Cerebral Deposition of Drugs at Low Temperatures*

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At low temperatures, sodium fluorescein stains the extravascular tissues of the brain. This vivid intracerebral deposition occurs after the brain has been cooled below 28°C for at least 20 minutes. Presumably, it is indicative of an alteration in cerebral permeability, since the negatively charged dye ordinarily does not pass the blood-brain barrier. Indeed, its passage suggests that other substances (usually excluded from the brain) may permeate the cerebral parenchyma under the extraordinary conditions created by the profound hypothermia.

In an empirical exploitation of this suggestion, d-tubocurarine, dimethyl penicillin, and diphenylhydantoin sodium were given by vein under comparable conditions of profound cerebral hypothermia. The brain substance then was assayed for evidence of cerebral deposition.

These drugs were chosen because of their pharmacological significance, chemical difference, and different predilection for cerebral deposition under ordinary conditions. Thus, according to Bovet, d-tubocurarine (in the circulation) ordinarily is excluded from the brain, while Noach et al. reported a significant cerebral deposition of diphenylhydantoin sodium from the circulation at normal temperatures. On the other hand, Rantz, Sollmann, and others found only traces of penicillin in the brain after intravenous injection under ordinary conditions. There are obvious chemical differences, while the several characteristic pharmacologic actions, such as muscle relaxation, antibiotic, and anticonvulsant, are well known, if not well understood.

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Materials and Methods

Thirty-six healthy Macaca rhesus monkeys (average weight 3.5 kg.) were used in this study.

a. Operative Technique. Twenty-eight animals were subjected to tracheotomy, intubation, and trepanation under careful local anesthesia (5 cc. Nupercaine 1/1500). The endotracheal tube was connected to a mechanical respirator arranged so as to provide 5 per cent supplemental oxygen with room air. A copper constant thermocouple probe was inserted over the parietal dura mater in the trepanation and sutured in place during closure of the overlying scalp. It was connected to a Minneapolis-Honeywell temperature reader. A rectal probe measured temperature by means of connection to a Yellow Springs recorder. An intravenous catheter was inserted in the right long saphenous vein and connected to a slow-running infusion of 5 per cent dextrose in water. Fluid volume given by this method, which was used as a vehicle for administration of drugs, never exceeded 50 cc.

Eight animals were subjected to left parieto-temporal craniotomy under local anesthesia after endotracheal intubation, induction with Fluothane and maintenance on oxygen and Anectine. In these cases, a cortical epileptogenic lesion was made by direct application of a wafer containing 3000 units of penicillin G. Later in these experiments, the wide area of cortex surrounding and including this lesion was removed by subpial dissection.

Scalp, cortical, and cardiac recordings were made on an 8-channel Grass electroencephalograph.

b. Cooling and Heat Exchange. In 14 animals, this was done by carefully packing the head and upper neck in ice wrapped about with Koroseal. The average time of cooling was 1 hr. in this group. In 8 animals (that underwent craniotomy and received penicillin lesions) the brain was cooled topically by irrigation with iced Elliot's solution in a technique which has been described recently. In the latter cases, brain temperature was recorded by intracerebral thermistor probe to a depth of 5 mm. to 1 cm., while rectal temperature was monitored as noted above. The average time of topical brain cooling was 10 min.

A total of 22 animals underwent regional or
topical hypothermia, while 14 were maintained at "normal" temperatures and served as controls.

c. Drugs. All drugs were given by vein as noted above. In the animals that were cooled, the time of administration was 30 min. after the lowest recorded brain temperature. The several average (1 kilo/body weight) doses were as follows:

d-tubocurarine: .86 mg./kg.
diphenylhydantoin sodium: 3 mg./kg.
dimethyl penicillin: 80 mg. (4000 units/kg.)

These levels of doses are considered analogous to therapeutic doses in clinical practice.

The rate of administration generally was uniform and slow. The average time of injection was 10 min. In the case of diphenylhydantoin sodium, administration was slowest and the total dose usually was divided into 6 equal parts, each of which was given over a 2-min. period with an interval of approximately 3 min. It was found necessary to regulate the administration of diphenylhydantoin sodium with great care as rapid, or even moderately rapid, injection promptly killed the animal. Similarly, a slow rate of injection of d-tubocurarine was advisable lest cardiac dysrhythmia occur.

The d-tubocurarine was labeled with C\textsuperscript{14} in the dimethyl position, while diphenylhydantoin sodium was also labeled with C\textsuperscript{14}, but in the C\textsuperscript{4} position.

d. Methods of Assay. The brain specimens were taken after sacrificing the animals in 28 cases. After exsanguination by severance of great vessels in the chest, the brain was removed carefully in the usual manner. Postmortem temperatures were taken from various areas and then samples of tissue from gray, white, and whole brain were taken from frontal, temporal, parietal, and occipital lobes, as well as pons and cerebellum. In 8 cases, the brain specimens were excised at operation as noted above.

The assay of labeled (C\textsuperscript{14}) drugs was done by Packard counter, using tissue homogenates from samples of known weight.

The quantity of dimethyl penicillin was estimated by the cylinder plate method, using \textit{Sarcina lutea} as the test organism.

All animals received 50 microcuries of Cr\textsuperscript{51}-labeled sodium chromate. The activity of chromium then was counted from a standard blood sample (1 cc.) which was taken just before sacrifice or immediately before cerebral excision (in the operative cases). The activity in this sample was compared to the Cr\textsuperscript{51} activity in a brain-tissue sample of known weight. Then by extrapolation from these figures, the percentage of blood in the sample was calculated. The resultant figure was used in further calculation of amounts of labeled drugs present in homogenates of tissue taken from the brain.

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**Fig. 1.** Brain charts indicating origin and amounts of d-tubocurarine in samples at different levels of temperature. Samples derived from both sides of the brain are summarized on the one chart. (a) 38°C. (b) 24°C. (c) 19°C. All figures \( \times 10^{-4} \) mg. of d-tubocurarine per gm. of brain.