RELATION BETWEEN THE ADRENAL CORTEX AND THE CENTRAL NERVOUS SYSTEM[1]

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[1] Original investigations reported herein were supported in part by a research grant (B-381) from the National Institute of Neurological Diseases and Blindness, National Institutes of Health, and from the USAF (contract No. AF 18(600)-921, monitored by the USAF School of Aviation Medicine, Randolph Field, Texas).

[2] The author wishes to acknowledge his special indebtedness to Dr. Louis S. Goodman who has provided advice, encouragement, and much help in the preparation of this review. The secretarial assistance of Lou Ann Robinson and Wildene Lund is gratefully acknowledged.

INTRODUCTION

It is the purpose of this review to summarize the available literature on the interrelationship of the adrenocortical hormones and the central nervous system. Limited aspects of this subject have been reviewed by Ramey and Goldstein (421), Glaser (181, 182), Cleghorn (72, 74, 75, 78), Hoagland (258, 259), Quarton *et al.* (419), and Woodbury (605, 616). Homeostatic regulation in the body is controlled by the nervous system and the endocrine system. Much research has been devoted to the physiology, biochemistry, and pharmacology of these two systems separately, but not to their interrelations. Since each system is subject to the regulatory influence of the other, it is evident that the nervous system must influence the endocrine system and *vice versa*.

With regard to the effects of the adrenocortical steroids on the nervous system, this review will include not only the effects produced by exogenously administered hormones, but also the effects of the endogenous hormones either released by the injection of adrenocorticotrophic hormone (ACTH) or by stimuli (drugs, cold, *etc.*) which cause release of endogenous ACTH, or secreted in the naturally occurring diseases of adrenocortical hyperfunction in man. The second major segment of the review will be concerned with the influence of alterations in central nervous system function on the activity of the adenohypophyseal-adrenocortical system.

Before beginning a detailed discussion of the interrelation of the adrenal cortex and the nervous system, it is pertinent to summarize quite briefly the general physiological effects of the adrenocortical hormones and the theories of the regulation of their secretion. For further details the interested reader is referred to the article by Thorn *et al.* (542) which contains a complete summary of the pharmacology and the physiology of the adrenocortical steroids. The adrenal cortex secretes three general types of steroids. The first type, characterized by cortisone and cortisol, is concerned mainly with regulation of metabolism of carbohydrate, protein, and fat. The second type, characterized by aldosterone and desoxycorticosterone, is concerned mainly with regulation of electrolytes.

The third type, probably represented by steroids such as 11-β-hydroxy-Δ^4-androstene-3,17-dione, is concerned with androgenic function. Steroids such as corticosterone and dehydrocorticosterone affect both carbohydrate and electrolyte metabolism.

The adrenocortical steroids (with the exception of aldosterone) are secreted in response to ACTH, released from the adenohypophysis or exogenously administered. One of the problems facing the adrenal physiologist is the mechanism by which ACTH is liberated from the pituitary gland. This subject has been reviewed by several authors (225–230, 333, 415) and only limited aspects will be discussed here. Three theories of regulation of ACTH release have developed, and there is evidence for and against each. The *cortical hormone titer theory* (467, 469, 533) states that a decrease in blood adrenocortical steroid titer acts as a stimulus for accelerated discharge of ACTH from the adenohypophysis; such a decrease in titer occurs when the rate of tissue utilization of adrenocortical steroids increases in response to exposure of the organism to a stressful stimulus. The *central neural mechanism theory* (226–229) emphasizes the importance of the hypothalamus in regulating ACTH release. Activation of certain hypothalamic nuclei by direct stimulation, by drugs, or by stressful stimuli causes release of a neurohumor which is transmitted by way of the hypothalamic-hypophyseal portal system to the adenohypophysis where it causes discharge of ACTH. The nature of the neurohumor(s) has not been established with certainty. The *epinephrine theory* (178, 333, 356) postulates that a stressful stimulus initiates the following chain of events: 1) hypothalamic stimulation; 2) transmission of sympathetic nerve impulses from the hypothalamus to release epinephrine from the adrenal medulla; 3) humoral transmission of epinephrine to the adenohypophysis; and 4) direct action of epinephrine on adenohypophyseal cells to release ACTH. Only the central neural mechanism theory will be discussed in this review (Section IV); but it would appear, in summary, as stated by Sydnor and Sayers (533) that ". . . available evidence suggests that regulation of ACTH involves both a humoral mechanism (blood-titer of adrenocortical hormone) and a neural mechanism (hypothalamus). The relative importance of these two has not been established; the nature and the duration of the PAS (*pituitary-adrenal system*) stimulus may determine the extent to which one mechanism is called into play as compared to the other. The immediate acceleration in ACTH release which follows application of a stressful stimulus may be called forth by the neural mechanism, the subsequent rate of discharge may be regulated by the titer of adrenocorticosteroids."

I. EARLY HISTORY

Ever since Addison in 1855 (4) first described the clinical manifestations of adrenocortical insufficiency, it has become increasingly evident that the adrenocortical hormones exert a profound influence on the functions of the central nervous system. Several of the cases reported by Addison exhibited neurological and psychological symptoms, including depression, anxiety, vocal weakness, delirium, "mind-wandering", *etc.* Thus Addison was aware of the characteristic

psychological and neurological alterations which occur in adrenocortical insufficiency.

In a study of 35 cases of Addison's disease, Greenhow [quoted by Cleghorn (72)], in 1875, described the terminal delirium which occurred in some of his patients and the localized neurological symptoms which developed in others. In 1899, Klippel (301) reported a case of adrenocortical insufficiency characterized by attacks of delirium and epileptic convulsions followed by coma. He ascribed this condition to cellular changes in the brain, particularly of the cerebellum, that were found *post mortem*, and described it as a diffuse encephalitis. Klippel also recorded psychic depression and decreased mental effort in some of his patients. At this same time Dufour and Roques de Fursac (117) reported that an extract of the adrenal cortex was effective in treating a woman with neurasthenia and asthenia (non-Addisonian) for a period of 20 months.[3] In addition, Brissaud, in the discussion following the paper by Dufour and Roques de Fursac, observed that extracts of the adrenal cortex were effective in treatment of the encephalopathy occurring in a patient with Addison's disease. Thus, at the beginning of the twentieth century, many of the characteristic mental and neurological changes which occur in Addison's disease were known and their treatment by adrenal cortical extract was appreciated. In addition, the treatment of neurasthenia by such extracts had been tested. With this information as a background and realizing the importance of endocrine glands in relation to the nervous system, Phillips (401) stated, "Internal secretion in its relation to nervous and mental diseases has not, until quite recently, been considered seriously or received the attention it deserves by those who are investigating the pathology of mental disorders." He described a patient with Addison's disease who exhibited depression, restlessness, tremors of the hands, lips, and tongue, delusions, and hallucinations of smell and taste.

One of the earliest suggestions relating the adrenal glands to epilepsy was reported in the papers by Fischer (139, 140) in 1920 and 1921; he postulated, on the basis of inadequate and poorly controlled experimental data, that reduction of adrenal substance in the body reduced the tendency to convulsions and that hyperfunction of the adrenal increased convulsive susceptibility. In an earlier paper, Fischer and Fischer (141) showed that convulsions induced by amyl nitrite inhalation produced enlargement of the adrenal glands. However, Wertheimer and Dubois (595) criticized Fischer because he used rabbits, animals which they thought were not subject to convulsions from cortical stimulation. Therefore, Wertheimer and Dubois used dogs and found that adrenalectomy did not hinder convulsions induced by intravenous injections of strychnine. In addition, Specht (508) found no difference in the susceptibility of intact and unilaterally adrenalectomized guinea pigs and rabbits to seizures induced by

[3] In the same discussion, this patient was also reported by Joffroy to be suffering from rheumatoid arthritis and the following quotation from his remarks is of interest in view of the current use of cortical hormones in the therapy of rheumatoid arthritis. "J'ajouterai qu'ayant suivi depuis longtemps la malade, j'ai constaté une amélioration physique non moins importante. Elle était atteinte autrefois de déformations multiples des doigts, comparables à celles du rhumatisme déformant. Celles-ci disparaissent de jour en jour."

amyl nitrite or tetanus toxin. In spite of the fact that other investigators had not confirmed his work, Fischer's claims apparently served as a stimulus for the clinical use of unilateral adrenalectomy in the treatment of epilepsy. Brüning (55) reported 14 patients treated in this manner; 5 patients were markedly improved, 5 patients showed some improvement, and 1 patient was not helped by the operation. Sandor (463) tried this procedure in 4 patients; 2 patients died from the operation and the other 2 patients were reported to have had milder and fewer seizures. However, these early reported successes were followed by many unfavorable results and the procedure was fortunately abandoned. [See review by Lennox and Cobb (321) for a discussion of the history of this medical aberration, and for references.] In the discussion of the article by Brüning (55), Peiper reported that removal of the adrenals from experimental animals resulted in coma, convulsions, and death; hence he was one of the earliest investigators to describe the central nervous hyperexcitability in experimental animals with adrenocortical insufficiency.

Further work on the effect of adrenocortical deficiency on the central nervous system was reported by Rowntree and Snell (453) in their monograph on Addison's disease. They noted the asthenia which accompanies this disease and believed that the psychic changes were a result of the asthenia. Other symptoms mentioned were inability to concentrate, drowsiness in some patients, restlessness and insomnia in others, irritability, apprehension, and disturbed sleep with disagreeable dreams and nightmares. Progression of the disease was stated to be associated with disorientation, confusion, visual and auditory hallucinations, and delusions. As to the origin of the mental symptoms in Addison's disease, Rowntree and Snell concluded: "The cause of mental symptoms is not known, but in all probability it is only part of the general picture, occasionally complicated by psychosis from exhaustion. Cerebral anemia probably plays a large part, as it does in the attacks of syncope or convulsions which are observed from time to time."

Hartman (232) was one of the first investigators to emphasize that the adrenocortical hormones have a direct effect on the central nervous system. He repeatedly called attention to the nervous manifestations in Addison's disease and was certain that the "vital" hormone of the adrenal affected the nervous system directly. Hartman and his coworkers (233, 235) showed that hypofunction of the adrenal cortex in man resulted in mental depression, nervousness, and hyperexcitability; administration of adrenocortical extract (ACE) alleviated the symptoms and produced a feeling of well-being, cheerfulness, tranquility, and even euphoria, an observation which antedates the recently reported euphoric effects in patients treated with cortisone for collagen diseases. The experimental work of Hartman and Lockwood (234) on the effect of adrenalectomy on reflexes in rats is discussed below.

The early studies on the effects of adrenocortical hyperfunction on the central nervous system were concerned mainly with the abnormal psychological states resulting from this condition. For example, Holmes (271) in 1925 reported a case of virilism associated with a suprarenal tumor; the patient developed mental changes which disappeared when the tumor was removed. This article was

followed by those of Broster *et al.* (51), and Maclay *et al.* (340), and in subsequent years many reports appeared [see Cleghorn for summary (76)]. Nearly all investigators viewed the mental changes only as side-effects of the disease and made no effort to assess the frequency or the nature of the psychic aberrations. However, in 1941, Engel and Margolin (130) attempted to determine the incidence of abnormal mental states in Addison's disease and to evaluate the effect of treatment; in addition, they studied the effects of hypocorticism on the electroencephalogram. Indeed, they were the first to demonstrate that the characteristic clinical picture was associated with a neurophysiological defect.

It is thus evident that early investigators recognized the important relationship between adrenocortical function and the central nervous system. However, no systematic study of the problem was forthcoming and the crucial contributions had to await parallel advances in the physiology and biochemistry of the adrenal cortex.

II. EFFECTS OF ADRENOCORTICAL INSUFFICIENCY ON THE NERVOUS SYSTEM

A. Neurophysiological aspects of adrenocortical hypofunction

1. Effects on reflex activity, neuromuscular function, and peripheral nerve. The work of Hartman and Lockwood in 1931 (234) demonstrated that the adrenalectomized animal has a decreased ability to support reflex activity and that administration of ACE corrects this defect. In adrenalectomized rats maintained on sodium chloride solution, they found that the average fatigue-time of the spinal reflex arc was only one sixth that of the ACE-treated, adrenalectomized rats. The various components of the reflex arc were measured by comparative stimulation of the contralateral and ipsilateral sciatic nerve and of the muscle itself. The experimental data suggested that adrenalectomized animals have a defect in transmission at the cord level, at the neuromuscular junction, and in muscle, and that all three sites are equally sensitive to the lack of adrenocortical hormones. As discussed below, this state of affairs is quite unlikely; the defect is probably in the supply of essential substrates to muscle and nerve, as a result of the inadequate circulation in adrenalectomized rats. Subsequent investigations have substantiated this view. For example, Hoagland and coworkers (258, 260, 496, 497) demonstrated that conduction time in the central nervous system (as measured by the time for an impulse initiated by tactile and/or electrical stimulation of the foot to reach the cerebral cortex) is significantly decreased (by 18%) in salt-maintained, adrenalectomized rats as compared to intact control rats. The decreased conduction time was found to be centrally determined and could be restored to normal by cortisone. Such data, along with those of Hartman and Lockwood, strongly suggest that adrenocortical insufficiency delays synaptic transmission in the central nervous system.

With respect to the neuromuscular junction, Torda and Wolff (556, 561) demonstrated that adrenalectomy and/or hypophysectomy in rats caused a decline of the amplitude and the area of the muscle action potential during repetitive, indirect stimulation (sciatic nerve). Since the magnitude of muscle contraction during direct stimulation decreased less than during indirect stimu-

lation, it was concluded that the neuromuscular fatigue which occurs in such animals is caused by moderate dysfunction of muscle and marked dysfunction of nerve; the possible role of the myoneural junction was not elucidated. ACTH, and to a lesser extent cortisone, restored the neuromuscular system of the hypophysectomized rats to normal. It is also of interest that Hoppe and Vogel (274) and Vogel and Westphal (584) demonstrated a decreased chronaxie (increased excitability) in the gastrocnemius muscle of adrenalectomized frogs; potassium chloride further decreased the chronaxie lowered by adrenalectomy. Administration of sodium chloride solution or ACE restored muscle excitability to normal. It was postulated that changes in muscle excitability were correlated with changes in the ratio of Na to K concentration in muscle and plasma, an observation consistent with the relation which exists between alterations in brain excitability and electrolytes in brain and plasma (see below).

The observations cited do not indicate clearly whether the neuromuscular defect noted in adrenalectomized animals is located at the myoneural junction or in the nerve itself. Several investigators have studied the effects of adrenalectomy on the function of peripheral nerve and have shown changes in excitability. Hoagland and coworkers (258–261, 496, 497) found that the excitability of rat sciatic nerve *in situ* was decreased moderately in the adrenalectomized animal and partially, but significantly, restored toward normal by the injection of ACE. However, sciatic nerves removed from normal and adrenalectomized rats and studied in a chamber exhibited no group differences in excitability. It was concluded, therefore, that an intact circulation is necessary for the occurrence of a decrease in nerve excitability in adrenalectomized rats.

The effects of adrenalectomy and of various adrenal hormones on the chronaxie of peripheral nerves have been extensively studied by Chauchard and Lecoq and their colleagues (62, 315, 316). The chronaxies of the nerves to the extensor and the flexor muscles of the big toe were determined in several species of animals, and of the median and radial nerves in man. Adrenalectomy increased peripheral motor nerve chronaxie (decreased excitability), an observation in agreement with that of Hoagland and coworkers discussed above. The decreased excitability of peripheral nerve produced by adrenalectomy is in sharp contrast to the increased brain excitability which occurs in such animals (see below).

Summary: it appears from the available evidence that animals with adrenocortical insufficiency exhibit the following changes: decreased central nervous system conduction time, decreased ability to sustain reflex spinal cord activity, decreased excitability of peripheral nerve, and increased excitability of skeletal muscle. The relation of these changes to metabolic alterations in adrenalectomized animals is discussed subsequently.

2. Effects on brain excitability. The effects of adrenocortical insufficiency on brain excitability have been studied by four different technics: 1) excitability as measured by threshold for electrically induced seizures (EST); 2) excitabilty as measured by threshold for pentylenetetrazol (Metrazol)-induced or insulin-induced seizures; 3) excitability as measured by susceptibility to audiogenic seizures; 4) occurrence of spontaneous seizures.

The effects of adrenalectomy on brain excitability as measured by EST were studied by Davenport (98) and Timiras *et al.* (548), and summarized by Woodbury (605). Davenport demonstrated that the EST of adrenalectomized rats placed on water to drink decreased progressively and after 4 days reached a minimum of 23% below the preoperative control threshold; the EST of rats maintained on 0.9% sodium chloride solution, desoxycorticosterone (hereinafter called DOC, regardless of the particular salt), or ACE was the same as that of non-operated controls. Administration of potassium chloride or magnesium chloride solutions accentuated the decrease in threshold produced by adrenalectomy alone; calcium chloride solution maintained the threshold approximately at normal. These results in rats have been extended to mice by Timiras *et al.* (548) who found that adrenalectomized mice given water to drink showed a progressive decrease in EST, to both 60-cycle a.c. (25% decrease) and low-frequency unidirectional current (25% decrease); adrenalectomized mice given 0.9% sodium chloride solution to drink exhibited no change in threshold as compared to intact animals. The changes in brain excitability noted by these investigators were found to be correlated with changes in brain and plasma electrolyte concentrations, as discussed later.

The influence of adrenocortical hypofunction on susceptibility to Metrazol-induced seizures was measured by Torda and Wolff (560) in adrenalectomized rats maintained on sodium chloride; no change from control values was observed. Cicardo (67, 68) also noted that the dose of Metrazol necessary to produce minimal convulsions was the same in adrenalectomized rats and adrenalectomized and hypophysectomized toads as in the intact controls. Adrenocortical hypofunction, therefore, does not appear to increase susceptibility to chemically induced convulsions as it does to seizures produced electrically. However, the problem of chemically induced convulsions in adrenalectomized animals is complicated by alterations in the absorption, fate, and excretion of the convulsant drug, and it is likely that adrenalectomy influences one or more of these factors; for example, if absorption of the convulsant is delayed, a larger dose would be required to produce a given effect. Although the experiments of Torda and Wolff rule out this particular factor of absorption since the Metrazol was administered intravenously, other factors such as those discussed by Swinyard *et al.* (532) are involved even when the convulsant is injected intravenously. More precise studies are necessary for a complete solution of the problem.

The average minimal convulsant dose of insulin was determined in normal, adrenalectomized, adreno-demedullated (with transplant of cortex), and hypophysectomized rats by Swann and Fitzgerald (529). The sensitivity to insulin convulsions was increased 24-fold by adrenalectomy, 2-fold by removal of the adrenal medulla, and 7-fold by hypophysectomy. Lack of adrenocortical steroids, therefore, results in increased susceptibility of the nervous system to the convulsant effects of insulin.

The effect of adrenalectomy on the incidence of audiogenic seizures in wild and domestic rats was studied by Griffiths (207). Intact and adrenalectomized wild rats, whether maintained on water or on sodium chloride, did not exhibit audio-

genic seizures in response to an air blast. In contrast, adrenalectomized domestic rats exhibited an enhanced susceptibility to audiogenic seizures when maintained on water but exhibited a decreased susceptibility to audiogenic seizures when maintained on large doses of sodium chloride. The explanation of these findings lies in the protection afforded by sodium chloride against the increase in brain excitability resulting from adrenalectomy. As discussed above, Davenport (98) demonstrated that sodium chloride restored the decreased EST of adrenalectomized rats to normal, and Woodbury *et al.* (607) have shown that excessive quantities of sodium chloride will elevate the EST to levels above normal in intact animals and (to a greater extent) in adrenalectomized animals. Griffiths also showed that adrenalectomy, whether in wild or domestic rats and whether the rats were treated or not, decreased the spontaneous activity of the animals, probably as a result of the muscle weakness so characteristic of adrenocortical insufficiency.

It has been observed, almost from the time that Addison's disease was first recognized, that patients in crises due to adrenocortical insufficiency exhibit convulsive episodes (72, 130, 301). Also, in experimental animals, Peiper (397) noted that adrenalectomy resulted in convulsions. Swingle *et al.* (531) were able to evoke convulsions in adrenalectomized dogs by giving them large amounts of water. It was observed that the adrenalectomized dogs convulsed after smaller quantities of water than were required in intact dogs. The normal dogs spontaneously recovered from water intoxication if fluid administration was discontinued at the time of onset of convulsions, whereas otherwise healthy and vigorous adrenalectomized dogs subjected to water intoxication did not recover unless injected intravenously with ACE or hypertonic sodium chloride solution.

Knobil *et al.* (302) studied the effects of adrenocortical insufficiency in rhesus monkeys and noted extreme weakness, occasional convulsions, prostration, and coma; such crises invariably occurred after a period of fasting occasioned by removal of food or by anorexia. The crises were associated with a marked decrease in blood sugar concentration; administration of glucose resulted in complete recovery from the crises in 5 to 60 min. The conclusion was reached that hypoglycemia was the immediate cause of death (and presumably of convulsions) in the monkey with adrenocortical insufficiency.

Although most investigators have explained the convulsions on the basis of the hypoglycemia which occurs in adrenal crises, Arnett *et al.* (17) observed that the frequency of cerebral symptoms in adreno-demedullated and adrenalectomized rats given insulin was unrelated to the blood sugar level. In addition, they found that insulin produced cerebral symptoms (depressed reflexes, coma, convulsions, and delta potentials in the EEG) in 84% of adrenalectomized rats but only in 16% of adreno-demedullated rats, although both groups had a similar degree of hypoglycemia. Thus the adrenalectomized animal is more sensitive than the adreno-demedullated animal to insulin-induced coma and convulsions, and it is evident that so-called hypoglycemic convulsions may be due to some other factor(s). The possible factors involved are discussed later in this review.

That convulsions are fairly common in Addison's disease has been pointed out

by Storrie (525), who also reported on EEG changes and seizures in 4 patients with this disease; all 4 had abnormal EEGs (generally diffuse slow waves), 3 of the 4 had grand mal seizures, and all 4 exhibited cerebral symptoms (confusion, stupor, and paranoid ideas). The fasting blood sugar in these patients was normal, again indicating that the seizures were not hypoglycemic in origin. Therapy with cortisone and DOC improved their condition and controlled the seizures.

Summary: it has been demonstrated that adrenalectomized animals are more susceptible to seizures, whether induced electrically or audiogenically or by insulin or water intoxication; but such animals apparently are not more sensitive to Metrazol-induced convulsions. Experimental animals and humans with adrenocortical insufficiency exhibit spontaneous seizures during crises. The relation of such changes in brain excitability to metabolic processes is discussed below.

3. Effects on the electrical activity of the brain. The EEG effects of hypocorticism in man were first reported by Engel and Margolin (130, 131) who found a characteristic picture of diffuse, slow activity with frequencies of 2 to 6/sec and voltages higher than those of alpha waves (up to 75 μV). Hyperventilation induced EEG changes more easily in patients with Addison's disease than in normal subjects, and glucose administration prevented such alterations. ACE but not DOC restored the EEG pattern to normal. A rough correlation was found between the EEG abnormalities and blood sugar level, and the EEG appeared to be improved by factors which improved carbohydrate metabolism, such as adequate replacement therapy in cases of Addison's disease.

The observations of Engel and Margolin in man have been amply confirmed by many investigators (46, 84, 146, 147, 270, 525, 540). Hoffman *et al.* (270) observed that 18 of 25 patients with Addison's disease exhibited definite abnormalities in the pattern of their resting EEGs. The changes were characterized by: 1) oscillations (5 to 8/sec) slower than the normal alpha rhythm, with a predilection for the frontal area and a relative refractoriness to the usual effect of opening the eyes; 2) an unusual exaggeration of the normal EEG response to voluntary hyperventilation; and 3) a reduction in incidence of low-voltage, high-frequency activity (beta waves). The EEG abnormalities progressed despite DOC therapy; in addition, treatment with ACE, vitamin B complex, and a diet high in carbohydrate failed to correct the EEG. Restoration of blood pressure, plasma volume, and electrolyte concentration prevented neither the occurrence of changes in the resting EEG nor the sensitivity to hyperventilation. Gorman and Wortis (199) also described high-voltage, slow bursts in all leads in the EEG of a patient with Addison's disease; the abnormality was exaggerated by hyperventilation. Thorn and his colleagues (147, 540) reported that cortisone abolished the EEG alterations (essentially the same as those reported by Engel and Margolin and by Hoffman *et al.*) in patients with Addison's disease; however, "nervousness" was not relieved. Corticosterone has been observed to correct both the EEG abnormalities and the nervousness and excitability of patients with Addison's disease and, like cortisone, to produce a feeling of well-being (85). 11-Dehydrocorticosterone appears to produce the same corrective results as corticosterone (146).

It is of interest that the dominant frequency of the EEG is below normal in adrenalectomized rats as well as in patients with Addison's disease; on the other hand, hypophysectomy in rats does not change the EEG (29, 32, 560). The normal pattern can be restored by treating adrenalectomized rats with ACE and pregnenolone but not with DOC (29, 32). The relation between the EEG and metabolic changes is discussed in Section II, B.

4. Effects on the responses of animals to centrally acting drugs. It is well known that the adrenalectomized animal is more sensitive to various drugs, including those acting on the central nervous system. At least two explanations are possible. The first is that, since the regulatory influence (see below) of adrenocortical hormones on the central nervous system is removed, the brain is more sensitive to drugs which produce either excitation or depression. The second is that the absorption, fate, and excretion of the drugs are modified so that their dose-effect curves are shifted. An examination of the literature provides evidence for both explanations. That the adrenalectomized animal is more sensitive to the central nervous depressants is indicated by the following data. Sindram (495) observed that adrenalectomized rats were more susceptible to urethane. The toxicity of thiopental was greater in adrenalectomized than in normal rats (122, 435). Tureman *et al.* (567, 568) and Robillard *et al.* (440) noted that the duration of pentobarbital-induced sleep was approximately doubled in adrenalectomized rats as compared to intact controls; cortisone decreased the susceptibility of both groups to pentobarbital; DOC did not affect pentobarbital-sleep time of adrenalectomized rats in low doses, but prolonged it slightly in high doses. In addition, adrenalectomy was found by Shibata and Komiya (492) to induce a 4-fold prolongation of sleep induced by thiopental; pretreatment with cortisone or cortisol prevented this prolongation, but DOC and isotonic sodium chloride solution were ineffective. Komiya and Shibata (304) also observed that adrenalectomy decreased the induction time and prolonged the duration of intravenous barbital anesthesia in mice, and that pretreatment with cortisone or cortisol prevented such changes; DOC and isotonic sodium chloride solution had no effect.

There is no evidence that the enhancement of barbiturate-induced anesthesia by adrenalectomy is due to a central effect of the lack of adrenocortical steroids; however, there is evidence that the influences of certain adrenocortical steroids on drug-induced depression are due, at least in part, to their central effects. Cortisone and cortisol increase brain excitability, whereas DOC decreases it. Thus the decrease produced by cortisone in the duration of pentobarbital-induced sleep in intact and adrenalectomized rats, the slight but significant increase caused by high doses of DOC in the duration of pentobarbital-induced sleep in adrenalectomized rats, and the delay produced by cortisol in the onset of barbital anesthesia in adrenalectomized mice are probably explainable on the basis of the central excitatory effects of cortisone and the central depressant effects of DOC.

Evidence that adrenalectomy prolongs barbiturate-induced sleep by modification of the absorption, fate, or excretion of the drug is based on the following

considerations. Adrenalectomy impairs absorption of drugs from the gastrointestinal tract and from parenteral sites of injection, mainly as a result of the inadequate circulation in the adrenalectomized animal. The prolonged sleep time could possibly be explained by impaired drug absorption if the absorption took place over a more protracted period and at a rate sufficient to maintain sleep. Since this possibility is unlikely, another explanation is necessary. That impaired hepatic detoxification of pentobarbital is the cause of the prolonged sleep time observed in adrenocortical insufficiency is suggested but not proved by the experiments of Robillard *et al.* (440) who demonstrated that pentobarbital was metabolized at a slower rate by the liver of adrenalectomized rats than by the liver of intact rats; cortisone was thought to exert its effect by enhancing hepatic degradation of pentobarbital. Komiya and Shibata (304) attributed the prolongation of barbital anesthesia by adrenalectomy to a demonstrated higher concentration of barbital in the brain; cortisone and cortisol prevented the increase in brain barbital concentration and shortened the duration of anesthesia, whereas DOC had little effect. Since barbital is not metabolized in the body, these data suggest an influence of adrenocortical steroids on the tissue distribution of the drug; although an effect of these steroids to hasten the renal excretion of barbital has not been ruled out, such a change would probably tend to lower the barbital concentration in the brain. Measurements of the plasma to brain ratio of barbital and of the rate of excretion of barbital in the urine are needed to obtain an answer to this problem.

From the above discussion, it is evident that the absorption, fate, excretion, and intensity of effect of drugs acting on the central nervous system can be modified by a deficiency or excess of adrenocortical steroids. The net effect on the excitability of the brain is thus the algebraic sum of these several factors.

The anticonvulsant drug diphenylhydantoin moderately elevates the EST of salt-maintained adrenalectomized rats, whereas it has little or no effect on the EST of intact controls (605, 613, 616). The diphenylhydantoin-elevated EST of intact or adrenalectomized rats can be prevented by the administration of cortisone. Thus the central effects of this anticonvulsant can be modified by both an excess and a deficiency of adrenocortical steroids. Further evidence that adrenocortical hormones modify the central effects of diphenylhydantoin is presented in Section V.

5. Psychic and behavioral changes. a. Man. It has been recognized since the first report by Addison that adrenocortical insufficiency profoundly influences the psyche, and many investigators have since noted the mental aberrations in patients with Addison's disease. Several reviews have summarized the psychological aspects of adrenocortical insufficiency (72, 75, 77, 81, 199).

The early reports on mental alterations in Addison's disease mentioned such changes merely as oddities, of little importance to the disease as a whole. However, it has become increasingly evident that psychological derangements are an integral part of the disease syndrome. Isolated cases of psychosis in patients with Addison's disease have been reported by Parot (391), Larue (312), Rushton *et al.* (455), and Chatagnon *et al.* (61); some transient improvement followed

therapy with sodium chloride, alone or with DOC. Gorman and Wortis (199) reported two cases of paranoid psychosis in Addison's disease, both of which responded briefly to DOC and sodium chloride. Craddock and Zeller (91) described a case of acute, severe depression with suicidal tendency in a patient with Addison's disease; thought at first to be due to cortisone treatment, the depression persisted on withdrawal of the hormone; improvement followed electroconvulsive therapy. A case of Addison's disease with unusual and protracted mental changes was reported by Quandt (418). Presenting features were coma, fibrillary twitching, facial grimacing, and choreiform and serpentine movements of the limbs. Despite therapy with fluid, electrolytes, and ACE, the patient remained dull and incoherent; however, treatment with cortisone restored the physical and mental status to normal.

Engel and Margolin (130, 131) were the first investigators to assess the *incidence* of mental disorders in their patients with Addison's disease. They found that 16 of 25 cases manifested neuropsychiatric alterations; three patients were frankly psychotic. In some instances, the disturbances encountered appeared most prominently immediately before or during crises; in other cases, the appearance was unrelated to the severity of the metabolic changes. Therapy with DOC, high carbohydrate diet, and various vitamins did not completely abolish the mental disturbances, but administration of ACE was markedly beneficial. Cleghorn (72) reviewed 25 cases of Addison's disease; the incidence of psychological deviations, as summarized by him, was as follows:

Psychological Deviation	No. of Cases	%
Apathy (psychic)	21	84
Negativism	20	80
Seclusiveness	12	48
Depression	12	48
Irritability	12	48
Suspiciousness	4	16
Agitation	2	8
Paranoid delusions	1	4

Therapy of the psychic changes in Addison's disease should be designed to abolish the mental abnormalities, if possible, and certainly to prevent their progression. Treatment with sodium chloride and DOC provides temporary remissions in some patients, but usually the psychic changes ultimately progress. The addition of cortisone or cortisol results in a much greater restoration of physical and mental capacities. However, cortisone itself may produce psychic changes (see below), and it appears that Addisonian patients are more sensitive than normal patients to this effect of cortisone. Cleghorn and Pattee (81) described 3 cases of psychoses resulting from cortisone treatment of patients with adrenocortical insufficiency; 2 patients became psychotic 3 days after the start of treatment, and one patient had an exacerbation of a psychosis which had developed during DOC therapy. It is of interest that Conn (85) has observed that

corticosterone, a secretory product of the adrenal cortex which exerts a "normalizing" effect on brain excitability in animals, is more effective than cortisone in maintaining the physical and mental status of patients with Addison's disease. The "normalizing" factor of the adrenal cortex and its regulation of central nervous system function are discussed in Section V.

It is evident from the available literature that individuals with Addison's disease frequently exhibit personality changes of varying degree of severity and that such changes can be overcome by adequate replacement therapy, usually with a combination of cortisone and DOC or with corticosterone.

b. Experimental animals: effect on spontaneous and rhythmical activity. Adrenalectomy decreases the spontaneous running activity of rats (domestic and wild), as demonstrated by Griffiths (207); treatment with sodium chloride repairs the deficiency to some extent. Richter and Wood (437) observed that spontaneous running activity of domestic and wild rats is also decreased by hypophysectomy; the decrease was more marked in the domestic animals. In view of the fact that both adrenalectomy and thyroidectomy (49, 222, 436) diminish spontaneous activity, it is likely that most of the effect of hypophysectomy is due to the resulting deficiency in thyroid and adrenocortical hormones. Richter (436) noted that gonadectomized domestic rats (which have much smaller adrenals and less adrenal cholesterol, ascorbic acid, and hormone than do wild rats) exhibit a marked decrease in spontaneous running activity; in contrast, gonadectomized wild rats (which have very large adrenals) exhibit no such decrease. Cortisone or ACE treatment restored normal activity but DOC had little effect. These results indicate that the 11-oxysteroids, which are necessary for normal carbohydrate metabolism and which are most potent in restoring normal function in adrenalectomized rats, are the most effective in restoring spontaneous activity to normal in gonadectomized domestic rats, and suggest that the decreased activity is probably the result of muscle weakness. The central nervous system might also play a role in the changes in spontaneous running activity induced by cortisone, as indicated by the fact that this steroid increases such activity in normal mice and in rats with adrenal insufficiency; in contrast, DOC, which decreases brain excitability, does not affect spontaneous activity although it might be expected to do so because of its central depressant properties. It is also of interest in this regard that Goldman and Abood (188) found a striking correlation between phosphate metabolism of the hypothalamic-pituitary system and the level of spontaneous activity. In adrenalectomized rats exhibiting decreased spontaneous activity, the creatine phosphate in the hypothalamus and pituitary was diminished and the inorganic phosphate was increased; cerebral cortical tissue showed no such changes. The full significance of these findings is not yet understood. An effect of adrenalectomy on the eosinophil rhythm in mice has been noted by Halberg *et al.* (220); adrenalectomy abolished the morning "high" and the early night "low" of the eosinophil rhythm. (The high and low eosinophil levels were found to coincide, respectively, with the rest and the activity phases known to occur in mice.) It is likely that the adrenal gland regulates the spontaneous activity rhythm by an influence on the central nervous system. The

observations of Goldman and Abood (188) cited above are of interest in this connection.

B. Metabolic effects of adrenocortical hypofunction on the central nervous system

1. Effects on electrolyte metabolism. The effects of adrenocortical hypofunction on brain and plasma electrolyte distribution and brain excitability have been described by Davenport (98) and Timiras *et al.* (548), and summarized by Woodbury (605). Davenport found that, whereas the plasma Na concentration of adrenalectomized rats given water to drink decreased markedly and plasma K concentration increased markedly, there was no change in total cerebral cortical Na, K, and Cl. However, recalculation of her data indicates that intracellular Na concentration of the brain, predicated on the basis that chloride space is a measure of extracellular fluid volume, was increased and that the ratio of brain extracellular to intracellular Na concentration was decreased. A direct correlation between plasma Na concentration and electroshock seizure threshold was also reported by Davenport.

In adrenalectomized mice given water to drink, Timiras *et al.* (548) observed a decrease in plasma Na level and an increase in plasma K level, whereas in the cerebral cortex there was a marked increase in total brain Na concentration and no change in K concentration. Calculation of brain intracellular electrolytes revealed a marked increase in Na concentration and no change in K concentration; the ratios of extracellular to intracellular Na and of intracellular to extracellular K were decreased. Thus, despite a decrease in extracellular Na, brain Na concentration was increased. In contrast, the concentration of Na in skeletal muscle cells was decreased. The increase in intracellular brain Na (decrease in brain Na ratio) was associated with an increase in brain excitability. Bergen and Hoagland (30), Stern *et al.* (524), and Flanagan *et al.* (142) reported that the total brain Na and K did not change after adrenalectomy in rats and dogs, but brain intracellular values of these cations were not calculated.

Since adrenalectomy increases intracellular brain Na concentration, it is of interest to note the effect of this procedure on the turnover of radiosodium by brain. Stern *et al.* (524) observed that the relative activity of brain (a measure of turnover rate) of adrenalectomized rats was slightly decreased by adrenalectomy; this finding, coupled with the increase in brain intracellular Na concentration in such animals, indicates that adrenalectomy decreases the active transport of Na out of brain cells (see Section III, B).

The influence of adrenalectomy on radiopotassium turnover by the brain has been studied extensively by Hoagland and colleagues (30, 33, 258, 267) and by Leiderman and Katzman (319). Hoagland and Stone (267) found that 36 hours after K^{42} injection adrenalectomized rats accumulated 24% more brain K^{42} than did the controls. Since the total K of brain was unchanged (30, 98), adrenalectomy would appear to increase the turnover of K in the brain. Realizing that the data of Stone and Hoagland could be interpreted in this manner, Leiderman and Katzman (319) studied brain K exchange in normal and adrenalectomized rats. The influx and outflux values for brain K were calculated graphically, by means

of the general exchange equation developed by Solomon (505). The influx rate of K into the brain of normal adult rats was found to be 2.89 mEq/kg/hr; the outflux rate, 3.64 mEq/kg/hr; and the influx ratio, 0.80. They concluded that, since a steady state obtains at the end of 72 hours, outflux must be equivalent to influx. Since total brain K is 100 mEq/kg and the influx to outflux ratio is 0.8, then 20 mEq of K per kg of wet brain are not exchangeable with K^{42} and might represent chemically bound, nonexchangeable K. In contrast, in adrenalectomized rats maintained on sodium chloride for 5 to 7 days postoperatively and then injected with K^{42}, Leiderman and Katzman observed that adrenalectomy did not appreciably change the influx rate of K in rat brain, and that the ratio of influx to outflux was now 1.04; this ratio would indicate that all brain K was exchangeable. Therefore, it was concluded that the nonexchangeable K compartment of brain tissue disappears as a result of adrenalectomy. Cortisone treatment of adrenalectomized rats restored the nonexchangeable compartment, whereas DOC and sodium chloride treatment did not.

If it is true that there is a nonexchangeable fraction of K in normal rat brain, this is of great importance. Several investigators have attempted to verify the findings of Leiderman and Katzman. Hoagland (258, 259) and Bergen *et al.* (33) repeated the experiments of Katzman and Leiderman and found no difference in total brain K in normal and adrenalectomized rats; but they did find that an increase in K^{42} of 16% over normal controls occurred in 36 hours in brains of adrenalectomized rats (in confirmation of their earlier work). In order further to determine whether there is a chemically bound K fraction in brain, ultrafiltration procedures were carried out and the K turnover rates determined; these rates were found to be the same in the ultrafiltrable fraction as they were in total brain, for both normal and adrenalectomized animals; thus the percentage increase in K^{42} amounted to 16% in both filtrable and nonfiltrable portions. However, Bergen *et al.* (33) found that the lower K^{42} content of normal rat brain as compared to adrenalectomized rat brain was due to the greater dilution of K^{42} by potassium ingested in the food; since adrenalectomized rats are anorexic, the fasted normal and fasted adrenalectomized rats were compared and there was no difference in the rate of K^{42} uptake by the brain in the two groups. Also, in a study of the K^{42} uptake in the brain of normal rats, Woodbury (606) was unable to demonstrate any nonexchangeable fraction. It is thus evident that the provocative results of Katzman and Leiderman have not been substantiated to date; further investigation is needed.

In *summary*, the brain of the adrenalectomized animal exhibits an increased concentration of intracellular Na, a decreased ratio of extracellular to intracellular Na concentration, and a decreased turnover of Na; total brain K concentration is unchanged, but the ratio of intracellular to extracellular K concentration is decreased and the turnover of K is questionably increased. Accompanying these changes in electrolytes there is an increase in brain excitability, a slowing of the frequency of the EEG, a decrease in central conduction time, and behavioral changes. From the data presented and additional evidence to be discussed later, it is suggested by the reviewer that changes in brain excitability are

correlated with changes in brain Na, whereas some of the other neurophysiological alterations are correlated with changes in brain K and oxidative metabolism.

2. Effects on cerebral blood flow and cerebral oxygen consumption. The effects of adrenalectomy on cerebral blood flow and cerebral oxygen consumption *in vivo* and on brain metabolism *in vitro* have been studied and reviewed by Hoagland and his collaborators (258, 260, 261). Based on the assumption that the electrocorticographic changes in adrenalectomized rats kept in good condition by sodium chloride therapy are the result of a decrease in cerebral circulation and an accompanying cerebral oxygen deprivation, these investigators studied "head blood flow" and oxygen consumption in adrenalectomized as compared to normal rats. A significant reduction of 61% in head blood flow was observed in adrenalectomized rats; there was a concomitant significant decrease of 43% in oxygen consumption. The administration of ACE, 5-pregnenolone, or cortisone restored head blood flow and oxygen consumption to within normal limits in 2 hours; on the other hand, DOC had little restorative effect. In later experiments, using modified and more accurate technic to measure cerebral blood flow, the same investigators (258) found in adrenalectomized rats that cerebral blood flow was decreased 57% and oxygen consumption was reduced 18%; cortisone therapy fully restored normal values for both cerebral blood flow and oxygen consumption. Hoagland and colleagues (258) concluded "that the evidence supports the hypothesis that reduced brain oxygen consumption following adrenalectomy slows the electrocorticogram. The reduced oxygen consumption in turn appears to result from decreased cerebral circulation brought about by general reduction in cardiovascular tone and responsivity." In addition, it was noted that those agents which restored cerebral blood flow and oxygen consumption (ACE, 5-pregnenolone, and cortisone) also restored the electrocorticogram to normal. Whether these effects of adrenalectomy on cerebral blood flow and metabolism in rats can be correlated with the increase in brain excitability produced by adrenalectomy requires further study. However, the fact that cerebral blood flow and oxygen consumption are reduced in adrenalectomized rats maintained on sodium chloride solution and that such maintenance therapy prevents a reduction in EST would suggest that brain excitability changes are unrelated to these two factors.

In contrast to conditions of hypercorticism (see below), the effect of adrenal hypofunction in man (Addison's disease) on cerebral blood flow has been little studied. Hafkenschiel *et al.* (218) measured cerebral blood flow and oxygen consumption in 7 patients with severe essential hypertension before and after a reduction in blood pressure achieved by removal of 90% of the adrenal tissue, alone or combined with sympathectomy. They found that the mean values of oxygen consumption, jugular venous oxygen content, and jugular venous oxygen tension remained essentially unchanged and that cerebral blood flow increased slightly after such surgical procedures; the high cerebral vascular resistance associated with the severe hypertension was lowered toward the normal range. Whether cerebral blood flow and cerebral vascular resistance are decreased in patients with Addison's disease or would be lowered by adrenalectomy in normal patients

is not yet known. It is of interest, however, that Gordan *et al.* (194) have observed a slightly decreased cerebral blood flow and oxygen consumption in patients with hypopituitarism; part of the decrease can certainly be attributed to the associated thyroid deficiency, since Gordan *et al.* also noted a decrease in brain oxygen consumption in patients with hypothyroidism; but whether the associated hypoadrenalism also contributes to the reduction is yet to be determined. These investigators state: "Despite our interest in the effects of corticoids upon cerebral metabolism, we have thus far lacked the courage to perform studies upon patients with Addison's disease. The tenuous metabolic balance of such patients precludes withdrawal of supportive therapy for a sufficient period of time to obtain data which could be considered as representative of a basal state."

Nevertheless, Scheinberg [cited by Engel (129)] did measure cerebral blood flow, cerebral oxygen consumption, and cerebral glucose utilization in two cases of Addison's disease and in one case of hypopituitarism. Engel reported on one of these patients who was having what was clinically a perfectly characteristic hypoglycemic reaction at the time the cerebral blood flow was being studied, although the blood sugar level was 72 mg%; no change in cerebral blood flow, oxygen consumption, or glucose utilization was detected. When glucose solution and ACE were administered into the jugular vein, no change occurred in either cerebral blood flow or glucose utilization, but there was a slight decrease in oxygen consumption. Thus the meager data available indicate that cerebral blood flow and oxygen consumption are essentially unchanged in patients with adrenocortical insufficiency, a situation in agreement with the lack of effect of adrenalectomy on oxygen consumption of brain tissue *in vitro*, a topic now to be discussed.

The effects of adrenalectomy on cerebral oxygen consumption *in vitro* have been studied by several investigators. Although Himwich *et al.* (252) noted a decrease in the oxygen consumption of minced brain obtained from adrenalectomized animals *in extremis*, most investigators have not observed any change in oxygen consumption of brain slices and homogenates (31, 92, 550). Bergen *et al.* (31) confirmed earlier observations that adrenalectomy does not influence oxygen consumption of brain slices and homogenates, but in addition found that the activity of cytochrome oxidase and succinic dehydrogenase in these same brain slices was normal. Whereas such data obtained *in vitro* agree with the lack of effect of adrenocortical insufficiency on cerebral blood flow and metabolism in man, there remains the fact that hypoadrenalism in experimental animals appears to decrease cerebral oxygen consumption and blood flow. The discrepancy remains to be resolved.

3. Effects on acetylcholine metabolism of brain. Greenberg (203) measured the level of activity of choline acetylase of acetone-dried brain powders obtained from stressed and unstressed adrenalectomized and sham-operated groups of rats, and found no difference between the levels in any of the groups even when acetylcholine synthesis was increased by addition of coenzyme. He concluded that adrenalectomy and stress, alone or combined, did not consistently change either the choline acetylase or coenzyme levels of brain tissue. These observations were confirmed by Torda and Wolff (561) who demonstrated that acetylcholine

synthesis in brain minces was unaffected by adrenalectomy but was decreased about 45% in hypophysectomized rats. However, ACTH and adrenal steroids were found by Torda and Wolff to affect acetylcholine metabolism (see below). Since the brain metabolism of acetylcholine is not influenced by adrenalectomy, the EEG and brain excitability changes observed in adrenocortical insufficiency must be independent of acetylcholine synthesis.

4. Effect on brain carbohydrate, protein, and fat metabolism. The influence of adrenocortical insufficiency on brain carbohydrate, protein, and fat metabolism has been little studied, despite the considerable research carried out on the animal as a whole and on discrete tissues other than the brain. Adrenal insufficiency in experimental animals and man is characterized by low blood glucose levels during fasting, depletion of liver but not of muscle glycogen, decreased urinary excretion of nitrogen, high respiratory quotient, increased sensitivity to insulin, and increased rate of oxidation of carbohydrate. Since marked changes in the metabolism of carbohydrate, protein, and fat occur in the animal with hypocorticism, it might be expected therefore that the brain would also show these same alterations. Little work has been done on the brain to prove this possibility. It has been observed that the oxygen consumption and the R.Q. of brain tissue removed from animals with adrenal insufficiency are not different from those of normal animals. However, Hoagland's group found that cerebral blood flow and oxygen consumption are decreased in adrenalectomized rats (see above), and Gordan *et al.* (194) showed that surgical hypophysectomy of a patient resulted in a decreased rate of oxygen consumption but an increased rate of glucose utilization by the brain. These observations are consistent with the suggestion that adrenalectomy increases the rate of oxidation of glucose by the brain but also indicate that oxidative metabolism is simultaneously inhibited. However, as mentioned earlier, patients with Addison's disease exhibit no change in glucose utilization by brain. Much further work is necessary to resolve this problem.

Vaccari and Rossanda (572) noted that the brains of adrenalectomized rats fasted for 32 hours and receiving sodium chloride solution to drink had lower concentrations of glycogen and slightly lower concentrations of total carbohydrate than did the brains of similarly treated intact rats. This again indicates an increased rate of utilization of carbohydrate by brain tissue as a result of adrenalectomy. However, unpublished experiments (606) have shown that adrenalectomized rats, whether on water or on sodium chloride solution to drink, exhibit no change in brain and muscle glycogen despite a marked reduction in liver glycogen. Sass-Kortsák (465) also observed no effect of adrenalectomy on brain glycogen content. The glycogen content of rat brain is decreased by hypophysectomy and can be restored to normal levels by treatment with ACTH (2, 606); whether this decrease is due to adrenocortical deficiency has not been established. More definitive studies on the carbohydrate metabolism of the brain under conditions of adrenocortical insufficiency are necessary before further conclusions are warranted.

The influence of hypoadrenalism on free amino acid concentration in brains of

rats has been studied by Vernadakis and Woodbury (581); as might be expected from the fact that adrenalectomy increases protein synthesis in other tissues, the total free amino acid concentration of the brain was markedly decreased, with the exception that the concentrations of glutathione and cysteic acid were inincreased. The amino acids, γ-aminobutyric acid (GABA), glutamine, glutamic acid, taurine, valine, and cystine, were markedly decreased in concentration by adrenalectomy; aspartic acid concentration was unchanged. These observations suggest that brain is similar to other tissues with respect to protein and carbohydrate metabolism. The decrease in GABA is of interest in view of the recent suggestion that GABA may be an inhibitory mediator substance in the central nervous system (26, 126). A decrease in GABA, as occurs in adrenalectomy, might be related to the increased brain excitability known to occur in adrenalectomized animals.

From the meager data available, it is evident that the brain of adrenalectomized animals oxidizes carbohydrate at a higher rate than normal and that protein synthesis is accelerated. No reports have come to the reviewer's attention concerning the fat metabolism of the brain in adrenocortical insufficiency.

5. Summary. In summary of the cerebral metabolic effects of adrenocortical insufficiency, it may be stated that the brain of adrenalectomized rats is deficient in its ability actively to pump sodium, and that a secondary defect in potassium metabolism is associated with this deficiency; the resulting brain electrolyte changes are associated with an increase in brain excitability. In addition, adrenal hypofunction results in a decreased cerebral metabolic rate, apparently related to the EEG alterations observed in adrenalectomized animals and in patients with Addison's disease. Finally, an increased utilization of carbohydrate and an increased synthesis of protein have been observed in the brain of the adrenalectomized animal. All the foregoing changes may very well be the cause of the variegated neurophysiological abnormalities occurring in the animal with adrenocortical hypofunction.

C. Pathological changes in the nervous system as a consequence of adrenocortical insufficiency

A summary of the early literature (1881–1915) on the pathological changes in the nervous system of patients with Addison's disease can be found in the article by Gordon (198), which cites several authors as finding a variety of such changes. A careful reading of the available reports leads one to the conclusion that specific pathological changes in the central nervous system in Addison's disease are rare or nonexistent.

In well-controlled experiments, Burns *et al.* (56) demonstrated a great variety of degenerative changes in autonomic ganglion cells (superior cervical, stellate, and coeliac) of cats showing classical signs of adrenocortical insufficiency. Whether these changes cause functional defects in ganglia and whether adrenocortical steroids can prevent the changes await further investigation. The Nissl substance in cell bodies of the spinal cord was found to disappear on forced muscular exercise in normal rats but remained intact in adrenalectomized rats

(107); this finding would appear to support the view that the ready fatigability of animals with hypocorticism is not of central nervous system origin. Other pathological changes in the cerebrospinal axis have not been described in animals with experimental adrenal cortical insufficiency.

III. EFFECTS OF ADRENOCORTICAL HYPERFUNCTION ON THE CENTRAL NERVOUS SYSTEM

A. Neurophysiological aspects of adrenocortical hyperfunction

1. Effects on peripheral nerve, reflex activity, neuromuscular transmission, and skeletal muscle. The influence of the various adrenocortical hormones on peripheral nerve have been extensively investigated by Chauchard and Lecoq and their collaborators (62, 315, 316). These investigators employed rats, pigeons, and guinea pigs as experimental animals and also performed some experiments on man. The changes in peripheral nerve excitability (as measured by chronaxie changes) produced by adrenocortical hormones were as follows: 1) single small doses of DOC increased excitability, whereas large doses decreased excitability; intermediate amounts elicited a diphasic response, hyperexcitability followed by depression; chronic treatment with DOC increased excitability. 2) ACE had an action similar to that of DOC. 3) Cortisone always decreased nerve excitability, whether the dosage was acute or chronic. 4) Corticosterone resembled DOC in its effects on peripheral nerve. 5) Hydrocortisone and 11-desoxy-17-hydroxycorticosterone (substance S) had the same effects as cortisone. In addition, Chauchard and coworkers (62, 315, 316) noted that all the adrenocortical hormones referred to above increased excitability in both preganglionic and postganglionic sympathetic fibers. ACTH decreased excitability of somatic motor nerves. The attempt made by these investigators to explain the changes in peripheral nerve excitability on the basis of changes in acid-base balance produced by the various hormones is quite unconvincing; such an explanation is not compatible with the findings of Hendley *et al.* (246) that acidosis decreases whereas alkalosis increases nervous system excitability and those of Lorente de Nó (334) that nerve is relatively unresponsive to changes in pH between the limits of 5.5 and 8.0. Furthermore, both DOC and cortisone, in experimental animals and man, produce a hypokalemic, hypochloriemic alkalosis and hence have the same effects on acid-base balance despite opposite influences on peripheral nerve excitability. However, the described effects of adrenal steroids on peripheral nerve excitability are opposite to those on brain excitability (see below), and an explanation for this difference is not available at present.

The effects of adrenocortical steroids on *reflex activity*, as measured by the righting reflex and other tests, have been investigated by Negrete and del Pozo (377) who noted that large (anesthetic) doses of DOC in rats produced marked depression of reflex activity. When cortisone was given prior to DOC, the depression was shorter in duration, the induction time was longer, and recovery occurred sooner. Thus cortisone antagonizes the effects of DOC on reflex activity as it does on brain excitability. A detailed study of the effects of adrenocortical steroids on spinal reflex activity has not been undertaken.

A fair amount of information is available concerning the influence of adrenocortical steroids and ACTH on neuromuscular transmission and skeletal muscle function. The effect of ACTH on neuromuscular function of patients with myasthenia gravis was studied by Torda and Wolff (557, 558, 561) who found that the hormone largely prevented the characteristic decline in the amplitude of the muscle action potential caused by repetitive indirect stimulation. ACTH also improved the work performance of myasthenic patients. In normal rats, Torda and Wolff (561) observed that ACTH and cortisone did not affect the amplitude of the muscle action potentials evoked by indirect or direct stimulation; but in hypophysectomized rats, both agents restored toward normal the decreased amplitude of such action potentials. Thus the hormones improve neuromuscular and muscular function only when such function is abnormal.

It is not the purpose of this review to discuss in detail the effects of adrenocortical steroids on skeletal muscle function. The interested reader is referred to the work of Ingle and collaborators (283, 286, 287). However, a brief account of some changes in skeletal muscle function similar to those in the nervous system might prove useful in elucidating the mechanism by which the adrenocortical steroids affect the properties of excitable tissues in general.

It was quite early recognized by Hartman and Thorn (235) that ACE improved the muscular weakness in patients with Addison's disease, and consequently the effect of ACE on various non-Addisonian patients with asthenia was determined. Ergographic measurements in patients with asthenia secondary to Graves' disease, muscular dystrophy, osteomyelitis, and diphtheria showed that ACE increased their ability to work without fatigue; however, patients with neurasthenia and myasthenia gravis were not improved. The marked impairment in muscle strength in acute adrenocortical insufficiency was found to be counteracted by adrenocortical steroids; in order of decreasing potency were ACE, cortisone and cortisol, corticosterone, dehydrocorticosterone, and DOC. However, none of these steroid preparations elevated muscle work output to normal in the adrenalectomized rat, or increased the work capacity in normal animals (286, 287).

In contrast, del Pozo *et al.* (105) found that, in striated muscle of normal cats, intravenous or intra-arterial injection of cortisone hemisuccinate (water-soluble) caused an immediate although rather small and transitory increase in amplitude of the response to indirect electrical stimulation. The enhancement of muscular contraction seemed to result from an action of cortisone on contractile tissue since the same effect was observed in denervated muscle stimulated directly. In addition, these investigators found that cortisone delayed the appearance of the fourth stage (fatigue) of neuromuscular transmission. Given at a time when the fifth stage (synaptic recovery) was present, the steroid produced an immediate and long-lasting increase in tension, but when given beforehand this state did not appear; the mechanism of these effects of cortisone is not known. Finally, del Pozo *et al.* demonstrated that cortisone increased the resistance of muscle to the effects of ischemia secondary to arterial occlusion.

However, not all clinical data support the view that cortisone improves neuro-

muscular function. Merritt (364) has summarized the literature on the effects of ACTH and cortisone therapy in 36 patients with myasthenia gravis. In a small percentage of the cases, no clinical improvement was noted; in the majority of patients, the therapy caused a temporary exacerbation of the symptoms, followed by a temporary remission of variable degree. Such remission was rarely complete, and neostigmine was still required. In some cases treated with cortisone, the temporary improvement appeared following withdrawal of the drug during the period of relative adrenocortical insufficiency caused by such therapy. It is of interest in this latter connection that the symptoms of myasthenia gravis may be somewhat ameliorated by the oral administration of large amounts of potassium salts (190), and it is therefore possible that the symptomatic improvement following withdrawal of ACTH or cortisone is the result of an increase in plasma K associated with the relative adrenocortical insufficiency.

Clinical evidence for a direct effect of adrenocortical steroids on muscle itself has been presented by Shy *et al.* (493) who observed that cortisone significantly reduced the myotonic response in patients with myotonia dystrophica; Reese and Peters (426) also noted a decrease in myotonic symptoms in 7 such patients. Glaser and Merritt (186), however, found no change in the myotonic response in three cases of this disease treated with ACTH or cortisone. Since it has been demonstrated that potassium salts may intensify the symptoms of myotonia congenita (457) and that DOC (which lowers plasma and muscle K concentration) may abolish the myotonic response in goats and in man with congenital myotonia (52, 379), it would appear that ACTH and cortisone decrease myotonia by an effect on K metabolism similar to that produced by DOC. Further experimentation is necessary in order to establish the role of adrenocortical steroids in neuromuscular transmission and on the excitatory and contractile processes in muscle.

2. Effects on brain excitability. a. Effect on brain excitability as measured by electroshock seizure threshold. The effect of DOC on seizure threshold was first tested in rats by Spiegel (509) and Spiegel and Wycis (510) who found that this steroid elevated threshold only at high dose levels; related steroids had only a slight effect.

The effects of chronic administration of adrenocortical steroids and ACTH on brain excitability, as measured by changes in electroshock seizure threshold (EST) in rats, have been summarized by Woodbury (605) who found that DOC increased EST (decreased brain excitability) to the greatest extent, 11-desoxy-17-hydroxycorticosterone increased EST slightly, corticosterone had no effect in the dose used (2 mg per rat), 11-dehydrocorticosterone slightly decreased EST (increased brain excitability), and cortisol and cortisone markedly decreased EST (603); ACTH slightly increased EST, an observation confirmed by De Salva *et al.* (106) and Ercoli and De Salva (133). The latter workers also noted that rats became tolerant to the effect of chronic ACTH administration. Other steroids such as cholesterol, pregnenolone, and acetoxypregnenolone did not affect brain excitability in rats (605). However, some of the newer synthetic steroids also influence EST (343). Certain quantitative data of interest are

provided by the results of Holtkamp *et al.* (272) who found, in adrenalectomized rats, a linear relation between the EST effects of cortisone and DOC and the log of the dose.

The influence of various steroids in combination on brain excitability was also tested (603). The DOC-elevated seizure threshold could be lowered by ACTH, ACE, cortisone, cortisol, corticosterone, and dehydrocorticosterone; 11-desoxy-17-hydroxycorticosterone, cholesterol, pregnenolone, acetoxypregnenolone, and testosterone did not alter the DOC-elevated threshold. On chronic administration, ACTH and cortisone prevented the DOC-induced elevation in seizure threshold; conversely, ACTH and dehydrocorticosterone partially prevented and DOC completely prevented the cortisone-induced decrease in threshold. On acute administration to intact and adrenalectomized rats, corticosterone prevented both the increase in threshold caused by DOC and the decrease in threshold caused by cortisol. The respective effects of DOC, cortisol, and cortisone on threshold were greater in adrenalectomized than in intact rats (605, 610). Administration of 0.9% sodium chloride solution as drinking water enhanced the EST-elevating effect of DOC in both intact and adrenalectomized rats (610). The interpretation of the above results with steroid combination will be discussed in Section V.

The observations in rats, that DOC decreases and cortisone increases susceptibility to seizures evoked either by 60-cycle a.c. or by low-frequency direct current, have been confirmed in mice by Timiras *et al.* (548). The changes in electrolytes found by these workers to accompany the changes in brain excitability in mice are discussed below (Section III B 1).

Anticonvulsant drugs influence the brain excitability changes induced by DOC and cortisone (138, 604). Diphenylhydantoin, phenobarbital, and trimethadione enhanced the decrease in excitability produced by chronic treatment with DOC. Also diphenylhydantoin and phenobarbital protected against the increase in excitability produced by chronic treatment with cortisone (138). On withdrawal of the anticonvulsant drugs, however, the hyperexcitable state was restored within 2 days; this indicates that anticonvulsant drugs merely mask and do not prevent the increase in excitability induced by cortisone.

Summary: it is evident that the adrenocortical steroids produce definite changes in brain excitability, as measured by the EST technic. The steroids which predominantly affect electrolyte metabolism (DOC, 11-desoxy-17-hydroxycorticosterone) decrease excitability; those which predominantly affect carbohydrate metabolism (cortisone, cortisol) increase excitability; those with intermediate metabolic effects (corticosterone, 11-dehydrocorticosterone) have intermediate effects on excitability. The relation of the chemical structure of adrenocortical steroids to their action on brain excitability has been described by Woodbury (603, 605). The relation of the brain excitability changes to the influence of adrenocorticosteroids on brain electrolyte, carbohydrate, and protein metabolism is discussed below (Section III B).

b. Effect on brain excitability as measured by central chronaxie and by direct stimulation of cerebral cortex. The effects of adrenocortical hormones on central

excitability as measured by chronaxie in animals have been studied by Chauchard and Lecoq and their colleagues (62, 315–317). Their results were as follows: DOC and ACE increased central excitability; cortisone, cortisol, and 11-desoxy-17-hydroxycorticosterone decreased central excitability; corticosterone increased excitability only after chronic administration. These results are opposite to those reported by investigators using other technics. Even clinical reports indicate that DOC-like and cortisone-like steroids have effects opposite to those described by the French investigators. It appears likely that the measurement of central chronaxie is not an accurate method for measurement of brain excitability.

In a series of articles, Pasolini (392–395) reported the effects of adrenocortical steroids and ACTH on seizures evoked by electrical stimulation of the cerebral cortex in dogs; the study was undertaken because of the observation of Longo [cited by Pasolini (392)] that normal dogs became predisposed to evoked seizures after they were adrenalectomized. In intact and adrenalectomized dogs, injection of DOC increased the threshold for direct stimulation of the cerebral cortex and prevented seizures in some animals. In sharp contrast, cortisone and ACTH decreased the cortical threshold and increased the incidence of evoked convulsions, and cortisone antagonized the effects of DOC. The above described effects of the adrenocortical steroids on brain excitability as measured by direct cortical stimulation in dogs are in agreement with those obtained by the EST technic in rats and mice, except that ACTH increases brain excitability in dogs but produces little or no change in rats. This single discrepancy can be explained by the fact that ACTH in rats increases the adrenal output of corticosterone, a steroid which does not alter brain excitability, whereas ACTH in dogs enhances adrenal secretion of cortisol, a steroid which increases brain excitability.

The phenomenon of cortical "irradiation" (spread of the response from electrically stimulated areas of cerebral cortex to distant areas) was quantified in rabbits by Misrahy and Toman (370), and the effect of cortisone was determined. Ipsilateral electrical responses were compared with concurrent contralateral responses, and thresholds were measured on both sides for primary fast response, secondary slow-wave responses, and secondary spindles. Cortisone reduced the ratio of contralateral to ipsilateral threshold for all responses (an excitant effect of cortisone), despite variable effects on ipsilateral threshold. Such results emphasize the belief that factors other than a direct change in neuronal threshold may predominate in determining the over-all "excitant" or "depressant" action of pharmacological agents.

c. Effects on chemically-induced seizures in animals. The effects of ACTH and adrenocortical steroids on the sensitivity of rats to pentylenetetrazol (Metrazol) seizures have been studied by several investigators (322, 532, 559, 560). Acute administration of ACTH and cortisone increased susceptibility to Metrazol (560); in sharp contrast, chronic administration of ACTH decreased the susceptibility to such seizures (560). Leonard *et al.* (322) found that neither cortisone nor DOC influenced the susceptibility of mice to Metrazol. However, Swinyard *et al.* (532) observed that DOC increased susceptibility of mice to intravenously injected Metrazol, an effect opposite to its influence on electroshock seizures.

DOC was found to protect against seizures induced by cocaine in dogs (5). Methionine sulfoximine has been shown to be the convulsant substance in agene-treated flour (363, 427). Various steroid hormones have been examined for their influence on seizures induced in dogs by injection of agenized zein. DOC and progesterone protected against "agene"-induced seizures, whereas ACTH and cortisone exacerbated such seizures as evidenced by a decrease in their time of onset and an increase in their severity (87). Thus, as is true for electrically induced seizures, DOC decreases and cortisone increases brain excitability. The increase in seizure susceptibility induced by ACTH in agene-treated dogs can be explained by the fact that ACTH in this species causes the secretion mainly of cortisol; this steroid increases brain excitability.

d. Effect on audiogenic seizures. A relation between the adrenal cortex and the susceptibility to audiogenic seizures has been postulated by a number of investigators (83, 180, 282, 582). However, the experimental results provide no clear-cut picture of the effects of various adrenal steroids and ACTH on sound-induced seizures. Colfer (83) found that DOC decreased susceptibility of rats to seizures induced by an air blast; he also noted that brain electrolytes changed as a result of DOC treatment. In 30-day-old dba mice with an allegedly predictable seizure incidence, cortisone raised the incidence of convulsions in females to that characteristic of the males of this strain (180). On the other hand, Vicari *et al.* (582) observed that pregnenolone moderately decreased, and cortisone and ACE slightly decreased, not only the incidence of audiogenic seizures in mice but also the resulting high mortality. Hurder and Sanders (282) found that ACTH did not influence the susceptibility of rats to audiogenic seizure; the adrenals of their seizure-susceptible group were larger than those of the control nonsusceptible group; whether the large adrenals were the cause or the result of the seizures was not determined.

e. Effects of adrenocortical steroids and ACTH on seizure incidence in experimental animals and man. Further evidence for a central excitatory effect of the adrenocortical steroids of the cortisone type is provided by the fact that convulsive episodes occasionally occur in experimental animals and in man treated with such steroids. In rabbits, Pincus *et al.* (407) noted that ACTH treatment often produced convulsions, particularly when the dose was high. When newborn mice and rats were treated for 3 days with cortisone, Hicks (251) reported that convulsive episodes developed in the second or third week; pathological changes were also observed in the brains of these animals. Adult animals similarly treated did not exhibit seizures. These results demonstrate the extreme susceptibility of young animals to factors favoring convulsions.

Many clinical reports attest to the fact that both cortisone and ACTH increase brain excitability in man. In patients with no previous history of seizures, generalized convulsions have occurred during treatment of collagen diseases with ACTH and cortisone (20, 21, 22, 40, 96, 124, 175, 288, 336, 408, 591). Status epilepticus has also resulted (114, 523). In patients with lupus erythematosus, a disease known to effect the central nervous system and to cause convulsions, therapy with cortisone and ACTH has resulted in variable effects, including

precipitation of seizures (22) as well as a decrease in seizure frequency (456). Since ACTH elicits the secretion mainly of cortisol in man, a steroid which increases brain excitability, and mainly of corticosterone in rats (see 605), a steroid which has little influence on brain excitability, it is evident why ACTH predisposes to seizures in man but not in rats.

Although spontaneous seizures in Cushing's disease are said to be infrequent (181), Starr (521) reported that 4% of his patients had convulsions. There are no reports of spontaneous seizures in cases of adrenogenital syndrome associated with adrenocortical hyperplasia; it is possible that the increased amount of androgenic hormone(s) secreted by the adrenals in this disease protects against any increase in brain excitability which would occur from an excessive secretion of cortisone-like steroids. This possiblilty is supported by the observation of Henneman (248) that patients with this syndrome are notably resistant to the excitatory effects of cortisone even when large doses are given.

f. Anticonvulsant effects of adrenocortical steroids. The effect of DOC in epilespy was first examined by McQuarrie and associates (361, 362) who found that this hormone decreased the incidence of spontaneous grand mal seizures in two patients, and also antagonized the seizure-evoking effect of hydration produced by vasopressin administration. These provocative observations were not confirmed by Aird (5) who reported that DOC did not decrease the incidence of grand mal seizures in two epileptic patients. In a later paper, however, Aird and Gordan (6) demonstrated that DOC, given in combination with conventional anticonvulsant drug therapy to otherwise refractory epileptics, reduced the incidence of petit mal and to some extent of grand mal seizures. The effects of ACTH, DOC, and cortisone in 6 epileptic children, 5 of whom were on anticonvulsant drug therapy, were tested by Klein and Livingston (300); 4 of the 6 were benefited by ACTH, and one (with pure petit mal) showed no definite improvement. The single patient not on drug therapy was not benefited by DOC, cortisone, or ACTH; in fact, the ACTH had to be withdrawn because of the appearance of choreiform movements, motor deficit, and abnormal personality. Other investigators have not found cortisone or ACTH to be of any value in convulsive disorders; indeed, they must be considered as contraindicated because of their marked tendency to increase rather than to decrease brain excitability, and to predispose to or actually precipitate seizures. Only rarely is DOC employed in epilepsy; in an occasional refractory case, it has been temporarily used as an adjuvant agent. Since 11-desoxy-17-hydroxycorticosterone (substance S) has been shown to elevate EST in rats (603) without producing significant electrolyte distortions, its usefulness in combination with conventional anticonvulsant therapy in epileptic patients merits investigation.

3. Effects of adrenocortical steroids on recovery processes in the central nervous system. In addition to their effects on excitable processes in the central nervous system, the adrenocortical steroids also influence the central recovery processes. For example, in patients undergoing insulin-shock therapy, cortisone was found to be markedly beneficial in hastening emergence from deep hypoglycemic coma and in decreasing postictal depression (217). Experimentally, cortisol shortened

the duration of the postictal depression which follows electroshock seizures in animals pretreated with insulin (547); the decrease in blood sugar level produced by insulin in these animals was also prevented by cortisol administration.

Chronic treatment of rats with cortisol was found to shorten the recovery time (RT50) from maximal electroshock seizures and to increase the blood sugar concentration. Chronic treatment with DOC, however, did not modify the RT50 nor the blood sugar concentration (547). The relation of the changes in recovery time to changes in blood sugar is discussed below (Section III, B). The tonic-clonic pattern of the maximal electroshock seizure was also modified by cortisone (547). The duration of tonic flexion was shortened and that of tonic extension was lengthened. The increase in duration of the tonic extensor component is an indication of increased brain excitability, an observation which is in agreement with the previously noted decrease in EST produced by cortisone. The effects of ACTH and of steroid hormones other than DOC, cortisone, and cortisol on the recovery process have not been studied.

4. Analgesic, hypnotic, and anesthetic effects of adrenocortical hormones. a. Relation of adrenocortical hormones to analgesia. Because ACTH and cortisone relieve pain and joint swelling in patients with rheumatoid arthritis, some investigators believe that these hormones have analgesic properties. Several studies of the analgesic properties of ACTH and certain adrenocortical steroids have been published. Cortisone and ACTH had no effect on cutaneous, dental, or visceral pain in man or on pain from radiant heat in rats (208, 573). Compound S has been reported to lower tooth-pain threshold without influencing wrist-pain threshold (318). Jacob and Szerb (290, 291) found that repeated injections of ACTH or cortisone in mice progressively increased the thermal pain threshold, and claim that their method is more sensitive than those of workers who were unable to detect analgesic effects of the two hormones. In a well-controlled series of experiments, Winter and Flataker (598) studied the effects of DOC, cortisone, and ACTH on the responses of animals to analgesic drugs. The reaction time of the tail-flick response to thermal stimuli was measured in normal rats under various treatments. Cortisone, DOC, and ACTH did not alter normal reaction time; but cortisone and ACTH markedly reduced and DOC increased the reaction time prolonged by morphine or methadone in intact and spinal rats. In addition, cortisone exerted a synergistic effect with the narcotic antagonist, nalorphine, enhanced the well-known excitatory effect of morphine in cats, and moderately increased the LD50 of methadone in mice. Since death from methadone results from respiratory depression, it is likely that cortisone, by increasing central excitability, antagonizes the methadone-induced respiratory depression. Since cortisone inhibited the effect of morphine in spinal animals and antagonized the hypnotic and respiratory depressant effect of the analgesic drugs, Winter and Flataker concluded that cortisone is stimulatory to the entire cerebrospinal axis. This conclusion is certainly in harmony with the evidence so far presented in this review. DOC was found by Loewe (331) to diminish morphine-induced mania in cats, an observation previously made by Winter and Flataker.

The effects of cortisone and ACTH on the acute abstinence symptoms of

patients undergoing morphine withdrawal have been reviewed and critically evaluated by Fraser and Isbell (155). They found that neither cortisone nor ACTH relieved these symptoms; in fact, ACTH caused the withdrawal symptoms to appear earlier and the patients to complain more. These data in man are in agreement with those of Winter and Flataker obtained in animals, as presented above.

Certain observations have linked epinephrine to the analgesic effect of morphine. Harris and Friend (163, 231) and Gross *et al.* (209) demonstrated that the analgesic response to morphine in rats and dogs is markedly reduced after removal of the adrenal medulla (transplantation of the cortex to the eye). Epinephrine and certain of its congeners are moderately potent analgesics (289, 320), and morphine causes the discharge of epinephrine from the adrenal medulla (100). Therefore it has been concluded that epinephrine released from the medulla mediates, at least in part, the analgesic effect of morphine. The observation of Zauder (618) that morphine, meperidine, and methadone still produced analgesia in hypophysectomized rats indicates that these drugs have a central analgesic effect not mediated through the hormones of the hypophysis, but does not rule out an effect through stimulation of epinephrine release from the medulla. However, the finding of Way *et al.* (590) that morphine exerts its full analgesic effect in adrenal-demedullated rats excludes epinephrine as an intermediate in the analgesic effect of morphine. Puharich and Goetzl (417) observed that cortical extracts were without influence on the analgesic effect of morphine. The available data appear to indicate that the adrenal cortex plays no role in the analgesic effect of morphine. Yet, as discussed previously, the observations of Winter and Flataker show that the adrenocortical steroids do modify the analgesic effect of morphine, and those of Jacob and Szerb indicate that they may have a central analgesic effect *per se*. It is also quite clear that certain of the central depressant effects of morphine can be antagonized by cortisone and synergized by DOC.

Clinically there is little doubt that patients who receive cortisone and ACTH for rheumatoid arthritis obtain relief of joint pain. Such relief of pain is probably due to improvement in the pathological condition causing the pain. However, the known euphoric effect of cortisone and ACTH may also be important. Recurrent reports of the relief of pain by cortisone and ACTH in various conditions can usually be explained on the basis of the anti-inflammatory and euphoric effects of these hormones.

b. Relation of adrenocortical hormones to drug-induced sleep. The effects of adrenocortical hormones on the duration of sleep induced by hexobarbital in mice have been studied by Winter and Flataker (599) who found that cortisone and ACTH shortened sleeping time whereas DOC had no effect. In addition, the markedly prolonged sleeping time of mice receiving a combination of hexobarbital and diphenhydramine was also decreased by cortisone, but the effect of the steroid could be fully accounted for by its antagonism to the action of the barbiturate; thus cortisone was without influence upon the central depressant effects of diphenhydramine. Winter and Flataker concluded that cortisone was an "analeptic" drug, but that its central stimulant action was different in nature

from that exhibited by caffeine and amphetamine. It is of interest that the anticonvulsant effect of phenobarbital (elevation of EST) can be enhanced by DOC (604) and antagonized by cortisone (138); thus the depressant effect of phenobarbital, like that of pentobarbital, can be altered by DOC and cortisone. Clinically, Boswell (42) and Fraser *et al.* (156) reported that cortisone was useful in the treatment of the barbiturate-withdrawal syndrome. The rationale for this use is not apparent, particularly because the syndrome is characterized by central excitation (delirium, convulsions); perhaps the psychic effects of cortisone account for the reported benefit.

c. Relation of adrenocortical hormones to anesthesia. An "anesthetic" effect of DOC, progesterone, and other "hormonally active" steroids in rats, mice, guinea pigs, rabbits, pigeons, and fish was reported by Selye (477–484, 600, 601). Large doses given intraperitoneally to susceptible rats (immature females weighing 50 to 100 g or partially hepatectomized rats) produced deep anesthesia, characterized by quiet respiration and not preceded by any obvious signs of excitation; the animals recovered without ill effects. Prolonged abdominal operations could be performed on rats anesthetized with DOC or progesterone. Death from large doses was apparently caused by central respiratory paralysis; significant pathological changes were absent. The safety margin between the anesthetic and the lethal dose was comparatively wide, and the anesthesia was accompanied by pronounced muscular relaxation (482). The anesthetic effect of progesterone was enhanced by treatment of animals with glucose or epinephrine, whereas it was antagonized by treatment with insulin or exposure to excessive heat or cold (600). The anesthetic effect of progesterone or DOC could be counteracted by Metrazol and, conversely, otherwise fatal doses of Metrazol were readily survived without convulsions by rats receiving anesthetic doses of the steroids (482).

Other investigators (58, 297, 308, 583) have confirmed the anesthetic effect of certain adrenal steroids in experimental animals. In man, progesterone has been reported to produce somnolence in minimal anesthetic doses (365). On the other hand, some workers (134) are of the opinion that the depression produced by DOC and progesterone is not true anesthesia, because the animals can be aroused and exhibit reflex activity to externally applied stimuli, a situation that would not obtain if the animals were as deeply anesthetized as claimed by Selye.

However, some reports (125, 137, 196, 197, 305, 314, 323, 373, 390) indicate that the intravenous injection of a hormonally inactive steroid (21-hydroxypregnane-3,20-dione sodium succinate [hydroxydione]) will produce true anesthesia in experimental animals (cats, dogs, and monkeys). It has also been used as a "safe, convenient and practical basal anesthetic for surgical procedures in man" (197, 314). The depressant activity of this compound in mice and rats is said to be equal to that of thiopental sodium and its toxicity is claimed to be much less; purported advantages of hydroxydione anesthesia are minimal respiratory depression, rapid uncomplicated recovery, and minimal postanesthetic depression [(323, 373), however, see (275)]. Little or no hormonal activity could be demonstrated after administration of large doses in experimental

animals. Therefore, it appears that certain steroids (with or without hormonal activity) can produce an anesthetic effect which is related more to their intrinsic steroid properties than to their specific hormonal activity. Further experimentation in this area is necessary.

5. Effects of adrenocortical steroids and ACTH on electrical activity of the brain. a. Effects of adrenocortical steroids and ACTH in man. EEG changes induced by adrenocortical steroid hormones and ACTH have been reported by many investigators (39, 85, 101, 102, 146, 161, 162, 185, 186, 200, 269, 378, 408, 420, 422, 527, 569, 591, 592). The first extensive report of the effects of ACTH and cortisone on the EEG in man was that of Hoefer and Glaser (269) who found that ACTH and particularly cortisone caused the appearance of a significant amount of moderately slow wave activity (4 to 7/sec), and an increase in sensitivity to hyperventilation; however, the incidence of these changes was variable. In 4 epileptic patients, Klein and Livingston (300) observed that ACTH therapy decreased the incidence of seizures and improved the EEG pattern. In contrast, Glaser and Merritt (186) noted that ACTH and cortisone increased the incidence of abnormalities in the EEG in epileptic patients and did not reduce the frequency of seizures. It is of interest that all but one of the patients treated with ACTH by Klein and Livingston (300) were on standard anticonvulsant medication; the patient not on an anticonvulsant developed a severe reaction (choreiform movements, and abnormal personality) which necessitated withdrawal of the ACTH. In view of the fact that diphenylhydantoin and phenobarbital protect against cortisone-induced hyperexcitability in rats (138), it seems likely that, in the patients observed by Klein and Livingston, any central excitatory effects of cortisone and ACTH were masked by the concomitant anticonvulsant medication; in the single case in which anticonvulsant medication was not used, excitatory phenomena appeared.

The effects on the EEG produced by intravenous administration of cortisol and ACTH were measured by Glaser *et al.* (185) who found that both hormones increased theta activity (5 to 7/sec) in the EEG. Cortisol seemed to exert this effect more consistently and to a greater degree than did ACTH. The effect was somewhat greater in epileptic subjects with previously abnormal EEGs. In two epileptic patients cortisol increased the incidence of 2 to 3/sec spike-wave seizure discharge. No correlation between EEG alterations and serum electrolyte changes was found, despite the fact that there was an increase in serum K concentration in 5 of the 7 patients given cortisol intravenously.

A tentative hypothesis for the mode of action of cortisone on the EEG has been advanced by Streifler and Feldman (527), based on the following observations: ACTH and cortisone act on the hypothalamus and thalamus; electrical stimulation of the basal structures of the brain modifies the electrical activity of the cortex in experimental animals; hypothalamic lesions slow cerebral cortical activity. These observations, coupled with those of Castor *et al.* (57) that cortisone and ACTH cause pathological changes in the hypothalamus and thalamus, led Streifler and Feldman (527) to suggest that the EEG changes induced by these hormones may, to some extent, be due to their direct action on diencephalic

structures. The fact that most of the EEG changes induced by the 17-oxysteroids are in the direction of slower activity is compatible with the hypothesis of Streifler and Feldman, and indicates more specifically an effect either to depress the mesencephalic reticular activating system or, more likely, to enhance the recruiting response in the diffuse thalamic projection system (see 399). The fact that cortisone has general excitatory properties on the nervous system indicates that it probably is acting to enhance the recruiting response in the thalamus, rather than to depress the arousal response from the mesencephalic reticular activating system. It could, however, excite inhibitory pathways in this area and thereby produce the observed effects on the EEG. No evidence for or against this possibility is available. The fact that 17-oxysteroids decrease the low-frequency EST (548) suggests that this steroid does enhance the recruiting response in the diffuse thalamic projection system. Low-frequency seizures appear to originate in this area and then spread to the cerebral cortex (360). Further research to localize the anatomical site of cortisone action is needed. Corticosterone and 11-dehydrocorticosterone have both been shown to correct the EEG abnormalities in patients with Addison's disease (85, 146), but these steroids have not been studied for their EEG effects in patients with collagen diseases or in normal individuals.

DOC has little influence on the EEG; however, Aird and Gordan (6) did note a small, but consistent, decrease in the frequency of abnormal waves in 6 epileptic patients treated with this steroid. Ward *et al.* (588) found that aldosterone did not alter the EEG pattern of patients with rheumatoid arthritis.

b. EEG changes induced by hypercorticism: Cushing's disease and adrenogenital syndrome. EEG changes in Cushing's syndrome are similar to those induced by ACTH and cortisone and need be mentioned only briefly (183, 409, 503). The main change is a decrease in the frequency of the alpha rhythm to a value of 3 to 7/sec. This shift appears to be correlated with an enhanced sensitivity to seizures. Two of 7 patients in one series developed seizures (183). No reports have come to the reviewer's attention concerning the EEG pattern of patients with adrenogenital syndrome.

c. Effects of adrenocortical steroids and ACTH in experimental animals. Relatively few experiments have been performed to test the effects of adrenocortical hormones on the electrical activity of the brain in intact animals, in contrast to animals with adrenocortical insufficiency (204–206, 386, 416, 507, 560). In cats, ACE has been reported to increase the amplitude and the frequency of the EEG and to prevent the flattening of waves associated with the edema resulting from exposure of the brain (204–206, 416). Similarly, Torda and Wolff (560) demonstrated in normal rats that ACTH increased the EEG voltage and produced occasional spiking and paroxysmal runs of low-frequency, high-voltage waves. Anoxia-induced disappearance of brain waves in rats was delayed by ACTH administration (507). The relation between these reported EEG effects of ACTH and ACE and their effects on brain excitability is not clear from the meager data available.

6. Effects of adrenocortical hyperfunction on psyche and behavior. Of all the

effects of adrenocortical activity on the nervous system, none has been studied as extensively as has that on the psyche. The magnitude of the subject permits only a general summary in this review. Reference is made to several key articles on the subject, some of which review the literature (44, 50, 53, 54, 60, 69, 70, 73, 74, 76, 78, 116, 120, 143, 151–153, 179, 183, 191, 245, 269, 311, 324, 329, 335, 342, 389, 425, 441, 443–446, 458, 513, 538, 542, 565); particular attention is called to the provocative review by Quarton *et al.* (419).

a. Observations in man: Cushing's disease and the adrenogenital syndrome. That adrenocortical hyperfunction is associated with mental disturbances has been reported by numerous investigators [see Cleghorn (76, 78) for a review of earlier literature]. The mental changes are more severe and more prevalent in patients with Cushing's disease than in patients with the adrenogenital syndrome (296, 503). The difference between the two diseases apparently is that plasma 17-ketosteroid levels are high and plasma 17-hydroxysteroid levels are normal or low in the adrenogenital syndrome, whereas the plasma concentrations of both 17-ketosteroids and 17-hydroxysteroids are elevated in Cushing's disease. The 17-hydroxysteroids seem to be the more potent in producing mental changes and can even antagonize the 17-ketosteroids. The use of the 17-ketosteroid, dehydroisoandrosterone, for the treatment of certain types of mental disorders (306, 526) would seem to support this point of view.

Mental changes in *Cushing's syndrome* have been described by many investigators (36, 86, 183, 239, 240, 409, 475, 504, 511, 521, 566). Spillane (511) has summarized the literature on 50 cases of Cushing's disease reported prior to 1951, and in addition described 7 new cases, 5 of which manifested significant mental and/or neurological disturbances. He points out that 2 patients became psychotic in the early stages of the disease, even prior to the development of the pathognomonic physical characteristics of the syndrome. A similar observation has been made by Trethowan and Cobb (566). Thus mental symptoms can be an early feature of this disease. The reported incidence of psychic changes in various series ranges from as high as 67 to 84% (409, 511) to as low as 20% (see 566). Of the 25 cases described by Trethowan and Cobb (566), 4 were severely disturbed, 6 markedly disturbed, and 8 mildly disturbed; 3 patients had quite minimal psychiatric symptoms; only 4 patients were thought to be mentally normal. These authors state, "It is obvious that no single clear-cut psychiatric picture emerges from the galaxy of mental symptoms that these patients present. If to these be added the manifestations described by other authors, the catalogue of symptoms becomes so extended as to cover a large part of the total range of known psychiatric phenomena." they continue, "Depression of some degree, often, though not invariably, associated with retardation, is perhaps the state most frequently encountered. Retardation, when absent, appears to be replaced by irritability in the form of agitation, anxiety, crying spells, or non-cooperative behavior, or both retardation and irritability may appear in the same patient at different times." They point out that the mental disturbances which occur in association with ACTH and cortisone therapy are also characterized, like those in Cushing's disease, by variability in the nature of the mental symptoms and

by the fact that depression, often associated with pronounced irritability and the appearance of paranoid ideas, is the most frequent phenomenon. Mental changes in Cushing's disease are often, but not always, accompanied by the EEG changes previously summarized.

Adequate recovery from the neuropsychiatric changes ensues upon treatment of the disease, usually by surgery; hence the changes must be considered as reversible except when brain damage has occurred. Often treatment of the disease results in hypofunction of the adrenal cortex, whereupon the mental changes characteristic of Addison's disease may appear; such changes respond well to therapy with cortisone plus DOC.

Mental abnormalities in the *adrenogenital syndrome* were first reported by Holmes (271). The characteristic changes, as described by Soffer (503), Allen (9), and Kepler and Locke (296), are as follows: severe depression, irritability, psychotic changes, occasionally mania, periods of excitement and paranoid confusion, and thoughts of suicide; again, depression is the most common symptom. Thus mental changes occur in both of the diseases of adrenocortical hyperfunction. The psychic disturbances are more marked in Cushing's syndrome. They are reversible with proper treatment of the disease. The relation between the metabolic disturbances and the psychic changes induced by adrenocortical hormones is discussed in Section III B.

b. Observations in man: effects of ACTH and adrenocortical steroids. Hartman and coworkers (232, 233, 235) were probably the first investigators to emphasize that adrenocortical steroids affected mental function. They noted that ACE exerted a beneficial effect on mental outlook in patients with various functional and organic diseases of the nervous system; patients with profound depression or irritability often became cheerful and calm. These observations remained relatively unnoticed until Hench and coworkers (244, 245) reported nervousness or euphoria in 6% of individuals given large doses of cortisone and ACTH for rheumatoid arthritis. Their observations were quickly confirmed by many other workers, and it is now universally appreciated that these hormones exert profound effects on the psyche and behavior. The wide variety of psychic reactions include irritability, sleeplessness, euphoria, manic behavior, depression, ambivalence, hypomania, frank psychosis, and often an increase in appetite.

The reported incidence of mental disturbances induced by ACTH and adrenocortical steroids varies with different investigators, largely as a result of different criteria employed for assessing psychic alterations. An incidence as high as 60 to 70% has been reported in some series. Patients with severe and chronic diseases seem to be more susceptible, perhaps because large doses are employed in such individuals (342). The euphoria which occurs early in the course of treatment has been attributed to the relief of pain or disability; however, cortisone produces euphoria even in normal subjects (542).

None of the investigators in this field questions the occurrence of psychological changes from therapy with adrenocortical steroids; the main argument centers around the cause of such changes. Quarton *et al.* (419) have reviewed the various theories advanced to explain these mental disturbances. Their article contains

the following statement: "After reviewing the many specific hypotheses purporting to explain mental disturbances associated with ACTH and cortisone, we are obliged to conclude that at the present time there is no completely satisfactory hypothesis. The greatest problem is that we lack certain key information needed to accept or reject the more important possibilities."

Rome and Braceland (443–446) scored the psychological reactions to ACTH and adrenocortical hormones into four grades of increasing severity, as follows: Grade I comprised deviations in mood, usually in the direction of elevation. The patients felt more vigorous than they actually were, and stated that their thinking was accelerated and that they never felt better in their lives. Mood alterations were often correlated with the amelioration or disappearance of the underlying disease, but sometimes they appeared considerably in advance of such a remission. Grade II included the mood alterations noted in Grade I, in more marked degree, and also restlessness, insomnia, and an increase in motor activity; mental activity was markedly accelerated. Approximately 60 % of the large number of patients in the series reported by Rome and Braceland exhibited responses in grades I and II. Grade III comprised a wide variety of responses, including marked anxiety, phobias, obsessional preoccupations, lethargy, indifference, crying, agitation, feelings of hopelessness, excitement, and ideational flights. Approximately 25 to 30 % of their patients were in this group. Grade IV included only the grossly psychotic reactions. A large majority of patients with this type of response had a history of previous psychiatric illness. Ten per cent of the series of cases were scored as Group IV. These investigators also pointed out that patients with Addison's disease were more vulnerable to untoward responses to steroid therapy than were those with normal adrenocortical function, an observation also reported by other investigators (70, 73, 74, 151, 419, 542).

The relative potency of the various adrenocortical steroids in producing abnormal mental reactions may be summarized as follows: When given in excess, DOC seems to exert untoward actions on the psyche (74), although it can counteract some of the psychic effects produced by cortisone, especially the stimulatory effects. Corticosterone is effective in patients with Addison's disease and imparts a feeling of "pep" and well-being to such patients, without producing nervousness (85). The mental effects of corticosterone given in excessive amounts to patients with normal adrenocortical function have not been adequately described. 11-Dehydrocorticosterone resembles corticosterone in its psychic actions. Cortisol, like cortisone, restores to normal the disturbed mental condition occurring in Addison's disease, and produces less nervousness in such patients than does cortisone (542). Cortisol given to patients with rheumatoid arthritis, in doses capable of producing marked metabolic effects, causes considerably less euphoria than is experienced after equivalent doses of cortisone (71). However, Rome and Braceland (444–446) and Perera *et al.* (400) have reported mental disturbances as a result of cortisol therapy; but the frequency and severity of the reactions are less than with cortisone. The effect of 11-desoxy-17-hydroxycorticosterone on the psyche has not been adequately evaluated, but it is probably similar to that of DOC. ACE apparently has not caused mental disturbances

comparable to those induced by metabolically equivalent doses of cortisone and ACTH (419). ACTH has been variously reported to cause more psychic disturbances than does cortisone (329), fewer than does cortisone (245), and not to differ from cortisone (153, 541, 542). Fleminger (143) believes that ACTH and cortisone exert opposite effects on mood, cortisone elevating and ACTH depressing mood level. Since cortisone decreases whereas ACTH increases 17-ketosteroid excretion, Fleminger suggested that cortisone and ACTH may influence mood by changing the ratio of circulating androgens to cortisone (or its equivalent). This suggestion deserves further investigation; its relation to the regulation of central nervous system activity by adrenocortical hormones is discussed in Section V.

All types of frank psychotic reactions to ACTH and cortisone have been described (3, 9, 12, 70, 120, 154, 183, 237, 295, 445, 459, 565). The reported incidence ranges from as high as 19 % to as low as 3 %. Glaser (183) has described two major patterns of such psychoses, a primarily affective disorder, either manic or depressive, and, more frequently, an organic (toxic) psychosis with associated paranoid hallucinatory and/or affective components similar to those occurring in Cushing's disease. However, Clark *et al.* (70) believe that "toxic psychoses," that is, disorientation and confusion, are not characteristic of psychotic reactions to ACTH and cortisone therapy; they noted that many of the symptoms and mechanisms seen in the schizo-affective group of psychoses were in evidence, and that disorientation and confusion appeared only in patients who were ill from a medical standpoint. The psychoses induced by adrenocortical hormones are reversible upon withdrawal of hormonal therapy.

c. Observations in experimental animals: effects of adrenocortical steroids and ACTH on behavior. In contrast to the mass of literature on the psychic and behavioral effects of ACTH and adrenocortical hormones in man, only meager information is available on such effects in experimental animals. The first report of the influence of adrenocortical steroids on behavior in experimental animals was published by Liddell and coworkers (326, 327) who tested the effect of ACE on experimental conditioned neuroses in sheep. Chronic administration of ACE subcutaneously produced a "dramatic effect"; the neurotic animals became calm, their conditioned reflexes were more precise and vigorous, and tic-like movements were noticeably decreased. Further experiments are indicated, especially to test the effects of the individual steroids, such as DOC and cortisone, on experimentally-induced neuroses. Mirsky *et al.* (367, 368) studied in monkeys the effects of ACTH upon conditioned fear reactions linked to bar-pressing required to obtain food. ACTH-treated animals were found to make a greater number of food-getting responses and were less frightened, more aggressive, and more exploratory in their behavior than were the controls.

7. Miscellaneous central nervous system effects of adrenocortical hyperfunction. a. Antipyretic effect of adrenocortical hormones. Early in the clinical use of ACTH and cortisone, it was observed that a prompt fall in temperature occurred in febrile diseases (245, 293). Kass and Finland (292) further confirmed this apparent antipyretic effect of the adrenocortical hormones by demonstrating that

the duration and the intensity of the febrile response to an injection of killed typhoid bacilli in man and rabbits was reduced by prior administration of ACTH. The antipyretic property of cortisone has been demonstrated in rabbits given pyrogenic bacterial vaccines (313, 424). The mechanism of the antipyretic action is not known. Cortisone and ACTH exert anti-inflammatory effects on tissues, and the fever which results from an inflammatory process would thus be expected to decrease under such therapy. However, the possibility has not been ruled out that these hormones might also influence the hypothalamic thermoregulatory centers.

b. Effect of adrenocortical hormones on appetite. In their first report on the use of adrenocortical hormones in rheumatoid arthritis, Hench *et al.* (244) commented upon the marked effect to increase appetite. Others have confirmed the high frequency with which hyperphagia occurs in association with cortisone and ACTH treatment (408, 542). However, in rats, van Putten *et al.* (578) found that ACTH and cortisone did not increase the spontaneous food intake of normal or stressed rats, and concluded that the appetite stimulating effect observed clinically is the result of a general improvement in the patient's condition. The mechanism of the hyperphagic action of ACTH and cortisone remains to be disclosed, and it is not absolutely certain that the increase in appetite is merely secondary to improvement in the underlying disease process. In view of the known role of the hypothalamus in the control of appetite, it is possible that the hyperphagic action of adrenocortical hormones may be due in part to their effect on the central nervous system.

B. Metabolic effects of adrenocortical hyperfunction on the central nervous system

1. Effects on electrolyte metabolism. The effects of adrenocortical steroids on electrolyte metabolism of tissues other than brain have been examined in considerable detail. DOC has been most extensively studied with respect to tissue electrolytes, including brain, whereas cortisone, hydrocortisone, and ACTH have been less thoroughly examined. In tissues other than brain, it has been shown that DOC causes a rise in intracellular Na concentration and a concomitant loss of intracellular K. In contrast, cortisone and ACTH exert only a mild effect on such tissues. In rats, cortisone causes a slight loss in skeletal muscle Na with little influence on K distribution, whereas ACTH has no effect.

The effects of DOC on brain electrolytes were studied by Woodbury and Davenport (609) who found that total brain Na and K concentrations were not altered but that brain intracellular Na concentration, calculated on the assumption that chloride space is a measure of extracellular fluid volume, was markedly decreased; although brain intracellular K concentration remained unchanged, the ratio of intracellular to extracellular K in brain was increased by DOC treatment. The decrease in brain intracellular Na was associated with an increase in EST (decrease in brain excitability), an observation consistent with that discussed above for adrenalectomized rats and mice. That a fundamental difference exists in intact rats between the effects of DOC on brain and other tissues (particularly skeletal muscle) is indicated by the fact that only in brain does DOC

decrease intracellular Na concentration; in other tissues studied (muscle, heart, liver, skin), intracellular concentration of Na is increased while that of K is decreased (606). This is strong evidence that the decrease in brain excitability induced by DOC is a result of the decrease in brain intracellular Na concentration. The above described brain electrolyte effects of DOC have also been reported by Colfer (83), Hoagland (258), and Timiras *et al.* (548).

The influence of DOC treatment on the turnover of radioactive Na in brain and other tissues of dogs was studied by Overman *et al.* (387) who found that DOC increased the turnover of brain Na in adrenalectomized but not in intact dogs; since the measurement of the Na^{24} uptake was made only 30 min after injection of the isotope, it is hard to interpret these results. The reviewer suggests, on the basis of his own experiments (606), that correct analysis of the effects of agents on the uptake of radioelectrolytes in brain requires data on the complete activity-time curves for periods up to 24 hours. Although it is likely that DOC actually does increase the turnover of Na^{24} in brain cells, more convincing information is necessary.

Some unpublished experimental results (545) are of interest in relation to the effects of DOC on brain electrolytes and excitability. DOC administered chronically to unilaterally nephrectomized, castrated, *adult* rats given 0.9% sodium chloride solution to drink caused a decrease in brain excitability and in brain intracellular Na concentration, an increase in brain extracellular Na concentration, and an increase in the ratio of brain intracellular to extracellular K concentration; cerebral edema did not occur. However, in *young* rats prepared and treated in exactly the same manner, brain excitability was decreased only during the first 11 days of DOC administration, and then increased until the time of sacrifice for electrolyte analyses on the 50th day; the large (toxic) doses of DOC caused marked cerebral edema and the extracellular water content of the brain was elevated. In these young rats, instead of the usual pattern of electrolyte changes caused by DOC, intracellular brain Na increased despite the fact that the brain K ratio was enhanced. Thus, in non-toxic doses in the adult animals, DOC decreased brain excitability and intracellular brain Na concentration, whereas toxic doses in the young animals increased brain excitability and intracellular Na concentration, a change in Na that DOC produces normally in other tissues. (Changes in brain amino acids induced by DOC in these animals are discussed in Section III B 4.) The experimental results indicate that DOC in low doses stimulates the active pumping of Na out of brain cells; but, under special conditions and in the presence of excess Na, this effect on the Na pump fails, toxicity results, and brain excitability increases. The toxic side effects of DOC, such as the convulsions induced in rats by high doses, may be related to this effect on brain Na.

The changes induced by aldosterone in brain and skeletal muscle electrolytes have been studied in mice (614). This steroid increases the ratio of extracellular to intracellular Na concentration and intracellular to extracellular K concentration in both brain and muscle. Thus aldosterone and DOC produce similar effects on brain electrolytes but opposite effects on muscle electrolytes. This discrepancy

was resolved by Withrow and Woodbury (602) who found that DOC had the same influence as aldosterone on Na and K concentrations in muscle in nephrectomized, partially eviscerated rats. Thus the action of DOC to increase Na and decrease K concentration in muscle of intact animals is secondary to the marked effect of this hormone to increase the renal and gastrointestinal excretion of K. The effect of large doses of DOC to increase intracellular Na concentration in young rats might be explained by the renal actions of this steroid.

The influence of other adrenocortical steroids and ACTH on brain electrolytes has been studied by Woodbury (605, 606) in rats and by Timiras *et al.* (548) in mice. The results may be summarized as follows: In *rats*, chronic administration of ACTH, cortisone, cortisol, corticosterone, dehydrocorticosterone, and 11-desoxy-17-hydroxycorticosterone had no effect on brain electrolytes in the doses used and for the period administered (28 days), although they markedly affected brain excitability. In *mice*, on the other hand, hydrocortisone increased brain excitability and markedly increased brain Na and Cl spaces. The increase in both Na and Cl spaces indicates either an affect of cortisol on the permeability of brain cells, such that both Na and Cl enter the cells without a net increase in intracellular Na concentration, or an effect on the glial tissue of brain. The increase in brain Cl space induced by cortisol in mice suggests that extracellular space is influenced by this steroid; an increased permeability may occur, that is, the ground substance and glia may become more fluid. This possibility is borne out by an observation discussed below that cortisone affects growth and proliferation of glial cells in tissue cultures of cerebral cortex. Further experiments on the connective tissue effects of cortisone in relation to the extracellular space of brain are being conducted in the reviewer's laboratory.

The influence of *acute* administration of cortisol (and DOC) on brain electrolyte metabolism has also been studied (581, 616). The results for DOC are the same as noted above for chronic injection of this steroid. However, the acute administration of cortisol differed from the chronic in that it increased brain intracellular Na concentration, decreased the brain Na ratio, and increased brain excitability. Thus the changes in brain electrolytes induced acutely by cortisol correlate with the observed changes in excitability. The results differ from those noted above for *chronic* cortisol treatment in which no measurable changes in intracellular brain electrolytes were noted. In this particular situation, the effect of chronic treatment on the connective tissue space of brain, or the shift of hydrogen ions across cell membranes which occurs during chronic cortisol administration and in Cushing's disease (512, 536), may obscure the real electrolyte shifts and thereby modify brain excitability. Acute administration of DOC and cortisol affects brain amino acid as well as brain electrolyte metabolism; the relation between these two effects is discussed in Section III B 4.

The observation that chronic administration of cortisone and related steroids increases brain excitability without a significant change in brain electrolyte metabolism tends to confirm the conclusion that the central effects of DOC and adrenalectomy are mediated through an influence on electrolyte metabolism. If the electrolyte changes were secondary to the depressant or excitant effects of

DOC and adrenalectomy, respectively, then cortisone, cortisol, and dehydrocorticosterone, three steroids which increase brain excitability, would be expected to cause an increase in brain cell Na concentration; this is not the case. Since cortisone and cortisol do not greatly influence electrolyte metabolism on chronic administration, the mechanism of their central action is still unexplained.

2. Effects on cerebral blood flow, and on brain oxygen and glucose consumption in vivo and in vitro. a. In vivo observations in man. The effects of ACTH and cortisone on cerebral blood flow in man have been studied by several investigators. Schieve *et al.* (473), who were the first to study the problem, observed that ACTH decreased cerebral blood flow in the 14 subjects tested, and that this decrease was associated with an increase in cerebral vascular resistance, a slight increase in mean arterial blood pressure, and no change in cerebral metabolic utilization of oxygen or glucose. However, both Alman and Fazekas (10) and Sensenbach *et al.* (488) found no changes in cerebral blood flow or metabolism in subjects treated with ACTH or cortisone; similar negative results were obtained in 2 patients with Cushing's syndrome (488). Although an increase in cerebral vascular resistance was noted in the experiments of Sensenbach *et al.*, this was paralleled by an increase in mean arterial blood pressure, and hence there was no change in cerebral blood flow. It must be concluded that the results of these studies provide no explanation for the mental, EEG, and brain excitability changes that occur during the administration of cortisone and ACTH.

The effects of DOC on cerebral blood flow and metabolism have been studied by Bentinck *et al.* (28), Gordan *et al.* (192–194), and Schieve and Wilson (474). Although Bentinck *et al.* found that DOC produced no change in mean arterial blood pressure or cerebral blood flow, the steroid did cause a rise in the sugar concentration in cerebral venous blood over that in arterial blood. This increase indicates that DOC caused a liberation of sugar from the brain, probably galactose mobilized from brain cerebrosides (193, 194), as discussed in Section III B 4. However, Schieve and Wilson (474) were unable to confirm the above described results; in their experiments, DOC did not cause an increase in sugar concentration in cerebral venous blood.

b. In vitro observation in animals. [See review by Gordan *et al.* (192–194).] The effects of various steroids on the respiration of rat brain homogenates were studied by Gordan and Elliott (195). DOC and progesterone and other nonadrenal steroids were compared with cholesterol, with respect to their influence on oxidation of glucose, succinate, and pyruvate. The inhibition of respiration in the presence of glucose or pyruvate (194) produced by DOC and progesterone and the lack of effect produced by cholesterol ran parallel with the reported anesthetic potency of these steroids. However, these steroids had little effect upon the oxidation of succinate. The effects of cortisone and cortisone-like steroids on brain oxygen consumption *in vitro* have not been studied.

The depression of brain respiration by DOC, as observed by Gordan and Elliott (195), has been confirmed by Eisenberg *et al.* (123) who found a linear relation between the logarithm of the dose and the per cent inhibition of respiration. Hayano *et al.* (238) also noted that DOC inhibited oxygen consumption of

rat brain slices and homogenates in the presence of a variety of oxidizable substrates. However, the inhibition was not the result of an interference with the cytochrome C-cytochrome oxidase system since DOC did not block this system. In an earlier study, Tipton (550) demonstrated that ACE and corticosterone depressed the oxygen consumption of rat brain tissue.

Gordan *et al.* (194) have concluded that the locus of steroidal inhibition of oxidation of glucose or pyruvate, not reversed by methylene blue, is at the level of the dehydrogenases. They further point out that, since anesthetic agents are believed to produce their biological effects by inhibiting the utilization of carbohydrate at the cytochrome level, it appears that steroids have a different mode of action than do the usual anesthetics. The observations of Hayano *et al.* support these conclusions.

The oxygen consumption is high in brains removed from castrated male rats. If such rats are first treated with ACTH, DOC, testosterone, progesterone, or other steroids, the *in vitro* oxygen consumption of their brains is reduced to normal. The efficacy of ACTH in this respect indicates that the adrenal steroids released by it can also inhibit oxygen consumption of rat brains *in vivo*. The relation of these findings to carbohydrate, protein, and fat metabolism of brain is discussed in Section III B 4.

The observations of Roberts and Keller (438) have demonstrated that cortisone injected intravenously reduces the oxygen consumption of rat adenohypophyseal tissue within 4 hours, but increases the respiration and aerobic glycolysis of posterior hypothalamic tissue. In contrast, epinephrine enhances respiration and aerobic glycolysis in both tissues. It was suggested that both cortisone and epinephrine activate neurohumoral pathways in the posterior hypothalamic-adenohypophyseal system, cortisone to produce an inhibitory effect and epinephrine to cause stimulation. The relation of these findings to the regulation of ACTH secretion is discussed in Section IV.

3. Effects of adrenocortical hyperfunction on acetylcholine and ammonia metabolism in the brain. In a series of publications Torda (551) and Torda and Wolff (554, 555, 562) reported their research on the effects of ACTH and adrenocortical steroids on the synthesis of acetylcholine by brain tissue, and came to the conclusion that, whereas ACTH increased brain acetylcholine synthesis (even in adrenalectomized rats), cortisone and cortisol had little effect. One would expect the effect of ACTH to be duplicated by cortisol and cortisone, but this was not the case. Since no important metabolic changes result from ACTH administration in adrenalectomized rats, it appears that the ACTH-induced increase in acetylcholine synthesis reported by these workers was due to some contaminant in their ACTH preparation. Torda (551) also reported that ACTH rapidly increased the ammonium ion concentration of rat brain, and she concluded that this ion, as well as acetylcholine, accounted for the enhanced electrical activity evoked by ACTH administration. However, there is no correlation between the effects of adrenocortical steroids and ACTH on acetylcholine metabolism and their effects on brain excitability; yet it is possible that the action of these hormones on ammonia metabolism in brain may explain their EEG effects.

4. Effects of adrenocortical hyperfunction on carbohydrate, phosphorus, protein, and fat metabolism. a. Carbohydrate. The influence of adrenocortical steroids and ACTH on carbohydrate metabolism of the brain has not been extensively studied. Much of the pertinent literature has been summarized by Gordan *et al.* (194) and by Gordan (192). The over-all effect of ACTH and cortisone-like steroids is to inhibit the oxidation of glucose in the tissues and to increase the deposition of glycogen, presumably derived from increased gluconeogenesis from proteins. Brain seems to be no exception. Increased deposition of glycogen in brain as a result of treatment with small doses of cortisone, and with DOC to a lesser extent, has been reported by Vaccari and Rossanda (572) in adrenalectomized rats; total carbohydrate content of brain was also increased by cortisone. After large (anesthetic) doses, Vaccari and Malaguti (570) noted that DOC increased the glycogen and total carbohydrate content of rat brain, whereas cortisone and pregnenolone in large doses had no such metabolic effect and did not cause anesthesia. Since other anesthetic agents (ether, barbiturate) increase the glycogen and total carbohydrate content of the brain, it was concluded that the DOC-induced effect was the result of reduced carbohydrate utilization during anesthesia (158). Timiras *et al.* (547) have demonstrated that small doses of cortisol increase the deposition of glycogen in brain, muscle, and liver of rats, and that this increase is associated with an elevation in blood sugar concentration and an enhanced recovery from electroshock seizures. Additional findings of these investigators established a clear association between speed of recovery from postictal depression and the level of blood sugar; pancreatectomized rats and intact rats treated with alloxan, glucagon, glucose, and cortisol recovered rapidly and had high blood sugar levels, whereas insulin-treated rats recovered slowly and had low blood sugar levels. It was therefore concluded that the process of postictal recovery is intimately associated with carbohydrate metabolism, particularly with brain glucose utilization; in contrast, the excitability process is associated with alterations in brain Na ratio. Since the blood is the main source of glucose for the brain (the glycogen stores being small), procedures or drugs that influence blood sugar concentration consequently affect brain metabolism and the process of recovery from post-excitatory depression.

The effect of cortisol on glycogen concentration of brain may be attributed, as it is in other tissues, to a dual effect of this hormone, namely, inhibition of glucose utilization and acceleration of gluconeogenesis. Since glucose is the main source of energy in the brain *in vivo*, it can hardly be expected that the inhibitory action of cortisol on the rate of oxidation of glucose plays any important role in the increase in storage of glycogen observed in brain after administration of this hormone. Rather, it is suggested that cortisol increases brain glycogen concentration by modifying protein and amino acid metabolism so as to accelerate gluconeogenesis.

Gordan *et al.* (194) reported that cerebral glycogen and cerebral galactose may be mobilized in man by DOC in some instances; this suggests that glycogen can serve as a source of rapidly available energy. Abood and Kocsis (2) noted in rats that the brain glycogen content, reduced by hypophysectomy, could be restored to normal by ACTH. Thus brain glycogen seems to be markedly influenced by

adrenocortical steroids, cortisone-like steroids increasing and DOC-like steroids decreasing brain glycogen. The decrease in glycogen produced by DOC is probably the result of a decrease in gluconeogenesis from protein. Indeed, Timiras and Woodbury (545) have noted that DOC increases the concentration of many free amino acids in rat brain, a fact which might indicate a decrease in gluconeogenesis from amino acids.

Still other effects of adrenocortical steroids on brain carbohydrate metabolism have been described. Ascorbic acid levels of organs other than adrenal glands do not change following the injection of ACTH, cortisone, or ACE. However, stress causes a fall in ascorbic acid concentration not only in the adrenal but also in liver, brain, heart, and skeletal muscle; in contrast, blood and kidney ascorbic acid is increased by stress (571). The role of ascorbic acid in brain metabolism has not been established. Cortisone caused an increase in intensity of the histochemical reaction for succinic dehydrogenase in cerebellum of intact rats and restored the decrease in intensity produced by adrenalectomy to normal (43). Cochran and DuBois (82) found that a variety of steroids, including estrone, cortisone, cholesterol, and ouabain, did not inhibit oxygen consumption and citrate synthesis by liver, kidney, and brain homogenates, whereas testosterone, DOC, progesterone, and diethylstilbestrol did inhibit citrate synthesis and oxygen consumption. These observations suggest that DOC-like steroids, but not the 11-oxysteroids, affect the enzyme concerned with citrate formation from acetyl and oxalacetate. Inhibition of citrate synthesis would prevent entrance of acetate into the Krebs' tricarboxylic acid cycle and might shunt it into fatty acid synthesis. Henneman *et al.* (247) suggest that cortisol and ACTH inhibit the metabolic pathways whereby pyruvate and lactate enter the tricarboxylic acid cycle and facilitate the pathways whereby citrate is utilized.

b. Phosphorus metabolism. The effects of ACTH on phosphorus metabolism have been studied by Torda, and Torda and Wolff (552, 553, 563, 564) in the forebrain of mice and by Loeb *et al.* (330) in the hypothalamus and the brain stem of monkeys. Torda and Wolff found that, after acute but not chronic administration, ACTH increased the amount of phospholipid phosphorus and P^{32}-labeled phosphorus without altering other phosphorus-containing fractions of the brain (553, 564); it was concluded that ACTH increases brain phospholipid synthesis. However, Loeb *et al.* (330) noted that chronic treatment with ACTH increased turnover of P^{32} in all brain phosphorus fractions (acid-soluble, phospholipid, pentosenucleic acid, and phosphoprotein), but did not change the total amount of phosphorus in any of these fractions; they concluded that ACTH increased metabolic activity of the brain areas examined. Based on this conclusion, and assuming that ACTH secretion is under control of the hypothalamus, Loeb *et al.* suggested that hypothalamic stimulation inhibits the secretion of ACTH, a suggestion also made by Roberts and Keller (438). Reiss *et al.* (429) studied the effects of hypophysectomy and ACTH on phosphorus metabolism of the central grey matter of rats, and noted that hypophysectomy increased the P^{32} uptake of the total acid-soluble fraction of whole brain and that ACTH prevented the increased uptake. Phospholipid-P^{32} uptake, 125 hours after injection of the isotope, was also enhanced by hypophysectomy and even to a greater ex-

tent by ACTH. However, Kocsis (303) found ACTH decreased phospholipid-P^{32} uptake in the brain, but the values were determined one hour after injection of the isotope. Reiss *et al.* concluded that the increased activity of the brain with regard to phosphorus metabolism in hypophysectomized rats may possibly be due to an enhanced carbohydrate utilization, and that ACTH restores normal metabolism by a decrease in carbohydrate utilization. These observations are supported by the earlier results of Reiss and Rees (431) who found that hypophysectomized and adrenalectomized rats exhibited an increase in hexokinase activity and anaerobic glycolysis, and that the latter function was restored to normal by ACTH. However, neither hypophysectomy nor ACTH affected the oxygen uptake of slices of grey matter removed from rat brains.

c. Protein and amino acid metabolism. The influence of adrenocortical steroids on protein and amino acid metabolism of brain has not been adequately studied, although their affect on other tissues has received considerable attention. If the data obtained on other tissues can be applied to brain, it would be expected that ACTH and cortisone-like steroids would decrease the synthesis and increase the breakdown of proteins and accelerate gluconeogenesis, and that adrenalectomy would have the opposite effects. The observations of Loeb *et al.* (330) that ACTH increased the turnover of P^{32} in the pentosenucleic acid fraction of the monkey hypothalamus might indicate an increase rather than a decrease in the rate of synthesis of cellular protein. However, direct determination of protein synthesis and breakdown under the influence of adrenocortical hormones is necessary before any conclusions are warranted.

The effects of DOC on brain amino acid metabolism have been studied more extensively. Gordan *et al.* (193) observed that the conversion of glutamic acid to glutamine in human brain was prevented or reversed by DOC. Timiras and Woodbury (545) studied the influence of DOC on the free amino acid content of cerebral cortex in young and old rats and correlated these changes with alterations in brain excitability and electrolytes. The most striking findings were changes in the glutamic acid-glutamine system and in aspartic acid. In line with the evidence presented by Gordan *et al.* (193), the data obtained in the experiments of Timiras and Woodbury demonstrate that castration increases the conversion of ammonia and glutamic acid to glutamine and that DOC restores the normal relationship found in the intact controls. An interpretation of the changes noted in the other amino acids cannot be made at this time. The observations are also consistent with those reported by Gordan *et al.* (194) that castration increases brain Q_{O_2} and that DOC restores brain Q_{O_2} to normal values, and the data suggest that increased oxygen consumption by brain results in increased utilization of glutamic acid and/or increased conversion of glutamic acid to glutamine, whereas DOC decreases such utilization and/or conversion.

Certain observations may now be summarized for purposes of correlation. *Adult* animals treated with DOC exhibit an increase in threshold for seizures, a decrease in brain Na concentration, an increase in brain glutamic and aspartic acid concentrations, and a decrease in brain glutamine. In contrast, *young* animals treated with DOC exhibit a decrease in threshold for seizures, an increase in

brain Na concentration, and an increase in brain glutamic and aspartic acid concentrations. These facts suggest that glutamic acid and glutamine and aspartic acid are associated with brain electrolyte alterations and thereby influence brain excitability. Further experiments are necessary to evaluate this suggestion. It is of interest, moreover, that Terner *et al.* (537) have associated the transport of K across brain cells with glutamic acid metabolism.

The effects of acute and chronic administration of DOC and cortisol on brain amino acids have been measured in intact and adrenalectomized rats (581, 616). Cortisol (acute and chronic treatment) increased the concentration of most free amino acids in brain with the exception that the concentration of glutamine and γ-amino butyric acid (GABA) was decreased. DOC (acute and chronic treatment) had opposite effects than cortisone on glutamic acid, glutamine, and GABA. The ratio of glutamic acid to glutamine (GA/Gl) in brain was increased, an observation consistent with the results of other experiments (611) which indicate a correlation of the GA/Gl ratio with the brain Na ratio. As the GA/Gl ratio increases, the brain Na ratio decreases, and *vice versa*. Since the brain Na ratio is inversely correlated with brain excitability, the GA/Gl ratio must be directly correlated with brain excitability. In addition, the decrease in brain concentration of GABA induced by cortisol is consistent with other evidence that the brain concentration of this amino acid is correlated with brain excitability (581,611, 617). Thus the cortisol-induced increase in brain excitability is associated with a decrease in brain GABA, whereas the DOC-induced decrease in brain excitability is associated with an increase in this amino acid.

It is therefore evident that adrenocortical hormones have a marked effect not only on the GA/Gl system but also on GABA. The GA/Gl system influences brain excitability via the regulation of the Na concentration in brain neurons; GABA may function as an inhibitory substance in the brain (26, 126).

d. Fat metabolism. The effects of adrenocortical hormones on fat metabolism, particularly in brain, are not clear; much more information is needed. A single injection of ACTH in mice transiently increased the total phospholipid content of cerebral cortex and accelerated the turnover of P^{32} in this fraction; however, chronic treatment with ACTH, DOC, cortisone, hydrocortisone, progesterone, or 21-acetoxypregnenolone had no effect on total phospholipid concentration (533, 564). In contrast, Loeb *et al.* (330) noted that chronic administration of ACTH in the monkey increased the turnover of P^{32} in the phospholipid fraction of the hypothalamus. The meager data suggest that ACTH increases synthesis and breakdown of brain phospholipid. The effects of cortisone and DOC on P^{32} turnover in phospholipids are not known. The relation of phospholipid metabolism to changes in brain excitability and electrical activity remains to be ascertained. The postulation by Bernheim (34) that adrenocortical hormones are concerned in the metabolism of brain linolenic acid requires confirmation.

C. Neuropathological changes induced by hyperfunction of the adrenal cortex

1. Effects of ACTH and cortisone. The development of neuronal, neuroglial, and microglial elements of the nervous system are markedly influenced by adrenocortical steroids of the cortisone-like type. For example, Hicks (251) noted that

acute and chronic administration of cortisone induced marked necrosis of neuroblasts and young neurons in embryos and newborn mice and rats. In adult animals, cortisone and ACTH produced marked neuronal necrosis in the striatum and cerebral cortex, and hyperchromatism and necrosis of nuclei of oligodendroglia, microglia, and endothelial cells. In the neonatal animals in which marked neuronal necrosis was present, convulsive episodes often occurred.

Field (136) studied the effect of cortisone on the development of microglia in the brain of mice, rats, sheep, goats, and human embryos. Mature microglia (of mesodermal origin) were observed in early stages of embryonic development in mice, rats, sheep, and human embryos but not in goats. Following birth, the so-called Hortega "fountains" of microglial cells appear in the brain in increasing numbers and then disappear as the adult stage is reached. Cortisone was found to suppress the development of Hortega's neonatal microglial "fountains" and also considerably to delay myelination. The total number of microglial cells was reduced by cortisone; the microglial cells present, however, were in the mature, branched form and were not ameboid in character. The author suggested that cortisone impedes the migration and phagocytic activity of ameboid microglia, which then revert to the branched inactive form. Since microglial cells become ameboid and phagocytic when inflammation occurs in the nervous system, it is evident that cortisone can impede the inflammatory process in the nervous system as it does in other tissues.

Similar observations on the effect of cortisone on neuronal and neuroglial elements have also been made in tissue culture by Geiger and Behar (170); cortisone prolonged the survival time of grey matter neurons and completely suppressed the growth of glial cells, scavenger cells, and gemistocytes; fibroblasts were only rarely seen; mitosis in developing neurons was markedly increased. Thus it is quite clear that cortisone suppresses glial cell development *in vitro* and *in vivo*. This suppression of connective tissue in brain by cortisone is similar to its effect on connective tissue in other organs [see reviews by Dougherty (115) and Thorn (542)].

The effects of chronic treatment with cortisone and ACTH on the adult brain have been variously described. Although certain investigators (57, 166, 506) have reported that ACTH and cortisone caused abnormal cellular changes in the hypothalamus and thalamus of rats, Malamud and Saver (341) observed no evidence of pathological change in the hypothalamus and thalamus of patients treated for prolonged periods with ACTH and cortisone for disseminated lupus erythematosus. Also, Halmi (223) reported that large amounts of cortisone given to rats and cats did not cause changes in the hypothalamus, and Gädeke and Betke (166) found no pathological changes in the hypothalamus of mice treated for 14 days with ACTH. Thus it is evident that the neuropathological effects of ACTH and cortisone on the diencephalon are either absent or variable. The significance of the changes, if any, cannot be assessed at this time.

The effects of cortisone on healing of injured nerve and on Wallerian degeneration have been studied by McColl and Weston (354) who observed that prolonged hormone treatment did not affect the edema formation which normally

follows sciatic nerve section in cats, but did decrease the tensile strength of such degenerated nerves and appeared to inhibit the anabolism of protein (probably collagen) during Wallerian degeneration. The usual decrease in concentration of lipids in the myelin sheath of degenerating nerves was not altered by cortisone. Thus connective tissue development appears to be inhibited by cortisone in nerves undergoing Wallerian degeneration; this inhibition probably accounts for the decrease in tensile strength.

Because of the anti-inflammatory effects of cortisone-like steroids, wound healing is usually delayed (see 115). Brain is no exception to this rule. For example, Ortiz-Galvan (385) demonstrated in cats that cortisol delayed the formation of a leptomeningocerebral cicatrix which developed from a stab wound; the early inflammatory reaction, the phagocytic activity of the microglia, and the fibroblastic and vascular proliferation were depressed.

2. Effects of DOC. The effects of DOC overdosage on the brain of experimental animals have been reported by Selye and collaborators (485–487, 543) and by Masson *et al.* (348) who found that brain tissue developed vascular lesions similar to those observed in other tissues, such as heart, pancreas, and kidney. Prolonged administration of DOC in suitably susceptible rats (unilateral nephrectomy, 1.0% NaCl solution as drinking water) produced changes in brain parenchyma, generalized brain edema, and cerebrovascular lesions. The perivascular spaces were distended and contained erythrocytes, the cells of the choroid plexus and the ependyma were hypertrophied, the meninges were thickened and infiltrated with polynuclear cells, the arteriolar walls showed a high degree of hyalinization and cellular infiltration, and the brain parenchyma was necrotic as a result of vascular thromboses. Glial proliferation was manifest especially in the regions most severely damaged by the vascular disturbance. The brain lesions were associated with "clear-cut motor disturbances" and, in young animals, with marked enlargement and rounding of the skull due to the cerebral edema. The glial proliferation is of interest in view of the fact that DOC-treated animals have a relative deficiency of cortisone-like steroids (608); since cortisone supresses glial development, the proliferation may be the result of this relative deficiency. Thus marked cerebral vascular and necrotizing parenchymal changes can occur in the brain of experimental animals as a result of prolonged over-treatment with DOC. The clinical data on such changes are too meager to warrant comment.

3. Neuropathological changes in Cushing's syndrome. The pathological changes which develop in the brain as a result of hyperfunction of the adrenal cortex in man have been reviewed by Trethowan and Cobb (566). Heinbecker (239) and Heinbecker and Pfeiffenberger (240) noted atrophy of the paraventricular and supraoptic nuclei and some internal hydrocephalus in several cases of Cushing's syndrome. Other pathological changes occasionally observed were patchy loss of cells in the posterior hypothalamic and mammillary nuclei, fibrous thickening of leptomeninges, and subarachnoid hemorrhage. In 2 cases of Cushing's disease, Cope and Raker (86) noted cerebral atrophy and dilatation of the ventricular system, and suggested that these changes may be the result of alterations in the

supporting tissues of the brain. However, Trethowan and Cobb (566) found only minor pathological changes in the brains of 4 cases of Cushing's syndrome.

IV. CENTRAL NERVOUS SYSTEM REGULATION OF ADRENOCORTICAL SECRETION

A. Relation between central nervous system activity and adenohypophyseal secretion of ACTH

Despite an enormous literature devoted to the problem, the role of the central nervous system in the regulation of anterior pituitary function is incompletely understood. Only a brief summary will be given in this review. Adequate summaries of the different theories and points of view have been published (48, 103, 178, 226–229, 268, 277, 281, 333, 415, 448).

Three important hypotheses have been proposed to explain the control of ACTH secretion by the adenohypophysis, as follows: 1) control by the systemic blood level of adrenocortical hormones; 2) control by the systemic blood level of epinephrine; 3) control by the hypothalamus. The first and second hypotheses have been thoroughly studied by Sayers and colleagues (467, 469), Long and associates (178, 332, 333, 356), and Vogt (585); they will not be discussed here except as they pertain to the third hypothesis. The third hypothesis was first propounded by Hume and associates (276, 279) and Harris and coworkers (103, 226–229). Several methods have been developed for studying the neural control of ACTH secretion, including 1) stimulation of the hypothalamus and measurement of ACTH secretion under various conditions; 2) placing of lesions in the hypothalamus and subsequent measurement of adrenocortical activity; 3) recording of electrical activity of the hypothalamus during periods of ACTH secretion induced by various stresses; 4) examination of the effect of centrally acting drugs on secretion of ACTH.

Since the data obtained on ACTH secretion are only as good as the methods used to assess the amount of ACTH secreted, it is pertinent to mention the various indices for measuring ACTH activity. These include blood eosinophil levels (rat, cat, dog, monkey, man), blood lymphocyte levels (rabbit), adrenal ascorbic acid concentration (rat, guinea pig), and plasma levels of 17-hydroxycorticosteroids (guinea pig, dog, man). It is generally agreed that the last-named method is the best of those currently available. However, blood lymphocyte levels in rabbits, eosinophil levels in dogs, and adrenal ascorbic acid concentration in rats appear to be fairly reliable secondary indices of adrenocortical activity and hence of ACTH secretion.

1. Effect of hypothalamic stimulation upon ACTH secretion. De Groot and Harris (103) and Hume and Wittenstein (279) were the first to provide information in this field. De Groot and Harris showed that electrical stimulation of the posterior region of the tuber cinereum or of the mammillary body in unanesthetized, unrestrained *rabbits* resulted in a lymphopenia which was similar in time and magnitude to that following an emotional stress; neither cervical sympathectomy nor electrical stimulation of other regions in the hypothalamus or of the pars

distalis, pars intermedia, and infundibular stalk abolished this response. Hume and Wittenstein (279) found that, in unanesthetized, unrestrained, normal or totally sympathectomized *dogs*, stimulation of the anterior hypothalamus caused a marked eosinopenia; posterior hypothalamic stimulation was much less effective. Porter (414) stimulated various regions of the hypothalamus in *cats* and noted an eosinopenic response only when the tuberal and mammillary areas were stimulated; these results in cats agree with those obtained in rabbits, but the effective areas are posterior to those reported in the dog. In the *monkey*, Porter (415) noted that electrical stimulation of the lateral tuberal and posterior regions of the hypothalamus elicited a pronounced eosinopenia; a significant response was also obtained from stimulation of the medial tuberal region and from certain areas of the cerebral cortex, especially the orbital surface of the frontal lobe. Similar hypothalamic and cortical stimulation in monkeys with the spinal cord sectioned at the 7th cervical level evoked a response comparable to that in intact animals. Pituitary stalk section completely prevented the eosinopenic response to hypothalamic stimulation. Eosinopenia induced by stress (epinephrine injection) could be prevented by stimulation of the hippocampal region, the uncus in particular. Thus cortical centers can exert both excitatory and inhibitory influences on the hypothalamic control of ACTH secretion. It would be of interest to repeat these experiments with more direct measurements of adrenocortical function, such as levels of corticoids and of ACTH activity in the blood. The observations of Mason (346) and of Pool *et al.* (410) are of interest in this connection.

2. Effect of hypothalamic lesions upon ACTH secretion. The data on the effect of hypothalamic lesions on adrenocortical activity are in general agreement with the results obtained with hypothalamic stimulation, with respect to the anatomical location of the effective areas. In the dog, paramedian lesions in the hypothalamus and at the juncture of the middle and posterior hypothalamus were found to abolish the usual eosinopenic response to epinephrine and insulin, and to decrease the response to operative trauma; lesions in the supraoptic nuclei were ineffective (277, 279). According to De Groot and Harris (103), lesions in the zona tuberalis, in the posterior region of the tuber cinereum, or in the mammillary body abolished or diminished the lymphocytopenia of stress in the rabbit, whereas lesions in the posterior part of the pars distalis, in the pars intermedia, or in the infundibulum did not influence the lymphocytic response to stress. They concluded that secretion of ACTH is under neural control via the hypothalamus and the hypophyseal portal vessels of the pituitary stalk. Posterior but not anterior hypothalamic lesions in the cat were shown by Porter (414) to prevent the eosinopenic response to epinephrine, formalin, and histamine. Thus the sites of the effective lesions in the cat and the rabbit are more posterior than those observed by Hume and colleagues in the dog. In another species, the rat, McCann (349) found that lesions in the median eminence completely blocked the adrenal ascorbic acid depletion which normally occurs in the remaining adrenal within an hour after the stress of a unilateral adrenalectomy; the eosinopenic response to subcutaneous epinephrine was also abolished. Complete stalk section

with interruption of the hypophyseal portal vessels also abolished the stress response and resulted in anterior lobe damage and adrenal atrophy. Partial lesions in the median eminence and in the adjacent areas and lesions of the mammillary bodies or paraventricular nuclei did not abolish the normal response.

In subsequent experiments on dogs, Ganong and Hume (168) noted that hypothalamic lesions involving one half or more of the median eminence prevented the adrenal hypertrophy which normally occurs with repeated acute stress and after unilateral adrenalectomy. Whereas hypophysectomized dogs normally exhibit marked adrenal atrophy, adrenal atrophy did not occur in dogs with the above described lesions. Administration of cortisol induced the same degree of adrenal atrophy in dogs with destructive lesions of the median eminence as in normal dogs. It would appear from these data that cortisol suppresses the release of ACTH by a direct inhibitory effect on the pituitary rather than on the hypothalamus or other cerebral centers; however, further work is required.

In still later experiments Hume and Nelson (278) measured the levels of ACTH in arterial blood and of 17-hydroxycorticosteroids in adrenal venous blood, in normal control dogs and in dogs with hypothalamic lesions. Animals with lesions in the anterior portion of the median eminence had no detectable ACTH activity in their blood following operative trauma, whereas the controls had activity levels between 3 and 8 milliunits/100 ml arterial blood; the output of 17-hydroxycorticosteroids in the animals with lesions averaged 1.8 μg/min compared with 12.5 μg/min in the controls. Lesions in other areas of the hypothalamus produced marked to complete suppression of ACTH secretion, depending on their location. There was no correlation between the occurrence or non-occurrence of diabetes insipidus and the presence or absence of a normal pituitary-adrenal response.

Laquer *et al.* (310) placed stereotactic lesions in the hypothalamus of the cat, and then studied the adrenocortical responses to stressful stimuli (injection of epinephrine, laparotomy), as measured by the eosinophil count, steroid levels in adrenal venous blood, and histological examination of the adrenal cortex. Cats with lesions in the suprachiasmatic area and in the posterior hypothalamus exhibited normal responses to the stressful stimuli, but cats with lesions in the median eminence and the adjacent hypothalamus showed very little response. The findings were interpreted to mean that an intact median eminence is necessary for the release of ACTH in response to certain stimuli, but that ACTH release from the adenohypophysis is not completely under control of the hypothalamus. Destruction of the median eminence did not cause atrophy of the adrenal cortex such as occurs when the anterior lobe is removed, and there were no obvious signs of adrenocortical hypofunction. Laquer and colleagues believe that only the release of ACTH in response to acute stressful stimuli is subject to hypothalamic control. This view is supported by the observations of other workers. No explanation is apparent for the finding of De Groot and Harris (103, 104) and Porter (414) that posterior hypothalamic lesions prevent the adrenocortical response to stress, as compared to the finding of Laquer *et al.* that such lesions do not abolish the response. Further experiments must be performed to resolve this difference, and particular attention should be paid to the use of the same species and the same indices of adrenocortical activity.

Fulford and McCann (164) studied the effect of hypothalamic lesions in rats on the hypertrophy of the remaining adrenal which occurs after unilateral adrenalectomy, and observed that such hypertrophy was absent in animals with hypothalamic lesions producing diabetes insipidus. However, if such rats were exposed to a severe stress, adrenal hypertrophy developed.

Wilson *et al.* (597) used urinary steroid excretion as an index of adrenocortical function in female dogs with lesions in the central nervous system. Transection of the spinal cord at C7 induced a 2- to 3-fold increase in urinary steroid excretion which lasted for 4 days, and laparotomy caused the same increase. In contrast, neither transection of the midbrain nor a subsequent laparotomy one month later produced any significant change in urinary steroid excretion. It was concluded that activation of ACTH secretion is blocked by midbrain transections.

Keller *et al.* (294), in contrast to other workers, concluded that neither function nor structure of the adrenal cortex in dogs is dependent upon the integrity of the ventral half or more of the hypothalamus plus the hypophyseal stalk, or upon the vascular channels connecting the adenohypophysis and the hypothalamus. This conclusion was based on the observations in chronic ventral hypothalamectomized dogs that there was no adrenal atrophy, no tendency to adrenocortical insufficiency *per se*, and no impairment in the eosinopenic response to major stresses such as unilateral sympathectomy and pancreatectomy. However, an examination of their data indicates some evidence of adrenocortical insufficiency, such as a slight decrease in insulin tolerance; also since the tests were made at least 3 weeks after the hypothalamectomy, the possibility of regeneration of hypothalamico-hypophyseal portal vessels was not ruled out. Yet even if regeneration of the portal vessels did occur, the lack of the all-important ventral hypothalamic structures should still prevent a normal adrenocortical response; since a normal response to severe stress was still present, the role of the hypothalamus as a mediator of ACTH release in severe stress is cast in doubt. These observations of Keller and associates would favor the evidence presented by Fortier (149, 150) of a dual control of ACTH release, as follows: 1) control through the hypothalamico-hypophyseal portal system in response to certain stresses (emotional, pain, *etc.*), and 2) reflex activation of the hypothalamus and/or direct activation of the adenohypophysis by systemic stresses which result in tissue damage, metabolic changes, and alterations in the chemistry of the blood. That release of ACTH is mediated at least in part through the hypothalamus was conclusively demonstrated by McCann and Sydnor (353) who found that the increase in blood level of ACTH induced by adrenalectomy (533) does not occur in rats with hypothalamic lesions.

3. Electrical activity of the hypothalamus during periods of stress-induced release of ACTH. Further evidence for a role of the hypothalamus in regulation of ACTH release is provided by data on the electrical activity of the hypothalamus during induced stress. Porter (413, 415) noted a definite increase in the electrical activity (amplitude and frequency) of the hypothalamus in cats and monkeys, induced by epinephrine, insulin, or hypoxia. Enhanced electrical activity was encountered only in the posterior and tuberal regions of the hypothalamus and in the mammillary bodies; a similar effect recorded in the anterior nucleus of

the thalamus was shown to be relayed from the hypothalamus. Stress also markedly increased the electrical activity in the anterior cingulate gyrus and to a lesser extent in the posterior cingulate and hippocampal gyri. Decerebration and decortication did not alter the enhanced electrical activity induced in the hypothalamus by epinephrine. However, electrolytic lesions in the hypothalamus abolished the enhanced electrical activity in the cerebral cortex. Since adrenalectomy annulled the increased electrical activity of the hypothalamus in response to epinephrine, and since maintenance doses of cortisone or cortisol restored the normal response, the latter is dependent upon the presence of circulating adrenocortical steroids. In addition, prior treatment with ACTH and ACE (but not with cortisone, cortisol, or DOC) suppressed the enhanced neural discharge induced by epinephrine. Therefore, Porter concluded that the augmented electrical activity in response to epinephrine stress is not the result of the increased secretion of ACTH or adrenocortical steroids, since the administration of these hormones failed to evoke such an augmentation.

4. Effects of centrally acting drugs on secretion of ACTH. The above described observations that the hypothalamus and the cerebral cortex are intimately involved in the regulation of ACTH release from the adenohypophysis are based on experiments involving neurophysiological technics. Further evidence for a role of the central nervous system in the regulation of ACTH release has been derived from studies of the effects of various drugs which act on the central nervous system and on the pituitary-adrenal system (see 211, 616).

a. Central nervous depressants and anesthetics. The effect of barbiturates on adrenocortical function was first tested by Hume and Wittenstein (279) who found that pentobarbital decreased the eosinopenic response to trauma (abdominal operation) in normal dogs. Ronzoni (447) demonstrated that, in deeply pentobarbitalized rats, a decrease in adrenal ascorbic acid concentration did not occur in response to cold, but did occur in response to hemorrhage and hyperthermia. Harwood (236) observed in monkeys that the level of 17-hydroxycorticosteroids in plasma was depressed by pentobarbital. Munson and Briggs (371) noted in rats that pentobarbital blocked the stress effect of morphine, as measured by the adrenal ascorbic acid depletion test. Ether, on the other hand, enhanced the stress effect of trauma in dogs, as measured by the production of eosinopenia (279). Since the barbiturates have been shown to have inhibitory effects on hypothalamic nuclei (347) and on the reticular activating system (16, 159, 299), the depressant effect of barbiturates on ACTH release provides additional support for a role of the hypothalamus and mesencephalic centers in the regulation of ACTH secretion.

Sydnor and Sayers (533) noted that ether enhanced ACTH release in adrenalectomized rats as well as in intact rats; this observation provided direct evidence that a centrally acting drug could stimulate the release of ACTH. An increase in serum concentration of free corticoid has been observed following ether anesthesia in children (494) and adults (462). Since ether has been demonstrated to block the reticular activating system (16, 159, 299) and the diffuse thalamic projection system (299), these systems would appear to be important in central regulation

of ACTH release. Other anesthetic agents (thiopental, cyclopropane) also increase the plasma 17-hydroxycorticosteroid level; spinal anesthesia, however, does not change the level (462).

The effects of ethanol on the pituitary-adrenal system have also been examined (144, 145, 464, 499, 500). The available data indicate that both low and high doses of ethanol cause a decrease in adrenal ascorbic acid, depletion of adrenal cholesterol, and regression of the thymus. A full interpretation of this adrenocortical-stimulating effect of ethanol has not been made, but one might speculate that the depression of higher cerebral centers by alcohol with the resulting release of lower centers (reticular activating system and/or hypothalamus) might result in activation of release of ACTH.

b. Anticonvulsants. The effects of anticonvulsant agents on adrenocortical function have been examined by a number of investigators. The influence of diphenylhydantoin on the pituitary-adrenal system has been most extensively studied (41, 45, 90, 127, 128, 514–520, 604, 605, 612, 613, 616). When the data obtained in various species on different dose schedules are compiled and analyzed, the following picture emerges. Acute or subacute administration of low doses of this drug causes adrenocortical stimulation. A single large dose or prolonged treatment with small doses depresses adrenocortical function; with chronic medication, the adrenal cortex is inhibited by diphenylhydantoin despite the concurrent adrenal hypertrophy produced by the stress effect of the drug. Hypophysectomy abolishes the adrenocortical stimulation evoked by single low doses of the anticonvulsant. The relatively small amounts of diphenylhydantoin employed in the therapy of epileptic patients stimulate the adrenal cortex during the early weeks of medication, but subsequently cause depression (90). As examples of the type of work on this problem, it was observed in rats that single doses of the drug or small doses repeated for 12 days caused adrenocortical activation as measured by adrenal hypertrophy, thymic atrophy, and an increased level of corticosterone in the plasma (616); however, if large doses were given to rats for either short or long periods, the depletion of adrenal ascorbic acid induced by stress was blocked, despite the fact that the adrenals of such animals responded, in an attenuated manner, to massive doses of ACTH (41). The effect of prolonged treatment with diphenylhydantoin on blood corticosteroid levels has not been studied in experimental animals. However, in epileptic patients on long-term therapy with this anticonvulsant, depression of adrenocortical function occurs (45, 90, 549). Since diphenylhydantoin in low doses synergizes with the seizure-evoking effect of 30% carbon dioxide, salicylate, and pentylenetetrazol (agents which activate the adrenal cortex), and since convulsions produced by these agents are thought to be of subcortical origin (615), it is likely that the locus of the adrenocortical-activating effect of diphenylhydantoin is in the hypothalamus. The subcortical effects of CO_2 are thought to be localized in the reticular formation of the posterior hypothalamus (171, 172), the region believed to control the release of ACTH. Thus the evidence suggests that diphenylhydantoin activates the adenohypophysis to release ACTH by stimulation of the reticular activating system. In high doses, however, the anticonvulsant prevents CO_2-induced sei-

zures (615) and, according to Gangloff and Monnier (167), also depresses subcortical centers; thus, chronic administration of large doses of the drug causes depression of the reticular activating system and thereby inhibits the release of ACTH. Some clinical observations also indicate that certain hydantoins can depress adrenocortical function; for example, Mesantoin can cause pigmentation of the skin similar to that produced by adrenocortical insufficiency (280), and diphenylhydantoin can produce periarteritis nodosa (579).

The influence of other anticonvulsants on adrenocortical function has not been studied extensively. A congener of diphenylhydantoin, 5,5-diphenyltetrahydroglyoxaline-4-one, has no effect on the pituitary-adrenal system on acute administration; however, when the drug is given for 2 weeks, it causes adrenal hypertrophy, an increase in plasma corticosterone level, and a decrease in plasma cortisol level, but not thymic atrophy (616). Phenobarbital, primidone, trimethadione, and Mesantoin were tested for their ability to deplete adrenal ascorbic acid in intact rats (612); of the four, only trimethadione was effective in this respect. Since trimethadione specifically antagonizes the subcortical seizures induced by pentylenetetrazol, it is possible that it also acts subcortically to activate the pituitary-adrenal system.

c. Analgesics and antipyretics. Morphine. Morphine resembles diphenylhydantoin in that it can stimulate the pituitary-adrenocortical system under some conditions and can block it under others (47, 173, 371, 375, 382, 534). Single analgesic doses of morphine stimulate the adrenal cortex of intact but not of hypophysectomized rats, as measured by depletion of adrenal ascorbic acid (173, 371, 375); this acute effect of morphine is completely blocked by pentobarbital and nalorphine (47, 132, 371) and by destruction of the median eminence of the hypothalamus, and partially blocked by cortisone administration (173). Since the adrenal ascorbic acid-depleting activity of morphine is only slightly impaired by adrenal demedullation or by depletion of tissue histamine (375), epinephrine and histamine are not responsible for this effect of morphine. When morphine is chronically administered, an entirely different situation exists; the drug no longer is capable of depleting adrenal ascorbic acid (371) and it prevents such depletion ordinarily induced by histamine, epinephrine, vasopressin, laparotomy, unilateral adrenalectomy, and abdominal surgery, but not that induced by ACTH (371); yet the adrenal gland is hypertrophied (338, 339, 476, 528, 534). Thus morphine has a dual action on the release of ACTH, initial stimulation of such release and subsequent inhibition. The available data indicate that the activating and inhibiting effects of this narcotic on the adrenal cortex appear to be exerted via the hypothalamus. The mechanism of the initial excitatory action of morphine on the pituitary-adrenocortical system is not known, but it may be related to the direct stimulation of the hypothalamus by the drug (596); in contrast, the subsequent inhibitory action of this narcotic is probably a result of the depressant effect of morphine on the reticular activating system or on the hypothalamus. Sawyer *et al.* (466) demonstrated in rats that the release of ovulating hormone from the adenohypophysis was blocked by doses of morphine which caused slowing of the frequency, increase in amplitude, and hypersynchrony of electrical

activity recorded in the parietal and frontoparietal cortex and in the hypothalamus. In addition, morphine elevated the threshold for elicitation of the arousal response upon stimulation of the reticular formation. These effects of morphine are similar to those produced by pentobarbital; since both drugs block pituitary release of ACTH in response to stress, it is suggested that morphine blocks ACTH release by an inhibitory influence on the reticular activating system and the hypothalamus.

Methadone. Both dextro- and levo-methadone deplete adrenal ascorbic acid in reasonably small doses; pretreatment with nalorphine inhibits the ascorbic acid-depleting effect of levo-methadone but not that of dextro-methadone (173). As would be expected, hypophysectomy abolishes the effect of the methadones on adrenal ascorbic acid. The loci of the various conventional effects of methadone on the central nervous system are not too well known (596) and even less is understood concerning their site of action with respect to causing pituitary-adrenocortical activation. Whether multiple doses of methadone can block the effect of stress stimuli on the pituitary-adrenocortical system, as is true for morphine, has not been determined.

Analgesic antipyretics. A number of observations attest to the fact that various analgesic antipyretic compounds stimulate the pituitary-adrenal system and in many ways mimic the effects of the adrenocortical steroids (25, 35, 59, 64, 65, 93, 94, 112, 113, 118, 135, 173, 174, 187, 189, 219, 249, 337, 366, 380, 381, 396, 442, 450, 501, 535, 574–577). Evidence for adrenocortical activation by such agents (salicylate, acetophenetidin, cinchoninic acids, gentisate, *etc.*) is based on the following facts: 1) salicylate and related compounds cause depletion of adrenal ascorbic acid and/or cholesterol in intact but not in hypophysectomized rats (35, 59, 93, 94, 135, 173, 187, 249, 366, 380, 442, 535, 574); 2) these agents cause histological changes indicative of adrenocortical activation (59, 442); 3) an increase in urinary excretion of reducing steroids but not of neutral 17-ketosteroids occurs in salicylate-treated patients (577); 4) eosinopenia results from large doses of salicylate, an effect abolished by hypophysectomy (396, 450, 574); 5) salicylate in large doses, and sometimes in therapeutic doses, increases plasma 17-hydroxycorticosteroid concentrations in experimental animals and in man (112, 113, 189). In addition, the evidence accumulated has established that the activation of the pituitary-adrenal system by the analgesic-antipyretic group of drugs (particularly salicylate) is mediated through the hypothalamus (93, 174). The work of George and Way (174) demonstrated that lesions of the median eminence in the rat completely blocked the adrenal ascorbic acid depletion which normally occurs within one hour following the administration of acetylsalicylic acid; thus the integrity of the hypothalamus is essential for the action of this drug on the pituitary-adrenal system. The fact that the antipyretic effect of salicylate is mediated through the hypothalamus provides additional support for this statement. The ability of pentobarbital to block salicylate-induced depletion of adrenal ascorbic acid also suggests a central neural or even a hypothalamic effect of salicylate (93). The observations of Christy *et al.* (64, 65) that aminopyrine blocks both the increase in temperature and the rise in plasma 17-hydroxycorti-

costeroid levels, but not the other systemic effects, produced by intravenous injection of typhoid vaccine in patients also indicate that aminopyrine acts through the hypothalamus to effect release of ACTH. However, salicylate has central excitatory properties, similar to those produced by CO_2 and low doses of diphenylhydantoin; in fact, both CO_2 and diphenylhydantoin enhance the seizure-producing effect of salicylate; since both agents probably act on the reticular activating system, it appears that the ACTH-releasing effect of salicylate may be a result of stimulation of this system. Further experiments are necessary to prove this hypothesis.

d. Neurohypophyseal hormones and hypothalamic extracts. The effects of the neurohypophyseal hormones on the pituitary-adrenocortical system have been determined by a number of workers (344, 345, 350–352, 357–359, 371, 374, 468, 502, 522). The results suggest that vasopressin and, to a much smaller extent, oxytocin stimulate the release of ACTH. In fact, the evidence indicates that vasopressin or a related substance may be the neurohumoral mediator which links the hypothalamus with the adenohypophysis, to cause release of ACTH. Rothballer (452) and Barrnett (23) demonstrated that painful stimuli cause a rapid release of Gomori-positive neurosecretory material from the infundibular process and median eminence into the hypothalamico-hypophyseal portal vessels. Previous workers (202, 388, 472) found considerable neurosecretory material close to the hypophyseal portal vessels, in the median eminence and the infundibular process. Such material, thought to be posterior pituitary hormone(s), is thus located near the hypothalamic sites which regulate the release of ACTH. In addition, Mirsky *et al.* (369) reported that various noxious stimuli (including adrenalectomy) elevate the titer of antidiuretic substance in the blood even before ACTH is released. This antidiuretic substance is thought to be vasopressin released from the hypothalamus. [However, the accuracy of the various methods for determination of antidiuretic activity in plasma is open to question and the nature of the antidiuretic substance is yet to be determined (see 241).] Mirsky *et al.* proposed that the antidiuretic hormone (vasopressin) and oxytocin may serve as the hypothalamic "neurohormones" responsible for ACTH release in response to various stimuli. Further evidence for this concept was advanced by McCann and Brobeck (351) who found in rats that hypothalamic lesions which produced diabetes insipidus blocked the secretion of ACTH. Rats with such lesions exhibited a decrease in adrenal ascorbic acid in response to stress (unilateral adrenalectomy, ether anesthesia, epinephrine, histamine), but secretion of ACTH could still be elicited by injection of vasopressin. A direct correlation was observed between the degree of ascorbic acid depletion and the severity of the diabetes insipidus (as measured by water intake). Only lesions involving the supraoptico-hypophyseal stalk produced the results noted; other tracts entering the median eminence were not involved. In addition, McCann and Sydnor (353) found that the elevation in blood ACTH concentration which normally follows stress fails to occur in the above described rats with severe diabetes insipidus. Injury to the supraoptico-hypophyseal tract caused a decrease in adrenal weight (351); such an observation denotes a decrease in the basal secretion of ACTH.

However, in rats with severe diabetes insipidus, adrenal weight was increased, a fact which indicates that secretion of ACTH may occur in severe stress independently of hypothalamic control.

Several workers have presented evidence that the neurohypophyseal hormones, particularly vasopressin, stimulate the pituitary-adrenocortical system as assessed by a variety of acceptable tests (344, 345, 350–352, 357–359, 371, 468, 502). Munson and Briggs (371) demonstrated that the adrenocortical stimulating effect of vasopressin and epinephrine was blocked by the combination of morphine and pentobarbital, and thus concluded that neither of these agents is the postulated neurohormone. However, Sevy *et al.* (489) noted that chlorpromazine blocked the effects of most stress agents except vasopressin. This observation suggests that vasopressin might be the postulated neurohormone. In contrast to the results of Munson and Briggs, McCann (350) observed that the combination of pentobarbital and morphine anesthesia blocked the adrenal ascorbic acid depleting effect of unilateral adrenalectomy but did not prevent the effect of intravenously administered vasopressin, epinephrine, or ACTH; large doses of cortisol blocked the response to unilateral adrenalectomy but not that to vasopressin. McCann (350, 352) also demonstrated that rats with acute or chronic hypothalamic lesions resulting in severe, permanent diabetes insipidus responded to commercial and synthetic vasopressin but not to unilateral adrenalectomy, histamine, epinephrine, or oxytocin. He also noted a direct correlation between pressor potency and ACTH-releasing activity in various fractions of vasopressin separated by chromatographic procedures. These results are consistent with the hypothesis that vasopressin is the neurohormone which causes the release of ACTH in response to acute stress.[4]

In vitro, rat anterior pituitary tissue releases a small amount of ACTH; Saffran *et al.* (460, 461) observed that this release of ACTH could be enhanced by the combined addition of epinephrine (or norepinephrine) and rat cerebral cortex, hypothalamus, and neurohypophysis. Addition of neurohypophyseal tissue was particularly effective. Purified vasopressin, but not oxytocin, also stimulated the release of ACTH when added to this *in vitro* system. Further purification of the vasopressin preparation resulted in loss of ACTH-releasing but not antidiuretic-pressor activity. The ACTH-releasing activity was found to reside in an impurity in the original vasopressin preparation. The observation of Saffran *et al.* were confirmed by Guillemin (210, 212, 215) who found that the addition of hypothalamic tissue extracts and commercial vasopressin, but not of purified vasopressin, caused the release of ACTH from anterior pituitary tissue *in vitro*;

[4] *Note added in proof:* However, Royce and Sayers (Fed. Proc. *17:* 136, 1958) demonstrated that vasopressin enhanced the depletion of adrenal ascorbic acid by blood of 24-hour hypophysectomized rats and of acutely decapitated rats with functioning circulatory systems. This elevation was greater than could be accounted for by the inherent ACTH activity of the vasopressin and suggests that vasopressin releases ACTH or substances with properties similar to ACTH from tissue storage sites. They concluded that the identity of vasopressin with a neurohumor, which acts directly on the adenohypophysis to release ACTH, remains to be established.

without such addition the pituitary tissue was unable to release ACTH for any significant length of time. These data plus those of Saffran and Guillemin *et al.* (212, 214) demonstrate that purified vasopressin *per se* is not the ACTH-releasing neurohormone but that the latter is closely associated with vasopressin. The exact form in which antidiuretic hormone is physiologically released is not known, and it is possible that purified vasopressin may be merely a small part of a larger, naturally secreted molecule necessary for ACTH release. Guillemin (212) demonstrated that Fraction D (a small peptide isolated from hypothalamus, posterior pituitary, substance P of gut origin, and equivocally from brain cortex) stimulated ACTH release from incubated anterior pituitary tissue; Fraction D was found not to be vasopressin, oxytocin, ACTH, histamine, acetylcholine, epinephrine, norepinephrine, or 5-hydroxytryptamine. He speculated that a substance in Fraction D may be the hypothalamico-adenohypophyseal neurohumor and, in addition, that this substance may be released by severe stress from the many other body tissues where it is found. This could explain the ACTH release which occurs as a result of severe non-specific stress in the absence of the normal hypothalamico-adenohypophyseal relationship. This attractive hypothesis requires experimental evaluation in an *in vivo* system.

Finally, Porter and Jones (411) and Porter and Rumsfeld (412) demonstrated that plasma and lyophilized plasma obtained from hypophyseal-portal blood, but not from carotid artery blood of hypophysectomized dogs, caused depletion of adrenal ascorbic acid in cortisol-treated intact rats but not in hypophysectomized rats. Thus hypophyseal-portal blood contains a substance which causes the release of ACTH. The nature of this substance has not been determined, but it appears to be similar to the substance extracted from the hypothalamus by Guillemin (212) and Slusher and Roberts (498), and to that extracted from commercial vasopressin by Swingle *et al.* (530). If this substance proves to be the neurohormone which causes ACTH release, then it is necessary to ascertain whether drugs which act on the hypothalamus to affect ACTH release do so by influencing the synthesis, degradation, or release of the neurohormone or by a direct action on the nervous pathways leading to the site of neurohormonal release.

e. Hypoxia, hyperoxia, and hypercarbia. Many of the systemic alterations induced by an excess or deficiency of O_2 and CO_2 can be accounted for on the basis of the central nervous system effects of these gases. Inasmuch as changes in O_2 and CO_2 concentration alter adrenocortical function, it is important to determine whether such alterations are mediated through the hypothalamico-adenohypophyseal system.

Hypoxia. The influence of low oxygen tensions on adrenocortical function in experimental animals has been studied by a number of investigators (157, 221, 467, 539, 616). The only evidence that this influence is mediated through the nervous system is the fact that hypoxia increases the excitability of the nervous system (172, 616) and stimulates adrenocortical function in normal but not in hypophysectomized rats; animals with hypothalamic lesions must be tested before it can be established whether this area of the brain is important for the

adrenocortical stimulation elicited by hypoxia. The nature of the adrenocortical hormones secreted following exposure to low oxygen tensions suggests a central origin, at least in part, of the effects of hypoxia. The data of Hale *et al.* (221) in man indicate that in severe hypoxia there is an increase in plasma 17-hydroxycorticosteroids and corticosterone-like steroids; in addition, the increase in Na/K ratio in the urine noted by them suggests that aldosterone secretion was enhanced. The observations of Woodbury *et al.* (616) that hypoxia increases brain excitability to a greater extent in adrenalectomized than in intact mice and rats are also pertinent in this regard. These investigators suggested that the lesser effect of hypoxia in intact animals can be explained by the release of aldosterone. It has been demonstrated that aldosterone secretion may be regulated in part by the central nervous system (423). Since this steroid reduces brain excitability (616), it is necessary to entertain the possibility that hypoxia can release aldosterone via stimulation of the central nervous system.

Hyperoxia. There is some evidence that inhalation of 50 to 100% oxygen at atmospheric pressure results in the release of an aldosterone-like substance from the adrenal (616), since such concentrations of oxygen cause less reduction in brain excitability in intact than in adrenalectomized mice and rats. When oxygen is administered under pressures greater than atmospheric [oxygen at high pressures (OHP)], adrenocortical secretion is increased, as measured by a decrease in adrenal ascorbic acid (177), by adrenal hypertrophy (27), and by histological changes in the gland (27). The central nervous system excitatory properties of OHP are well known, and an effect on the hypothalamus has been noted (27). To what extent the action of OHP to release ACTH can be attributed to its influence on hypothalamic function cannot be stated at present.

Hypercarbia. Many studies in various species have demonstrated that acute and chronic exposure to CO_2 enhances the release of ACTH, as measured by a decrease in adrenal ascorbic acid (298, 309), a decrease in adrenal cholesterol (309, 470), an increase in adrenal weight (148, 470), and an increase in concentration of 17-hydroxycorticosteroids in adrenal venous blood (434). The degree of adrenocortical stimulation varies directly with the concentration of CO_2 inhaled and with the duration of exposure. For example, Richards and Stein (434) observed that dogs exposed to 2.5, 5, 10, 20, and 30% CO_2 for one hour exhibited a progressive increase in the 17-hydroxycorticosteroid levels of adrenal venous blood; maximal adrenocortical stimulation was elicited by exposure to 20 to 30% CO_2, and the response to such exposure was abolished by hypophysectomy. Richards (433) also found that adrenocortical stimulation occurred in dogs with a profound decrease in arterial pH and bicarbonate concentration in the presence of a normal arterial CO_2 tension, and also in dogs with an increase in arterial CO_2 tension and bicarbonate concentration in the presence of a normal arterial pH. He concluded that concomitant alterations in arterial pH and CO_2 tension are not required to evoke an adrenocortical response, and that an appropriate change in either of these factors can act as a stimulus for ACTH release.

Carbon dioxide has many actions on the central nervous system. Among the most prominent, are its effects on the hypothalamus and the reticular activating

system (171, 172). In high concentrations, CO_2 stimulates the hypothalamus and reticular activating system, as indicated by release of epinephrine (171), production of clonic seizures (615), and activation of the EEG (171, 615). Therefore, it can be assumed with considerable justification that CO_2 acts on the hypothalamus to promote ACTH release (see 172, 615). Information on the effect of various concentrations of this gas on ACTH release in animals with hypothalamic lesions would provide a clear-cut answer to this problem.

f. Miscellaneous agents, conditions, and procedures. 1) Tranquilizing agents. Only the effects of chlorpromazine and reserpine on ACTH release will be discussed in this review. On acute administration, chlorpromazine causes activation of the adrenal cortex, as measured by depletion of adrenal ascorbic acid, increase in the 17-hydroxycorticosteroid level in adrenal venous blood, and increase in urinary excretion of 17-hydroxycorticosteroids; pentobarbital blocks this effect of chlorpromazine (121, 224, 236, 376, 489). In contrast to the results of many other investigators, Holzbauer and Vogt (273) observed that chlorpromazine did not inhibit the adrenal ascorbic acid depletion induced by epinephrine or surgical stress; an explanation of this discrepancy is not apparent. On chronic administration, chlorpromazine inhibits ACTH release in response to a variety of stress stimuli but not to vasopressin (18, 63, 66, 224, 383, 384, 489). In schizophrenic patients, chlorpromazine blocks the rise in plasma concentration of 17-hydroxycorticoids induced by high doses of insulin (66). Reserpine has also been demonstrated to enhance ACTH release on acute administration (169, 449) and to inhibit such release on chronic administration (593), as measured by the various tests described above for chlorpromazine. However, Cronheim and Koster (95) found that a mixture of rauwolfia alkaloids did not block the effect of salicylic acid to deplete adrenal ascorbic acid.

2) Autonomic agents. Despite an enormous literature on the influence of various autonomic drugs on adrenocortical function, it is often impossible to distinguish between the central nervous system and visceral nervous system effects of these agents. Only epinephrine and amphetamine will be discussed in this review. Epinephrine has been studied extensively. The fact that the ACTH-releasing effect of epinephrine is abolished in animals with hypothalamic lesions not involving the adenohypophysis (277, 349, 415) suggests that this effect of epinephrine depends, at least in part, on an intact hypothalamico-adenohypophyseal system. Epinephrine probably causes activation of hypothalamic nuclei; this probability is also suggested by the metabolic studies of Roberts and Keller (438). Amphetamine, a drug with predominantly central nervous system effects, also has been shown to stimulate the release of ACTH, as measured in rats by a decrease in adrenal ascorbic acid but not adrenal cholesterol, and in man by an increase in plasma 17-hydroxycorticosteroid level (24, 355).

3) Hormones. Most of the hormones, other than those secreted by the adrenal cortex, stimulate the release of ACTH; thyroxine, triiodothyronine, estrogens, and insulin are particularly effective in this respect (7, 38, 111, 119, 165, 491, 544, 586, 587); in contrast, adrenocortical hormones inhibit ACTH release (467, 469). On the basis of presently available data, it cannot be decided whether the various

hormones influence ACTH release by an action on the central nervous system or by a direct effect on the adenohypophysis. The well-established fact that adrenocortical steroids inhibit the pituitary-adrenocortical system is the basis for the "cortical hormone titer" theory of regulation of ACTH release (see 467). This theory assumes that adrenocortical steroids inhibit ACTH release by a direct action on the adenohypophysis. However, certain data suggest that the adrenocortical steroids may inhibit ACTH release by virtue of their action on the central nervous system. For example, Dingman and Thorn (110) and Dingman and Despointes (109) have suggested, on the basis of their studies in man, that the diuretic action of cortisone, cortisol, and prednisolone may be related to an inhibitory effect on the hypothalamus to suppress ADH secretion. Since cortisone and cortisol generally have excitatory effects on the nervous system, it is possible that cortisone excites inhibitory hypothalamic pathways. The observations of Porter cited above (Section IV A 3) that ACTH and ACE suppress the enhanced electrical activity of the hypothalamus induced by epinephrine also indicate an action of adrenocortical steroids on the hypothalamus. It would be of interest to know whether the adrenocortical steroids are able to inhibit ACTH release in animals with hypothalamic lesions.

4) Psychic states. The effect of psychic and emotional states on adrenocortical activity has been the subject of some experimental and much clinical investigation. This aspect of the relation of the central nervous system to the adrenal cortex merits a separate review, and will not be discussed in this article. The interested reader is referred to selected references in this field (7, 11, 14, 15, 24, 37, 80, 99, 108, 152, 160, 176, 184, 250, 253–257, 264–266, 307, 372, 402–406, 428, 430, 432, 580).

5) Naturally occurring and experimentally induced convulsions. Many investigators have demonstrated that convulsive states, regardless of the manner in which they are produced, stimulate the release of ACTH, as assessed by a variety of acceptable tests (8, 13, 19, 38, 45, 79, 88, 89, 97, 201, 216, 242, 243, 262, 263, 398, 451, 454, 471, 490). The results of these experiments provide further evidence for regulation of ACTH secretion by the central nervous system; however, since few if any of the studies yield specific information on the localization of the precise areas concerned with such regulation, this topic will not be discussed further.

B. Relation between central nervous system activity and secretion of aldosterone

Although the hypothalamico-adenohypophyseal system is known to regulate the secretion of some of the adrenocortical steroids via ACTH, it does not necessarily follow that the secretion of all adrenocortical steroids is regulated in this manner. The secretion of aldosterone by the adrenal cortex appears to be controlled by a mechanism distinctly different from that for cortisol (328). The secretion of aldosterone is responsive to changes in water and electrolyte metabolism, whereas the secretion of cortisol is regulated by release of ACTH (328). Sodium deprivation results in a large increase in aldosterone output in the urine whereas sodium excess causes a decrease in aldosterone output; neither procedure

affects 17-hydroxycorticoid (cortisol) excretion. ACTH administration causes a much larger urinary excretion of cortisol than of aldosterone. Suppression of ACTH release by cortisone or by damage to the pituitary reduces cortisol secretion markedly but has little effect on aldosterone secretion. The finer mechanisms of the regulation of aldosterone release have not been elucidated, but the observations of Rauschkolb and Farrell (423) indicate that the central nervous system is involved. They observed in dogs that secretion of aldosterone was markedly reduced by decapitation and decerebration, but unaltered by spinal cord transection and decortication; these findings suggest that a regulatory center for aldosterone secretion may be located in the diencephalon. In line with this evidence for central regulation of aldosterone secretion are the clinical observations (325, 594) that injury to certain areas of the brain, particularly the hypothalamus, can result in hypernatremia. Whether the hypernatremia is a result of altered secretion of aldosterone, or whether changes in aldosterone secretion occur secondarily as a result of the hypernatremia (see above), cannot be determined from the available data. In order to elucidate further the intimate mechanisms regulating aldosterone secretion, simultaneous measurements of electrolyte concentrations in plasma and urine and the rate of aldosterone secretion should be performed in animals with discrete central nervous system lesions.

V. ADRENOCORTICAL REGULATION OF BRAIN EXCITABILITY

Evidence is presented in Section IV that adrenocortical secretion of hormones regulating carbohydrate and electrolyte metabolism is under control of the central nervous system; cortisol secretion is regulated via the hypothalamico-adenohypophyseal system and aldosterone secretion via some area in the diencephalon. Also, evidence is presented in earlier sections that the adrenocortical steroids in excessive amounts cause marked changes in brain excitability; cortisol-like steroids increase excitability, whereas DOC-like steroids decrease excitability. Whether such effects of the adrenocortical steroids on brain excitability operate under physiological and pathological conditions remains to be elucidated. Various workers have delineated three separate functional roles of the adrenal cortex, "permissive", "active", and "homeostatic", and there is evidence that all three are concerned with the regulation of central nervous system functions. The term "permissive" ("supporting") has been used by Ingle (284, 285) to characterize the relationship of the adrenocortical hormones to certain metabolic responses which fail to become overt in animals with adrenocortical insufficiency, but which reappear when doses of adrenocortical hormones adequate to maintain a state of eucorticism are administered. The reappearance of such metabolic responses cannot be attributed to an increase in secretory activity of the adrenal cortex, because even the adrenalectomized animal can be restored to normal by appropriate therapy. The adrenocortical steroids thus "permit" but do not cause a given effect to occur. An example of the permissive role of the adrenocortical steroids in nervous system function is the observation of Porter (415) that the enhanced electrical activity in the hypothalamus induced by epinephrine is annulled by adrenalectomy and restored by maintenance doses of cortisone or

cortisol; excessive amounts of these steroids do not augment the effect of epinephrine.

However, many of the central nervous system effects of adrenocortical steroids cannot be ascribed to their permissive role, and an "active" role must be invoked. For example, the increase in brain excitability induced by thyroxine in intact rats is almost twice as great as that in adrenalectomized rats (546); the attenuated effect of thyroxine on brain excitability in the adrenalectomized rat has been attributed to the lack of even a minimal amount of adrenocortical steroids and to the consequent decrease in responsivity of the brain. This possibility is in accord with the "permissive" effect just described. If this proposal is correct, then maintenance doses of adrenocortical steroids given to adrenalectomized, thyroxine-treated rats would be expected to restore the normal response to thyroxine, and brain excitability should be markedly increased. The experiment was performed and the expected result did not occur. Instead, ACE not only prevented the usual moderate enhancement in excitability which thyroxine induces in adrenalectomized rats but actually prevented any increase in excitability. These results indicate that the adrenal cortex actively participates in the response of the central nervous system to thyroxine. Approximately half of the effect of large doses of thyroxine on the nervous system is the result of adrenocortical stimulation; the other half is the result of a direct excitatory action of thyroxine itself on the brain.

The above experimental results also illustrate another aspect of the effect of adrenocortical hormones on nervous system function, namely, their ability to "normalize" or regulate brain function when it has deviated from normal (605, 616). The concept of a "normalizing" or regulatory role of the adrenal cortex is also based on additional observations (603, 605, 616), as follows: 1) Adrenocortical steroids with an oxygen at C-11 antagonize the decrease in brain excitability induced by DOC. 2) ACTH and 11-dehydrocorticosterone, given chronically, partially antagonize the increase in brain excitability induced by cortisone. 3) A single dose of corticosterone prevents to a large extent the decrease in excitability induced by DOC and the increase in excitability induced by cortisol. 4) DOC, cortisol, and many other agents cause a greater change in brain excitability in adrenalectomized than in intact animals. 5) Experimental studies of the effects of salt and water loads on brain excitability of intact and adrenalectomized animals demonstrate that such loads alter excitability of the adrenalectomized rat much more than that of intact animals. 6) Certain centrally acting drugs which alter brain excitability stimulate the hypothalamico-adenohypophyseal system to release ACTH (see Section IV A 4); the adrenocortical hormones secreted as a result of such stimulation tend to antagonize the alteration in brain excitability induced by the drug. These data suggest that some secretory product of the adrenal cortex, released as a result of ACTH stimulation, regulates central nervous system excitability in such a way as to restore an abnormally increased or decreased excitability to normal. Evidence that the regulatory hormone of the adrenal cortex, at least in the rat, is corticosterone has been summarized by the reviewer (605) and will not be discussed here. As discussed above, both hypoxia

and hyperoxia probably cause the release of aldosterone from the adrenal cortex by virtue of their central nervous system effects. This suggests an additional mechanism for regulation of brain excitability. Aldosterone decreases excitability (616) and hence counteracts in part the direct increase in excitability induced by hypoxia; as would be anticipated, hypoxia causes a greater increase in brain excitability in the adrenalectomized than in the intact animal. Aldosterone augments the decrease in brain excitability induced by hyperoxia; again as anticipated, hyperoxia causes a greater decrease in brain excitability in the intact than in the adrenalectomized animal.

Thus two mechanisms exist for regulation of brain excitability by adrenocortical steroids, one operating via the hormones secreted as a result of ACTH stimulation of the adrenal cortex and the other operating via aldosterone. Corticosterone acts to restore abnormal brain excitability to normal, regardless of the direction of the original deviation. However, this regulatory influence of corticosterone may be compromised if the original cause of the change in excitability also activates the adenohypophyseal-adrenocortical system so as to alter the normal pattern of adrenocortical secretion, or if the original cause of the deviation activates the release of aldosterone. It can therefore be concluded that the adrenocortical hormones have the three influences on central nervous system function, as described above: a *permissive* influence in that normal brain excitability is not maintained in the absence of adrenocortical hormones, an *active* influence in that the concentration and pattern of steroids in the blood exert a direct effect on brain excitability, and a *regulatory* influence in that factors which alter brain excitability also cause adrenocortical steroids to be released which tend to counteract the original change in excitability.

The possible metabolic factors involved in the regulation of brain excitability by the adrenocortical hormones require brief summary. Evidence has been presented that brain excitability is inversely related to the ratio of extracellular to intracellular brain Na concentration and also inversely related to the concentration of GABA in brain cells (611, 617), and that the effect of a drug or procedure on brain excitability is the algebraic sum of its separate effects on brain Na ratio and brain GABA concentration (611). In addition, it has been demonstrated that cortisol decreases whereas DOC and diphenylhydantoin increase brain GABA concentration in adrenalectomized but not in intact rats. In both intact and adrenalectomized rats, cortisol decreases brain Na ratio whereas DOC and diphenylhydantoin increase this ratio. With these facts in mind, it is possible to present a metabolic explanation for the regulation of brain excitability by adrenocortical steroids. Since cortisol decreases brain Na ratio and brain GABA concentration in the adrenalectomized rat but decreases only the brain Na ratio in the intact rat, brain excitability is not increased as much by this hormone in the intact as in the adrenalectomized animal. Conversely, since both DOC and diphenylhydantoin increase brain Na ratio and brain GABA concentration in the adrenalectomized rat but increase only the brain Na ratio in the intact rat, brain excitability is not decreased as much by these two agents in the intact as in the adrenalectomized animal. It is thus evident that the brain

of the *intact* rat is less susceptible to agents which alter its excitability; this protection can be explained by the fact that agents (cortisol, DOC, diphenylhydantoin, *etc.*) which alter brain excitability cause the secretion of corticosterone, the regulatory hormone of the adrenal cortex; corticosterone prevents the change in brain GABA concentration induced by such agents. Only when corticosterone is not secreted, as in the adrenalectomized rat, do these agents alter brain GABA concentration. Still other examples of the regulatory influence of corticosterone on brain GABA concentration have been observed (581, 611). It seems fairly well established, therefore, that the active and the regulatory influences of adrenocortical hormones on brain excitability are exerted via their effects on Na and GABA metabolism in the brain.

A final problem which deserves mention is the nature of the active adrenocorticosteroids in the brain and whether such steroids actually enter the brain substance. Only low levels of 17-hydroxycorticosteroids are observed in cerebrospinal fluid; this has been interpreted to mean that the blood-brain barrier limits their entrance into the brain (1). However, the experiments of Waterbury and Woodbury (589) have demonstrated that radioactive cortisol very rapidly enters the cerebral cortex; the rate of entrance and the amount present parallel the course and the intensity of the changes in brain excitability induced by cortisol. In addition, the compound which enters the brain has been identified as cortisol by chromatographic methods. Thus cortisol *per se* acts on the nervous system to increase brain excitability. Further studies with other isotopically labeled steroids, particularly corticosterone, DOC, and aldosterone, are needed.

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