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-
EFFECT OF ADRENAL CORTICAL SUBSTANCES ON CNS

Refection 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. × 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