OBSERVATIONS ON SELECTIVE BRAIN HEATING IN DOGS*

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This investigation was prompted by the knowledge that heat destroys tumor cells more readily than normal ones9,18 and by the recent demonstration of Woodhall et al.11,12,19,20 that hyperthermia enhances the cytotoxic effect of certain chemotherapeutic agents on malignant tumors.

The observation that the brain can be cooled selectively by regional perfusion10,21 suggested the possibility of heating the brain selectively by similar technique, thus avoiding the undesirable effects (electrolyte imbalance, peripheral vascular collapse) of total-body hyperthermia. We considered it important to determine the duration and limit of excessive heat that are compatible with normal function of the brain and also the physiological changes that occur during selective hyperthermia of the brain.

We measured blood pressure, pulse, respiration, electrocardiograms and electroencephalograms incident to heating. Blood electrolytes, pH and hemoglobin as well as morphology of erythrocytes also were studied. In addition the effect of heat on cortical excitability was tested by recording changes in the evoked visual response while varying the temperature of the brain. Finally, all animals were observed for variable periods of time (18 hours to 3 months) and gross and histological examinations were made of the brains.

METHOD

One hundred adult dogs were studied under light Nembutal anesthesia. The technique employed was a modification of that used by Lourie et al.19 for selective cooling of the brain. Ninety animals were intubated with an endotracheal tube, paralyzed with Flaxedil and carried on artificial respiration; the remainder were allowed to breathe spontaneously. The carotid arteries were exposed bilaterally beyond their bifurcation and small craniectomies (1 cm. in diameter) were made over both parietal areas and cerebellum. All animals were given heparin (3–5 mg./kg.).

By utilizing an extracorporeal shunt (Fig. 1) it was possible to achieve brain temperatures of 42°C. (107.6°F.) to 46°C. (114.8°F.) for 30 min., esophageal temperatures not rising above 38°–40°C. The 30-min. period was decided upon arbitrarily. Carotid blood was detoured through a Sigma motor pump, propelled through a stainless-steel coil immersed in a water bath, and returned to the carotid circulation at a flow rate of 50 cc.per min. The extracorporeal system had a capacity of 100 cc.

At any temperature 50 ml. per min. was found to be the safe ceiling of flow rate regardless of body weight. Brain weight bears no relationship to body weight, the former remaining relatively constant in animals of disparate body weights. Flow rates above 50 ml. per min. result in concomitant lowering of blood pressure and pulse rate and breakdown of the blood-brain barrier during perfusion. In such animals neurological deficit, blindness and death could occur, post-


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mortem examination revealing infarction, hemorrhage and edema of the brain as well as ocular hemorrhages.

To attain brain temperatures of 42°–43°C, it was necessary to ligate the external carotid and occipital arteries on the side of perfusion and maintain water-bath temperatures at 47°–49°C. Furthermore, it was essential to control respiration at a fixed rate (24/min.) since excessive panting induced by hyperthermia lowered brain temperature. To achieve temperatures higher than 45°–46°C the common carotid artery, contralateral to the side of perfusion, had to be ligated and water-bath temperatures of 48°–51°C were necessary.

Temperatures were monitored on a telemeterometer using calibrated bead thermistors to measure extradural temperatures from both hemispheres, posterior fossa and esophagus; for intracerebral readings a #20 hypodermic thermistor was used. A standard mercury thermometer registered rectal and water-bath temperatures. Extradural temperatures were found to parallel intracerebral ones closely, showing no more than a 0.5°C. difference. Therefore, in the majority of animals only extradural temperatures were monitored.

Femoral-artery pressures were measured with a standardized Statham transducer and recorded on a Grass polygraph simultaneously with pulse rate, electroencephalogram and electrocardiogram. A single pair of stainless-steel needle electrodes were used to record electroencephalograms. One electrode was placed in periosteum to the right of the mid line at the level of the vertex, the other into nasal periosteum.

Blood was taken variably from femoral artery and vein, carotid artery and extracorporeal circuit for determination of pH, Na⁺, K⁺, Cl⁻, and hemoglobin as well as for morphological examination of red cells. In some animals blood electrolytes and hemoglobin were examined daily for 1 week in addition to being measured during hyperthermia.

The cortical visual response was evoked by electrical stimulation of optic nerve and recorded extradurally. The critical electrode was placed over the right lateral gyrus, the reference one on nasal periosteum. Stimulating electrodes were ordinary small sewing needles. One insulated to its tip was thrust into left optic nerve within the orbit, the other bared 7 mm. from its tip was inserted into orbital periosteum. Stimuli of 1–5 volts

Fig. 1. Conditions necessary to achieve brain temperatures of 42°–46°C.