The Effects of Preanesthetic Medication, Anesthesia and Hypothermia on the Endocrine Response to Injury

E. E. Van Brunt, M.D., and W. F. Ganong, M.D.

THE TRAUMA of surgery triggers a series of endocrine phenomena which are part of the widespread response of the body to injury. The response to injury in man has been documented in detail in the classical studies of Moore and his associates.[61] A central event in this response is an increase in the circulating levels of adrenocortical hormones due largely, although not exclusively, to increased secretion of ACTH from the pituitary. The physiological mechanisms which bring about the elevation in adrenocortical hormone levels, and the effect on these mechanisms of drugs used for preanesthetic medication, of anesthetics and of hypothermia are the subjects of this review.

The importance of the increased hormone levels in injured individuals deserves emphasis. The adrenal cortex secretes three types of steroid hormones; glucocorticoids, mineralocorticoids, and sex hormones. Small amounts of the glucocorticoids, which affect primarily carbohydrate and protein metabolism, and the mineralocorticoids, which control the distribution and excretion of sodium and potassium, are adequate for survival in the absence of stressful stimuli. However, adrenalectomized patients who get along quite well on maintenance doses of these steroids become hypotensive and die when subjected to stresses such as surgery, unless their intake of steroids is increased.[96] It is not known for certain why increased amounts of hormones are necessary. Some investigators feel that part of the answer is the interaction between glucocorticoids and the catecholamines, norepinephrine and epinephrine. In man, norepinephrine is the mediator liberated at the postganglionic sympathetic nerve endings, while epinephrine is the principal hormone secreted by the adrenal medulla.[104] When glucocorticoids are absent, the constrictor effect of norepinephrine on blood vessels is deficient,[80] and glucocorticoids could therefore play a role in preventing shock during surgery. There is also evidence that the catecholamines fail to exert their "metabolic" effects, *i.e.*, mobilization of free fatty acids from adipose tissue and of glucose from the liver, in the absence of adrenocortical steroids [18]; mobilization of these emergency fuel supplies may be an important part of the response to injury. However there are probably other effects of the adrenocortical hormones that make an increase in their circulating level so important.

The authors are in the Department of Physiology, School of Medicine, University of California Medical Center, San Francisco, California.

Secretion and Fate of Adrenocortical Hormones

The principal glucocorticoids secreted by the adrenal cortex are cortisol and corticosterone. The only mineralocorticoid normally secreted in physiologically important amounts is aldosterone. The major sex hormones secreted are the estrogen, estradiol, and the androgen, dehydroepiandrosterone (fig. 1). The secretion of all of these hormones, including that of aldosterone [24] is increased by ACTH from the pituitary gland. The levels of glucocorticoid secretion, and probably adrenal sex hormone secretion, are solely determined by the circulating ACTH level, but other factors, particularly renin from the kidney, affect the secretion of aldosterone.[10,63-65] Unfortunately, statements implying that the pituitary plays little or no part in the control of aldosterone secretion are frequently found in reviews and texts. There is a clear-cut increase in aldosterone secretion during surgery, and this increase, unlike that produced by salt depletion, is blocked by hypophysectomy.[47, 55] An increase in aldosterone secretion, presumably due to an increase in ACTH secretion, is also produced by anxiety,[101] and in patients facing major surgical procedures this may contribute to the increase in aldosterone secretion produced.

The events that follow an increase in ACTH secretion, and the fate of the secreted cortisol are shown diagrammatically in figure 2. The metabolism and excretion of corticosterone and aldosterone differ only in a few details. Since the adrenal sex hormones do not appear to play any role in the response to injury, they are not discussed in this review.

ACTH stimulates the synthesis and release of adrenocortical hormones. In the dog, the increase in glucocorticoid secretion is proportional to the dose when small amounts of ACTH are injected,[7,12] but a maximal level of glucocorticoid secretion is soon reached. Large doses of ACTH have a more prolonged effect, but do not produce any further increase in the rate of adrenocortical secretion (fig. 3). A similar "ceiling on output" exists in the rat [40, 53, 54] and in man.[14, 53] This maximum is generally reached during major surgery, and if ACTH is injected during an operation, there is no further increment in glucocorticoid output.

All but a small fraction of the secreted cortisol is promptly bound in the circulation, primarily to an α-globulin known as transcortin.[9] Small amounts are also bound to albumin. Apparently, only the unbound cortisol is physiologically active, and the hormone bound to transcortin represents a circulating reserve of hormone. In the liver, cortisol is converted to and is in equilibrium with cortisone. In man and in most animals, this derivative of cortisol is not secreted by the adrenal gland.[2] Cortisol and cortisone are converted in the liver to the tetrahydro-derivatives of these steroids, then promptly conjugated, primarily to glucuronic acid. These physiologically inactive "steroid conjugates," unlike cortisol, are not bound to protein. They are freely soluble in water, and are promptly excreted in the urine. 17-Ketosteroids and other physiologically inactive metabolites of cortisol are also formed in the liver and excreted in the urine.[2]

The fate of corticosterone is similar to that of cortisol, except that less of it is bound to protein. Aldosterone is secreted in much smaller amounts than the other hormones (fig. 1), but not bound to protein to any degree. Therefore, essentially all of the unconjugated

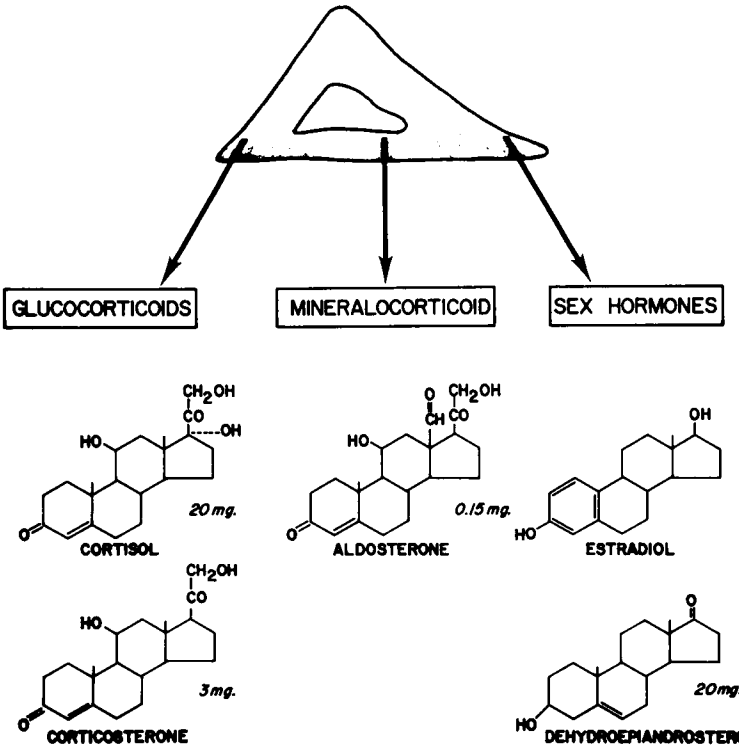

FIG. 1. The principal hormones secreted by the adrenal cortex. The values beside each hormone are 24 hour outputs based on secretion rate determined in resting man.

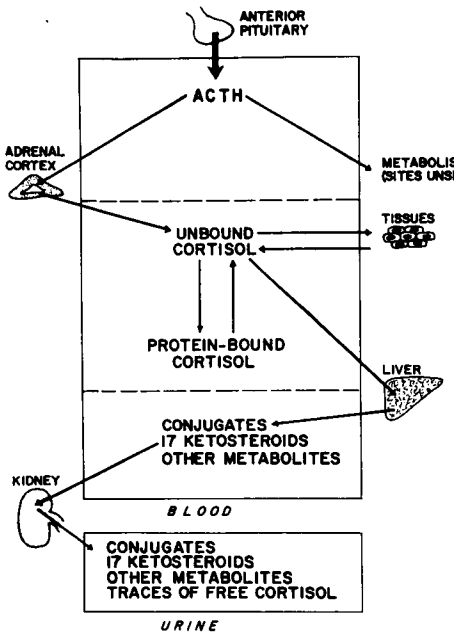

FIG. 2. Schematic representation of the factors affecting the concentration of unbound cortisol in plasma.

aldosterone in the circulation is in the physiologically active form. Like cortisol and corticosterone, it is metabolized in the liver and the conjugated metabolites are excreted in the urine.[48]

Measurement of Adrenocortical Activity in Man

The advantages and the limitations of the various methods used to determine the level of adrenocortical activity in man become apparent when they are discussed with reference to figure 2.

The tissue effects of glucocorticoids include lysis of circulating eosinophils and lymphocytes, and changes in the number of these cells in the blood have been used as indicators of adrenocortical activity.[96] Theretically, they reflect changes in the levels of unbound, active glucocorticoids. Unfortunately, both the lymphocyte and the eosinophil count are unreliable for this purpose, because both are affected by other endocrine and non-endocrine factors.[97] It is frequently stated that in cases of unexplained hypotension, the diagnosis of adrenal insufficiency can be ruled out if no eosinophils are found in a smear of the peripheral blood, or if a direct blood eosinophil count is low (less than 50 cells/cu. mm.). In animals, however, some surgical procedures cause eosinopenia in the absence of the adrenals (fig. 4). It therefore seems wise to use other, more direct methods for evaluating adrenocortical function.

Measurement of the 24-hour excretion of adrenocortical steroids in the urine is a widely used and valuable index of adrenocortical ac-

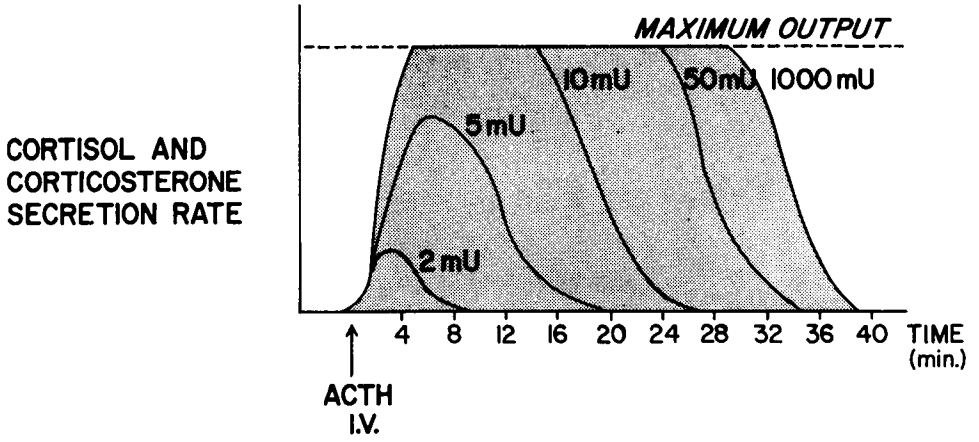

FIG. 3. Graphic representation of the effect of intravenous ACTH on adrenocortical secretion of cortisol and corticosterone in the hypophysectomized dog. Each curve represents the response to that dose of ACTH indicated. (Reproduced, with permission of the publishers, from Ganong, W. F.[26])

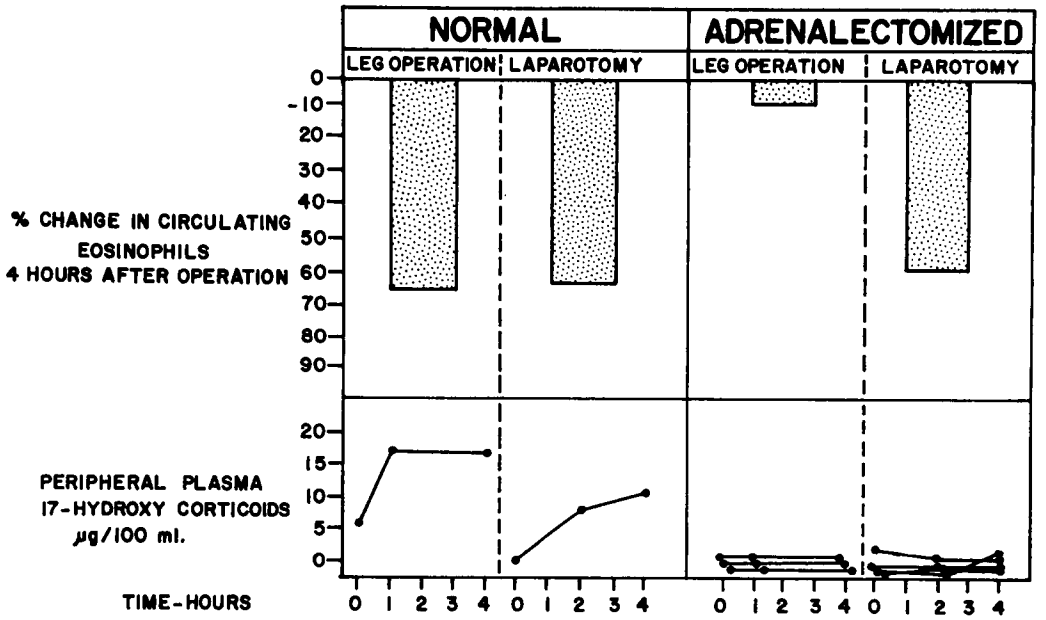

FIG. 4. Comparison of the changes in circulating eosinophils and peripheral plasma 17-hydroxycorticoids following surgical trauma in normal and adrenalectomized dogs. (Data of Steenburg, R., and W. F. Ganong, reproduced with permission from Ganong, W. F., Review of Medical Physiology, Los Altos, California, Lange Medical Publications, 1963, In press.)

tivity. Because only small amounts of the steroids in the urine are free, and most are conjugated to glucuronic acid, it is important to hydrolyze the conjugates by incubation with β-glucuronidase before measuring the steroid content (table 1). Individual steroids can be measured, but a much more common procedure for evaluating glucocorticoid secretion is determination by the Silber-Porter reaction of the content of 17-hydroxycorticoids, *i.e.*, cortisol and the steroids related to it, principally cortisone and 11-desoxycortisol, which have an —OH group in the 17 position (fig. 1). Corticosterone, which does not have an —OH group in the 17 position, can be measured by other techniques. The 17-ketosteroids include a heterogeneous group of adrenal androgens and derivatives of testosterone, as well as cortisol metabolites, and are not a reliable index of glucocorticoid secretion.

Determinations of urinary steroid excretion provide an "average" of the level of adrenocortical secretion during the time the urine was collected. Twelve and even six-hour collections are sometimes analyzed to provide information concerning short term changes. Values obtained in this way must be compared to values for similarly time control collections, because there is a marked diurnal fluctuation in steroid secretion and excretion.[77] The urinary steroid level reflects not only the rate at which steroids are secreted, but the rate of their hepatic metabolism and their excretion by the kidney. This consideration is particularly pertinent because during anesthesia, ether, cyclopropane, thiopental and meperi-

TABLE 1. Plasma and Urine 17-Hydroxycorticoids and Plasma ACTH in Man, at Rest and After Maximal Adrenocortical Stimulation

	Average Basal Values	Typical Values Following Maximal Adrenocortical Stimulation
Urine 17-hydroxycorticoids (mg/24 hours)		
Free	0.1	0.5
Total (Free + conjugates)	8	30
Plasma unconjugated 17-hydroxycorticoids (µg/100 ml.)	10*	50–70
Plasma ACTH (mU/100 ml.)	0.3*	2–5

Values based on data of various authors. *AM values; evening values are lower.

dine all cause a transient depression of hepatic and renal function.[17, 33, 87]

Measurement of steroid secretion rates by isotope dilution is a relatively new technique which permits the measurement of the rates at which individual steroids are secreted over a period of time.[99] A radioactive steroid such as cortisol is injected intravenously in a dose which is too small to have any significant physiological effect by itself. The degree to which the labelled steroid is diluted by "cold" steroid, *i.e.*, the rate at which the endogenous steroid is secreted, is determined by chemically isolating the steroid or one of its metabolites in a timed urine specimen, and determining the specific activity of the product isolated. Since the radioactive and the endogenous steroid are presumably metabolized and excreted in the same way, secretion rate values are essentially unaffected by variations in hepatic and renal function. The values listed in table 1 for the 24-hour output of individual steroids in resting man were determined in this way. The major drawback of the method is that, like determinations of steroid excretion, it cannot be used to measure short term changes in hormonal secretion.

Methods for measuring the unconjugated 17-hydroxycorticoids in plasma, which in man consist of cortisol and small amounts of other steroids, and the circulating conjugated 17-hydroxycorticoids, are now available. It should be emphasized that plasma contains free, unbound corticoids, protein-bound corticoids, and corticoid metabolites, principally glucuronide conjugates formed in the liver (fig. 2), and that the unconjugated 17-hydroxycorticoids, as usually measured, include both unbound and protein-bound 17-hydroxycorticoids. The unconjugated plasma 17-hydroxycorticoids are often called the "free" 17-hydroxycorticoids, or simply the "plasma 17-hydroxycorticoids," but to avoid confusion, the term unconjugated 17-hydroxycorticoids is preferable. Determination of the conjugated 17-hydroxycorticoids is largely of research interest,[93] but measurement of the unconjugated moiety is the simplest and most widely used method for evaluating adrenocortical function during and immediately after operation, and for following rapid, serial changes in adrenocortical function. However, caution must be exercised in inferring that a high plasma level, *per se*, indicates a high rate of adrenocortical secretion because this, like the level of any substance in blood, is determined by a balance between the rate at which it is added to the blood stream and the rate at which it is removed. In the dog and in man, surgical trauma and certain anesthetics, ether and cyclopropane, decrease the rate at which the liver removes unconjugated 17-hydroxycorticoids from the blood stream.[84, 92] This is why the unconjugated 17-hydroxycorticoid level in peripheral plasma is higher in patients undergoing major operations than when doses of ACTH sufficient to produce maximal hormone output are injected.[98]

Another problem in interpretation is posed by the fact that the unbound physiologically active corticoids make up only part of the total unconjugated plasma 17-hydroxycorticoids. Therefore, changes in unconjugated 17-hydroxycorticoid levels may be due to changes in the amount of bound, rather than unbound hormone. In pregnancy, for instance, plasma unconjugated 17-hydroxycorticoids rise to high levels, but there is little or no clinical evidence of glucocorticoid excess because the rise is due mostly to an increase in bound corticoids.[11] The plasma unbound 17-hydroxycorticoid level can be measured by determining the unconjugated 17-hydroxycorticoid level before and after dialysis of the plasma sample, but this method is too complex for routine use.[11] However, there is generally a proportional rise in the unbound 17-hydroxycorticoids when the total unconjugated 17-hydroxycorticoids rise, as long as there is no change in the amount of binding protein in the circulation.[107] Actually, the rise in the unbound hormone level is proportionally greater than the rise in the total unconjugated hormone level, because the binding capacity of the proteins is exceeded when the rate of adrenocortical secretion is increased. For example, the unbound cortisol level rises from about 0.5 μg/100 ml., when the unbound plus bound level is 10 μg/100 ml., to about 7 μg/100 ml. when the unbound plus bound level is 35 μg/100 ml.[107] There have been no reports of changes in binding protein titers in surgical patients, and anesthetic drugs are not known to affect these substances. Therefore, changes in plasma un-

conjugated 17-hydroxycorticoid levels during anesthesia and surgery are probably accompanied by corresponding changes in unbound circulating glucocorticoid levels.

Measurement of hormonal output in adrenal venous blood is the most direct technique for measuring adrenocortical secretion. The concentration of the hormones in adrenal venous blood is a poor index of their rate of secretion, and sampling adrenal venous blood by inserting a needle into the adrenal vein during abdominal surgery is of relatively little value, because, in both instances, at any given level of output, concentration varies reciprocally with adrenal blood flow. There are, however, a number of studies of hormonal output during abdominal operation in man, in which care was taken to collect all the effluent from one adrenal and to calculate hormonal output by multiplying adrenal venous hormonal concentration by adrenal blood flow.[36, 44, 46] Hume, Bell, and Bartter[46] have also reported values for adrenocortical hormonal output in man with indwelling adrenal venous catheters and choker devices brought out through the skin. This permitted intermittent collection of all the blood coming from the left adrenal gland at various periods up to 24 hours after operation. Their results, which provide a definitive picture of the adrenocortical response to major surgery in man, are summarized in table 2.

Another method for evaluating pituitary-adrenocortical function in man is the measurement of the plasma ACTH content by injecting the plasma into hypophysectomized assay animals, and comparing the effect on some parameter of adrenal function to that of a known amount of ACTH. In the most sensitive assay presently available, the adrenal venous output of corticosterone[54] in hypophysectomized rats is determined. With this method, ACTH has been detected many times in the plasma of unstressed human beings in the morning hours when adrenocortical secretion is at its diurnal peak.[53] It is not detectable in all subjects, but if the zero values and the measurable values for a series of subjects are averaged, a mean morning ACTH value of about 0.3 mU/100 ml. plasma is obtained (table 1). In the evening, when adrenocortical secretion is at its diurnal low point, ACTH is not detectable in any of the subjects. During major surgical procedures, the plasma ACTH level rises to 2–5 mU/100 ml., falling again to low levels 24 hours postoperatively.[8, 53]

TABLE 2. Summary of data of Hume, Bell and Bartter,[46] showing mean adrenal venous output of adrenocortical hormones in 21 human beings during major abdominal surgery, before and after the administration of ACTH, and in seven patients with indwelling adrenal vein cannulas 24 hours after operation, before and after the administration of ACTH.

	Mean Output From the Left Adrenal (μg/minute)	
	17-Hydroxy-corticoids	Aldo-sterone
During operation	33.1	0.072
ACTH during operation	30.5	0.074
24 hours after operation	3.1	0.024
ACTH 24 hours after operation	37.4	0.055

It is worth noting that the ACTH level in peripheral blood, like the circulating corticoid level, is determined by the balance between rate of secretion and the rate of removal from the blood stream. As yet little is known about the metabolism of ACTH. However, it is the amount of ACTH reaching the adrenal via the peripheral blood that determines the rate of adrenocortical secretion. It appears that both in the dog and in man, the amount of ACTH reaching the adrenal during surgery is greater than the amount necessary to produce a maximal glucocorticoid output.[26] Therefore, it is possible that in a particular experimental situation, a given anesthetic or preanesthetic medication might significantly depress the blood ACTH level without depressing it to the point where an actual decrease in glucocorticoid secretion would occur. The depressant effect would thus be missed unless the blood ACTH were measured.

Other Substances Activating the Adrenal Cortex

There are a variety of substances other than ACTH that can increase the secretion of adrenocortical hormones in experimental animals under certain conditions. Substances demonstrated to have this effect include vasopressin,[37, 43] serotonin,[43] histamine,[43] acetylcholine,[82] adenosine 3′-5′ monophosphate,[38] and

angiotensin II.[62] Their actions and the significance of their effects have been discussed in a recent review.[26] It should be emphasized, however, than in most physiological and clinical situations, ACTH and, probably, angiotensin II are the major factors and possibly the only circulating factors regulating adrenocortical secretion. The action of angiotensin II is primarily exerted on the secretion of aldosterone, but large amounts of this peptide also cause moderate increases in the secretion of cortisol and corticosterone.[62]

Activation of the Pituitary

Current evidence indicates that the increase in ACTH secretion produced by stressful stimuli such as surgical trauma, drugs, changes in blood chemistry, and strong emotions are mediated by a group of neuroendocrine reflexes which act through the hypothalamus, and that it is the hypothalamus that controls pituitary secretion. Lesions of the median eminence of the hypothalamus prevent the increase in ACTH secretion normally produced by these stimuli, and electrical stimulation of this portion of the brain increases ACTH secretion. Extracts of the hypothalamus contain a substance which increases ACTH secretion in animals with median eminence lesions. The substance is apparently a polypeptide, and is now generally known as corticotropin releasing factor (CRF). It is believed that stressful stimuli cause this material to be released from nerve endings in the hypothalamus, from which it is carried by a special set of blood vessels, the portal hypophyseal vessels, directly to the anterior pituitary. The experimental evidence upon which these conclusions are based are discussed in detail in two recently published books,[69, 95] and in a number of reviews.[19, 26, 107] At present, attention is focused on the mechanisms and pathways by which the various stressful stimuli activate the hypothalamus.

Since misconceptions are common it should be noted that, in the dog and man, epinephrine is not the factor responsible for activating the pituitary. Surgical trauma and other noxious stimuli increase epinephrine secretion, and since epinephrine increases ACTH secretion in the rat, it was logical to postulate that circulating epinephrine secreted from the adrenal medulla was responsible for the increase in ACTH secretion. However, in the dog and man, it appears that epinephrine and norepinephrine do not increase ACTH secretion. Infusions of these amines decrease, rather than increase, plasma 17-hydroxycorticoids [71] and fail to increase the secretion [73] or excretion [97] of adrenocortical hormones. Further evidence that the catecholamines are not the mediators is the observation in the dog, that marked increase in adrenal medullary secretion of epinephrine and norepinephrine produced by stimulation of the dorsal portion of the hypothalamus, cause no increase in adrenocortical secretion.[31] Even with stimuli such as hypoglycemia, which stimulates both the cortex and the medulla of the adrenal gland, the increase in cortical secretion precedes the medullary response.[29] The one observation that fails to fit the consensus of available data is a recent study by Vernikos-Danellis and Marks [102] in which epinephrine infusions produced a transient rise in plasma ACTH level in man. However, these investigators did not measure adrenocortical secretion in their subjects. Plasma ACTH levels as high as those reported in their study are associated with a high rate of adrenal secretion, yet as noted above, others report that epinephrine fails to increase adrenocortical secretion in man.

Epinephrine causes an eosinopenia in man, in the absence of the adrenal gland. Consequently, use of the degree of eosinopenia produced by epinephrine (Thorn test) as a "test of pituitary reserve" can no longer be considered reliable.[97]

A factor which does play an important role in determining the level of ACTH secretion is the circulating glucocorticoid level. In man, treatment with large doses of glucocorticoids or their synthetic derivatives inhibits ACTH secretion and leads eventually to marked adrenal atrophy and unresponsiveness to ACTH. The hormones probably act on the hypothalamus to produce this inhibitory effect, although they may act directly upon the pituitary as well.[26] One of the major actions of the steroids is the inhibition of ACTH synthesis, but they may have other effects as well.[39] This subject and its implications in terms of the clinical management of patients treated with corticoids

are discussed in detail elsewhere in this symposium.[74] Adrenal insufficiency is associated with a marked increase in ACTH secretion. The metyrapone (Metopirone, SU-4885) test, a method for assaying pituitary reserve in patients with endocrine disorders, makes use of this fact. Metyrapone, when infused in appropriate amounts, inhibits the biosynthesis of cortisol by blocking the enzymes responsible for hydroxylation at the 11 position of the steroid nucleus. The resultant drop in the circulating cortisol level apparently stimulates the pituitary, and the magnitude of the increase in ACTH secretion, as measured by the increase in urinary 17-hydroxycorticoids other than cortisol, is an index of the secretory capacity of the pituitary.[52] Thus, there is an inverse relation between the circulating glucocorticoid level and the amount of ACTH being secreted in man. However, the increase in ACTH secretion produced by a decrease in the circulating corticoid level is not initially very great, and takes some time to develop. For instance, in studies of normal subjects treated with metyrapone, there was no clear-cut rise in ACTH levels until treatment had been continued for 24 hours, and a similar relatively slow rise in blood ACTH levels occurs after steroid treatment is stopped in bilaterally adrenalectomized patients.[53] It should also be noted that in man, while relatively small doses of exogenous glucocorticoids inhibit ACTH secretion in the absence of stressful stimuli, large doses do not prevent the occurrence of a maximal increase in adrenocortical secretion during operation unless treatment has been continued long enough to produce adrenal atrophy or pituitary ACTH depletion.

The importance of factors other than the corticoid feed-back mechanism in the control of ACTH secretion is shown by the observation that when bilaterally adrenalectomized rats are subjected to operation, there is an increase in the blood ACTH level that is even greater than that which occurs in intact animals.[85] Factors which activate the hypothalamus to release CRF include impulses from afferent neural pathways converging on the median eminence and, possibly, humoral factors which act directly upon the hypothalamus. The level of ACTH secretion at any given time is probably determined by the balance between the activity of these stimulatory mechanisms and the inhibitory effect of the glucocorticoids, which is proportional to their level in the circulating blood. These interrelations are shown diagrammatically in figure 5.

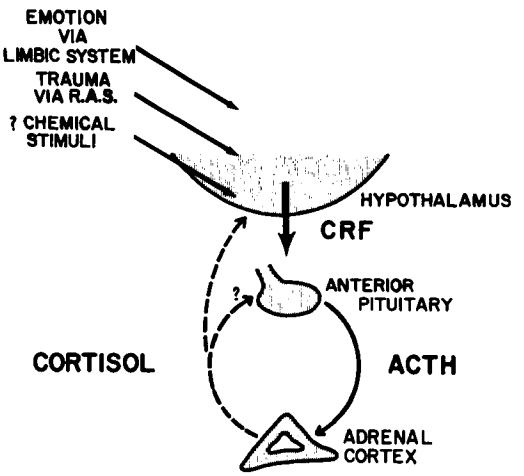

FIG. 5. Diagramatic representation of the interrelation of factors controlling ACTH secretion. The dotted lines represent inhibitory influences. RAS, reticular activating system. (Reproduced with permission from Ganong, W. F., Review of Medical Physiology, Lange Medical Publications, Los Altos, California, 1963, In press.)

Afferent nerve pathways which converge on the hypothalamus include fibers from the limbic system, the basal portion of the cerebral cortex which is concerned in the genesis of emotions and their expression.[70] Collaterals from the ascending pathways for pain and other cutaneous sensations apparently reach the hypothalamus via the ascending reticular system.[56] The former pathways mediate the response to emotions, such as fear and apprehension, which are potent stimulators of ACTH secretion,[25] while the latter play a major role in triggering the increase in ACTH secretion produced by surgical procedures. In experimental animals, denervation prevents the adrenocortical response to thermal trauma to a limb, and section of the spinal cord prevents the response to burns, electric shocks, and surgical procedures below the level of the section.[21, 43, 46, 81] According to Hume *et al.*,[46] there is no increase in adrenocortical secretion when major abdominal surgery is performed in paraplegic humans with lesions high in the

thoracic spinal cord. This failure to respond is not due to diminished responsiveness of the adrenal to ACTH.[15] Osborn and associates [75] concluded that the adrenocortical response to operation is not blocked in paraplegic human beings, but their data showed a failure of plasma unconjugated 17-hydroxycorticoids to rise during surgical procedures. The usual response in patients with intact spinal cords is a marked rise in plasma unconjugated 17-hydroxycorticoids during this period.[100] Osborn's patients showed a rise in urinary 17-hydroxycorticoid secretion on the second and third postoperative days, but this could have been due to psychic stimuli. After cord section, the adrenocortical responses to painful stimuli above the level of the spinal cord transection and to psychic and other stimuli which operate through mechanisms that do not involve spinal afferent systems, remain normal.[46, 81]

In view of the demonstrated importance of spinal pathways in the response to operation, it is not surprising that most investigators who have studied spinal anesthesia report that it reduces or prevents the adrenocortical response during the course of the operation,[34, 84, 103] however, an increase in adrenocortical secretion appears as the anesthetic wears off and transmission in spinal pathways returns to normal. It is also not surprising that an occasional patient shows increased hormonal levels during spinal anesthesia, because the mechanisms for response to emotional and other stimuli remain intact.

Even though the increase in ACTH secretion produced by burns and various major operations is blocked by interruption of neural pathways from the traumatized area, it is possible that, in some situations, chemical factors liberated from damaged tissue circulate via the blood stream to the head where they stimulate the hypothalamus or possibly, the pituitary itself to an increased production of ACTH. The question of the existence of such "wound hormones," discussed in considerable detail in the older literature, has recently been revived because of the report from two different laboratories that the secretion of 17-hydroxycorticoids in dogs is somewhat elevated after removal of the entire brain, except for the pituitary.[13, 106] Another group of investigators have reported that ACTH secretion is increased by laparotomy in rats in which all connections between the hypothalamus and the rest of the brain have been severed.[57] However, the meaning of these results in terms of normal function is still obscure, and at present, it cannot be said that the existence of any "wound hormone" has been proved.

Psychic Factors in Preoperative Patients

In view of the recognized effects on ACTH secretion of such emotional reactions as fear and apprehension, one might expect plasma unconjugated 17-hydroxycorticoid levels to be variably elevated on the day of operation before preanesthetic medication is given. Many investigators have reported such elevations.[22, 35, 79, 88] although they were not found in the studies of Hammond and his associates [34] and of Virtue *et al.*[103] It is not apparent why the patients in these latter two studies did not show the responses reported by others.

Effects of Preanesthetic Medication

Some of the drugs used for preanesthetic medication act on the neural mechanisms controlling ACTH secretion, to increase the output of this hormone, while others inhibit its secretion. Stimulatory effects are generally of little practical concern to the anesthesiologist or surgeon, but marked inhibition of ACTH secretion, and consequently of the adrenocortical response to injury, may have serious and even fatal consequences. Detailed studies of the effects of preanesthetic medication and anesthesia on adrenocortical function in man have been published by Hammond *et al.*[34] and by Virtue and his associates,[103] and this subject has been reviewed with emphasis on its practical implications by Vandam and Moore.[100]

Among the many drugs used for preanesthetic medication, morphine holds a unique position. When first injected, morphine causes a moderate increase in ACTH secretion in the rat, but prior administration of large doses of this drug inhibits the depletion of adrenal ascorbic acid produced by a variety of stressful stimuli.[66] This effect is prevented by nalorphine,[5] and is particularly marked when the morphine is given in combination with pentobarbital. It is generally stated on the basis of these and other experiments that morphine acts on the nervous system to block

stress-induced increases in ACTH secretion. However, there is currently considerable debate about the specificity of the "blocking" effect of morphine and the validity of adrenal ascorbic acid depletion as an index of adrenocortical secretion.[24, 25, 32, 91] The tranquilizing drugs, reserpine and chlorpromazine, also increase ACTH secretion when first injected, but inhibit the adrenal ascorbic acid depletion response to subsequent stressful stimuli. It is interesting in this regard that Montanari and Stockham [59] have recently reported that while a second dose of reserpine fails to deplete adrenal ascorbic acid, it does increase the circulating corticosterone level in the rat. The subject of "pharmacological blockade" of ACTH secretion is discussed in detail elsewhere in this symposium.[67]

In man, morphine apparently exerts a slight inhibitory effect on basal adrenocortical secretion,[58] but when given alone or in combination with a barbiturate and parasympatholytic agent in the doses usually employed for preanesthetic medication, it has no effect on plasma unconjugated 17-hydroxycorticoid levels and certainly does not significantly inhibit the adrenocortical response to surgery.[34, 103] Parasympatholytic agents by themselves, and barbiturates in subanesthetic doses, likewise have no inhibitory effect, although the sedatives may cause a slight decrease in resting blood hormone levels.[89]

Christy *et al.*[7] reported a diminished adrenocortical response to insulin hypoglycemia in chlorpromazine-treated patients; and Gold and his associates [28] found that chlorpromazine decreased the response to injections of metyrapone, although the response to operation was unaffected. However, Gold's data, and that of Sloane *et al.*[90] suggest that the inhibitory effects of chlorpromazine on adrenocortical responses in man are due to a moderately decreased adrenal sensitivity to ACTH, rather than inhibition of ACTH secretion. This decrease in adrenal sensitivity is apparently not severe enough to present any problem when surgical procedures are performed on chlorpromazine-treated patients, but when a patient has been receiving large doses of the drug for long periods of time, it might be wise to check his response to a test dose of ACTH before operation.

The effects of meperidine on adrenocortical function deserve further study. Bernis [4] reported that meperidine stimulated adrenocortical secretion, but his results have been criticized on the basis of methodology.[100] On the other hand, Han and Brown [35] found that anesthetic doses of meperidine supplemented by nitrous oxide inhibited the adrenocortical response to operation. In their patients, preoperative unconjugated 17-hydroxycorticoid levels were moderately elevated due to anxiety, but no further rise occurred during the course of surgery.

General Anesthesia

Ether anesthesia increases ACTH secretion in man,[34, 42, 50, 94, 100, 103] and its stimulatory effect in animals is so reproducible that it is used as a standard experimental stress. Cyclopropane has a similar but less marked effect. It has often been assumed that with these two anesthetics, ACTH is secreted in the excitement stage during induction, but Vandam [100] concluded that the magnitude of the adrenocortical response is directly proportional to the depth of anesthesia. Both agents probably increase the peripheral unconjugated 17-hydroxycorticoid levels by depressing hepatic and renal function, thus slowing the rate of removal of these hormones from the blood. Hypoxia complicating general anesthesia may increase ACTH discharge, but severe hypoxia decreases rather than increases the level of adrenocortical secretion,[6, 30] probably because it depresses the adrenocortical enzyme systems which are essential for biosynthesis of steroid.

The effects on adrenocortical function of thiopental anesthesia in man, and of pentobarbital anesthesia in animals have been studied in some detail. Thiopental does not stimulate ACTH secretion, and fails to exert any significant blocking effect on the response to operation.[34, 103] Anesthetic doses of pentobarbital have no effect on the level of adrenocortical secretion in the dog unless there is considerable excitement during induction.[49] It is often said that pentobarbital inhibits the pituitary-adrenal response to surgical procedures. There is some evidence that it decreases ACTH secretion in rats,[83] and subanesthetic doses lower plasma unconjugated 17-hydroxycorticoids to a slight degree in man.[89] How-

TABLE 3. 17-Hydroxycorticoid Output From the Right Adrenal Gland in Response to the Trauma of Adrenal Vein Cannulation in Normal Dogs

Anesthetic	17-Hydroxy-corticoid Output (μg/minute)	Number of dogs
Ether	6.9 ± 0.5	15
Pentobarbital (30 mg/kg.)	7.5 ± 0.8	12

ever, in the dog the output of 17-hydroxycorticoids produced by surgically exposing and cannulating the adrenal vein is just as great in pentobarbital anesthetized dogs as in those anesthetized with ether (table 3). The principal difference between the two types of anesthesia is that 17-hydroxycorticoid output remains elevated after operation as long as ether anesthesia is in effect, while there is a variable decline after surgical intervention in pentobarbital anesthetized dogs.[42] In the pentobarbital anesthetized dogs whose mean intraoperative value is shown in table 3, mean output three hours after the surgery was completed was 6.8 ± 0.7 μg/minute, and six hours after surgery was 4.2 ± 1.0 μg/minute.

Research stimulated by Selye's report [86] that certain steroid hormones have anesthetic effects led to the introduction of the steroid, 21-hydroxypregnanedione sodium succinate (hydroxydione) as a basal anesthetic. Because of its structural similarities to adrenocortical hormones, one might expect this compound to inhibit ACTH secretion, but Bernis [4] reported that it stimulates adrenocortical secretion, while others [51, 68] stated that it has no effect on the adrenal. Elliott stated that hydroxydione-induced changes in cerebral blood flow, oxygen uptake, and glucose uptake in man are similar to those induced by meperidine.[16]

Most authors found that spinal anesthesia exerts no stimulatory effect on the pituitary-adrenal system,[34, 41, 44, 103] and that, as noted above, there is little if any increase in adrenocortical secretion during surgical procedures carried out under this form of anesthesia. There is no reason for concern about the failure of 17-hydroxycorticoid levels to rise, however as the anesthetic wears off, adrenocortical secretion increases and there is an essentially normal adrenocortical response in the postoperative period.[34, 84, 100, 103]

A few comments about hypnosis seem in order because of the increasing use of this technique as an adjuvant to anesthesia, but there are no data on the effect of hypnosis on the adrenocortical response to operation. However, hypnotically-induced anxiety increases plasma unconjugated 17-hydroxycorticoid levels [78] as does anxiety in nonhypnotized subjects.[105] After an extensive review of other physiological functions in hypnotized subjects, Barber concluded that visceral and autonomic responses were probably altered no more by the hypnotic suggestion than by direct suggestion to nonhypnotized subjects.[1]

Hypothermia

The metabolic processes of the adrenal cortex, like those of other tissues, are depressed during hypothermia.[76] There still may be moderate increases in adrenocortical secretion following surgery when the rectal temperature is above 30° C., but when it falls below 28° C., the response to surgery is progressively reduced. Systemic blood pressure falls and adrenal blood flow decreases. There is no compensatory rise in adrenal venous hormonal concentration like that seen during hemorrhagic shock at normal body temperatures, and hormonal output falls to low levels.[23] In hypothermic animals the adrenal is unresponsive to injected ACTH, but the responsibility of the hypothalamic-pituitary system to stress is apparently also depressed because there is no detectable ACTH in the peripheral blood following operation.[45] However, in hypothermic dogs and man, the peripheral unconjugated 17-hydroxycorticoid levels are elevated during surgery because hepatic metabolism of the circulating glucocorticoids is inhibited to a marked degree.[3] Upon rewarming, there is a further increase in the circulating corticoid level, although the rise may not be quite as great as it is with extensive surgery at normal body temperatures.[3]

A Note on Adrenocortical Function in Shock

The problem of the relation between adrenocortical function, hypotension, and shock is one which has stimulated a great deal of discussion.

Comprehensive consideration of this subject would require a separate review, and only selected aspects of the problem can be considered here.

Adrenal blood flow decreases as systemic blood pressure falls, but except during hypothermia, there is a concomitant rise in the hormonal concentration in adrenal venous blood so that, over a wide range of blood pressures, hormonal output remains constant. There is, of course, a limit to this compensatory change, and when adrenal blood flow is less than 17 per cent of the control value, hormonal output can no longer be maintained.[20] However, renal and hepatic function [98] are depressed in shock, and the rate of metabolism of adrenal steroids is severely impaired. This is why, even in severe shock, peripheral 17-hydroxycorticoid levels are generally high.[21]

It should be emphasized that there is no good evidence that "adrenal exhaustion" occurs in man,[27, 60, 100] and patients who develop acute adrenal insufficiency during or after operation are those with pituitary or adrenal disease which usually has antedated surgery. They respond dramatically to the administration of steroids. On the other hand, as Vandam points out,[100] a few hypotensive patients with no demonstrable pituitary or adrenocortical deficiency appear to "do better" when given supplemental adrenocortical hormones. For this reason improvement following steroid therapy in patients who develop hypotension during surgery, or in the immediate postoperative period, is not diagnostic of adrenal insufficiency. Laboratory confirmation of the diagnosis is essential.

It has been recommended that when faced with an emergency in which adrenal insufficiency is suspected, a blood eosinophil count be performed, or that a blood smear be searched for eosinophils, on the theory that if the eosinophil count is low, adrenal insufficiency is not present. This procedure is unreliable because, as noted above, eosinopenia can occur in the absence of the adrenal glands. Of course, the physician will not be able to wait for a plasma unconjugated 17-hydroxycorticoid determination to be performed, and he must proceed on the basis of his tentative diagnosis to institute the indicated therapy. However, if a blood specimen for this measurement is drawn before steroids are administered, the level, when subsequently reported, provides an essential datum on which to base further definitive management.

References

1. Barber, T. H.: The physiological effects of hypnosis, Psychol. Bull. **58**: 390, 1961.
2. Berliner, D. L., and Daughaday, T. F.: Hepatic and extrahepatic regulation of corticosteroids, Pharmacol. Rev. **13**: 329, 1961.
3. Bernhard, W. F., McMurrey, J. D., Ganong, W. F., and Lennihan, R.: The effect of hypothermia on the peripheral serum levels of free 17-hydroxycorticosteroids in the dog and in man, Ann. Surg. **143**: 210, 1956.
4. Bernis, R., and Vanek, R.: L'elimination des corticoids urinaires rédacteurs "totaux" dans le stress chirurgical, Acta Anesth. Belg. **9**: 116, 1958.
5. Burdette, B. H., Leeman, S., and Munson, P. L.: The reversal by nalorphine of the inhibitory effect of morphine on the secretion of adrenocorticotrophic hormone in stress, J. Pharmacol. Exp. Ther. **132**: 323, 1961.
6. Castagnoli, N., Jr., Goldfein, A., and Ganong, W. F.: Release of adrenal steroids during asphyxia, Fed. Proc. **20**: 178, 1961.
7. Christy, N. P., Night, N., Longson, D., and Jailer, N. W.: Inhibitory effect of chlorpromazine upon the adrenal cortical response to insulin hypoglycemia in man, J. Clin. Invest. **36**: 543, 1957.
8. Cooper, C. E., and Nelson, D. H.: ACTH levels in plasma in preoperative and surgically stressed patients, J. Clin. Invest. **41**: 1599, 1962.
9. Daughaday, T. F.: Steroid protein interactions, Physiol. Rev. **39**: 885, 1959.
10. Davis, J. O., Ayers, C. R., and Carpenter, C. C. J.: The renin angiotensin system in the control of aldosterone secretion, Physiologist **4**: 27, 1961.
11. Doe, R. P., Zinneman, H. H., Flink, E. B., and Ulstrom, R. A.: Significance of the concentration of non-protein bound plasma cortisol in normal subjects. Cushing's syndrome, pregnancy, and during estrogen treatment, J. Clin. Endocr. **20**: 1484, 1960.
12. Egdahl, R. H.: Pituitary-adrenal response following trauma to the isolated leg, Surgery **46**: 9, 1959.
13. Egdahl, R. H.: Further studies on adrenal cortical function in dogs with isolated pituitaries, Endocrinology **71**: 926, 1962.
14. Eik-Nes, K. B., Sandberg, A. A., Nelson, D. H., Tyler, F. H., and Samuels, L. T.: Changes in plasma levels of 17-hydroxycorticoids during the intravenous administration of ACTH: a test of adrenocortical capacity in the human, J. Clin. Invest. **33**: 1702, 1954.

15. Eisenstein, A. B., Wenneker, A. S., and Londe, A. M.: Effect of spinal cord transection on adrenocortical function, Proc. Soc. Exp. Biol. Med. **109**: 947, 1962.
16. Elliott, H. W., Krueckel, B. F., and Sutherland, V. C.: In vitro effects of a steroid anesthetic on brain metabolism, *In* Hormones, Brain Function and Behavior, Hoagland, H., p. 55, 1957.
17. Fairlie, R. W., Barss, T. P., French, A. B., Jones, C. M., and Beecher, H. K.: Metabolic effects of anesthesia in man: comparison of the effects of certain anesthetic agents on normal liver, New Engl. J. Med. **244**: 615, 1951.
18. Forsham, P. H.: *In* Textbook of Endocrinology, Williams, R. H. (ed.), Philadelphia, W. B. Saunders Co., 1962, p. 307.
19. Fortier, C.: Adenohypophysis and the adrenal cortex, Ann. Rev. Physiol. **24**: 223, 1962.
20. Frank, H. A., Frank, E. D., Korman, H., Macchi, I. A., and Hechter, O.: Corticosteroid output and adrenal blood flow during hemorrhagic shock in the dog, Amer. J. Physiol. **182**: 24, 1955.
21. Franksson, C., Gemzell, C. A., and von Euler, U. S.: Cortical and medullary adrenal activity in surgical and allied conditions, J. Clin. Endocr. **14**: 608, 1954.
22. Franksson, C., and Gemzell, C. A.: Adrenocortical activity in the preoperative period, J. Clin. Endocr. **15**: 1069, 1955.
23. Ganong, W. F., Bernhard, W. F., and McMurrey, J.: The effect of hypothermia on the output of 17-hydroxycorticoids from the adrenal vein in the dog, Surgery **38**: 506, 1955.
24. Ganong, W. F., and Forsham, P. H.: Adenohypophysis and adrenal cortex, Ann. Rev. Physiol. **22**: 579, 1960.
25. Ganong, W. F.: *In* Physiology of Emotions, A. Simon (Ed.), Springfield, Ill., Charles C Thomas, 1961.
26. Ganong, W. F.: The central nervous system and the synthesis and release of ACTH, *In* Advances in Neuroendocrinology, A. Nalbandov (Ed.), Urbana, Ill., Univ. of Illinois Press, 1963.
27. Ganong, W. F.: *In* Review of Medical Physiology, Los Altos, Calif., Lange Medical Publications, 1963, (In press).
28. Gold, E. N., Di Raimondo, V. C., Kent, J. R., and Forsham, P. H.: Comparative effects of certain non-narcotic central nervous system analgesics and muscle relaxants on the pituitary adrenocortical system, Ann. N. Y. Acad. Sci. **86**: 178, 1960.
29. Goldfein, A., Zileli, M. S., Despointes, R. H., and Bethume, J. E.: The effect of hypoglycemia on the adrenal secretion of epinephrine and norepinephrine in the dog, Endocrinology **62**: 749, 1958.
30. Goldfien, A., and Ganong, W. F.: The effect of anoxia on adrenal cortical and medullary secretion in the dog, Proceedings of the 41st Meeting of the Endocrine Society, pp. 57, 1959.
31. Goldfien, A., and Ganong, W. F.: The adrenal medullary and adrenal cortical response to stimulation of the diencephalon, Amer. J. Physiol. **202**: 205, 1962.
32. Guillemin, R., Clayton, G. W., Smith, J. D., and Lipscomb, H. S.: Measurement of free corticosteroids in rat plasma: Physiological validation of a method, Endocrinology **63**: 349, 1958.
33. Habif, D. V., Papper, E. M., Fitzpatrick, H. F., Lowrance, P., Smythe, C. M., and Bradley, S. E.: Renal and hepatic blood flow, glomerular filtration rate, and urine output of electrolytes during cyclopropane, ether, and thiopental anesthesia, operation, and the immediate postoperative period, Surgery **30**: 241, 1951.
34. Hammond, W. G., Vandam, L. D., Davis, J. M., Carter, R. D., Ball, M. R., and Moore, F. D.: Studies in surgical endocrinology: anesthetic agents as stimuli to changes in corticosteroids and metabolism, Ann. Surg. **148**: 199, 1958.
35. Han, Y. H., and Brown, E. S.: Pituitary blockade by meperidine in man, ANESTHESIOLOGY **22**: 909, 1961.
36. Hardy, J. D., and Turner, M. D.: Hydrocortisone secretion in man: studies of adrenal vein blood, Surgery **42**: 194, 1957.
37. Hilton, J. G.: Adrenocorticotrophic action of antidiuretic hormone, Circulation **21**: 1038, 1960.
38. Hilton, J. G., Kruesi, O. R. Nedeljkovic, R. I., and Scian, L. F.: Adrenocortical and medullary response to adenosine 3′–5′ monophosphate, Endocrinology **68**: 908, 1961.
39. Hodges, J. R., and Vernikos, J.: The effect of hydrocortisone on the level of corticotrophin in the blood and pituitary gland of adrenalectomized and of stressed adrenalectomized rats, J. Physiol. **150**: 683, 1960.
40. Holzbauer, M., and Vogt, M.: Functional changes produced in the adrenal cortex of the rat by administration or by the release of corticotrophin, J. Physiol. **138**: 449, 1957.
41. Hume, D. M., and Wittenstein, G. J.: The relationship of the hypothalamus to pituitary adrenocortical function, Proceedings of the First Clinical ACTH Conference, Philadelphia, The Blakiston Co., 1950, p. 134.
42. Hume, D. M.: The secretion of epinephrine, nor-epinephrine, and corticosteroids in the adrenal venous blood of the dog following single and repeated trauma, Surg. Forum **8**: 111, 1957.
43. Hume, D. M.: The method of hypothalamic regulation of pituitary and adrenal secretion in response to trauma, *In* Curri, S. and Martini, L. (Eds.), Springer-Verlag, Vienna, Pathophysiologica Diencephalica, 1958.

44. Hume, D. M., and Bell, C. C.: Secretion of epinephrine, norepinephrine, and corticosteroid in adrenal venous blood of the human, Surg. Forum **9**: 6, 1959.
45. Hume, D. M., and Egdahl, R. H.: Effect of hypothermia and of cold exposure on adrenocortical and medullary secretion, Ann. N. Y. Acad. Sci. **80**: 435, 1959.
46. Hume, D. M., Bell, C. C., and Bartter, F.: Direct measurement of adrenal secretion during operative trauma and convalescence, Surgery **52**: 174, 1962.
47. Jessiman, A. G., Matson, D. D., and Moore, F. D.: Hypophysectomy in the treatment of breast cancer, New Engl. J. Med. **261**: 1199, 1959.
48. Jones, K. M., Lloyd-Jones, R., Riondel, A., Tait, J. F., Tait, S. A. S., Bulbrook, R. D., and Greenwood, F. D.: Aldosterone secretion and metabolism in normal men and women, and in pregnancy, Acta Endocr. (Kbh) **30**: 321, 1959.
49. Kaada, B. R., Setekleiv, J., and Skang, O. E.: Effects of barbiturates and nitrous oxide on level of 17-OH-steroids and eosinophil cells in cat, Acta Pharmacol. (Kobenhavn) **16**: 87, 1959.
50. Klein, R., Papdatos, C., Fortunato, J., and Byers, C.: Acid-hydrolyzable corticoids of serum, J. Clin. Endocr. **15**: 215, 1955.
51. Laubach, G. D., P'an, S. Y., and Rudel, H. W.: Steroid anesthetic agent, Science **122**: 78, 1955.
52. Liddle, G. W. Island, D., Lance, E. M., and Harris, A. P.: Alterations of adrenal steroid patterns in man resulting from treatment with a chemical inhibitor of 11-hydroxylation, J. Clin. Endocr. **18**: 906, 1958.
53. Liddle, G. W., Island, D., and Meador, C. K.: Normal and abnormal regulation of corticotrophin secretion in man, *In* Rec. Prog. Horm. Res., G. Pincus (Ed.), XVIII, 125, New York, Academic Press, 1962.
54. Lipscomb, H., and Nelson, D. H.: Measurement of corticosterone in rat adrenal venous plasma as a bioassay for ACTH, Fed. Proc. Proc. **18**: 95, 1959.
55. Llaurado, J. G.: Aldosterone secretion following hypophysectomy in man: relation to urinary sodium/potassium ratio, Metabolism **6**: 556, 1957.
56. Magoun, H. W.: The Waking Brain, Springfield, Ill., Charles C Thomas, 1958.
57. Matsuda, K., Kendell, J. W., Duyck, C., and Greer, M. A.: ACTH secretion in the decerebrate rat, Proceedings of the 44th meeting of the Endocrine Society, 1962, p. 20.
58. McDonald, R. K., Evans, F. T., Weise, V. K., and Patrick, R. W.: Effect of morphine and nalorphine on plasma hydrocortisone levels in man, J. Pharmacol. Exp. Ther. **125**: 241, 1959.
59. Montanari, R., and Stockham, M. A.: Effects of single and repeated doses of reserpine on the secretion of adrenocorticotrophic hormone, Brit. J. Pharmacol. **18**: 337, 1962.
60. Moore, F. D., Steenburg, R. W., Ball, M. R., Wilson, G. M., and Myrden, T. H.: Studies in surgical endocrinology, Ann. Surg. **141**: 145, 1955.
61. Moore, F.: Metabolism in the Post-traumatic State, New York, Grune & Stratton, 1960.
62. Mulrow, P. J., and Ganong, W. F.: Stimulation of aldosterone secretion by angiotensin II. A preliminary report, Yale J. Biol. Med. **33**: 386, 1961.
63. Mulrow, P. J., and Ganong, W. F.: The effect of hemorrhage on aldosterone secretion in normal and hypophysectomized dogs, J. Clin. Invest. **40**: 579, 1961.
64. Mulrow, P. J., Ganong, W. F., Cera, G., and Kuljian, A.: The nature of the aldosterone stimulating factor in dog kidneys, J. Clin. Invest. **41**: 505, 1962.
65. Mulrow, P. J., and Ganong, W. F.: The role of the kidney and the reninangiotensin system in the response of aldosterone secretion to hemorrhage, Circulation **25**: 213, 1962.
66. Munson, P. L.: Pharmacological control of the secretion of ACTH, Biochem. Pharmacol. **8**: 25, 1961.
67. Way, E. L., and Sutherland, V. C.: Pharmacologically active brain substances and their relation to endocrine effects, ANESTHESIOLOGY **24**: 543, 1963.
68. Murphy, F. J., Guadagni, N. P., and DeBon, F.: Use of steroid anesthesia in surgery, J. A. M. A. **158**: 1412, 1955.
69. Nalbandov, A. (Ed.): Recent Advances in Neuroendocrinology, Urbana, Ill., University of Illinois Press, 1963.
70. Nauta, W. J. H.: Limbic system and hypothalamus: anatomical aspects, Physiol. Rev. **40** (Suppl. 4): 102, 1961.
71. Nelson, D. H., Sandberg, A. A., Palmer, J. G., and Glenn, E. M.: Levels of 17-hydroxycorticoids following intravenous infusion of epinephrine in normal men, J Clin. Endocr. **12**: 936, 1952.
72. Nelson, D. H., and Hume, D. M.: Corticosteroid secretion in the adrenal venous blood of the hypophysectomized dog as an assay for ACTH, Endocrinology **57**: 184, 1955.
73. Nelson, D. H.: Adrenocortical secretion and factors affecting that secretion, *In:* Stress, Selye, H., and Heuser, G. (Eds.), New York, M. D. Publications, 1956.
74. Nelson, D. H.: Present status of the problem of iatrogenic adrenocortical insufficiency, ANESTHESIOLOGY **24**: 457, 1963.
75. Osborn, W., Schoenberg, H. M., Murphy, J. J., Erdman, W. J., and Young, D.: Adrenal function in patients with lesions high in the spinal cord, J. Urol. **88**: 1, 1962.
76. Parkes, A. S. (Ed.): Hypothermia and the effects of cold, Brit. Med. Bull. **17**: January, 1961.

77. Perkoff, G. T., Eik-Nes, K., Nugent, C. A., Fred, H. L., Nimer, R. A., Rush, L., Sanuels, L. T., and Tyler, F. H.: The diurnal variation of plasma 17-OHCS in man, J. Clin. Endocr. **19**: 432, 1959.
78. Persky, H., Grosz, H. J., Norton, J. A., and McMurtry, M.: Effect of hypnotically-induced anxiety on plasma hydrocortisone level of normal subjects, J. Clin. Endocr. **19**: 700, 1959.
79. Price, D. B., Thaler, M., and Mason, J. W.: Preoperative emotional states and adrenal cortical activity, A. M. A. Arch. Neurol. **77**: 646, 1957.
80. Ramey, E. R., and Goldstein, M. S.: Adrenal cortex and the sympathetic-nervous system, Physiol. Rev. **37**: 155, 1957.
81. Redgate, E. S.: Spinal cord and ACTH release in adrenalectomized rats following electrical stimulation, Endocrinology **70**: 263, 1962.
82. Rosenfeld, G.: Stimulative effect of acetylcholine on the adrenocortical function of isolated perfused calf adrenals, Amer. J. Physiol. **183**: 272, 1955.
83. Royce, P. C., and Sayers, G.: Blood ACTH: effects of ether, pentobarbital, epinephrine and pain, Endocrinology **63**: 794, 1958.
84. Sandberg, A. A., Eik-Nes, K., Samuels, L. T., and Tyler, F. H.: The effects of surgery on the blood levels and metabolism of 17-hydroxycorticosteroids in man, J. Clin. Invest. **33**: 1509, 1954.
85. Sayers, G., and Royce, P. C.: Regulation of the secretory activity of the adrenal cortex, *In:* Clinical Endocrinology I, E. G. Astwood (Ed.), New York, Grune & Stratton, 1960.
86. Selye, H.: Anesthetic effect of steroid hormones, Proc. Soc. Exp. Biol. Med. **46**: 116, 1941.
87. Shackman, R., Grober, I. G., and Melrose, D.: Liver blood flow and general anesthesia, Clin. Sci. **12**: 307, 1953.
88. Shannon, I. L., Szmyd, L., and Prigmore, J. R.: Stress in dental patients, USAF School of Aerospace Medicine, 62–59: 4P, April, 1962.
89. Siker, E. S., Lipschitz, E., and Klein, R.: The effect of preanesthetic medications on the blood level of 17-hydroxycorticosteroids, Ann. Surg. **143**: 89, 1956.
90. Sloane, R. B., Saffran, M., and Cleghorn, R. A.: Steroid response to ACTH and the effect of ateractic drugs, *In:* Psychoendocrinology, M. Reiss (Ed.), New York, Grune & Stratton, 1958.
91. Slusher, M. A.: Dissociation of adrenal ascorbic acid and corticosterone responses to stress in rats with hypothalamic lesions, Endocrinology **63**: 412, 1958.
92. Steenburg, R. W., and Ganong, W. F.: Observations on the influence of extra-adrenal factors on 17-hydroxycorticoids in the surgically-stressed adrenalectomized animal, Surgery **38**: 92, 1955.
93. Steenburg, R. W., Smith, L. L., and Moore, F. D.: Conjugated 17-hydroxycorticosteroids in plasma: methods and significance in relation to surgical trauma, J. Clin. Endocr. **21**: 39, 1961.
94. Suzuki, T., Yamashita, K., and Mitamura, T.: Effect of ether anesthesia on 17-hydroxycorticosteroid secretion in dogs, Amer. J. Physiol. **197**: 1261, 1959.
95. Szentágothai, J., Flerko, Be., Mess, B., and Halász, B.: Hypothalamic control of the anterior pituitary, Budapest, Akadémiai Kiadó (English Ed.), 1962.
96. Thorn, G. W.: The Diagnosis and Treatment of Adrenal Insufficiency, ed. 2., Springfield, Ill., Charles C Thomas, 1951.
97. Thorn, G. W.: The eosinophil, ACTH, epinephrine and stress, Amer. J. Med. **14**: 139, 1953.
98. Tyler, F. H., Schmidt, C. D., Eik-Nes, K., Brown, H., and Samuels, L. T.: The role of the liver and the adrenal in producing elevated plasma 17-hydroxycorticosteroid levels in surgery, J. Clin. Invest. **33**: 1517, 1954.
99. Ulick, S., Laragh, J. H., and Lieberman, S.: The isolation of a urinary metabolite of aldosterone and its use to measure the rate of secretion of aldosterone by the adrenal cortex of man, Trans. Ass. Amer. Phys. **71**: 225, 1958.
100. Vandam, L. D., and Moore, F. D.: Adrenocortical mechanisms related to anesthesia, ANESTHESIOLOGY **21**: 531, 1960.
101. Venning, E. H., Dyrenfurth, I., and Beck, J. C.: The effect of anxiety upon aldosterone secretion in man, J. Clin. Endocr. **18**: 1005, 1957.
102. Vernikos-Danellis, J., and Marks, B. H.: Epinephrine-induced release of ACTH in normal human subjects: a test of pituitary function, Endocrinology **70**: 525, 1962.
103. Virtue, R. W., Helmreich, M. L., and Gainza, E.: The adrenal cortical response to surgery, the effect of anesthesia on plasma 17-hydroxycorticosteroid levels, Surgery **41**: 549, 1957.
104. von Euler, U. S.: Nor-adrenaline: chemical, physiological, pharmacological, and clinical aspects, Springfield, Ill., Charles C Thomas, 1956.
105. von Euler, U. S., Gemzell, C. A., Lennart, L., and Ström, G.: Cortical and medullary adrenal activity in emotional stress, Acta Endocr. **30**: 567, 1959.
106. Wise, B. L., Pont, M., and Ganong, W. F.: Failure of hind-brain removal to depress ACTH secretion in dogs with isolated pituitaries, Fed. Proc. **21**(2): 196, 1962.
107. Yates, F. E. and Urquhart, J.: Control of plasma concentrations of adrenocortical hormones, Physiol. Rev. **42**: 359, 1962.