INVESTIGATION of cerebral lesions following arrest of the cephalic circulation revealed a very striking picture which included the following:

a) Swollen cells—cells that are enlarged, may contain vacuoles, and whose staining properties have been altered. Some have enlarged nuclei surrounded by an edematous zone.

b) Perineuronal and generalized edema.

c) Dilated blood vessels; enlarged perivascular spaces and marked perivascular edema.

d) Marked changes in the blood vessel walls.

e) Cellular lesions appeared in many subcortical areas to be restricted to anatomic units (nuclei).

This combined picture of edema and changes in cell and vessel membranes with highly localized destruction, suggested two possible mechanisms of injury: (a) disturbance of the blood-brain barrier with permeability changes and shifts in electrolyte balance; and (b) possible interference with local enzyme systems primarily involving one or more of the intermediary steps in carbohydrate metabolism.

These two mechanisms immediately focused attention on the possibility that the adrenal cortex might play a role of major importance in the protection of the central nervous system from such damage, inasmuch as various fractions of the adrenal cortical hormone are known to influence both electrolyte balance and carbohydrate metabolism.

However, before attempting to test this hypothetical hormonal activity under the severe conditions of complete circulatory arrest, it was necessary to obtain some base-line of an adrenal cortical effect on the central nervous system in normal and less severely injured cases, as well as to determine whether or not the hormonal action would be reflected in activity of the brain as measured by the electroencephalograph. The use of exposure edema to produce a relatively mild form of injury was suggested by the report of Prados, Strowger and Feindel who showed that after trephination and re-
reflection of the dura, exposure to air resulted in an acute reaction characterized as being one of edema due to a primary alteration in the integrity of the circulation with secondary cellular alterations. Adrenal cortical hormone was shown to prevent many of these changes. We have extended these observations and included a study of the effects of adrenal cortical substances on the uninjured brain.

METHODS AND MATERIALS

Two groups of experiments were performed. The first group was designed to test the possible influence of adrenal hormones on relatively mild injury— injury in the form of exposure edema. Three criteria were used as indices of the anatomic and functional status of the brain tissue:—(a) the electroencephalogram as a measure or correlate of function; (b) reaction to injection of 1 per cent trypan blue as an indication of integrity of the blood-brain barrier, and (c) microscopic sections for changes in morphology.

The second group of experiments was set up to determine the effect of the adrenal substances on the electroencephalogram of the intact, unoperated control animal. A variety of species were used—cats, rabbits, rats, and man (in two experiments). The procedure was carried out on unanesthetized and curarized animals, as well as on animals anesthetized with pentobarbital sodium, urethane-ether, chloralose, “evipal” and “dial.” Each experiment was carried out in duplicate, except for the titration experiments which were carried out on 6 cats.

The electroencephalogram was recorded in the usual way, employing a standard 3-channel ink-writing oscillograph with differential amplifiers. The scalp was incised and the temporal muscles were reflected. Phonograph needle electrodes were driven into the skull following induction of anesthesia with intraperitoneal sodium pentobarbital (“nembutal,” Abbott; 35 mg./kg.). A pair of cats was used in each experiment of the exposure edema series; one received adrenal cortical hormone, while the other served as a control. Both animals were prepared by making a skull defect, measuring 1.3 cm. X 2.0 cm., in one hemisphere, located in the midparietal region. The dura was reflected and the brain exposed to air. In some cases a strong lamplight was focused on the head, both to increase drying of the brain and to keep the animal warm over a long period of time. Aqueous adrenal cortical extracts were administered intramuscularly 1 hour before, immediately following, and 3 hours after exposure of the brain. At the time of exposure, 10 cc./kg. of 1 per cent trypan blue were injected into the saphenous vein. This was repeated at the time of sacrifice, usually 12 or 24 hours after exposure. Death was induced by intrathoracic injection of chloroform, following which the brains were removed and examined grossly and microscopically (with thionin stain).

OBSERVATIONS

Fig. 1 shows the results obtained in control and adrenal treated animals following brain exposure. The preoperative record in the injected animal
demonstrates markedly greater amplitude and faster frequency than in the control, these being consequent to an intramuscular injection of total extract 1 hour before exposure. It is to be seen that in the untreated animal, complete flattening of the brain waves has appeared 3 hours following operation; even 24 hours later the record is still abnormal. However, no significant abnormality can be seen in the electroencephalogram of the adrenal treated animal 3 hours after exposure, nor does it show any of the slow frequency seen in the control 24 hours later. Both animals received two injections of 10 cc./kg of 1 per cent trypan blue into the saphenous vein; one 3 hours after exposure, and another just prior to removal of the brain for sectioning. (In the normal animal, trypan blue fails to stain the central nervous system—i.e.,

![AN EFFECT OF ADRENAL CORTICAL EXTRACT ON BRAIN EXPOSURE](image)

**Fig. 1**

does not pass the blood-brain barrier—except for the tuber cinereum and region of the chiasm, the pituitary, the choroid plexuses and the area postrema.) On gross examination, the brain of the untreated animal showed marked blue staining extending into the white matter at the area of exposure. The adrenal treated brains showed no staining in some cases; in others a much less extensive area of faint staining was evident. In some cases, the staining reaction was somewhat equivocal, but in no case did the staining in the treated animals approach the intensity observed in the controls. Two associated points are to be noted. First, during the course of the experiments, gross edema was observed only in the controls, evidenced by bulging of the brain substance through the trephine hole in the calvarium, accompanied by disappearance of the brain pulsations. Secondly, examination of thionin stained sections revealed the presence of marked intra- and intercellular edema in the controls; a pathologic picture that was absent following injection of the adrenal cortical extract.

It was pointed out that in the preoperative post-injection record (Fig. 1) of the treated animal, marked changes could be observed in contrast to the preoperative tracing in the control. The observation that the hormone appeared to influence the electrical activity of the brain in the unoperated, intact animal attracted immediate attention. Consequently, the electroencephalogram of a normal animal was recorded following pentobarbital an-
EFFECT OF ADRENAL CORTICAL SUBSTANCES ON CNS

Fig. 2 shows the normal record obtained from three leads, as well as the changes following intramuscular injection of 2 cc./kg. of aqueous adrenal cortical extract. Twenty-one minutes after the injection, marked changes in amplitude are obvious; the increase in voltage is carried still further 32 and 50 minutes post-injection. This procedure was carried out in a series of animals in all of which similar changes in amplitude and frequency were observed.

However, there remained the possibility that these effects were in some
way related to the anesthesia—in other words, that there might be some combined action of the hormone with pentobarbital. For this reason, both lipoadrenal cortical hormone (Upjohn) and aqueous adrenal cortical hormone

were injected intramuscularly and intravenously in the unanesthetized animal (Fig. 5) and man (Fig. 6), as well as in the curarized animal (Fig. 4), and in animals anesthetized with urethane-ether (Fig. 3), “evipal,” chloralose, and “dial.” The results already obtained were confirmed by these ex-
experiments. In man only one experiment has been carried out thus far, in which incipient changes in amplitude and frequency (of the same nature as those seen in the experimental animals) appeared consequent to the intravenous injection of 0.5 cc./kg. of aqueous adrenal cortical extract. The changes, in both animals and man, appeared 5–10 minutes after intravenous injection, and 20–30 minutes after intramuscular injection. The minimal effective dose and time of latency of the recorded reaction remained to be determined. This was done by the intravenous injection of 0.25 cc./kg. doses at 8 minute intervals (Fig. 7).

With this procedure, it was observed that definite changes appeared in the electroencephalogram 8 minutes after a total of 0.5 cc./kg. had been injected. These changes progressed following doses up to 1–2 cc./kg., at which point an asymptote was reached. No further increase in amplitude or frequency could be produced with greater amounts of the hormone. In extremely large doses the bursts of marked activity in the electroencephalogram alternate with periods of depression. In one animal which was given up to approximately 20 cc./kg. of the hormone, the bursts of enhanced voltage still appeared at intervals.

The question arose as to whether or not individual fractions of the total cortical hormone could produce or were producing the observed reaction. The first attempt to answer this question was the injection of desoxycorticosterone acetate, the results of which are shown in Fig. 8. It appears that the DCA produces the same type of increase in amplitude as that brought about

---

**EFFECT OF ACH AND DCA IN OIL ON TWO ANESTHETIZED CATS**

**CAT1. 2KG. PRE-INJ. RF-RO 7 M2**

**CAT2. 2KG. PRE-INJ. RF-RO 7 M2**

**CAT1. 6 HRS. POST-INJ. IM. ACH IN OIL**

**CAT2. 6 HRS. POST-INJ. IM. DCA IN OIL**

50µV. 1 SEC.

---

**Fig. 8**
by the total adrenal hormone itself, but the frequency changes are apparently not of a like nature. If anything, the enhanced amplitude following DCA was accompanied by slow frequency in contrast to the fast frequencies seen after injection of total extract. Further experiments with DCA and other similar compounds remain to be performed.

DISCUSSION

In the light of our knowledge at the present time, there can be little question of the validity of the thesis that the adrenal glands profoundly influence resistance and defense mechanisms of the body. There is an ever increasing mass of clinical and experimental data serving to point out and attempting to explain changes in the adrenal cortex following poisons and infections and in conditions of stress or shock, as well as the role of the cortical hormones in the formation of antibodies and other physiological events. Evidence has been obtained demonstrating that the adrenal cortex is related to carbohydrate metabolism, to salt and water metabolism, to utilization of certain of the vitamins, and is intimately concerned with processes of tissue respiration. Perla and Marmorston summarize these relationships in the following statement:

It would seem probable that the mechanism of natural resistance is dependent on the maintenance of normal cellular metabolism and that procedures that impair oxidation and reduction processes depress the resistance of the somatic cells to all abnormal stimuli, whether marked variations in temperature or poisons, toxins or infectious agents. When the physiologic action of the cortical hormone is better understood, the exact chemical nature of the life-prolonging hormone identified, and its relation to oxidation-reduction systems determined, a new approach to the problem of the mechanism of natural resistance in the body may be available.

Following this line of reasoning, we instituted a course of injections of adrenal cortical hormone in a case of post-traumatic concussion syndrome in man (about one month after injury). The results have indicated that further clinical and experimental investigations of this problem should be carried out. Using a minimum dose of 20 cc. of aqueous extract per day (from our findings we now suggest a level of at least 0.5 cc./kilo/day) it was noted that by the third day of this therapy the incessant headache had disappeared. An electroencephalogram taken 2 weeks after treatment was begun, showed no abnormality whatsoever—the slowing and irregularity seen 1 month before was no longer in evidence. The patient has been followed up to the present time and has shown no recurrence of any of the symptoms. Other problems relative to these findings will be discussed below. An indication of confirmation of these results is suggested in the report of Aird who states:

Neurophysiological studies on cerebral concussion have demonstrated that the permeability of the blood-brain barrier is increased after concussion and that this effect persists ... in apparent association with the post-concussional dysrhythmia observed electroencephalographically.... When measures were taken to decrease the permeability of the blood-brain barrier, these effects could be prevented in large part. Preliminary clinical studies, which are at present under way, suggest that adrenal cortical extracts may have some beneficial effects on the post-concussional state.
It is possible that this patient's electroencephalogram would have recovered in any case, but the findings would suggest that further work of this nature is indicated.

We are primarily interested in the way in which these mechanisms can be related to the central nervous system. In earlier days, when little or no definite knowledge was available relative to the action of the adrenal glands, it was suggested that they played a major role in epilepsy and subtotal adrenalectomies were performed in such cases. It was observed that in some instances the seizures diminished and the associated lymphocytosis and eosinophilia disappeared. It is now known that hydration can precipitate an epileptic crisis, and that restriction of the water intake or enforced diuresis are anticonvulsive. Surgical removal of the adrenal, therefore, had probably produced a negative NaCl balance and a significant degree of dehydration.

In Addison's disease patients tend to show symptoms of insomnia, restlessness, abnormal sensory reactions, apathy, anxiety, fatigability and general ineffectiveness—a picture described as subacute adrenal deficiency. These symptoms may precede or occasionally overshadow other clinical symptoms or biochemical findings to such an extent that the patient is sent to a psychiatric service. Improvements in vision, insomnia, fatigue and tremor occur with adequate adrenal cortical extract therapy. Engel and Romano reported abnormal electroencephalograms in Addison's disease during all stages of therapy. The records were most abnormal during the crisis, showing marked slowing with an average frequency of about 7 per second. With adequate adrenal cortical treatment (100 cc. over 5 days) the electroencephalogram returned to normal, showing an average frequency of 9–10 per second. Other reports of the ineffectiveness of cortical extract in such cases appear to have been due to low, inadequate dosage.

Engel and Romano also found that desoxycorticosterone acetate would only partially restore the electroencephalogram. From our findings thus far it seems that desoxycorticosterone has more effect on amplitude than on frequency. It may be that both electrolyte balance and carbohydrate metabolism must be affected in order to produce the complete result. Later experiments may afford the answer to this question.

A further point of interest relative to the picture produced by Addison's disease, is the increased susceptibility and sensitivity to drugs. The patient is unusually sensitive to narcotics such as morphine and codeine, and to sedatives, including paraldehyde, bromides and barbiturates. Coma and respiratory failure may follow administration of usual therapeutic doses of these compounds. Restoration of adrenal cortical levels overcomes this susceptibility to central nervous system depressant drugs.

In bilaterally adrenalectomized rats as in the Addisonian patient, there is fatigue and a disinclination for exercise. The animals lose interest in their surroundings, and at times may become almost comatose. In some cases they become easily irritated or disoriented. The reflexes of these animals
are more easily fatigued than the normal. The resistance to the reflex fatigue may be increased as much as sixfold following adrenal cortical administration (Hartman, Beck and Thorn⁴). Furthermore, Liddell⁵ has observed that adrenal cortical extract exerted a marked ameliorative influence on the manifestations of “experimental neurosis” in sheep.

It appears then, that adrenal cortical extract exerts a profound effect on the central nervous system, which is reflected to some extent, at least, in the activity of the brain as measured by the electroencephalograph. Part of this influence may be transmitted through a metabolic mechanism, but unquestionably a large part is manifested as a control or regulation or preservation of the blood-brain barrier and its permeability. Our experiments with the hormone in cases of exposure edema have definitely confirmed those of Prados, Strowger and Feindel who first reported the efficiency of these glandular preparations in preventing leakage of trypan blue through capillary walls after exposure. They observed that, “... as a result of exposure the capillary endothelium becomes more permeable. This allows not only an increased outflow of fluid into the interstitial spaces, but the leakage of substances which in normal conditions are not permeable to the so-called blood-brain barrier.” There is considerable evidence in the literature that adrenal hormones influence capillary permeability,⁶ and that the capillaries of the adrenalectomized animal are dilated and abnormally permeable. The edema which can follow such abnormality, and which has been seen after arrest of cephalic circulation, concussion, exposure, etc., should, therefore, be affected by adrenal extracts. Our experiments would suggest that such, in fact, is the case.

It is possible that the electroencephalographic findings may also be of value in relation to the problem of the origin of the electroencephalogram itself. The present observations, plus results of experiments in progress, should lead to at least one more correlate of nervous system activity and its reflection in the electroencephalogram. If adrenal hormones cause neurones to fire in some specific way, there should be the possibility at hand of localizing some of the basic physiological factors underlying electroencephalographic activity.

SUMMARY AND CONCLUSION

Evidence has been obtained of the passage of adrenal cortical extract across the blood-brain barrier. Adequate doses of adrenal cortical extracts have been shown to protect the cerebral cortex against structural and functional abnormalities elicited by exposure. In addition, these hormones have produced marked changes in the electroencephalographic picture of normal animals, and indication of their effectiveness in overcoming symptoms of the post-concussional state has been obtained.

It is felt that the results have important physiological and clinical implications.
REFERENCES


