Experimental Postoperative Cerebral Edema*

FRANK D. MANN, M.D., AND DARIO D. TRAVAINI, B.S.
Division of Neuropathology, Barrow Neurological Institute of St. Joseph's Hospital, Phoenix, Arizona

Since postoperative cerebral edema remains an important cause of morbidity and mortality in neurosurgery there is need for an experimental model that closely resembles this clinical condition. Prados et al. exposed the cerebral cortex of cats to air; edema of moderate degree, permitting closure of the dura mater, usually followed but rarely and unpredictably there was marked swelling. Luse and Harris reported swelling of the brain following craniotomy in the rabbit; they stated that this technique was not a suitable method for the consistent production of cerebral edema. This communication reports a method for the consistent production of a marked degree of postoperative cerebral edema together with some observations on the edema thus produced.

Material and Methods

Rats were chosen as the experimental animal in order to make more convenient observations on large numbers of animals. In agreement with the results of Prados et al. on cats and Luse and Harris on rabbits, well marked cerebral edema was found to follow craniotomy only occasionally and unpredictably. Craniotomy was performed on 113 rats in working out the following technique for consistent production of postoperative cerebral edema.

Rats weighing 150 to 200 gm. were anesthetized with sodium pentobarbital (30–60 mg. per kg. intraperitoneally). It was necessary to individualize the dosage on the basis of response to an initial relatively low dose. A small, high-speed, thin-bladed, circular saw obtained from a hobby shop was used to remove a piece of skull approximately 1 cm. square, the anterior border being the frontoparietal suture lines. The dura mater then was stripped from the area of brain beneath, avoiding the mid-sagittal sinus. A Gelfoam sponge was pressed gently but firmly over the operative area to maintain hemostasis. Thirty min. after completion of the operative procedure 0.1 ml. of epinephrine 1–1000 was injected into the gastrocnemius muscle. Rapid marked swelling of the brain followed. Swelling was usually maximal within 30 min. and often within 5–10 min. At maximal swelling the edema usually extended several mm. above the upper surface of the skull.

At the elected time the rats were sacrificed by decapitation with a cleaver. The brains were removed and fixed in 10 per cent formalin. Coronal sections were cut through the entire brain at the level of the edematous area and histologic sections were prepared and stained with hematoxylin and eosin.

Observations were made on cerebral edema produced in 22 rats by the foregoing technique. Controls were the brains of 11 rats which either died or were sacrificed immediately after the operative procedure.

Observations

All of the brains rendered edematous by this method showed unequivocal swelling of the cytoplasm of the oligodendrocytes (clear cells) as shown in Figs. 1–3. (It should be noted at this point that there is sharp division between authorities as to whether the cells affected in cerebral edema are oligodendrocytes or astrocytes. In accepting one point of view it is not implied that the issue is settled.) There was also unmistakable “loosening” of the structure of the white matter with clear spaces between the fibers in the more severely affected brains. There was some artifactual shrinkage around vessels in the control brains; hence this change was not used as a criterion of edema. Of all the various histological descriptions of cerebral edema, the above picture resembles most closely that described by Perret and Kernohan.

Histologically as well as grossly the edema was localized definitely to the area of cortex exposed by the craniotomy and it extended

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fairly deeply into the brain to the level of the corpus callosum.

Two rats were given the same dose of epinephrine as that used to produce edema but were sacrificed ½ hour later without performing craniotomy. No edema resulted.

*Response of Cerebral Edema to Urea.* Ten of the 22 rats in which cerebral edema was produced were treated with urea (1–4 ml. of 30 per cent urea injected intraperitoneally). In all 10 the edema disappeared with amazing speed and the brain then shrunk below the level of the skull further than it had previously protruded. With the larger doses, there was marked shrinkage within 5 min. and maximal shrinkage within 30 min. It should be emphasized that this marked shrinkage with urea was localized to the previously edematous part of the brain. The adjacent brain did not shrink so the resulting gross appearance was that of a striking localized hollow below the opening of the craniotomy.

In 3 of the 10 rats, following shrinkage of the brain with urea, the skin was sutured over the craniotomy and the animals were returned to their cages. By the following day the animals were active and looked relatively normal. After 48 hours the incisions were re-opened and the brain was once more found to be very edematous. Two of the rats were treated a second time with urea and again showed a good response. The third rat, which was not treated a second time with urea, showed an extreme secondary edema. The brain of this rat was the only one of the series that histologically showed edema at a considerable distance from the area exposed by the craniotomy.

The histologic picture of the brains of the urea-treated rats was the surprising finding of this research. In all instances, these brains showed edema on histologic examination unmistakably more severe than the animals not treated with urea although the gross picture was that of extreme shrinkage (Fig. 3). Urea in the largest dosage used, without epinephrine, was administered to 2 rats that were sacrificed 30 min. later without craniot-

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**Fig. 1.** Control brain. Hematoxylin and eosin, ×480.
omy. These brains showed grossly a slight general shrinkage away from the skull, in striking contrast to the marked localized shrinkage of the urea-treated edematous brains. With the technique used no edema and indeed no evident histologic change were noted in the brains of the 2 animals treated with urea only.

**Discussion**

Edema was produced consistently following experimental craniotomy and administration of epinephrine and was confined to the area of the cerebrum exposed by the craniotomy. Thus the edema would appear to be closely related to the experimental surgical procedure although its consistent production required a large dose of epinephrine in addition to the surgical procedure. Epinephrine alone produced no edema. Experimental and clinical observations agree that the effect of operative trauma alone in producing cerebral edema is highly unpredictable. Can epinephrine or some analogous substance be a factor? It is unlikely that the amount of epinephrine administered in these experiments can be formed in the body. However, probably only a small fraction of the dose administered actually reached the brain. Furthermore it is possible that epinephrine or an analogous substance may be formed in the brain. Therefore it seems justifiable to raise the question of whether antagonists of epinephrine might be helpful in preventing clinical postoperative cerebral edema. Can this experimental effect of epinephrine be related to the clinical effectiveness of cortisone in preventing cerebral edema, as reported by Rasmussen and Gulati? It is possible that epinephrine might act by increasing capillary permeability and cortisone by decreasing it.

Luse and Harris found that the swelling of the oligodendrocytes produced by distilled water is completely reversed by dehydration with hypertonic solutions. In striking con-
trast the oligodendrocytes of experimental postoperative edema are made more swollen by urea even though the urea specifically shrinks the edematous area to a great degree. Luse and Harris\(^2\) believed that the oligodendrocytes have the important function of transporting fluid and nutrients through the brain tissue. Thus edema or dehydration caused by changes in the osmotic pressure of the blood may be regarded essentially as an exaggeration of physiologic changes. On the other hand in experimental postoperative cerebral edema produced by the method described herein it appears that the combination of operative exposure and epinephrine produces injury of the oligodendrocytes which is possibly irreversible. Following this line of reasoning it is suggested that the urea treatment of the edematous brain completely removes the fluid from the injured swollen edematous oligodendrogial processes which are in contact with the blood vessels over a large surface. However, the cell bodies of the oligodendrocytes which were visualized in our routine histologic preparations and which presented but little surface to the blood vessels were not dehydrated, but instead it appeared that fluid may have been forced into them from the collapsed injured processes. This interpretation would explain the paradoxical finding of extreme swelling of the cytoplasm of the oligodendrocytes in brains that grossly showed extreme shrinkage caused by urea. If the disproportionately large shrinkage of the edematous area produced by urea as compared to the normal area is caused by collapse of the injured swollen oligodendroglia, then it follows that these cell processes must indeed make up a large part of the volume of the normal brain. This would be in agreement with the view of Luse and Harris\(^2\) that the volume of the oligodendroglial cytoplasm corresponds to the chloride space in the brain which is known to be disproportionally large compared to the volume of extracellular fluid.

Whatever the explanation the oligodendrocytes appear histologically more abnor-

![Image](image_url)

**Fig. 3.** Cerebral edema, after treatment with urea. Hematoxylin and eosin, X430.
mal after treatment with urea than before even though grossly the swelling is replaced by shrinkage. If, as seems likely, this histologic picture indicates severe functional damage, the strong tendency to secondary development of edema after treatment with urea is understandable.

Summary

Cerebral edema of marked degree was produced consistently in rats by craniotomy plus intramuscular injection of a large dose of epinephrine. Histologically, the brains rendered edematous by this method consistently showed swelling of the cytoplasm of oligodendrocytes. This change was confined to the edematous area. Intraperitoneal injection of urea caused rapid extreme localized shrinkage of the edematous area. After extreme shrinkage with urea the previously edematous area nevertheless histologically showed more swelling of the cytoplasm of the oligodendrocytes than was the case before treatment with urea.

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References