ADRENOCORTICAL MECHANISMS RELATED TO ANESTHESIA

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As recently as twenty years ago any discussion of the relationship between the surgical experience of which anesthesia is a part and the adrenal cortex would have been highly speculative. Such lack of information in what is now a fruitful field of investigation represents a long interval from the time of Addison's\(^1\) description in 1855 of adrenal cortical failure and Brown-Séquard's\(^2\) demonstration of the vital necessity of the adrenal gland. It took time to establish the reality of the ancient belief in body humors, the final barrier having been broken at the beginning of the century with the investigation of the pharmacological properties and synthesis of epinephrine. Perhaps it was the more spectacular nature of the medullary hormone which for 25 years concealed from research eyes the more subtle actions of the cortex. Then once again the uniformly fatal disease recognized by Addison led to the employment of adrenal extracts in therapy and in 1933\(^3\) the first successful recovery from a major operation in a patient with Addison's disease was reported.

Soon there was a growing recognition of a pervading syndrome in surgical patients. A common pattern of response to trauma embracing alterations in body water, salt and nitrogen, began to emerge. In 1943-Albright\(^4\) likened the post-traumatic state to that of Cushing's disease. World War II emphasized the need for the study of trauma and investigations suggested a relationship between the urinary excretion of ketosteroids of adrenal origin and the metabolic changes noted above.\(^5\) Selye\(^6\) correlated many observations of endocrine change into an all-inclusive theory of stress and the response to it which he called the general adaptation syndrome. This broad concept had been anticipated by the outstanding investigators in their eras, among them Beaumont, Pavlov, Claude Bernard, and Cannon.\(^7\)

Anesthetists long have been concerned over the problem of anesthetic care for the patient with possible adrenal insufficiency.\(^8\)-\(^14\) Further interest in the adrenals has been aroused by the increasing number of operations on the endocrine glands, among them adrenalectomy and hypophysectomy. While adrenal cortical function in relation to anesthesia has received some recognition, greater attention has been paid to the adrenal medulla and sympathetic nervous system.\(^15\)-\(^18\) Here the more obvious adrenergic action has compelled attention. Cannon's principles of homeostasis\(^19\) are hardly more evident in any area than in the responses to anesthetic drugs. The relationship between anesthesitess and the sympathetic-medullary system will not be discussed at length in this paper, save to refer to the interaction of the catechol amines and adrenal cortical hormones.*

Elucidation of the physiology of the adrenal cortex has come from laboratories of medicine and from investigations of the patient's response to operation or trauma. It must be emphasized that the use of anesthetic drugs is only one component of the surgical experience and that any effect of anesthetics upon adrenal function can only be additive to all other events associated with operation. Yet it is important to learn what anesthetics per se will do. Anesthesia may affect adrenal function and adrenal function may influence the course of anesthesia. This is the perspective from which a review of anesthetics and adrenal function must be approached.

* It has been of great interest that a steroid related in structure to the adrenal cortical hormones has been tested as an anesthetic agent.\(^20\) Though experience with this steroid indicates that there is much to be desired, it is a promising start in the search for anesthetic substances which may not share the disadvantages of the commonly used hydrocarbons.
PHYSIOLOGY OF THE ADRENAL CORTEX

To comprehend how anesthetics may affect adrenal cortical secretion it is necessary to review current concepts of cortical action.† The adrenocortical processes as we understand them in man are based to a large extent on observations of adrenal disorders, studies in normal volunteers, in vitro study of human adrenal tissue, and interpolation of information gathered from experiments in other species.

In the normally functioning adrenal cortex there is a continuous biosynthesis of steroids of which more than 28 individual substances have been recognized.22 The production of steroids as investigated by adrenal perfusion with C14-labeled products depends largely upon cholesterol as a precursor with intrinsic synthesis hinging upon enzymatic activity and pantothentic acid, triphosphopyridine and ascorbic acid as possible cofactors. How corticotrophin of the anterior pituitary gland acts as the major regulator of cortical secretion has not yet been clarified.23 Neurogenic regulation of secretion is not deemed necessary to explain the facts. Adrenal exhaustion as a possible aftermath of anesthesia or prolonged illness and trauma often has been postulated but never demonstrated in the normal gland.24 On the contrary, prolonged or repeated stimulation results in continued secretion of cortical hormones with resultant cortical hypertrophy. The response of the cortex to stress in the aged is no less than that in the young.25 but the total excretion of 17-ketosteroids may be less in the aged or infirm because of the diminished output of androgens.

The hormones secreted by the cortex are of three general types: glucocorticoids, mineralocorticoids, and the sex hormones. This is rather an arbitrary classification since the hormones in each group share some of the physiological effects of the others. There are major species differences in the quantities of the individual corticoids secreted.26 In the glucocorticoid group in man, Compound F or 17-hydroxy cortisol (Cortisol) is the chief substance and Compound B or corticosterone quantitatively next in importance.27 28 These substances are active in intermediary carbohydrate and protein metabolism. Absence of the glucocorticoids leads to failure of interconversion of food stuffs with the result that the Addisonian develops hypoglycemia and cannot long survive starvation. The increased secretion of hormones found in cortical hyperplasia often results in hyperglycemia and glycosuria. Although hydrocortisone is commonly employed to treat arterial hypotension and vascular collapse there is no hint in the actions mentioned thus far of a specific action on the vasculature. Yet hydrocortisone will elevate the blood pressure in adrenal insufficiency and produce increased vasomotion in mesenteric vessels.29 As suggested later in the discussion of hormonal interactions, an appropriate electrolyte concentration in the vascular cells seems to be necessary for a satisfactory pressor response either spontaneously or following the use of pressor agents. The glucocorticoids have some effect on sodium and potassium exchange but these electrolytes are largely under mineralocorticoid control. Of the latter aldosterone is most important 30 and deoxycorticosterone less significant in daily regulation. From an anesthetic viewpoint little need be said of the androgens other than to point out that they are of little importance in survival following stress.

The presence of the anterior pituitary gland and release of adrenocorticotropic hormone are necessary for glucocorticoid and sex hormone production. Aldosterone, on the contrary, seems to be largely independent of pituitary influence.20 22 The cortex loses its ability to respond to ACTH and atrophies some time after hypophysectomy. However, the zona glomerulosa does not atrophy following hypophysectomy, and electrolyte metabolism is not disturbed as much as after adrenalectomy. Decreases in the effective circulating extracellular fluid and blood volume, the general level of sodium in the body, increases in potassium, and decreases in the Na/K ratio seem to be the regulating factors in aldosterone secretion.30 31 32

Corticotrophin or ACTH is a poly peptide available for therapy in the form of a purified powder obtained from the pituitary gland of domestic animals. Potency is expressed in terms of biological units based on the effect
on the adrenal cortex in animal assay. At one time the in vivo assay of ACTH secretion depended upon observations of depletion of ascorbic acid or of cholesterol in the adrenal cortex of the hypophysectomized rat. The specificity and quantitative relationship of ascorbic acid depletion to cortical secretion have not been established. Nelson and Hume have assayed ACTH by measurement of the output of corticoids in the adrenal vein of the acutely hypophysectomized dog. With this method it has been found that secretion of ACTH occurs rapidly after stress, within 15 seconds of stimulation, suggesting a neurogenic rather than a humoral mechanism of release. The activity of ACTH lasts but a short time, probably due to its rapid removal from the circulation. Extremely small quantities are effective in cortical stimulation and the daily secretion, with a diurnal variation higher in the morning, is responsible for the output of approximately 15 to 50 mg. of hydrocortisone daily. The output of ACTH is lowest in the newborn but of equal magnitude in children and adults, including the aged. Recently another method for the determination of ACTH in serum has been described using the production of Compound B from the adrenal gland of the hypophysectomized rat as an index. With this technique ACTH has been readily demonstrated in normal human serum, and found to vary between 0.3 and 0.7 millinits/100 ml. serum.

From the standpoint of interpretation of anesthetic effects on the cortex the means by which adrenal cortical function is measured must be made known. Assay techniques for ACTH have already been discussed and there are bioassay, physicochemical and isotope tracer techniques for aldosterone. Adrenal cortical function can be measured in a number of ways, most of these in reality also indirectly determine the activity of ACTH. Early investigators approached the problem by measurement of the total urinary output of steroids, which included not only the androgens but conjugated compounds which had lost biological activity. As an over-all indication of cortical function in a certain time period this is a useful method. Fractionation of steroids and methods of greater specificity now permit the quantitative assay of 17-hydroxycorticoids in urine. A suggested simple means of detecting adrenocortical insufficiency has been the simultaneous determination of serum and urinary sodium concentrations. This test is not specific and suffers from the defect that nephritis among other abnormalities may produce increased urinary levels of sodium. In peripheral blood the eosinophil cell count has been employed with the development of eosinopenia as a sign of increased cortical activity. Following stress a blood smear showing no eosinophils is the normal finding. A smear with eosinophils is abnormal and a resting eosinophil count above 300 is suggestive of Addison's disease or of an allergic reaction, whereas a count below 50 suggests adrenal activation. In a very strict sense the response of eosinophils to an intravenous injection of ACTH provides a gross index of cortical responsiveness. This has been the basis of a commonly employed clinical test. As an evidence of a satisfactory cortical response to stress, however, eosinopenia is a nonspecific reaction which may occur in the adrenalectomized animal in response to the injection of epinephrine alone, and under other circumstances. Eosinopenia, therefore, should not be interpreted as a quantitative index of cortical activity and of hydrocortisone secretion.

The Porter-Silber reaction as applied to urine is a colorimetric reaction specific for 17-hydroxycorticoids, either free or conjugated. Nelson and Samuels and others have adapted this reaction to the measurement of the circulating levels of free 17-hydroxycorticoids in circulating blood. The value of these techniques resides in the fact that the biologically active concentration of hormone affecting the tissues may be determined. Recently, attention has been drawn to the fact that even the "free" or unconjugated steroids may not all be physiologically active since in normal individuals the major fraction is bound to a protein with an extremely high affinity. This protein, labeled transcortin, binds approximately 20 gamma per cent leaving as little as one gamma in the truly "free" state. The blood concentrations of corticoids found are a reflection not only of cortical secretion but of the rapidity of conjugation, urinary excretion rate, and perhaps of tissue utilization (fig. 1). The miscible pool, turnover rate, and ultimate
fate of the corticoids have been observed by following the course of C\textsuperscript{14}-labeled cortisone and hydroxycortisone.\textsuperscript{54-56} Studies of hydrocortisone metabolism indicate that conjugation is due to an enzyme formed in the liver.\textsuperscript{57-60} Excretion of the corticoids is dependent upon normal renal function.\textsuperscript{52, 61} Since the peripheral blood level of unconjugated hydrocortisone is influenced by so many factors, the estimation of corticoid output in the adrenal venous blood is a much more direct method of detecting secretory levels.\textsuperscript{62-67} This technique has proved feasible in animals and man with the accumulation of worthwhile quantitative data under various circumstances.

Having discussed the peripheral hormonal structure, it now remains to treat of those factors that influence ACTH secretion. A dogmatic presentation should not belie the fact that one is dealing with theories which at any time may be modified in the light of new evidence. All experiments, however, favor the hypothesis that the hypothalamus plays the dominant role in ACTH release.\textsuperscript{68, 69} Destruction of the median eminence\textsuperscript{70, 71} prevents the response to stress, while direct stimulation of this same area increases the output of ACTH. Experimental evidence suggests that the hypothalamic centers may be stimulated either reflexly or directly. These matters are of importance in elucidating the mechanism whereby general anesthetics act as stimulants to the output of adrenal corticoids. Hume\textsuperscript{65, 69} has outlined the neurogenic pathways which mediate the stress response in experimental peripheral trauma. An intact peripheral nervous system is necessary. Selection of the spinal cord in dogs at the sixth to eighth thoracic level also blocks the response to trauma, further evidence of the neurogenic factor in thalamic activation. A humoral substance from damaged peripheral tissue acting on the hypothalamus was once thought to be the factor in the cortical response to major trauma or burns, but this theory has not been substantiated.\textsuperscript{68}

The output of ACTH is thought to be due to the release of a humoral substance from the hypothalamus carried over the portal system of blood vessels which surround the pituitary stalk.\textsuperscript{68, 69, 72, 73} Whether the responsible humor is epinephrine, acetylcholine, or vaso-
pressin has not been established. Recent work suggests that a small polypeptide, labeled CRF for corticotropin releasing factor, is responsible for the transmission of the stimulating effect received in the hypothalamic area and signaled to the pituitary to release ACTH. Section of the pituitary stalk with the surrounding portal vessels obviates the response to stress but does not result in adrenal atrophy. Transplantation of the pituitary gland to the anterior chamber of the eye produces survival of the hypophysis and maintains the adrenal cortex, but the latter does not respond to stress. Epinephrine has been considered to be a stimulus to ACTH production, an observation based upon the development of eosinopenia and depletion of ascorbic acid in the cortex. While epinephrine may be synergistic with ACTH, it alone is not a factor in cortical secretion.

As a final consideration in this section the manner whereby exogenously administered adrenal products depress the output of corticoids and lead to cortical atrophy is an important one for anesthetists. Sayers advanced the concept that the circulating levels of corticoids in peripheral blood regulate the output of ACTH. In short, tissue utilization with subsequent lowering of peripheral blood concentrations could provide the stimulus for the further secretion of ACTH. Increased concentrations of corticoids would reduce the secretion of adrenocorticotropic. This theory has been questioned by several observations, the chief of which has been the demonstration that prolonged elevated levels of corticoids in peripheral blood do not lessen the continued response to stress. If there be any inhibition of ACTH by circulating concentrations of corticoids this probably takes place at the hypothalamic level. More recently the suggestion has been advanced that the level of ACTH per se influences the output of additional corticotropin. The important practical fact arising from this information is that exogenous or increased endogenous sources of corticoids in some manner obviate the need for ACTH secretion which then results in lack of responsiveness and eventual atrophy of the adrenal cortex. Cortisone has been found to depress the uptake of oxygen, inhibit glycolysis and depress the content of corticotrophin in the isolated anterior lobe of the pituitary. Within one to two minutes of the administration of hydrocortisone to the intact animal the release of ACTH may be inhibited. Treatment with cortisone may result in cortical atrophy as severe as that following hypophysectomy, and withdrawal of steroids may be followed by adrenal crisis. The duration of treatment rather than the total dose of steroid administered seems to be the major factor in residual cortical depression. During steroid therapy the simultaneous administration of ACTH may maintain adrenal cortical responsiveness, but this in no way minimizes the hypothalamic or pituitary inhibition which may be the more serious problem. In cortical therapy alternation of larger doses with periods of respite has been suggested as a means to avoid depression but this technique requires further study. It has not been determined how long it may take for recovery of adrenal function after cessation of therapy. It is often said that a period of three weeks is sufficient. In any case, however, the knowledge that a patient has received steroids should raise the possibility of adrenal deficiency.

THE EFFECTS OF ANESTHETICS UPON ADRENAL CORTICAL FUNCTION

Having reviewed fact and theory of adrenal cortical function one may now turn to the effect of anesthesia upon this process. Such information is important for the researcher who would distinguish anesthetic effect from experimental result in adrenal studies. The surgeon may wish to know which anesthesia is best for states of adrenal dysfunction. The anesthetist shares the surgeon's viewpoint and seeks to harmonize the effects of anesthetics with adrenal activity. Many questions will remain unanswered. Is heightened adrenal activity deleterious? Will this add to the composite burden of metabolic change in the chemically sick patient? Is cortical function as important as that of the sympathetic nervous system in homeostasis? Should the adrenal response be eliminated deliberately and, may adrenal insufficiency develop during the course of operation?

Few pure studies of anesthetic action on adrenal cortical function have been reported,
those of Virtue\textsuperscript{81} and Hammond\textsuperscript{82} being almost alone in this respect. Dissection of the anesthetic experience in terms of preoperative emotional tension, effect of preanesthetic medication, role of anesthetic agent versus technique, depth of narcosis in general anesthesia and degree of nervous interruption in spinal anesthesia, have been attempted as a complete study in only one paper.\textsuperscript{85} But there are many isolated studies of these various facets. A natural tendency for the clinician to apply newly devised tests of adrenal cortical function to the study of anesthetics has frequently resulted in failure to consider some of the pitfalls in method. For example, reports of circulating concentrations of 17-hydroxy-corticoids may fail to declare normal laboratory variations, neglect the factor of diurnal variation or fail to take into the account the effect of anesthetics on hepatic\textsuperscript{82, 84} and renal function\textsuperscript{85} in the interpretation of elevated concentrations of corticoids. In other instances the development of eosinopenia has been interpreted as an infallible sign of increased cortical activity.\textsuperscript{86, 87} Most commonly the effect of anesthetics has not been considered apart from the trauma of operation, although this approach must be considered a realistic one from the standpoint of the entire operative experience.

Preoperative anxiety is not a major stimulus to adrenal cortical secretion, though some papers\textsuperscript{85, 86} suggest that emotional upset may activate the pituitary-adrenal-cortical system. Roehe\textsuperscript{89} employing the eosinophil count found varying degrees of eosinopenia during the immediate preoperative period, while Hammond\textsuperscript{82} detected occasional eosinopenia but no changes in circulating levels of corticoids. The eosinopenic effect might easily have been due to sympathetic stimulation since the preoperative patient exhibits so many signs of adrenergic activity. Franksson\textsuperscript{91} found minor elevations in circulating 17-hydroxycorticoids prior to operation.

Preanesthetic medication may result in definite cortical change especially if morphine or the barbiturates are employed. Morphine may block the release of ACTH at the hypothalamic level.\textsuperscript{92} The effects of barbiturates are uniformly depressive to cortical activity with the locus of action not settled. More will be said of the barbiturates in the ensuing discussion. Bernis\textsuperscript{92} reported a stimulating effect of hydroxydione in urinary excretion studies of corticoid production during surgery. In general it seems safe to conclude that the role of small quantities of preanesthetic medication is not a very significant one in the assessment of the adrenal cortical response to anesthesia.

In all species studied the short acting barbiturates, with pentobarbital the chief compound investigated, are the least active stimulants to the cortex. The longer acting barbiturates have not been investigated to any great extent. Studies of peripheral blood levels\textsuperscript{84, 85, 86} (fig. 2) and adrenal vein secretory levels of corticoids\textsuperscript{87} during barbiturate anesthesia substantiate the general impression of the depressant characteristics of these drugs probably at the hypothalamic level.\textsuperscript{89} Failure to detect an increase in the output of adrenal venous corticoids after the injection of ACTH suggests that the barbiturates may inhibit enzymatic synthesis of adrenal products. Ronzoni\textsuperscript{86} found that barbiturate anesthesia in rats failed to stimulate the adrenal cortex and prevented ascorbic acid depletion after stress. The stress response to cold has been blocked by these drugs.\textsuperscript{87, 89} Excitement during induction of anesthesia in the cat with pentobarbital and allobarbital led to increases in circulating corticoids and to eosinopenia.\textsuperscript{88} When the barbiturates have been employed in balanced techniques of anesthesia as in the thiopental, nitrous oxide, relaxant sequence, rises in peripheral and adrenal venous levels of 17-hydroxycorticoids were not observed.\textsuperscript{81, 83, 89}

Upon the experimental background that activation by trauma of the hypothalamic-pituitary axis is prevented by peripheral de-nervation\textsuperscript{85, 86} it was to be expected that local and block anesthesia might decrease the cortical response to operation. Local anesthetic injection \textit{per se} causes no increase in cortical activity.\textsuperscript{82} Almost all reports of the effect of spinal anesthesia on adrenal activity utilizing peripheral blood levels of corticoids (fig. 3), eosinopenic responses and urinary excretion of corticoids indicate that adequate spinal anesthesia is an effective means of preventing adrenal cortical stimulation.\textsuperscript{81, 82, 85} Similar
findings have been reported in the one case of epidural anesthesia studied. When the effect of the nerve block has dissipated the adrenal cortical response to surgery becomes quite apparent. In those cases wherein a rise in circulating corticoids has been detected during spinal anesthesia either anesthesia had not attained a sufficient level or the rises in blood concentrations of corticoids were not very significant. In the interpretation of these results it must be remembered that spinal anesthesia also blocks the response of the sympathoadrenal system in ratio to the height of anesthesia. The absence of cortical effect should be interpreted in this light. The fact that the blocking effect is a transient one lasting only during the time of operation raises the question of the value of employing this technique to block the cortical response to the surgical procedure. With this limitation, spinal or block anesthesia may be a good choice for patients with adrenal cortical hyperactivity such as cortical hyperplasia, adenoma, or Cushing's disease which require adrenalectomy, or states of sympathetic overactivity such as thyrotoxicosis and pheochromocytoma.

Diethyl ether and cyclopropane to a lesser extent have been shown to stimulate the cortex probably in direct ratio to the depth of narcosis.
and possibly in relation to the stress of induction and emergence. Ether has been studied the most, cyclopropane to a lesser extent and the other general anesthetics little or not at all to our knowledge. Peripheral blood and adrenal venous levels of corticoids during ether anesthesia have been significantly elevated in most studies 67, 81, 82, 102, 104 (fig. 4). When the stimulatory effects have not been prominent, the preoperative use of barbiturates, induction with thiopental, or light levels of narcosis may have accounted for the lesser effects.92 The well-known attribute of ether in stimulating the sympathetic-medullary system 15, 16, 18, 105 again provides a background for interpretation of the cortical effects. In the analysis of the elevation in blood levels of circulating 17-hydroxycorticoids, the effect of general anesthesia, particularly of ether and cyclopropane on hepatic and renal function, must be considered. A decreased rate of conjugation during ether anesthesia has been noted but denied by others. Decrease in the urinary output of corticoids due to diminished renal blood flow is a distinct possibility. If it can be said that spinal anesthesia is the better choice of anesthesia for patients with sympathetic or adrenal or cortical hyperactivity then ether should be avoided on similar theoretical grounds. Clinical experience, however, does not suggest any adverse effects from the use of ether in the presence of thyrotoxicosis or for adrenal surgery.9

As a conclusion to this section the work of Virtue 81 and Hammond 92 in studies of anesthetized volunteers and anesthesia studied before operation again must be cited. Results of their studies have been inserted in the previous discussion. Hammond studied emotional responses, preanesthetic medication, local anesthesia, spinal, ether, cyclopropane, and thiopental anesthesia under uncomplicated circumstances measuring circulatory and urinary concentrations of corticoids, eosinophil responses and the metabolic reaction in the form of sodium, potassium, chloride and

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**Fig. 3.** Effect of spinal anesthesia on circulating blood level of free 17-hydroxycorticoids. During a bilateral inguinal herniorrhaphy there is no rise in steroid in the blood. When the anesthesia wears off there is a residual tendency to rise. (Reproduced with permission from Moore, F. D.: Metabolic Care of the Surgical Patient, Philadelphia, W. B. Saunders & Company, 1959.)
nitrogen balance. Despite the obvious cortical stimulating effect of ether and to a lesser extent that of cyclopropane the only metabolic change noted as a result of anesthesia alone was a tendency toward sodium retention in several cases of ether anesthesia. Whether this was secondary to the cortical response, or secondary to the effect of anesthesia on renal blood flow could not be determined in those experiments.

**A Consideration of Anesthetic Techniques That Block Adrenal Cortical Activity**

Although the adrenal cortical response seems to be a major one only in the case of ether anesthesia, and the accompanying metabolic alteration minor consisting for the most part of sodium retention, the over-all response to operation is marked by a more sustained adrenal effect. Whether coincidental or the result of corticoid influence salt and water retention and potassium and nitrogen loss take place in proportion to the magnitude of the surgical trauma. If there were any reason to decrease adrenal cortical activity deliberately it might be found in the hope of preventing these metabolic changes in the already ill patient who was to undergo surgery. An example of such a case is the patient with mitral stenosis in heart failure, already burdened with extra water and salt. Additional salt and water retention would add to the circulatory load and the loss of potassium complicate management of failure with the digitalis and similar preparations. If mitral valvuloplasty or some operation were contemplated it might be reasoned that here would be the need for the least stressful of anesthetic agents even though the period of anesthesia were short. It has already been noted that local or spinal anesthesia and the barbiturates fulfill this goal. This they seem to do without elimination of the basal level of corticoid production necessary for homeostasis during operation and a satisfactory response afterwards.

Hypothermic techniques of anesthesia block the adrenal response to stress with the additional virtue of diminished metabolic activity.
Khalil discussed the depressant effect of hypothermia on the hypothalamic-pituitary response to stress. Bernhard and Swan found no further change during operation in peripheral serum levels of 17-hydroxycorticoids in the dog and man during hypothermia. Egdahl, in dogs and Hume, in man, employing adrenal vein catheterization found unchanged concentrations of corticoids but a decrease in blood flow which led to a total decrease in output during hypothermia. Those animals which had been anesthetized with pentobarbital and stressed by the surgical procedure of catheterization of the adrenal vein failed to respond to maximal stimulating doses of ACTH indicating that the adrenal cortex had been depressed by cold. After rewarming adrenal cortical responses returned to the control levels. In order to prove that decreased blood flow per se was not responsible for this effect of hypothermia hemorrhagic shock was induced in another group of animals and the consequent decrease in adrenal blood flow was found to be associated with a heightened output of corticoids. Barlow found unchanged levels of peripheral blood corticoids during hypothermia but retention of responsiveness to ACTH. The differences in these experimental results may in part be explained by anesthetic agent employed, the presence or absence of surgical trauma, and the degree of cooling. In any case the decrease in metabolic activity during hypothermia has been considered to retard the enzymatic processes active in adrenal hormonal synthesis.

Other substances may block the response to stress. Although the phenothiazine group of drugs, especially when employed in combination with barbiturates and narcotics in the technique of artificial hibernation are said to minimize stress and prevent irreversible shock, few quantitative data on their effects have been reported. Most of the reports appear in the foreign literature. Bernis using the total daily urinary output of reducing corticoids as an index of activity during operation found evidence of stimulation after the use of Diparol and meperidine, and little change when Thiopan, a ganglionic blocker, was employed. The least change occurred following the use of neuroplegic agents. But these studies were deficient in many respects and the results with ether anesthesia entirely at variance with other work. Christy observed an inhibitory effect of chlorpromazine upon the adrenal cortical response to insulin hypoglycemia in man. Harwood found an elevation in circulatory corticoids after the administration of chlorpromazine to monkeys. Aron noted that hypothermia added to the pituitary suppression produced by chlorpromazine and that chlorpromazine prevented the release of ACTH after stress.

In clinical medicine amphetamine has been employed to suppress the secretion of 17-hydroxycorticosterone in the treatment of hyperfunctional adrenal states. The output of aldosterone is likewise suppressed. Another drug with a similar depressant effect is di-chloroethane. Whether there is a place for these compounds in anesthesia and surgery remains to be seen.

Hormonal Interrelationships

It is irrational to treat of adrenal cortical function alone without establishing the essential facts of hormonal interaction. Full comprehension of cortical action is only possible, though not made easier, by a consideration of this matter. Nor is it convincing enough merely to point out that in addition to the cortex other endocrine glands are under the trophic influence of the anterior pituitary or that alterations in the function of the hypophysis, anterior and posterior pituitary, gonads, thyroid, pancreas, adrenal cortex and medulla are common features in the recovery from injury or operation. Perhaps Addison's graphic description of adrenal failure will help initially to make clarification of this problem easier: "The leading and characteristical features of this morbid state to which I would draw attention are anaemia, general languor and debility, remarkable feebleness of the heart's action, irritability of the stomach, and a peculiar change of colour in the skin, occurring in connection with a diseased condition of the supra-adrenal capsules." Other features, not stated, are poor tolerance for fasting, low blood sugar concentration, difficulty in retaining salt, poor tolerance to with-
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...drawal of salt, and difficulty or delay in the excretion of water. It is difficult to define the exact areas of action of the corticoids and in a specific case to explain why the administration of 17-hydroxycorticosterone may restore blood pressure to normal in certain states of hypotension. The parallel between the concept of the permissive nature of the adrenal corticoids and the established homeostatic activity of the sympathetic-medullary system is evident and suggests a relationship between the two. Special note, therefore, must be made of the fact that all hormonal interactions those of the cortex and medulla are most intimate.

Ramey and Goldstein have reviewed the various aspects of adrenal cortical and sympathetic activity. There is some confusion in comparing experimental data from adrenalectomized, sympathectomized, demedullated or decorticate preparations. While the emergency role of the sympathetic system is a recognized one, the sympathectomized animal does not fare well even during ordinary existence. Adrenalectomy further narrows the range of adaptation and results in a greater intolerance to stressful situations. However, the actions of the cortex and medulla are not interchangeable: epinephrine or norepinephrine alone will not restore the blood pressure in adrenal cortical insufficiency nor will the corticoids prevent postural hypotension in the completely sympathectomized preparation. There is, nevertheless, a recent report in man of the successful treatment with fluorohydrocortisone of orthostatic hypotension resulting from a disturbance in the release of norepinephrine at sympathetic nerve endings. Although the blood pressure could be maintained with infusions of norepinephrine alone other synthetic pressor amines were ineffective.

Ramey and Goldstein suggest that the cortex and sympathetic nervous system are permissive for mutual interaction. In the absence of the adrenal steroids the thresholds for action of norepinephrine and epinephrine are elevated. A clinical counterpart of this experimental finding may be found in the treatment of the hypotensive patient who does not respond to infusions of pressor drugs alone but who reacts satisfactorily with the added administration of steroids. This response does not prove that there is either medullary or cortical insufficiency and raises the possibility that the environment of the vasculature may be faulty. In experiments on the reaction of the blood vessels in the rat mesappendix Goldstein showed that the inability of adrenalectomized animals to adjust to environmental stress is a consequence of impaired vascular responses to stimulation from constrictor neurohormones of the sympathetic nervous system. Vascular collapse is in part due to this deranged response of minute blood vessels. When the appropriate cortical steroids are present, however, the response of the vascular apparatus to both endogenous autonomic humors and exogenous administration is restored to normal. Agents such as atropine, methanetheline, and Dibenamine, which block the autonomic nervous system at various points, protect these animals against stress. This is one of the experimental bases for the suggested use of ganglionic blocking agents or of chlorpromazine in the treatment of hemorrhage and shock. Zweifach, a pioneer in the study of the reactivity of minute blood vessels in the mesappendix of the rat, likewise pointed out that all four properties of the terminal vascular bed, intrinsic tone, reactivity, vasomotion, and vasoconstriction require the presence of the adrenal cortex. Von Euler, who has contributed much to the understanding of neurohumoral function, also found that lack of adrenal corticoids may exert an unfavorable effect on the vasoconstrictive system and that cortisone and ACTH potentiate the effects of norepinephrine. The objection to the conclusions suggested by these experiments resides chiefly in the applicability of studies on the rat mesappendix to problems in man. But there are enough clinical counterparts to suggest that the analogy holds.

The electrolyte environment of peripheral blood vessels is another factor of importance in the interaction of hormones on the vasculature. Mention has been made of the effect of adrenal steroids on water and salt metabolism, and Nickel has discussed the role of adrenal medullary hormones in sodium, potassium, and water exchange. Raab, a frequent contributor to this field, has reviewed the subject of the interaction on vascular cells of catechol amines, corticoids and electrolytes.
Aleksandrow studied the influence of chlorothiazide through its effect on sodium and potassium on the responsiveness of hypertensive subjects to the pressor effect of nor-epinephrine. A satisfactory response seemed to relate in part to the sodium content of vascular cells. On good experimental evidence the suggestion was made that pressor activity per se may be mediated through cationic shifts, perhaps as a result of reciprocal changes in sodium and potassium.

The greater part of this section has been devoted to a discussion of the interaction of cortex and medulla and electrolytes in the control of blood pressure through peripheral mechanisms. The same hormonal and chemical relationships apply to the maintenance of satisfactory myocardial contractility. The subsequent discussion on postoperative adrenal insufficiency and hypotension will employ these facts as a basis for discussion. Other hormonal responses to stress involving the thyroid and the posterior pituitary gland will not be discussed at length. In regard to the thyroid activity it has been observed that the basal metabolic rate may be increased after trauma. Goldenberg has reported a series of experiments which suggest participation of thyroid hormone in the pattern of postoperative reaction. Increases in plasma levels of thyroxine, increased utilization of this hormone, and a reciprocal relationship between the adrenal cortex and the thyroid have been documented. Hydovitz found no change in protein-bound iodine during thyroid surgery under ether anesthesia. Thyroidal responses to anesthesia and operation must not be overlooked but the effects at most seem to be minor. As a final consideration in the area of hormonal interrelationships, intraoperative and postoperative antidiuresis must be viewed not only in relation to anesthetic effects on renal function but in the general interplay of the posterior pituitary, adrenal medullary and cortical effects on water and salt exchange.

Postoperative Adrenal Insufficiency

Before the era of clinical investigation it was known that the Addisonian could be precipitated into adrenal crisis by acute infection, hemorrhage, operation or other trauma. Such crisis was characterized mainly by arterial hypotension and tachycardia terminating in shock and death. Today, with the increasing performance of adrenalectomy and partial lobectomy and the nonspecific therapeutic use of adrenal steroids which may result in complete or partial loss of adrenal reserve, the likelihood of encountering adrenal crisis after anesthesia and operation is enhanced and deaths have been reported. Concern over this problem is witnessed by the large volume of reports of postoperative hypotension which have been attributed to adrenal cortical insufficiency. Only a few of these papers can be cited in this review. The fact that many hypotensive patients have had satisfactory responses to the administration of large doses of corticoids along with other measures has been interpreted as establishing the diagnosis of cortical failure with no proof other than the response to therapy. It is of front-rank importance in this area to distinguish between a favorable response to a large pharmacologic dose of steroid and that to a small replacement dose in time of insufficiency. Many cases that might be considered as superficially resembling adrenal insufficiency have recovered after the correction of reduced blood volume, the use of pressor drugs, administration of sodium chloride and potassium, or the correction of disturbances in acid-base balance. It is clear that the usual case of postoperative hypotension is not the result of adrenal insufficiency. It is also true that actual adrenal insufficiency will respond transiently to saline and blood; the diagnosis is not always easy (see below). Adrenal failure after trauma has rarely been documented. Had there been the opportunity to make measurements of adrenal cortical function many cases of postoperative hypotension probably would have shown high peripheral blood concentrations of corticoids. It seems logical then to conclude that an excess of corticoids was necessary for recovery just as an extra amount of pressor substances was required.

It should be noted that adrenal cortical function has never been found to be seriously compromised in experimental shock. The reverse has often been observed along with an increased activity of the sympathetic nervous
system.\textsuperscript{47, 158} Hume\textsuperscript{157} in a comparison of the adrenal vein output of corticoids in hypothermia and hemorrhagic shock found a reduced blood flow in both but an increased concentration of corticoids in shock which resulted in an unchanged or augmented output. However, Frank\textsuperscript{158} was unable to document a sustained output of corticoids in the adrenal venous blood in hemorrhagic shock if the blood flow fell below a certain level. In other experiments the administration of cortical substances has failed to prolong survival or prevent development of irreversible hemorrhagic shock.\textsuperscript{159-161} Irreversibility then seems not to be related to adrenal cortical insufficiency. Occasional experiments reporting benefit from cortical replacement therapy relate to other types of shock and the beneficial result in some cases may be due to correction of water and salt disturbances.\textsuperscript{162}

Thorn\textsuperscript{162} has reviewed the current status of treatment of adrenal disorders. In addition to those individuals who have received steroids, adrenal insufficiency should be suspected in patients on anticoagulant therapy (because of the possibility of adrenal hemorrhage), patients with the clinical stigmata of Addison's disease (weakness, gastrointestinal symptoms, and unusual pigmentation), those with amyloid disease or disseminated tuberculosis, cases of long standing gastrointestinal disease, cases of sepsis (of which the Waterhouse-Friderichsen syndrome\textsuperscript{164} is the most virulent form) and lastly patients with chronic salt losing nephritis.\textsuperscript{121}

Types of Adrenal Insufficiency: Despite the many theoretic endocrinologic aspects of adrenal function relative to the problems of surgery and anesthesia, there are only two types of clinical situations that face the surgeon or the anesthetist. As he in turn faces the patient, he finds a problem in therapeutic adrenal hormone dosage. At the time of crisis—or even before a time of crisis—the anesthetist and the surgeon themselves may not know the endocrine status of the adrenal glands. Therefore, the two situations may be described as follows:

(1) Cortisone Therapy. This is the more common problem. The patient has been on cortisone therapy either for the disease for which he is going to be operated upon, for some other disease, or as replacement for previous adrenal insufficiency. Well-documented adrenal insufficiency is relatively infrequent and although the maintenance dose level of cortisone in this condition is lower than the therapeutic level for most diseases, the problem has many things in common with the much more frequent situation of long-term nonspecific cortisone treatment.

(2) Clinical Crisis Resembling Adrenal Insufficiency. This is the problem around which the controversy turns. How does one make the diagnosis of adrenal insufficiency during the period of crisis, hypotension, fever, or oliguria? Under what circumstances is one justified in giving cortisone therapy without a precise diagnosis?

The remaining section of this review will deal briefly with the two categories mentioned above.

Cortisone Therapy: As pointed out in the foregoing sections of this review, the adrenal cortex is driven both as to structural integrity and functional endocrine activity by ACTH. The principal action of cortisone on the adrenal glands themselves is traceable to its effect in inhibiting the production of ACTH. The administration of ACTH itself also inhibits the production of ACTH but produces a well-developed rather than an atrophic adrenal gland. The cortisone-like substances that have been developed by the pharmaceutical industry all share the property of inhibiting the anterior pituitary gland.

No one knows precisely how long the patient must be on cortisone therapy before significant pituitary inhibition is produced; likewise it is not known how long after discontinuance of cortisone therapy adrenal function can be assumed to be normal. Therefore, arbitrary rules on both these scores must be made pending more precise quantitative information; one must define safe maximum and minimum limits of treatment, lacking either the time or the opportunity to study each patient.

A safe general rule is that any patient who has been on cortisone for four days or longer may be considered to have subnormal adrenocortical function; any patient who has been on cortisone therapy within the past six months may also be considered to have such inhibi-
tion. It is immediately apparent that this rule is a very broad one, intentionally conservative to avoid disaster.

In such patients the rule for management during operation is to provide by therapeutic administration a blood steroid level that mimics the normal response to trauma. This can be done by giving hydrocortisone intravenously at the rate of 100 mg. every eight hours on the day of operation, reducing this gradually over the next several days, gradually adding ACTH and then tapering both to cessation. Under no circumstances should cortisone therapy be stopped in a surgical patient without giving ACTH to cover the last two or three days by means of adrenal stimulation.

If the patient has been on cortisone for a protracted period, the length of time that ACTH is to be given to restore adrenal function is appropriately longer and quantitative study of hormone excretion in the urine or concentration in the blood is advisable. Several interesting facets of replacement therapy are briefly listed below.

(1) If the patient is on cortisone therapy and starts to bleed from an ulcer, cortisone must temporarily be continued or even increased to cover the needs of the additional stress imposed by the gastrointestinal hemorrhage. Though superficially this may appear illogical, it is quite essential since the hemorrhage and tendency to develop shock will be rapidly fatal if adrenal support is withdrawn.

(2) By the same token, any patient on steroid therapy should be protected against peptic ulcer activation. The most dangerous form of steroid therapy is that given by mouth. Some sort of antacid regimen must accompany this.

(3) If the patient has been on steroids by mouth for a long time, he must be assured of an adequate intramuscular or intravenous dose of steroid several hours prior to induction of anesthesia. Oral steroids are very rapidly active but transiently, and it is dangerous to stop treatment just before anesthesia is begun. The actual dose level of steroid maintenance prior to the operation must be viewed realistically in relation to the operative needs. For example, a patient with true adrenal insufficiency treated with cortisone at a rate of 25-75 mg. per day, will require only twice this much to weather elective operation smoothly. In sharp contrast, the patient who has been on very high doses of steroids (300-500 mg. a day for example) for many months appears to achieve a "tissue habituation" to large steroid levels and needs much larger amounts of steroid (800-1,000 mg.) on the day of operation.

(4) The administration of steroids over a period of six months to a year in some patients may result in almost complete disappearance of the adrenal glands themselves. In others this does not occur. There is evidence to suggest that intermittency of corticosteroid administration spares adrenal structure. By this is meant that an occasional day (for example, two or three days a week) without steroid administration results in enough endogenous ACTH production to maintain more normal adrenal structure. When this is not done and high-dosage steroid therapy is given for a very prolonged period, the adrenal gland may become so atrophic that even the zona glomerulosa disappears and aldosterone or salt-retaining activity is likewise lost. Therefore, in patients who have been on very high doses of corticosteroids for prolonged periods of time, desoxycorticosterone acetate or other mineralocorticoid equivalent must be supplied.

ADRENAL THERAPY IN TIMES OF CRISIS: The above situations are fairly straightforward problems of endocrine therapy that can be analyzed in terms of known concentrations, known dose levels and known physiologic effects of hormone.

By sharp contrast are those situations in which a patient is critically ill, usually in a situation suggesting some aspect of "shock" and in whom the possibility of corticosteroid therapy is to be considered.

In approaching such a patient, it is well to bear in mind a general rule that has emerged from our observation of many such cases. It is this: that if a shock-like state emerges in the course of a fairly trivial or at least uneventful surgical operation, it is much more likely to be due to adrenal insufficiency than is a state of shock emerging after a very major or difficult operation, one involving infection, blood loss, respiratory insufficiency, renal insufficiency, or any other of the major physiological
and metabolic crises that attend surgery. In the latter situation, hypotension may be due to so many different things that the diagnosis of adrenal insufficiency necessarily is much less likely.

Despite this general rule, one must approach the patient in either category with a logical procedural sequence that may be drawn somewhat as follows:

1. Rule out as best as one can the common anatomic and physiologic causes for refractory hypotension, with or without fever, in the surgical patient. These include:
   - Unreplaced blood loss
   - Pulmonary embolus
   - Coronary occlusion
   - Continuing acute hemorrhage
   - Unrecognized or untreated sepsis
   - Pneumothorax
   - Mediastinal emphysema
   - Upper respiratory obstruction
   - Atelectasis
   - Massive collapse of the lung
   - Acute pancreatitis
   - Pelvic cellulitis
   - Endocarditis
   - Cerebrovascular accident

2. Measure the patient's venous pressure. This achieves three important objectives. First, it rules out the occasional instance of hemopericardium, pericardial tamponade, coronary occlusion or congestive heart failure as the primary cause of the patient's hypotension; second it provides a baseline against which transfusion may be carried out in liberal quantities; and thirdly, it sets the stage for replacement of blood volume to an end point of elevated venous pressure, to be followed later if necessary by phlebotomy. This latter, seemingly paradoxical course, is by far to be preferred than to a continuance of unrestored volume deficit.

3. The following indices are needed when the cause of hypotension and/or fever remains unidentified. A blood smear should be prepared and a search made for eosinophils. If there are no eosinophils whatsoever present in the smear, the likelihood of true adrenal insufficiency diminishes almost to the vanishing point. A pharmacologic need for supernormal dosage of cortisone is still possible but is statistically very small in all reported series.

4. A baseline blood sample is then taken for subsequent analysis for steroids. Urine collections are begun.

5. The patient is then ready for the start of corticosteroid therapy. If eosinophils have been detected in such a situation with shock and/or fever adrenal insufficiency is a likely possibility; in any event blind therapy may logically be started. Hydrocortisone is started at an initial dose of 100 mg. intravenously with an initial maintenance dose of 300 mg. a day, given continuously and intravenously, and with the concept that this will be discontinued within 48 hours unless the clinical results are dramatic.

6. As mentioned in the previous discussion it has been shown in man and animals that the effects of vasopressors are potentiated by corticosteroids and vice versa. For this reason, if hypotension is not immediately responsive to corticosteroid therapy, a small dose of vasopressor drug may logically be added to the infusion.

Once having started corticosteroid therapy in such a patient, it is incumbent upon the surgeon and the anesthetist immediately to consider further plans for steroid therapy. These fall into two sharply contrasting groups as follows:

a. If there is an immediate and favorable response to combined therapy, it should be continued with suitable anti-ulcer medication such as can be taken by an acutely ill patient. Steroids should be tapered off at the end of five to seven days, with appropriate endocrine studies of the blood and urine conducted either by the surgical laboratory or the medical or endocrinologic service. An immediate and dramatic restoration of blood pressure by corticosteroid therapy is in itself strongly suggestive of some underlying endocrine abnormality. The later treatment of the patient should of course be governed by the nature of this abnormality. In our experience over a twelve-year period we have uncovered only three patients in more than 60,000 operations, who have had actual continuing adrenal insufficiency.
(b) If the blood pressure maintenance effect of the combination of steroid and pressor drug is disappointing and not clear-cut, they should be discontinued as soon as possible and a very rigorous search for other causes of continuing hypotension should be carried out. The commonest causes for this continuing hypotension have in our experience been found in the above list of diagnostic possibilities. Particular emphasis must be laid on the presence of infection. All groups who have been interested in the problem have reported occasional patients with sepsis and shock in whom corticosteroid therapy combined with antibiotics has given good results. In such instances a very loose diagnosis of "endotoxin shock" has been made; this diagnosis is virtually meaningless since there is no way of identifying endotoxin in peripheral blood at the present time. The implication of such a diagnosis is merely that the patient's illness is due to an interaction between an antigenic endotoxin and the patient's blood or tissues and that this toxic interaction is abated or obviated by corticosteroids.

It was mentioned above that in a patient who started to bleed while on corticosteroid therapy, the steroid must paradoxically be increased at least for the duration of the critical period. An analogy may be found in a patient with sepsis. Increasing difficulty in controlling sepsis has often been reported during corticosteroid therapy. Nonetheless, when corticosteroid therapy is given, because of hypotension due to sepsis, one is justified in continuing steroids providing that the antibiotic therapy is rigidly controlled and intensively and aggressively employed.

**ADRENAL INSUFFICIENCY, APPARENT OR REAL?** Finally, for the sake of emphasis, a brief word about the diagnosis of adrenal insufficiency! One finds articles in the literature suggesting that a favorable response to adrenal therapy is equivalent to a diagnosis of adrenal insufficiency. This fallacy must be rooted out of the medical mind if we are to avoid a population of postoperative patients maintained on steroids for a lifetime. There is a wide spectrum of diseases that respond favorably to steroid therapy without any hint of adrenal insufficiency. These include arthritis, dermatitis, emphysema, asthma, certain diseases of the eye, colitis, enteritis, and hepatitis. The favorable response to large doses of steroids in these diseases is due to a variety of mechanisms, some of which previously have been discussed in this review. Certain aspects of illness after trauma may also partake of the nonspecific inflammatory and antigen-antibody characteristics underlying several of the diseases that respond to corticosteroids. But this is not tantamount to a diagnosis of adrenal insufficiency.

If one finds a patient who does respond favorably to corticosteroids, then, as mentioned above, it is incumbent upon the physician to diagnose precisely the status of adrenal function so that the future and continuing management of this patient may be based on endocrine reality rather than imaginary diagnostic criteria.

**SUMMARY**

Knowledge of the relationship between the adrenal cortical hormones and operation of which anesthesia is a part is of comparatively recent origin. Although anesthetists have been concerned about adrenal cortical insufficiency, more attention and study have been devoted to the adrenal medulla and the sympathetic nervous system. Investigation of the cortical response to trauma and operation have contributed much to the understanding of anesthetic effects. The medulla and the cortex are closely related in activity, and it has become apparent that anesthetics affect adrenal function and that adrenal hormones influence the course of anesthesia. To understand the problem, current concepts of adrenal cortical physiology have been reviewed with a description of the nature of the cortical hormones, the manner of their secretion and metabolism, methods of assay, and the relation to the hypothalamic-pituitary axis. Particular attention has been paid to the process by which therapeutically administered steroids affect endogenous cortical secretion.

The effects of anesthetics on adrenal cortical activity have been reviewed. Since some anesthetics stimulate and others depress cortical function, the implications of these effects were discussed. It is suggested that anesthetic techniques which do not stimulate or even diminish cortical secretion may be of value in certain instances wherein the metabolic response to
trauma adds a considerable burden to the already ill patient.

The later sections of this review approach the important subject of the relation of the cortical hormones to the circulation. Here it was necessary to establish the facts of medullary cortical interaction and the role of electrolytes in the responsiveness both of the peripheral vasculature and the myocardium. Other endocrine factors were noted.

Finally the problem of postoperative adrenal insufficiency has been treated at length. It was pointed out that true insufficiency is a rare event and that postoperative hypotension responding favorably to steroids does not connote adrenal failure. Two situations that face the surgeon and anesthetist are those involving cortisone therapy and the clinical crisis that resembles adrenal insufficiency. Suggestions for diagnosis, treatment and investigation of both these problems have been made.

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TRILENE IN OBSTETRICS Trichloroethylene anesthesia was given to 10,000 consecutive obstetric patients for vaginal delivery with no maternal mortality. It was administered by members of the regular obstetric nursing staff, not anesthetists. Breathing and crying times of infants were less delayed with trichloroethylene anesthesia than with cyclopropane anesthesia. The perinatal mortality was slightly lower in the group of infants delivered with trichloroethylene than among those delivered with other gas anesthetics. Five hundred consecutive electrocardiograms were taken, with one tracing during the first stage labor, one during trichloroethylene anesthesia, and one after delivery. Cardiac arrhythmias were found during about 25 per cent of trichloroethylene anesthetics. Labor itself has associated with it a surprising number of cardiac arrhythmias. Precautions necessary for a safe trichloroethylene obstetric anesthetic are good premedication, 5 minutes allowed for induction, and temporary removal of the mask if breathing becomes rapid or irregular. (Thierstein, S. T., and others: Trichloroethylene Anesthesia in Obstetrics, Obst. & Gynec. 15: 560 (May) 1960.)