BRITISH MEDICAL JOURNAL

LONDON SATURDAY FEBRUARY 26 1955

FACTORS INFLUENCING ADRENOCORTICAL ACTIVITY IN HEALTH AND DISEASE*

BY

R. I. S. BAYLISS, M.D., M.R.C.P.

Assistant Physician, Westminster Hospital

The heightened interest in the adrenal cortex and its secretory products over the last few years is largely due to two factors—the belief by some workers that several diseases of unknown aetiology, such as rheumatoid arthritis, are caused by an imbalance in the various hormones secreted by the adrenal gland, and the advent of pure adrenal steroids and corticotrophin (A.C.T.H.) in sufficient amounts for use in clinical medicine. There can be no doubt that these agents are of considerable value in the treatment of certain diseases, particularly in the control of status asthmaticus and rheumatoid arthritis, and also in testing adrenocortical function so that the diagnosis of certain endocrine diseases can be more accurate and founded on a truly scientific basis. The proper use of these agents requires some knowledge of the mechanism by which they and other factors influence adrenocortical function.

The many different hormones secreted by the cells of the suprarenal cortex can be classified under five main headings according to their chief physiological actions. These five categories comprise glucocorticoids, androgenic steroids, mineralocorticosteroids, oestrogenic steroids, and progestational steroids: very little is known about the last two groups, and they are not discussed further. These subdivisions are somewhat arbitrary, because the actions of these hormones often overlap. For example, glucocorticoids, which include such compounds as hydrocortisone (also known as cortisol and compound F) and corticosterone (Albright calls them the "S" or sugar hormones because of their influence on carbohydrate metabolism), not only affect protein, carbohydrate, and fat metabolism but influence salt and water metabolism as well. There is evidence, however, for a specific mineralocorticoid which controls salt and water metabolism—namely, aldosterone, a hormone recently isolated by Simpson *et al.* (1954). Little is yet known about its role in health and disease, although there is enough evidence to indicate that the factors which control its secretion are different from those which promote the formation of hydrocortisone (Simpson and Tait, personal communication; Prunty *et al.*, 1954). Androgenic steroids, which Albright has called the "N" or nitrogen-retaining hormones because of their ability to promote anabolism of protein in addition to their action on the secondary sexual manifestations, also appear to be controlled to some extent by different factors from those concerned with the formation of glucocorticoids and aldosterone. Thus in considering the factors which influence adrenocortical activity in health and disease it is necessary to define which particular adrenal function is under discussion. This report is concerned chiefly with the secretion of glucocorticoids: our knowledge is far from complete, and in a rapidly developing field of research this is inevitably in the nature of an interim report on work in progress in several different centres.

*A lecture given to the Postgraduate Medical School and the Institute of the British Postgraduate Medical Federation as part of the course on "The Scientific Basis of Medicine." Delivered at the London School of Hygiene and Tropical Medicine on November 25, 1954.

INDICES OF ADRENOCORTICAL ACTIVITY

Glucocorticoid Secretion

Research into the secretion of corticosteroids has been beset with difficulties largely owing to lack of satisfactory methods. In the past much valuable information has been obtained from animal experiments in which assessment of adrenocortical activity has been based on such indirect indices as the degree of ascorbic acid or cholesterol depletion in the adrenal glands—changes which have been accepted as evidence of increased secretion of corticosteroids. However, the significance of these changes is still uncertain, and in endocrinology, perhaps more than in any other subject, it is unwise to translate from animal experiments to man. In man, too, indirect indices of adrenocortical activity have been used. Some of these, such as the fall in eosinophils, have proved under certain circumstances to be misleading. The significance of these eosinophil changes is discussed later.

More direct assessment of adrenocortical function is obtained by measuring the concentration of corticosteroids in the blood and in the urine. In principle the technique of estimating plasma corticosteroids is simple. A sample of 15 ml. of plasma is extracted with chloroform. The extract is dried and then purified by column chromatography. The steroids are estimated by a colour reaction with phenylhydrazine in sulphuric acid which is specific for C-17 dihydroxy-ketones (Porter and Silber, 1950; Nelson and Samuels, 1952; Bayliss and Steinbeck, 1953). By working up large volumes of fresh plasma it has been found that the bulk of the material measured is hydrocortisone (Nelson and Samuels, 1952), although some of the colour is produced by metabolites such as tetrahydrocortisone (Bayliss and Steinbeck, 1953; unpublished observations). The identification of the compounds present has been made by paper chromatography, eluting the steroids off the

paper and then recording the characteristic absorption spectra they give when reacted with concentrated sulphuric acid (Zaffaroni, 1950, 1953).

There are certain shortcomings in using the plasma concentration of 17-hydroxycorticosteroids as an index of adrenocortical activity. First, the method does not measure corticosterone, which is a normal, but probably not a major, constituent of adrenocortical secretion. The second, and in this context the more important, shortcoming is that the concentration of 17-hydroxycorticosteroids in the plasma may not necessarily be an index of adrenal activity. The level in the plasma is

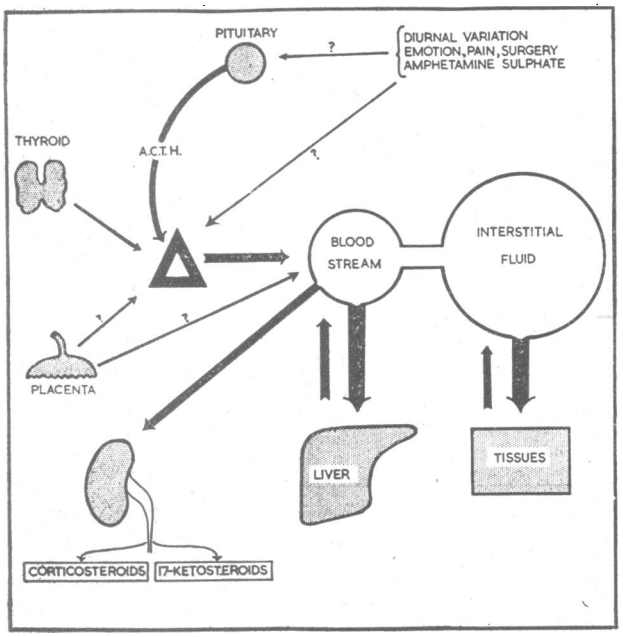

Diagram to illustrate some of the factors which influence the plasma level of 17-hydroxycorticosteroids.

the resultant of several factors (see Diagram)—the quantity being secreted by the adrenal glands, the quantity being metabolized and utilized in the tissues, and the quantity being excreted in the faeces and urine.

Secretion

Steroids secreted by the adrenal cortex pass into the blood stream and thence into the extracellular fluid. Paper chromatographic analysis of fluid removed from the pleural space or peritoneal cavity has shown the presence of hydrocortisone and also, in some specimens, very small amounts of tetrahydrocortisone (Cope and Hurlock, 1953, 1954). The 17-hydroxycorticosteroid content of pleural and ascitic fluid is of the same order as that found in blood samples, and this suggests that adrenocortical hormones diffuse readily from the vascular into the interstitial fluid compartments (Bayliss and Steinbeck, unpublished observations).

Utilization

Adrenocortical steroids are metabolized in the tissues and particularly in the liver. In the dog there is a considerable steroid gradient across the liver, and after giving cortisone by mouth the steroid concentration is much higher in the portal venous blood than in blood from the hepatic vein (Bayliss *et al.*, 1954b). In man a dose of 50 mg. of cortisone by mouth causes a rapid increase in the plasma steroid level, but the hormone disappears quickly from the blood stream and the plasma level returns to normal in four to six hours (Bayliss and Steinbeck, 1955).

Little is known of the metabolism of corticosteroids in peripheral tissues. Nelson *et al.* (1951) failed to find a significant arteriovenous difference across the limbs. This is perhaps not surprising, since Louchart and Jailer (1952) found that little disappeared when cortisone was incubated with slices of muscle or brain, but that large losses occurred in the presence of liver, kidney, or spleen slices. On the other hand, when hydrocortisone or cortisone is injected into a knee-joint the steroid is rapidly metabolized, and if some of the joint fluid is withdrawn half an hour later the hormone has been converted into other compounds (Wilson *et al.*, 1953).

It is possible that certain substances may interfere with the metabolism of cortisone or hydrocortisone. It was first observed in Holland that patients taking large amounts of liquorice were liable to develop oedema and hypertension (Borst, 1950). It was suggested that glycyrrhetinic acid, believed to be the active ingredient of the liquorice, exerted an effect similar to that of adrenocortical hormones, and that this might be the unwitting reason why salt-depleted miners in certain French coalfields sucked sticks of liquorice at the end of their day's work, just as British miners may add extra salt to their beer. When glycyrrhetinic acid was given to Addisonian patients conflicting results were obtained. Some patients showed clinical improvement and maintained their salt balance (Groen *et al.*, 1951 ; Card *et al.*, 1953) ; others did not (Borst *et al.*, 1953). It was observed that when an Addisonian patient was given cortisone a smaller dose combined with glycyrrhetinic acid produced the same therapeutic effect as a larger dose given alone. This suggests that liquorice may act by blocking the enzyme systems which metabolize corticosteroids. If in an Addisonian patient there is some residual adrenal function and small amounts of steroid are being secreted, glycyrrhetinic acid causes clinical improvement by preventing enzymic breakdown of the adrenal steroids ; if, on the other hand, adrenal atrophy is complete and no steroids are being secreted, glycyrrhetinic acid has no effect. Proof of this hypothesis has not yet been obtained.

Urinary Excretion

Although studies with C^{14}-labelled cortisone have shown that eventually about 80% of the radioactivity is eliminated in the urine, much of this material is probably no longer steroidal, because only 5 to 10% of a 50-mg. dose of cortisone is recovered in the urine as corticosteroids and an even smaller amount as neutral 17-ketosteroids. The quantitative estimation of urinary corticosteroids has proved difficult, because the hormones and their metabolites are excreted partly as free compounds and partly as conjugates. The difficulty has been to hydrolyse the conjugated compounds. The method evolved by Norymberski *et al.* (1953) circumvents this difficulty and is likely to prove a most valuable tool in the study of adrenocortical function. The method of Reddy *et al.* (1952) is also promising : it has the great merit of simplicity, but its accuracy has still to be proved. By estimating the 17-hydroxycorticosteroid concentration in plasma and urine the renal clearance of corticosteroids has been measured in the same way as the clearance of urea or creatinine is measured. About 1 ml. or less of plasma is cleared of 17-hydroxycorticosteroids per minute. Since data from studying the steroid concentration in ascitic and pleural fluid indicate that these hormones are diffusible, the low clearance must be due to active reabsorption in the tubular lumen, which is the method used for conserving substances important to the body economy.

These, then, are some of the factors which may influence the concentration of 17-hydroxycorticosteroids in the plasma.

In normal healthy subjects the plasma steroid level ranges from 3 to 17 μg. per 100 ml., with a mean of 9 μg. per 100 ml. It is necessary to point out, however, that isolated single determinations may be misleading, because there is evidence, discussed below, that emotional factors

may influence plasma steroid concentration and high values may occur in normal people during an emotional disturbance.

Androgenic Steroid Secretion

The urinary excretion of neutral 17-ketosteroids is generally accepted as an index of androgenic steroid formation in the body. The daily output in the adult male is on the average some 5 mg. higher than in the female—this amount being contributed by androgens of testicular origin. Unfortunately, hydrocortisone and cortisone are in part excreted as 17-ketosteroids, and the total excretion of 17-ketosteroids—derived from both corticosteroids and androgenic steroids and probably other precursors as well—is an imperfect index of androgenic hormone formation. By more complicated chromatographic techniques it is possible to separate 17-ketosteroids into several constituent fractions and determine how much of the total has been derived from corticosteroids and how much from androgenic hormones and other precursors (Dingemanse *et al.*, 1952; Kellie, 1953; Lakshmanan, 1954).

FACTORS INFLUENCING CORTICOSTEROID SECRETION

Corticotrophin

The pituitary trophic hormone A.C.T.H. is the principal factor directly regulating the secretion of corticosteroids (Sayers and Sayers, 1948; Sayers, 1950; Long, 1952). Whether corticotrophin is a protein or a polypeptide, and whether it is one hormone or several, is still undecided (Astwood *et al.*, 1952; Stack-Dunne, 1953; Forsham, 1955), nor is the mechanism by which it increases corticosteroid secretion fully understood. Perfusion studies of ox adrenal glands, carried out at the Worcester Foundation over a number of years, indicate that its action is to accelerate the early stages in the biosynthesis of hydrocortisone and corticosterone from cholesterol and acetate precursors (Pincus, 1954).

The degree of increased adrenocortical activity produced by A.C.T.H. is dependent upon two factors—the amount of hormone administered (Bayliss and Steinbeck, 1954a) and the length of time the stimulating action of the hormone is applied (Renold *et al.*, 1952).

If solutions of A.C.T.H. are infused over a constant time, the degree of adrenocortical stimulation produced is directly related to the dose given. Over a 6-hour period as little as 0.25 unit an hour will cause a significant increase in adrenal activity. If this response is plotted against the logarithm of the dose a straight-line relationship is obtained. The slope of the line is rather flat, so that with increasing doses above 2 units an hour there is little further elevation of the plasma steroid concentration, and for practical purposes it can be assumed that 2 units an hour over a six-hour period will cause maximum adrenal stimulation.

The degree of adrenocortical response to a constant dose of A.C.T.H. is directly proportional to the duration of A.C.T.H. administration (Renold *et al.*, 1952). If a single dose of 20 units is injected intravenously the response of the adrenal cortex is often short-lived and evanescent. In contrast the same amount of hormone dissolved in saline and infused over a six- or eight-hour period causes a profound increase in adrenocortical secretion. These differences are due to the rapid destruction of A.C.T.H. in the body (Sayers *et al.*, 1949; Greenspan *et al.*, 1950; Reiss *et al.*, 1951; Pincus *et al.*, 1952). If A.C.T.H. is dissolved in saline and injected intramuscularly it causes a relatively brief increase in plasma 17-hydroxycorticosteroid concentration lasting about four hours. If the same dose is given intramuscularly in a gelatin menstruum, combined with a zinc precipitant or an oxycellulose adsorbant, a more prolonged effect is observed, the vehicle allowing a gradual release of the A.C.T.H. and preventing its destruction at the site of injection (Bayliss and Steinbeck, 1954a; Oudsten *et al.*, 1954; Greene and Vaughan-Morgan, 1954; Ferriman *et al.*, 1954; Gemzell and Franksson, 1953).

The degree of adrenal stimulation obtained from intramuscular A.C.T.H. in saline or a gelatin menstruum is too variable from one patient to another and in the same patient at different times to allow a quantitative assessment of adrenocortical response. In our hands consistent results are observed only when the material is given by intravenous infusion (Bayliss and Steinbeck, 1954a). This has an important clinical application: the testing of adrenocortical function by giving intramuscular A.C.T.H. is meaningful only if a positive response is obtained. If the response is negative no conclusions can be drawn and the trophic hormone should be infused intravenously.

Deficiency of A.C.T.H. secretion due to pituitary destruction leads to adrenocortical atrophy and low plasma 17-hydroxycorticosteroid levels. The degree of adrenal atrophy is related to the degree of A.C.T.H. deficiency and this in turn to the degree of pituitary destruction. When pituitary destruction is total, or nearly so, the plasma level of 17-hydroxycorticosteroids may fall to zero, and such values are found in patients with gonadal, thyroid, and adrenal failure who require substitution therapy to remain alive. In others in whom the degree of pituitary destruction is less complete and the clinical features indicate only gonadal failure the plasma steroid levels are within the normal range.

Responsiveness of the Adrenal Gland

The amount of steroid secreted by the adrenal cortex depends not only on the degree of stimulation provided by A.C.T.H. but also on the responsiveness of the gland itself. In normal subjects a continuous infusion of A.C.T.H. calls forth a rapid response, which can be detected in the peripheral blood within 15 to 30 minutes of starting the infusion. After reaching a maximum in about an hour, the plasma steroid level remains relatively constant during the remainder of a six- or eight-hour infusion. When the infusion is stopped the increased adrenocortical activity ceases, and within two to three hours the plasma steroid level has returned towards the pre-infusion level. In normal subjects the level attained six to eight hours after starting an A.C.T.H. infusion at the rate of 2 units an hour is usually of the order of 25–35 μg. per 100 ml.—that is, 15 μg. or more above the pre-infusion level. As would be expected, repeated daily infusions cause progressively higher levels, and this suggests that the anatomical hypertrophy of the gland found after repeated infusions is associated with increased functional capacity and heightened steroidogenesis.

Some idea of the total steroid output from adrenal glands receiving maximum stimulation with A.C.T.H. is given by some studies made by Thorn *et al.* (1953). They observed the changes in urinary corticosteroid excretion, eosinophils, electrolyte, and blood glucose concentrations during a four-hour infusion of 3 units of A.C.T.H. an hour and found that quantitatively similar effects were produced in the same subject by infusing 12 mg. of hydrocortisone an hour. From this it may be tentatively inferred that under maximum stimulation the adrenal glands secrete the equivalent of about 300 mg. of compound F per 24 hours.

Addison's Disease

Decreased responsiveness of the adrenal cortex to A.C.T.H. is seen characteristically and diagnostically in Addison's disease. None of the patients we have studied has shown a significant increase in the plasma level after A.C.T.H. infusion. Even those who appear to have some slight residual adrenal function, as evidenced by their symptomatic independence of substitution hormone therapy and by the low but not negligible plasma steroid levels, show no response, and in them the steroid level may actually fall during the infusion, owing perhaps to utilization of the small amount of circulating hormone during

the stress of the procedure. Normal subjects infused with saline alone show little variation in their plasma steroid level, and if during this time there is increased steroid utilization a constant level is maintained by increased A.C.T.H. secretion and increased corticosteroid output. It is tempting to believe that in Addisonian patients with low normal plasma steroid levels, the few remaining adrenocortical cells are responding to their uttermost to large amounts of endogenously produced A.C.T.H. and no further response is possible to exogenous A.C.T.H.

Hypopituitarism

In patients with hypopituitarism the responsiveness of the adrenal glands is often less than in normal subjects, and there is evidence that the degree of responsiveness is related to the duration of the adrenal atrophy. Thus a patient, who was known to have had hypopituitarism for many years following implantation of radon seeds into the sella turcica, and then surgical extirpation of the remaining hypophysial tissue, showed a rise from 0 μg. per 100 ml. to only 6 μg. after a six-hour infusion of A.C.T.H., whereas in a patient who had only recently been hypophysectomized the level rose from zero to 36 μg.; this large increment may indicate, as occurs in animals, that shortly after hypophysectomy the target gland has a heightened response to its trophic hormone.

Adrenogenital Syndrome

In Addison's disease the activity of the adrenal cortex is impaired in all its functions and the formation of glucocorticoids, mineralocorticoids, and androgens is much reduced or absent. In contrast the adrenal glands of patients with virilization due to congenital adrenal hyperplasia have a more isolated defect which is limited to the biosynthesis of glucocorticoids, and in rare instances the mineralocorticoids as well. In most of these patients the circulating level of 17-hydroxycorticosteroids is abnormally low and there is little or no increase following stimulation with A.C.T.H., whereas the formation of androgens, as indicated by the urinary excretion of 17-ketosteroids, is increased and raised even further after A.C.T.H. (Kelley *et al.*, 1952; Bayliss *et al.*, 1954a; Bongiovanni *et al.*, 1954).

This condition provides information concerning the mechanism by which pituitary–adrenocortical activity is regulated. The secretion of A.C.T.H. is controlled by the plasma level of circulating glucocorticoids, and if the steroid concentration falls the pituitary secretes more A.C.T.H., thereby stimulating the adrenal cortex to maintain the plasma steroid concentration. Conversely, if the steroid level in the blood rises the activity of the pituitary is depressed and less A.C.T.H. is elaborated. In congenital adrenal hyperplasia it appears that because the biosynthesis of glucocorticoids is defective (probably through lack of a particular enzyme system) and the plasma concentration is low, the pituitary responds by secreting increased amounts of A.C.T.H. The adrenal glands are unable to secrete more glucocorticoids and respond to the A.C.T.H. by hypertrophying and elaborating large amounts of androgens which are responsible for the virilization of the patient and for the increased urinary excretion of 17-ketosteroids (Bartter *et al.*, 1951; Wilkins *et al.*, 1952; Jailer *et al.*, 1952).

The validity of this concept has been confirmed by the observation that if cortisone or hydrocortisone is given to such patients the activity of the pituitary is suppressed, less A.C.T.H. is elaborated, and the adrenal glands no longer secrete such large amounts of androgens (Wilkins *et al.*, 1951, 1952; Gardner and Migeon, 1952; Bayliss *et al.*, 1954a; Jailer *et al.*, 1954). Thus these patients are treated by the administration of cortisone in sufficient amounts to suppress pituitary activity and to reduce the urinary excretion of 17-ketosteroids to normal limits.

Cushing's Syndrome

In contrast to the conditions discussed above, in all of which the formation of glucocorticoids is reduced, Cushing's syndrome is characterized by abnormally high plasma steroid levels, whether the condition is associated with an adenoma of the adrenal cortex, bilateral adrenal hyperplasia, or a carcinoma. If the condition is due to bilateral adrenal hyperplasia an infusion of A.C.T.H. raises the already high steroid level even higher. This finding suggests a possible explanation for the underlying disorder in Cushing's syndrome of this type. Since the plasma level of corticosteroids is abnormally high, it seems probable that the primary defect lies in the pituitary gland itself, which is insensitive to the normal inhibitory influences of large amounts of circulating steroids. It is as though the "thermostatic" mechanism is set at too high a level and pituitary activity is not shut off until abnormally high plasma steroid levels are attained. Proof of this belief must await a reliable method for estimating the A.C.T.H. content of the blood, but it is significant that when hydrocortisone is infused into such patients there is a reduction in the urinary excretion of 17-ketosteroids, suggesting that the exogenously administered hormone raises the plasma level high enough to suppress pituitary activity. This response is not seen if the condition is due to an adrenal adenoma or carcinoma, and so may be of clinical value in determining the pathology of the disease before surgical exploration (Jailer *et al.*, 1954).

Myxoedema

The hormone secreted by the thyroid gland influences the metabolic rate of all tissues, and it might be anticipated that in severe myxoedema the activity of the adrenal cortex would be impaired and the rate of steroidogenesis retarded. However, in many patients with myxoedema the plasma steroid level is within the normal range, although, of course, in the myxoedematous state utilization may be decreased, and the rate of steroidogenesis correspondingly reduced. In a few patients abnormally low levels have been encountered, and these have risen to normal after substitution therapy with thyroid extract or L-thyroxine. In one patient with hypopituitarism characterized by severe secondary myxoedema, the plasma steroid level rose from 1 μg. per 100 ml. to 6 μg. when replacement therapy was given with thyroxine only.

In addition to A.C.T.H. and the state of the adrenal cortex, other factors influence adrenocortical activity. Most of these are still incompletely understood, and it is uncertain whether they exert their effect by direct action on the adrenal cortex, or by way of the hypothalamus and anterior pituitary, or by increasing tissue "utilization" of corticosteroids. Their importance lies in the fact that their influence is difficult to control and they may operate, unknown to the investigator, during physiological studies.

Diurnal Variation

Healthy adults show a diurnal variation in adrenocortical activity. It has been known for many years that the urinary excretion of 17-ketosteroids varies throughout the day (Pincus and Hoagland, 1943), and Thorn (1954) has reported that the urinary excretion of 17-hydroxycorticosteroids also varies over a 24-hour period. Similarly, the plasma steroid level varies: lowest values are found at night, around midnight, and the highest levels occur at about 6 a.m. (Tyler *et al.*, 1954; Bayliss, 1955). This variation persists whether the subject is up and about his daily work or whether he is confined to bed and receiving a constant amount of food every two hours. It is not related to the diurnal variation that occurs in the urinary excretion of water, sodium, and other electrolytes. What controls this diurnal change in activity remains unknown, and many obvious investigations need to be carried out: Is this rhythm reversed in night workers? Does it occur in blind people? What effect on it has a lesion of the hypothalamus? Is it disturbed in patients with psychiatric disorders or with Cushing's syndrome?

Emotional Factors

Emotional factors may influence adrenocortical activity in certain subjects. We first observed this phenonemon in 1952, and have since confirmed that in certain patients anxiety, frustration, and fear may cause a significant increase in the plasma 17-hydroxycorticosteroid concentration. Repeated venepunctures, although not more painful than usual, may activate the adrenal cortex by calling forth an emotional response. In certain subjects, delivering a lecture to a critical audience has a similar effect. It is because of these influences that it is difficult to define normal plasma steroid levels. A blood sample taken at random from an out-patient on his first attendance may give an erroneously high value because the patient may be suffering anxiety and tension at the time. Usually the levels induced by an emotional upset do not exceed 20 μg. per 100 ml. and are not therefore likely to cause confusion in the differential diagnosis of Cushing's syndrome, but in some instances higher levels are observed. In interpreting the results of physiological studies due allowance must be made for these emotionally prompted rises in plasma corticosteroids, and it is necessary to make repeated observations and to use adequate controls to be certain that the responses observed are due to the change in the specific experimental conditions being studied and not to an emotional upset.

Adrenaline

It is not yet known how emotional disturbances influence the plasma steroid level, but release of adrenaline is a possible intermediate mechanism. It has been thought for some time that, because adrenaline causes a fall in circulating eosinophils, directly or indirectly it stimulates the adrenal glands to secrete increased amounts of corticosteroids (Recant *et al.*, 1950). In normal but not in adrenalectomized subjects A.C.T.H. causes a fall in the number of eosinophils (Thorn *et al.*, 1948; Forsham *et al.*, 1948), and, since hydrocortisone or cortisone also causes a fall in eosinophils, it has rightly been assumed that the eosinopenia after A.C.T.H. indicates increased secretion of corticosteroids and a rise in the plasma concentration of adrenocortical hormones. It has been found, however, that adrenaline may cause an eosinopenia in patients who have had both adrenal glands removed (Kark and Muehrcke, 1952), and direct measurement of the steroid concentration in the plasma, and the steroid excretion in the urine after a single injection or a prolonged infusion of adrenaline in normal subjects, has failed to show any increase in adrenocortical activity (Sandberg *et al.*, 1953; Thorn *et al.*, 1953).

We were impressed that following A.C.T.H. the fall in eosinophils is greatest two to three hours after the maximum plasma steroid concentration has been obtained; and that following adrenaline the fall in eosinophils is greatest two hours after the injection. Hence it seemed that any increase in plasma steroids should be looked for within the first few minutes of giving the adrenaline. Despite taking multiple samples at this time, Hunter *et al.* (1955) have failed to detect any consistent increase in plasma steroids, and on the present evidence we must conclude that adrenaline does not cause a detectable increase in adrenocortical activity and is not responsible for the increased plasma steroid levels found in emotional disturbances. It must also be concluded that, although an eosinopenia after administration of A.C.T.H. is a valid index of increased adrenocortical activity, this is not necessarily so under other circumstances.

D-Amphetamine Sulphate

Amphetamine sulphate has many of the pharmacological properties of adrenaline, but a more prolonged action. In 1952 a patient with panhypopituitarism due to a large chromophobe adenoma which was also causing attacks of diencephalic epilepsy was found to have plasma corticosteroid levels above normal—22 μg. per 100 ml. This surprising result was obtained at a time when the patient was receiving amphetamine sulphate for his diencephalic epilepsy. When the amphetamine was stopped the plasma steroid level fell to the anticipated low value of 3 μg. per 100 ml. Subsequently Thorn (1954) has noted that some patients have increased urinary excretion of 17-hydroxycorticosteroids following "benzedrine," and we have found similar changes in the plasma steroid levels.

Stress

Selye (1946) has suggested that a wide variety of factors, such as infections, intoxications, trauma, nervous strain, heat, cold, muscular fatigue, and *x*-irradiation induce a state of general systemic stress which is associated with increased adrenocortical activity. Whether or not these many different factors do indeed cause increased cortical secretion remains to be proved. Thorn *et al.* (1953) have not observed an increase in the urinary excretion of 17-hydroxycorticosteroids after physical exertion, exposure to cold, anoxia, or mental exertion involving the use of an Air Force pursuit meter; but these results cannot yet be accepted with complete confidence because of the analytical method used. Increased steroid excretion was noted in members of the Harvard boat-race crew, but since the cox and the coach showed a similar response the increased adrenocortical activity seemed more attributable to emotional factors than to the physical exertion *per se*. The plasma steroid level shows no consistent change in patients receiving whole-body *x*-irradiation sufficient to cause radiation sickness.

Surgical operations do increase the urinary excretion of corticosteroids (Cope *et al.*, 1951; Thorn *et al.*, 1953) and raise plasma steroid levels (Franksson *et al.*, 1954), and increased adrenocortical activity is commonly observed in any painful condition. For example, an elderly patient with severe cephalgia due to temporal and occipital arteritis had consistently high values of 26 μg. per 100 ml., which returned to normal levels when the pain subsided, although the disease continued to be active. Patients with a myocardial infarct may show high levels. One admitted soon after the onset had a level of 50 μg. per 100 ml., which rose to 82 μg. per 100 ml. when she seemed on the point of dying. With recovery the plasma steroid level returned to a normal value of 9 μg. In several patients studied in the terminal stages of their illness very high steroid levels have been observed. This is not necessarily associated with urea retention and therefore is not attributable to failure of renal excretion. These findings may not, however, represent increased adrenocortical secretion: they may indicate failure of tissue utilization or impaired hepatic metabolism.

Salicylates

It has been suggested that salicylates exert their beneficial action in rheumatic affections by increasing adrenocortical activity (Hetzel and Hine, 1951; van Cauwenberge and Heusghem, 1951; van Cauwenberge and Betz, 1952). However, in ordinary therapeutic dosage salicylates do not cause a significant or constant increase in the plasma level of 17-hydroxycorticosteroids despite symptomatic relief and mild manifestations of salicylism (Bayliss and Steinbeck, 1954b), although poisoning with salicylates has been reported to increase the level (Done *et al.*, 1954).

Pregnancy

As judged by the urinary excretion of corticosteroids, there is evidence that the activity of the adrenal cortex is increased during pregnancy (Venning, 1946; Tobian, 1949; Cope *et al.*, 1951), and the plasma steroid level is also raised (Gemzell, 1953). Blood samples taken from 30 women at monthly intervals throughout pregnancy show a progressive increase in 17-hydroxycorticosteroids, the mean value for the group rising from 10 to 13 μg. per 100 ml. during the third and fourth months to 24 μg. during the last month. The concentration in blood taken from the umbilical cord

at the time of delivery was of the same order—27 μg. per 100 ml. During the post-partum period the level in the mothers' blood fell, the mean concentration for the group returning to normal by the eighth post-partum day. The levels in individual patients varied considerably from the mean values. About 45% showed a marked increase, with maximum levels exceeding 29 μg. per 100 ml.; another 45% had more moderate increases, with maximum values of more than 21 μg.; and in 10% the level did not exceed 20 μg. per 100 ml. (Bayliss *et al.*, 1955).

One important question which remains unanswered is the origin of this steroidal material. Does it arise in the mother or in the foetus? Since in newborn infants the urinary excretion of 17-ketosteroids, glycogenic corticosteroids, and reducing steroids, and the plasma level of 17-hydroxycorticosteroids are all low (Talbot *et al.*, 1943; Venning *et al.*, 1949; Day, 1948; Klein *et al.*, 1954) whereas the level of plasma 17-hydroxycorticosteroids remains high in the maternal circulation for a week after delivery, it seems probable that the site of origin is in the mother. Here three possible sites need consideration—the adrenal glands, which have an increased weight during pregnancy; the placenta, which is known to form other steroids such as progesterone; and the ovaries. Blood samples taken during caesarean section from a uterine vein or a maternal placental sinus and from a peripheral vein have not shown a significant difference in 17-hydroxycorticosteroid concentration, and if the steroidal material were elaborated mainly in the placenta it would be expected that after delivery the concentration in the mother would fall more rapidly than it does. However, observations made in Addisonian patients who have become pregnant suggest that adrenocortical-like hormones are formed in the placenta (Samuels *et al.*, 1943; Knowlton *et al.*, 1949; Jailer and Knowlton, 1950). There is also evidence that an A.C.T.H.-like hormone is formed in the placenta (Jailer and Knowlton, 1950; Opsahl and Long, 1951; Tarantino, 1951; Cohen and Kleinberg, 1952). Thus it may well be that in pregnancy increased amounts of adrenocortical steroids are formed both in the maternal adrenals and to a lesser extent in the placenta.

Two years ago Professor Long (1952) wrote: "I am of the opinion that the greatest obstacle to our understanding lies in the inadequacy of the methods at present employed for the detection of an increased secretory rate from either the anterior pituitary or adrenal cortex." Although some progress has been made, we are still lacking satisfactory methods, and the secretion of many hormones by the adrenal cortex makes a study of its activity complicated and often laborious. I have dealt with only glucocorticoid secretion and with only some of the factors which influence this particular activity, but enough has been said to indicate the changes that occur through the seven stages of man from the high levels in pregnancy, the low levels in the newborn infant, to again the high levels that may be found at the time of death.

Summary

The adrenal cortex elaborates a large number of different hormones which to some degree overlap in their physiological effects. Current investigations are chiefly concerned with 17-hydroxycorticosteroids (such as cortisone and hydrocortisone), androgenic steroids (as reflected in the urinary excretion of 17-ketosteroids), and in the compound which is probably responsible for the control of salt and water metabolism (aldosterone).

In the work reviewed here adrenocortical activity has been assessed by studying the plasma concentration of 17-hydroxycorticosteroids. The plasma level is influenced by the amount of material secreted by the adrenal glands (which is mainly controlled by the release of A.C.T.H. from the pituitary gland), by the "utilization" of the liberated steroids in the tissues (particularly in the liver), and by the rate of urinary excretion.

The plasma level of 17-hydroxycorticosteroids is the same in both sexes. It shows a diurnal variation, and increased values are found in pregnancy, Cushing's syndrome, certain emotional disturbances, following surgical operations, in painful conditions, and at the time of death. No consistent increase in adrenal activity has been observed after administration of adrenaline, salicylates, or deep *x*-irradiation in ordinary therapeutic dosage. Amphetamine sulphate increases the plasma steroid level in some subjects. The relationship between the adrenal response and the dose of A.C.T.H. and the duration of its administration is discussed.

Low plasma adrenal steroid values are found in Addison's disease (and there is evidence that in these patients adrenocortical failure may be complete or only partial), in patients with extensive pituitary destruction, in congenital adrenal hyperplasia associated with virilism, and in some patients with myxoedema.

References

Astwood, E. B., Raben, M. S., and Payne, R. W. (1952). *Recent Progr. Hormone Res.*, 7, 1.
Bartter, F. C., Albright, F., Forbes, A. P., Leaf, A., Dempsey, E., and Carroll, E. (1951). *J. clin. Invest.*, **30**, 237.
Bayliss, R. I. S. (1955). *Ciba Foundation Colloquia on Endocrinology*. In press.
—— Browne, J. McC., Round, B. P., and Steinbeck, A. W. (1955). *Lancet*, **1**, 62.
—— Broadbent, I. E., and Steinbeck, A. W. (1954a). Ibid., **1**, 434.
—— Dempster, W. J., Round, B. P., and Steinbeck, A. W. (1954b). *Clin. Sci.*, **13**, 377.
—— and Steinbeck, A. W. (1953). *Biochem. J.*, **54**, 523.
—— —— (1954a). *British Medical Journal*, **1**, 486.
—— —— (1954b). *Lancet*, **1**, 1010.
—— —— (1955). In press.
Bongiovanni, A. M., Eberlein, W. R., and Cara, J. (1954). *J. clin. Endocr.*, **14**, 409.
Borst, J. G. G. (1950). *Ned. T. Geneesk.*, **94**, 3608.
—— ten Holt, S. P., de Vries, L. A., and Molhuysen, J. A. (1953). *Lancet*, **1**, 657.
Card, W. I., Mitchell, W., Strong, J. A., Taylor, N. R. W., Tompsett, S. L., and Wilson, J. M. G. (1953). Ibid., **1**, 663.
Cohen, H., and Kleinberg, W. (1952). Ibid., **2**, 201.
Cope, C. L., Boysen, X., and McCrae, S. (1951). *British Medical Journal*, **2**, 762.
—— and Hurlock, B. (1953). Ibid., **2**, 753.
—— —— (1954). *Clin. Sci.*, **13**, 69.
Day, E. M. A. (1948). *Med. J. Aust.*, **2**, 122.
Dingemanse, E., Huis in't Veld, L. G., and Hartogh-Katz, S. L. (1952). *J. clin. Endocr.*, **12**, 66.
Done, A. K., Ely, R. S., and Kelly, V. C. (1954). *J. Pediat.*, **44**, 153.
Ferriman, D. G., Anderson, A. B., and Turner, P. P. (1954). *Lancet*, **1**, 545.
Forsham, P. H. (1955). *Ciba Foundation Colloquia on Endocrinology*. In press.
—— Thorn, G. W., Prunty, F. T. G., and Hills, A. G. (1948). *J. clin. Endocr.*, **8**, 15.
Franksson, C., Gemzell, C. A., and von Euler, U. S. (1954). Ibid., **14**, 608.
Gardner, L. I., and Migeon, C. J. (1952). Ibid., **12**, 1117.
Gemzell, C. A. (1953). Ibid., **13**, 898.
—— and Franksson, C. (1953). *Acta endocr. (Kbh.)*, **14**, 205.
Greene, R., and Vaughan-Morgan, J. (1954). *Lancet*, **1**, 543.
Greenspan, F. S., Li, C. H., and Evans, H. M. (1950). *Endocrinology*, **46**, 261.
Groen, J., Pelser, H., Willebrands, A. F., and Kamminga, C. E. (1951). *New Engl. J. Med.*, **244**, 471.
Hetzel, B. S., and Hine, D. C. (1951). *Lancet*, **2**, 94.
Hunter, J. B., Bayliss, R. I. S., and Steinbeck, A. W. (1955). In press.
Jailer, J. W., Gold, J. J., and Wallace, E. Z. (1954). *Amer. J. Med.*, **16**, 340.
—— and Knowlton, A. I. (1950). *J. clin. Invest.*, **29**, 825, 1430.
—— Louchart, J., and Cahill, G. F. (1952). *J. Amer. med. Ass.*, **150**, 575.
Kark, R. M., and Muehrcke, R. C. (1952). *Lancet*, **1**, 1189.
Kelley, V. C., Ely, R. S., and Raile, R. B. (1952). *J. clin. Endocr.*, **12**, 1140.
Kellie, A. E. (1953). *A.R. Brit. Emp. Cancer Campaign*, p. 397.
Klein, R., Fortunato, J., and Papadatos, C. (1954). *J. clin. Invest.*, **33**, 35.
Knowlton, A. I., Mudge, G. H., and Jailer, J. W. (1949). *J. clin. Endocr.*, **9**, 514.
Lakshmanan, T. K. (1954). *Recent Progr. Hormone Res.*, **9**, 179.
Long, C. N. H. (1952). Ibid., **7**, 75.
Louchart, J., and Jailer, J. W. (1952). *Proc. Soc. exp. Biol. (N.Y.)*, **79**, 393.
Nelson, D. H., and Samuels, L. T. (1952). *J. clin. Endocr.*, **12**, 519.
—— —— Willardson, D. G., and Tyler, F. H. (1951). Ibid., **11**, 1021.
Norymberski, J. K., Stubbs, R. D., and West, H. F. (1953). *Lancet*, **1**, 1276.
Opsahl, J. C., and Long, C. N. T. (1951). *Yale J. Biol. Med.*, **24**, 199.
den Oudsten, S. A., van Leeuwen, L., and Coers, R. J. (1954). *Lancet*, **1**, 547.
Pincus, G. (1954). Lecture to Society for Endocrinology.
—— and Hoagland, H. (1943). *J. Aviat. Med.*, **14**, 173.
—— Hopkins, T. F., and Hechter, O. (1952). *Arch. Biochem. Biophys.*, **37**, 408.
Porter, C. C., and Silber, R. H. (1950). *J. biol. Chem.*, **185**, 201.
Prunty, F. T. G., McSwiney, R. R., Mills, I. H., and Smith, M. A. (1954). *Lancet*, **2**, 620.
Recant, L., Hume, D. M., Forsham, P. H., and Thorn, G. W. (1950). *J. clin. Endocr.*, **10**, 187.
Reddy, W. J., Jenkins, D., and Thorn, G. W. (1952). *Metabolism*, **1**, 511

Reiss, M., Badrick, F. E., Halkerston, I. D. K., and Plaice, C. (1951). *Nature (Lond.)*, **168**, 206.
Renold, A. E., Jenkins, D., Forsham, P. H., and Thorn, G. W. (1952). *J. clin. Endocr.*, **12**, 763.
Samuels, L. T., Evans, G. T., and McKelvey, J. L. (1943). *Endocrinology*, 32, 422.
Sandberg, A. A., Nelson, D. H., Palmer, J. G., Samuels, L. T., and Tyler, F. H. (1953). *J. clin. Endocr.*, **13**, 629.
Sayers, G. (1950). *Physiol. Rev.*, **30**, 241.
—— Burns, T. W., Tyler, F. H., Jager, B. V., Schwartz, T. B., Smith, E. L., Samuels, L. T., and Davenport, H. W. (1949). *J. clin. Endocr.*, **9**, 593.
—— and Sayers, M. A. (1948). *Recent Progr. Hormone Res.*, **2**, 81.
Selye, H. (1946). *J. clin. Endocr.*, **6**, 117.
Simpson, S. A., Tait, J. F., Wettstein, A., Neher, R., Euw, J. v., Schindler, O., and Reichstein, T. (1954). *Experientia (Basel)*, **10**, 132.
Stack-Dunne, M. P. (1953). *Ciba Foundation Colloquia on Endocrinology*, **5**, 133.
Talbot, N. B., Butler, A. M., Berman, R. A., Rodriquez, P. M., and MacLachlan, E. A. (1943). *Amer. J. Dis. Child.*, **65**, 364.
Tarantino, C. (1951). *Folia Endocr. (Pisa)*, **4**, 197.
Thorn, G. W. (1954). Medical Research Society Lecture.
—— Forsham, P. H., Prunty, F. T. G., and Hills, A. G. (1948). *J. Amer. med. Ass.*, **137**, 1005.
—— Jenkins, D., and Laidlaw, J. C. (1953). *Recent Progr. Hormone Res.*, **8**, 171.
Tobian, L. (1949). *J. clin. Endocr.*, **9**, 319.
Tyler, F. H., Migeon, C., Florentin, A. A., and Samuels, L. T. (1954). Ibid., **14**, 774.
Van Cauwenberge, H., and Betz, H. (1952). *Lancet*, **1**, 1083.
—— and Heusghem, C. (1951). Ibid., **1**, 771.
Venning, E. H. (1946). *Endocrinology*, **39**, 203.
—— Randall, J. P., and Gyorgy, P. (1949). Ibid., **45**, 430.
Wilkins, L., Lewis, R. A., Klein, R., Gardner, L. I., Crigler, J. F., Rosemberg, E., and Migeon, C. J. (1951). *J. clin. Endocr.*, **11**, 1.
—— Gardner, L. I., Crigler, J. F., Silverman, S. H., and Migeon, C. J. (1952). Ibid., **12**, 257.
Wilson, H., Glyn, J., Scull, E., McEwen, C., and Ziff, M. (1953). *Proc. Soc. exp. Biol. (N.Y.)*, **83**, 648.
Zaffaroni, A. (1950) *J. Amer. chem. Soc.*, **72**, 3828.
—— (1953). *Recent Progr. Hormone Res.*, **8**, 51.

ENDOCRINE TREATMENT IN PSYCHIATRY*

BY

R. E. HEMPHILL, M.D., D.P.M.

Lecturer in Charge of Department of Psychiatry, University of Bristol; Medical Superintendent, Bristol Mental Hospitals Group

Endocrine therapy has a definite but restricted place in psychiatric practice; in some conditions its use is accepted, in others presumptive. With a few possible exceptions, such as cretinism, there are no psychiatric disorders in which an endocrine disturbance or deficiency has been proved to be an exclusive or major factor in causation. In contrast to the many papers published on research in the endocrinology of psychiatric illness in recent years, there are few about endocrine therapy and fewer that carry conviction.

Since the ductless glands are essential to adaptation and the preservation of physical and emotional stability, and can be disturbed by psychological upset, it is reasonable that psychiatrists should have looked to the field of endocrine treatment.

Although physiological disturbances and abnormalities of body constitution can be seen in any selection of chronic psychotics, the usual symptomatology of endocrine illnesses is rare in psychiatric disorders. Laboratory methods for investigating ductless gland function which have been evolved up to the present are probably not sufficiently precise or reliable to indicate and guide therapy in the absence of clinical signs of endocrine disease, and are not yet convenient for routine use. Thus endocrine treatment is still empirical, and the attempts to make it rational by laboratory methods have not yet been successful.

*From a Maudsley Bequest Lecture given in London on April 5, 1954.

Endocrine preparations may be used because of their physiological and pharmacological effect or as replacement; probably to some extent both aspects enter into successful therapy. It is improbable that lack of one hormone is responsible for any psychiatric disorder, and a replacement therapy is unlikely to be found.

An endocrine disturbance is only one factor in an illness which can be regarded as a reaction between physical and psychological components; but it may be responsible for great difficulties in adjustment. Endocrine therapy aims at improving this factor, so contributing to the total therapeutic effort by benefiting the adaptive or reactive capacity of the patient. It must be preceded by careful psychiatric assessment and investigation, and accompanied by adequate psychotherapy.

Endocrinology in psychiatry can conveniently be considered from the following aspects: (1) conditions encountered in psychiatric practice for which therapy is no longer experimental; (2) psychiatric aspects of endocrine disorders; and (3) experimental endocrine treatment of the psychoses and psychoneuroses.

Conditions Encountered

The Menopause

The features of menopausal depression, irritability, or neurosis need only be mentioned briefly here. There are few women who do not experience psychological changes during the months or years in which ovarian function is failing. The degree to which a woman is disturbed seems to depend upon her capacity for emotional adjustment, general stability, and reaction to ill-health. Many women who suffer most at the menopause report that they have usually experienced mood swings and physical discomfort at some part of the menstrual cycle. It is not correct to assume that a certain kind of personality suffers at the menopause, or is immune; but unbalanced and especially aggressive females often become unreasonable almost to the point of psychosis both at the menstrual cycle and at the menopause. A gradual menopause produces more discomfort than an abrupt cessation. Vasomotor disturbances and hot flushes correspond closely with mood swings. It is believed that these are due to a dysbalance in the relationship between pituitary-stimulating hormones and the peripheral ovarian hormones that are now failing, which has been suggested by high prolan excretion.

Treatment with synthetic or natural oestrones (stilboestrol, dienoestrol, or oestrone), or, in severe cases, oestroform by injection, in sufficient quantity to control hot flushes, is all that is required for the somatic disturbances, and makes psychotherapy easier. Stilboestrol is toxic to about 20% of women, especially the older; the dose is about 0.1 mg. daily. The usual dose of oestrone is from 0.2 to 1 mg. daily. A severe menopausal disturbance sometimes occurs years after artificial menopause by radium, or after hysterectomy if the ovaries remain; this is to be treated on the same lines as the normal menopause and is mentioned for this reason. Convulsive therapy—so effective in involutional melancholia—often aggravates menopausal depression and is contraindicated in the presence of hot flushes, because of its stimulating effect on anterior pituitary lobe function.

Involutional Melancholia

Unlike the menopausal reaction, this is a true psychotic depression, with ideas of guilt or of incurable illness, much agitation, and a marked tendency to suicide. It rarely follows a gradual menopause with vasomotor disturbances, and it usually occurs a year or more after sudden cessation of menses. The pre-psychotic personality is conscientious and inflexible, in contrast to the lability of the menopausal reaction. There is often an appearance of rapid physical ageing, and in some cases there seems to be an anterior pituitary insufficiency, which may be benefited by treatment