups error. In short, the ordinary test leads to a statistically significant result for the interaction but when repeated with the subjects within groups error which was larger, the results do not quite achieve significance ($0.20 > P > 0.10$, Table VII).

Examination of the data in Table IX shows that differences between the logarithm of the values at 10:00 P.M. are bigger than those at 7:00 A.M. or noon. This is apparently not statistically significant if one applies the conservative test. On the other hand, examination of the raw values of the same data in Table VIII shows that the biggest differences between patients and normals were obtained at 7:00 A.M. as compared with the other times. The discrepancy between the values obtained in Tables VIII and IX is due to the conversion of the raw values into logarithms which reduced the larger numbers to a greater extent than it did the smaller ones.

A graph of the raw values is shown in Figure 4. It is obvious in this figure that differences between patients and normals were greater at 7:00 A.M. than at noon or 10:00 P.M.

	SUBJECT	SEX	AGE IN YEARS	7:00 A.M.	12 noon	10:00 P.M.
Patients	1	F	48	29.00	20.50	18.75
	2	F	62	34.00	18.75	15.50
	3	M	70	31.00	19.25	12.50
	4	M	71	34.00	16.00	11.75
	5.	F	56	53.00	32.75	31.25
	6	F	64	61.00	37.25	23.50
	7	F	48	34.00	29.00	21.50
Normals	1	F	60	23.00	14.00	5.00
	2	M	66	17.00	13.50	2.75
	3	F	49	16.50	13.50	3.25
	4	F	65	22.50	16.50	6.00
	5	M	73	17.50	9.00	6.00
	6	F	53	15.50	11.25	9.50
	7	F	54	11.50	8.00	5.00

TABLE VI

Plasma Cortisol Levels (μg/100 ml.) in Normal Subjects and in Depressed Patients

SOURCE	SUM OF SQUARES	DEGREES OF FREEDOM	VARIANCE ESTIMATE
BETWEEN SUBJECTS	2.13080280	13	-
A (Effect of Depression)	1.70323989	1	1.70323989**
SUBJECTS WITHIN GROUPS	0.42756291	12	0.03563024
WITHIN SUBJECTS	1.69179551	28	-
B (Diurnal Variation)	1.30524173	2	0.65262087**
AB	0.14450158	2	0.07225079*
B x SUBJECTS WITHIN GROUPS	0.24205220	24	0.01008551

TABLE VII

Analysis of Variance Table for 2-Factor

Experiment with Repeated Measures

** Significant at the 0.05% level.

* Significant at the 2.5% level.

SUBJECTS	7:00 A.M. *	12 noon	10:00 P.M.	MEAN**	STANDARD ERROR
Patients	39.4	24.8	19.3	27.8	± 2.7
Normals	17.6	12.3	5.4	11.8	± 1.3
Mean ***	28.5	18.6	12.4		

TABLE VIII

Summary of Depression x Diurnal Variation Interaction

* The values shown for a given time is the mean of seven determinations.

** The values shown in this column are the mean of twenty-one estimations.

***The values shown in this row are the mean of fourteen estimations.

SUBJECTS	7:00 A.M.	12 noon	10:00 P.M.	TOTALS
Patients	11.0579	9.6219	8.8287	29.5085
Normals	8.6558	7.5326	4.8622	21.0506
Total	19.7137	17.1545	13.6909	50.5591

TABLE IX

Summary of the Log Values of Depression x

Diurnal Variation Interaction

CLINICAL RATING	NUMBER OF ESTIMATIONS	MEAN AND STANDARD ERROR
++++	21	27.8 ± 2.7 µg/100 ml.
+++	6	20.0 ± 14.2 "
++	9	13.9 ± 7.1 "
+	6	15.5 ± 10.6 "
0	9	10.5 ± 5.3 "

TABLE X

Plasma Cortisol Levels (µg/100 ml.)

According to Clinical Rating

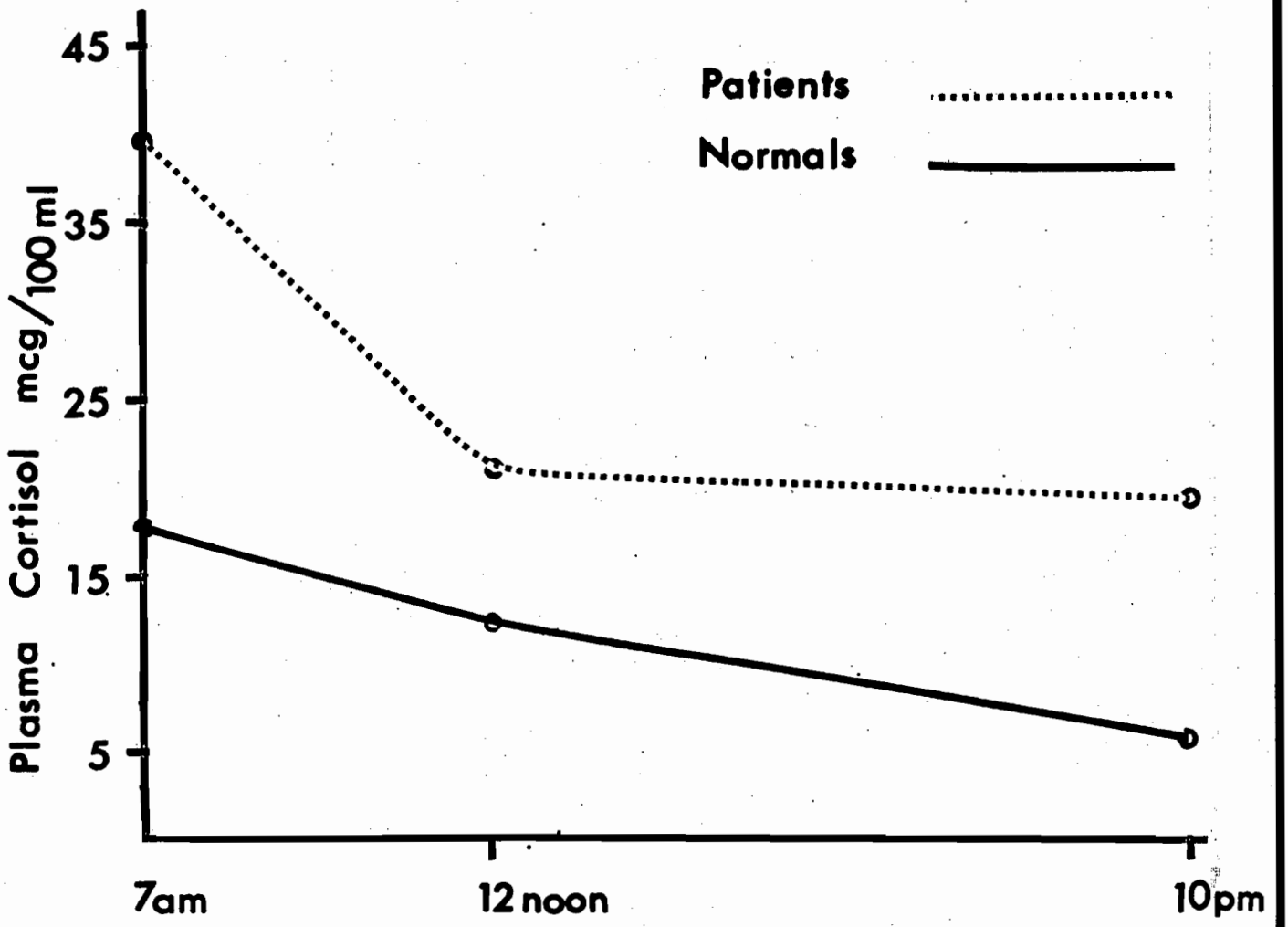

Fig. 4. The graph shows the diurnal variation in the plasma cortisol concentrations of normal and depressed subjects. In the analysis of variance it is represented by the depression X diurnal variation interaction (AB) which was statistically significant by the ordinary test ($0.02 > P > 0.01$) but not by the conservative test ($0.20 > P > 0.10$). The meaning of this is that the differences between the mean values of the patients and the normals were greater at some points than at others. Examination of the curves shows that this difference was considerably greater at 7 a.m. than at noon or 10 p.m.

DISCUSSION

The levels of plasma cortisol in this study were found to be very much higher in the psychotically depressed patients than in normal subjects of comparable age and sex. Beard et al. in 1957, limiting their investigation to examining morning samples of blood, showed that raised levels of adrenocortical hormone occurred in depressed patients at this time of day. The present results indicate that the high cortisol levels found in depressive illness extend throughout the twenty-four hour period with the highest values occurring in the early morning. In addition to the primary mood disturbance there were at least three additional factors contributing towards the initially high pre-treatment levels of cortisol. These included the stresses produced by being admitted to hospital (Mason, 1959; Mason et al., 1965), undergoing the procedure of venipuncture (Cleghorn and Graham, 1950) and the freedom from any sedative medication which might lower the hormone values (Shibusawa et al., 1955; Co Tui et al., 1960). The role played by these factors is probably only a minor one but they should be taken into consideration when evaluating the differences between the normal subjects and the depressed patients in this investigation.

A good correlation was found between the severity of the

clinical depression and the hormone levels in the plasma (Table X). The two cases with marked subjective and motor retardation had higher levels than the others, all of whom were agitated. This supports the findings of Board et al., 1957.

The levels of cortisol were found to vary at different times of the day in all patients in a similar fashion to that of normal subjects, with the highest level present in the morning, the next highest at noon and the lowest values in the evening. This suggests that in depressed patients the same mechanism which controls the normal diurnal rhythm of cortisol secretion is still operating but that it is greatly accelerated, causing a significant increase in the adrenocortical activity which in turn produces the high peripheral blood hydrocortisone levels. The recent work by Gibbons in 1964, using radioactive cortisol to determine the adrenocortical secretion rate, confirmed this increase in adrenal activity in depressed subjects, and it demonstrated that there was a high correlation between the elevated plasma cortisol levels and the cortisol secretion rate.

The shape of the diurnal curve in the depressed patients changed during the course of treatment. The high pre-treatment levels fell considerably after two weeks' treatment, with a further smaller decline after four weeks' treatment. The levels changed in exactly the same way in all patients so that with remission or significant improvement, the cortisol values resembled those of normal subjects

which meant that their diurnal variation curves were also in the normal range.

While the number of patients treated is small, the results show an effect which appears to be consistent. For the first two days of the investigation, no patient improved on placebo, in fact, they became worse, with aggravation of the depressive mood and insomnia. All five patients however responded favourably to the prescribed anti-depressant medication. Of the five cases who completed the study, four were treated with amitriptyline and one with imipramine. The two cases who had to drop out of the study had also been placed on imipramine. The effectiveness of the amitriptyline was clinically evident during the first week of treatment but much more so at the end of the second week. Then the clinical improvement was noticeable to the medical staff and also to the patients' relatives. The improved clinical picture was accompanied by a fall in the plasma cortisol levels. This fall was greatest in the peak morning values after the first two weeks. After four weeks, there was a further decline in the cortisol values with the levels moving towards more normal ones. The case treated with imipramine followed a similar course. Clinically the depression cleared up completely in three of the cases, and in the other two, only minor symptoms remained which cleared after a further two weeks of treatment. Since sedative

medications are known to lower the hydrocortisone values in the peripheral blood and since the only additional medication given to these patients was placebo, we can conclude that the drug influence on the plasma cortisol levels was due entirely to the prescribed antidepressant medication. The amitriptyline showed a consistently good response in lowering the plasma cortisol and the one case of imipramine did likewise. However, not all depressed patients respond as consistently and favourably as this. For example, the five depressed patients treated by Gibbons and McHugh (1963) with imipramine showed different responses. One improved clinically and showed a decline in plasma cortisol values but the other four had no clinical improvement. Two of them showed no change in the levels of cortisol and the other two had transient falls followed by a subsequent rise to the previous levels.

It is now an accepted fact that the effectiveness of any drug varies with each individual patient and so the question frequently rises whether to continue treatment with a specific medication which clinically does not appear to be having the desired effect. Under these circumstances, it seems reasonable to suggest that if there is not a substantial fall in the plasma cortisol levels, especially the early morning values, after two weeks, it is probably a good indication that the drug is not the medication of choice for that patient and should be changed.

In addition to the medication prescribed, there are a number of other factors which should be taken into account when considering the consistently good response of these patients to treatment. Each patient received much more individual attention than the average admission. Interviews taking the form of supportive psychotherapy were given three or more times during the day, by the author. The nurses, who were also incorporated into the treatment plan, spent more time with these patients than they normally would have. The part played by this personal supervision in improving the outlook and the determination of each patient to get better is difficult to evaluate, but it should not be underestimated.

The sleep disturbance in psychotic depression has a characteristic pattern quite distinct from that which occurs in neurotic depression. Patients usually state that they are able to get over to sleep without much difficulty but that they awaken in the early hours of the morning and cannot get back to sleep again. All seven depressed cases in this study had this typical disturbed sleep rhythm. On the other hand, the neurotic depression complains that he has difficulty getting to sleep but once asleep goes right through until morning.

A number of investigators have put forward explanations for this disturbance in sleep in depressed subjects. For instance, Swift and Klithorn in 1961 postulated that there was a primary hypothalamic

disturbance which resulted in an inversion of the sleep rhythm tending to produce increased wakefulness at night; Oswald et al., in 1963, after taking continuous nocturnal encephalographic recordings measuring eye movements and bed movements, reported that they failed to reveal any characteristic abnormality of sleep in patients with melancholia other than an excess of wakefulness.

The present findings suggest a somewhat different hypothesis to account for the insomnia. It appears to the writer that the primary disturbance in mood sets off a chain of events involving overactivity of certain hypothalamic functions (beginning possibly in the rhinencephalon) causing an increased output of ACTH which in turn produces overactivity of the adrenal cortex leading to an elevation of the plasma cortisol levels. The high peak morning values found in normal subjects fall throughout the day so that low levels occur at night, and even anxious subjects who have higher morning values than normal people are found to have very low or even nondetectable, i.e. zero, levels in the evening. In contrast, the depressed patients have extremely high morning values and even though these decline during the day, the evening levels are still very high. In the diurnal cycle, the secretion of cortisol commences in the early hours of the morning so the already high plasma cortisol levels are further increased until they reach their peak values between 6:00 A.M. and

8:00 A.M. Depressed patients have, therefore, very high plasma cortisol values throughout the twenty-four hours with the highest values occurring in the early hours of the morning, coinciding with the early morning awakening and the increased wakefulness. There is a significant amount of evidence to suggest that cortisol in high doses exerts an excitatory effect on the central nervous system so that it seems reasonable to suggest that the very high plasma cortisol values in these patients exert a stimulating action on the brain to produce the early morning awakening.

If this hypothesis is correct then by lowering the early morning cortisol values, we would eliminate the early morning awakening in the psychotically depressed patient. Nichols et al. (1965), in a recent publication, suggest a method whereby selective suppression of the adrenal cortex can be produced by giving small amounts of glucocorticoids. They found that by giving normal subjects one-half milligram of dexamethasone, they could almost completely suppress the secretion of cortisol over the following twenty-four hour period. Application of this test to psychotically depressed subjects with early morning awakening is an area for further investigation.

It may also be more than coincidence that the exacerbation of the depressed mood occurs at the same time as the very high levels of plasma cortisol, that is, first thing in the morning. In this investi-

gation, when the cortisol levels fell, the morning exacerbation of mood disappeared in all five cases.

Although we do not as yet know the function of the cortisol in depressive illness, it would appear to be a useful indicator of the severity of the illness, and a guide to the progress of treatment. Furthermore, there is the possibility that it may be responsible for at least two of the primary symptoms in this condition.

SUMMARY

The diurnal variation in plasma cortisol levels was studied in 14 subjects, 7 psychiatrically depressed patients and 7 normal persons of comparable age and sex. Five patients were treated with antidepressant medication and their plasma cortisol values estimated after 2 weeks and again after 4 weeks of therapy.

The levels were higher in the patients and remained high by normal standards throughout the 24 hours. The highest values occurred in the morning and the lowest at night. Good correlation was found between the severity of the clinical depression and the levels of plasma cortisol. Patients with marked retardation recorded the highest values.

No pathognomonic diurnal variation curve was found for psychotic depressive illnesses, instead, each patient had an individual curve which changed during the course of treatment.

It is hypothesized that cortisol is an indicator of the severity of psychotic depression and a guide to the progress of treatment. Furthermore, it may also be responsible for the early morning awakening and morning exacerbation of mood in this illness.

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