IN SPITE of considerable investigation into the natural history of subarachnoid hemorrhage caused by the rupture of intracranial congenital berry aneurysms, there is at present no agreement as to the efficacy of the various means of management of this condition. One avenue of approach to assist in the solution of this problem is the trial of different forms of therapy in experimental animals. This would require a technic for the production in such animals of aneurysms similar to those found responsible for subarachnoid hemorrhage in human beings. The purpose of this report is to present the findings in a series of attempts to produce such lesions in dogs by injecting various noxious agents into the walls of intracranial arteries.

McCune and associates reported a method for the experimental production of aneurysms in dogs by means of injections of nitrogen mustard into the wall of the aorta. Aneurysmal dilatation leading to rupture of the aorta was produced within 4 to 8 days depending on the concentration of the drug used. Although the detailed histology of the lesions was not reported, destruction of the media and dilatation of the vessel were described.

We have attempted to adapt the method of McCune et al. to the intracranial arteries of dogs.

MATERIALS AND METHODS

Mongrel dogs ranging in weight between 15.3 and 29.3 kg. were anesthetized by intravenous injection of pentobarbital sodium and a craniectomy 2 by 3 cm. was made in the left temporal bone just above the floor of the middle cranial fossa. The temporal lobe was retracted, and the 2nd and 3rd cranial nerves and lateral portions of the circle of Willis were exposed. Various procedures were then carried out on the left internal carotid artery between its juncture with the posterior communicating artery and its division into anterior and middle cerebral arteries. The wound was then closed. This routine was followed in 24 dogs.

The study was divided into two parts. In the first part 14 dogs were used. In 2 of the dogs a BD, Yale, Luer-Lok No. 51 needle on a BD, Yale, tuberculin syringe (the distal 8 to 5 mm. of the needle being bent at a 45-degree angle with the bevel of the point down) was placed into the wall of the artery. This was done twice in the first dog and once in the second. No solution was injected through the needle. The study of these 2 dogs was intended to reveal damage caused by the needle alone.

In the other 12 dogs various solutions were injected from 2 to 5 times into the walls of the arteries during a single operative procedure. Because the injected arteries were small, 1 to 2 mm. in diameter, often it was impossible to force a significant amount of solution into the arterial wall. This factor is believed to be the cause for failure to produce significant lesions in some of the dogs. One half cc. of each solution was drawn into the syringe, but during the injection much of this amount escaped into and outside the vessel because of its thin wall and the relatively large size of the needle.

The solutions used were as follows: isotonic saline to determine the effect of the injection of an innocuous solution; hypertonic solution (8% per cent) of sodium chloride because it is known to be irritating to tissues; hyaluronidase (150 and 300 U.S.P. units per cc.) to study its effects on the ground substance of the arterial wall; sodium morrhuate (10 and 5 per cent) because of its irritative effect on the walls of veins; 1 and 5 mg. of plasmocid (8-[3 diethylaminopropylamine]-6-methoxy quinoline) per cc. because of its toxicity for muscle; and 0.5 and 2 mg. of nitrogen mustard (methyl-bis [beta-chloroethyl] amine) per cc. because of its effect noted in the study of McCune et al.

In the second part of the study, 10 additional dogs were studied. The technic was identical to that used in the first part except that hypertonic
saline solution, having produced the best results in the first part, was used exclusively and suction was carried out through polyvinyl-formal (Ivalon) sponge instead of through cottonoid, since it was thought that the latter might have been partially responsible for a foreign-body reaction found around fragments of fiber at the site of injection in some dogs in the first study. Two or three injections were made in each arterial wall during a single operative procedure.

On the 21st day after operation, the dogs were sacrificed by rapid intravenous injection of pentobarbital sodium. The brains were removed immediately and were placed in a fixative solution of 10 per cent formalin. After fixation for 1 week, the brains were examined grossly and a triangular, prism-shaped (base ventral) section, including the injected artery and the adjacent brain, was removed and sectioned serially, the plane of the section being perpendicular to the surface of the brain and in the axis of the longest dimension of the block of tissue. Each section was 8 micra in thickness. Every tenth section was stained in hematoxylin and eosin. Where they served to point out the changes, Werlhoff elastic stains, counterstained after the method of van Gieson, and Mallory-Heidenhain stains were made.

RESULTS

Gross Findings. Examination of both fresh and fixed sections of brain tissue revealed little of interest as far as the gross arterial lesions were concerned. The slight thickening and clouding of the meninges that universally overlay the injected areas plus the fragment of Gelfoam that usually was adherent to the same area tended to obscure the lesions, which were relatively small (the largest being only 1.5 mm. in length). The only other findings were limited to the brain substance and resulted from the pressure of retraction during operation or from injection of an especially noxious substance.

Histologic Findings. (a) First study. In the specimens in which puncture with the needle only had been used, the effect was limited to the internal elastic membrane, which was disrupted in three lesions in 2 dogs. The defects in the membrane were less than 0.5 mm. in length. The torn ends were retracted and curled into the lumen, and the total lesion occupied about a fourth of the circumference of a cross section of the artery. The retraction of these torn ends presumably followed lines of stress normally applied to the elastic membrane. In one lesion the defect involved the muscularis which was replaced by fibrous tissue for a short distance. This lesion in the muscularis, which was found only once, was similar to but much smaller than the lesions seen in later dogs.

The lesions in the dogs that had injections of isotonic sodium chloride solution were similar to those that formed subsequent to puncture with the needle alone, except that in 1 dog no defect was seen in the internal elastic membrane.

When hypertonic solution (28 per cent) of sodium chloride was injected into the arterial wall, the 2 dogs had lesions that involved a considerable portion of the circumference of the arteries for a distance of 880 micra and 2.16 mm., respectively, and consisted of replacement of the internal elastic membrane and muscularis with homogeneous pink-staining material and fibrous tissue (Figs. 1 and 2). Thus they presented a pathologic picture similar to congenital berry aneurysms. A second lesion produced in the first of these dogs consisted of replacement of the muscularis with fibrous tissue. The internal elastic membrane was intact. The involved wall in the second of these dogs was folded in such a way that in life it may have bulged. It was felt that hypertonic saline was probably responsible for the more extensive lesions of the elastic membrane and muscularis as compared with those produced in the first 4 dogs.

When hyaluronidase was injected into the arterial wall, the first animal had two lesions which consisted of defects in the internal elastic membrane with minimal damage to the adjacent muscularis. No lesion was discovered in the second dog.

The injection of a 10 per cent solution of sodium morrhuate proved lethal to the dog within 12 hours and resulted in massive necrosis of all structures in the distribution of the internal carotid artery. When a 5 per cent solution of sodium morrhuate was used, no lesion was found.

A concentration of 1 mg. of plasmocid per cc. of solution did not produce a detectable