

CHANGES IN THE BRAIN AFTER ELECTRICALLY INDUCED CONVULSIONS IN CATS

BERNARD J. ALPERS, M.D.

AND

JOSEPH HUGHES, M.D.

PHILADELPHIA

The widespread use of electrically produced convulsions for the treatment of mental disorders naturally gives rise to the question whether such artificially induced convulsive states are associated with evidence of damage to the brain. No observations on such changes in the human brain have as yet been published, to our knowledge. There has been an abundance of articles on the clinical, but none on the pathologic, features of induced convulsions. For this reason we have studied the brains of 30 cats in which artificial convulsions were produced by the electric current in order to determine, in animals at least, what change such convulsions cause in the nervous system.

MATERIAL AND METHODS

Thirty cats were given electrically induced convulsions (table). The first group, cats 1 to 6 inclusive, received a series of 23 shocks; these were given daily except Sundays. The second group, cats 7 to 15 inclusive, were given a series of 18 shocks; these were also given six times weekly. The third group, cats 16 to 30 inclusive, received 10 shocks and were treated three times weekly.

No hypnotic drug or anesthesia was required in order to carry out this procedure, as the animals remained friendly throughout the experiment. From this it was judged that they had an amnesia for the shocks similar to that which is experienced by patients.

The electric shocks were administered through small disk electrodes, about 5 mm. in diameter, which were held in place by a rubber band slipped over the cat's head. In order to insure good contact the underlying hair was cut away and electrode paste rubbed into the scalp.

The animals were shocked with a strength of current which was of threshold value for producing the convulsive seizure. The apparatus to deliver this current was the same as that used clinically in the treatment of patients. It consisted of a step-down and step-up transformer operated by an electrical timing switch

This paper was read at a meeting of the American Association of Neuro-pathologists, Atlantic City, N. J., June 9, 1941.

This study was aided by a grant from the John and Mary R. Markle Foundation to the Institute of the Pennsylvania Hospital.

From the Department of Nervous and Mental Diseases, Jefferson Medical College, and the Institute of the Pennsylvania Hospital.

and so designed that the duration of the shock, the voltage and the milliamperage could be varied at the will of the operator. The apparatus operated on a 110 volt, 60 cycle, alternating current. It was not possible to state exactly the strength of current acting on the brain because of technical difficulties attending any attempts to measure what portion of the current penetrated the skull and reached the brain tissue. A current of a strength varying from 150 to 200 milliamperes was applied to the scalp. It has been estimated that about 10 per cent or less penetrated the cortex.

Summary of Data on Cats Subjected to Electric Shock Treatments

Cat Number	Number of Treatments per Week	Number of Snocks	Number of Convulsions	Total Number of Minutes in Convulsions
1.....	6	23	15	10
2.....	6	23	19	13
3.....	6	23	22	10.5
4.....	6	23	23	35.5
5.....	6	23	20	25.5
6.....	6	23	22	16
7.....	6	18	18	3.4
8.....	6	18	18	2.5
9.....	6	18	18	4
10.....	6	18	18	3.5
11.....	6	18	18	3.8
12.....	6	18	18	18.5
13.....	6	18	18	6.5
14.....	6	18	18	10
15.....	6	18	18	10.2
16.....	3	10	10	2.5
17.....	3	10	10	5
18.....	3	10	10	6.5
19.....	3	10	10	6
20.....	3	10	10	4.5
21.....	3	10	10	4.5
22.....	3	10	10	5
23.....	3	10	10	4.5
24.....	3	10	10	6
25.....	3	10	10	5
26.....	3	10	10	5.5
27.....	3	10	10	5.5
28.....	3	10	10	5
29.....	3	10	10	5
30.....	3	10	10	5

After the shock the animals were rendered unconscious, immediately after which they went into a tonic and clonic type of convulsive seizure. Occasionally convulsive seizures did not occur.

The cats were killed by section of the carotid artery. The brains were placed in dilute solution of formaldehyde U. S. P. and were sectioned within a few hours after this fixation. Embedding was both in paraffin and in pyroxylin. Special blocks were taken for formaldehyde-ammonium bromide treatment. In every instance studies were made with toluidine blue, cresyl violet and hematoxylin and eosin; with ponceau B for fat, and with stains for myelin (Weil), microglia and astrocytes.

PATHOLOGIC CHANGES IN THE BRAIN

The cats were divided into two series, of 15 animals each. In group 1 were included cats which were thought to have received more than

the equivalent of the human dose employed for ordinary routine treatment. For comparison, a second group of cats (group 2) was studied, in which the doses of electricity and the number and duration of the convulsions more closely resembled the situation for human subjects.

CATS SUBJECTED TO EIGHTEEN OR MORE ELECTRIC SHOCKS
(GROUP 1)

All parts of the cortex and the entire brain stem and cerebellum were studied in each of the 15 cats.

Meninges.—In all animals there was some degree of congestion of the pial vessels over the cerebral hemispheres. This was more marked in some cats than in others.



Fig. 1 (cat 2, second series).—Areas of hemorrhage in the subarachnoid space over the cerebrum and around the brain stem.

In 4 cats some degree of subarachnoid hemorrhage was observed. In 3 animals the hemorrhage was over the cortex and in 1 around the medulla. In all cases the hemorrhage was focal and confined to only a small part of the cortex. In 1 of the 3 cats with hemorrhage over the cortex the meningeal hemorrhage was on the mesial surface of one hemisphere. In 2 instances the hemorrhage was fresh, and in 2 others the red cells were disintegrated and hemosiderin granules were present. No damage to the adjacent pial vessels could be found.

In 3 of the 4 cats with subarachnoid bleeding there was some degree of fibroblastic proliferation in and around the hemorrhage. This undoubtedly represented efforts to organize the hemorrhage. This process was probably seen in its end stages in 2 other cats, both of which had focal areas of fibroblastic arachnoiditis. In 1 animal (cat 7) there were areas of thickened meninges here and there over the cortex. These areas were packed with fibroblasts, with resulting thickening of the

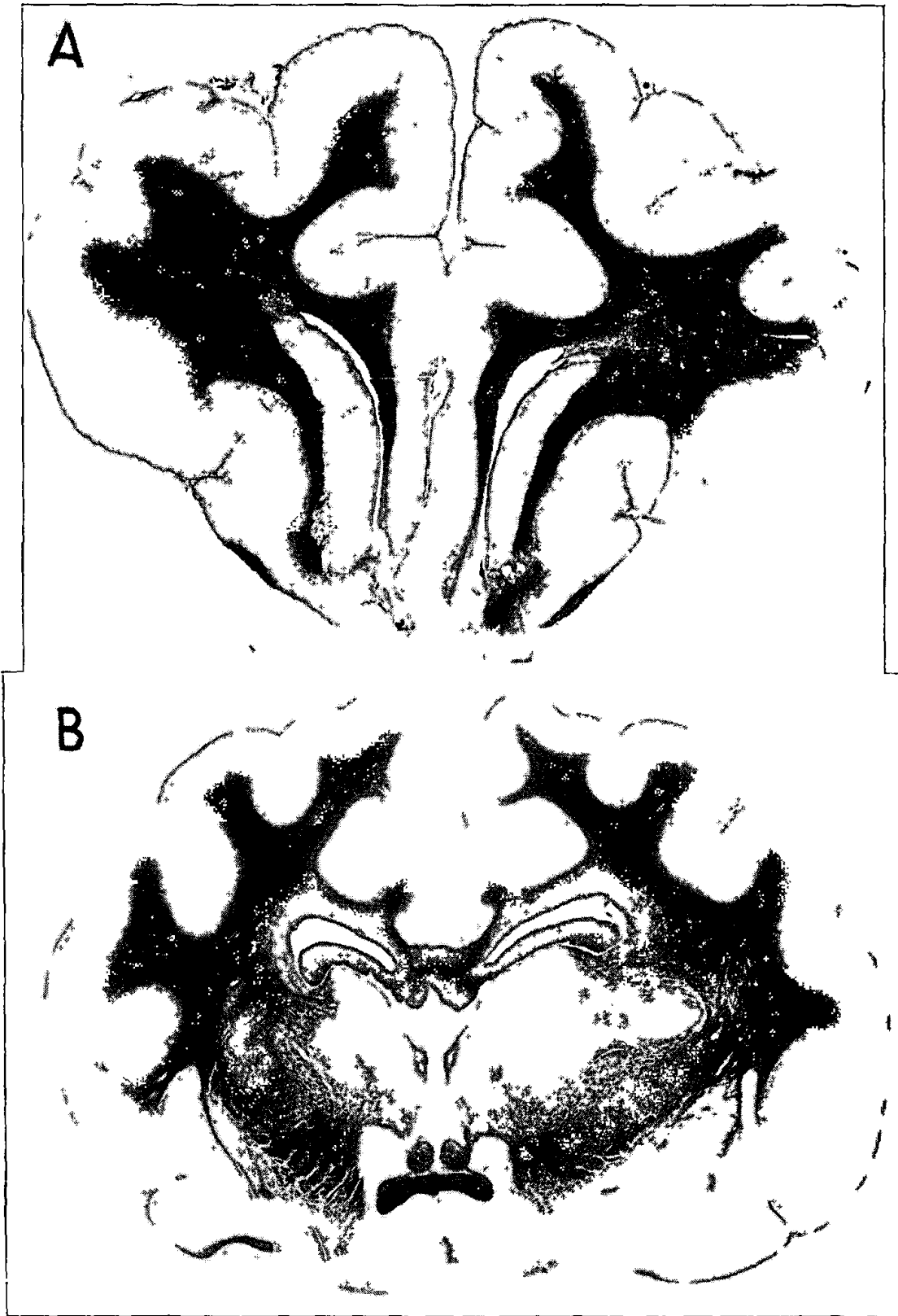


Fig. 2 (second series).—*A*, demyelination in the frontal area (cat 2); *B*, demyelination of the white matter around the lateral ventricles and in the internal capsule (cat 1).

arachnoid and firm adhesion of this membrane to the underlying cortex. This adherence was so strong in one area that the upper cortical layer was damaged and torn. In another animal (cat 8) there were scattered areas of mild fibroblastic thickening and arachnoiditis, but in one area of the cortex the arachnoid was greatly thickened and strongly adherent to the underlying cerebral cortex. It is quite probable that the changes in these 2 cats represent the end results of adhesive arachnoiditis in areas of subarachnoid hemorrhage.

Cerebral Cortex.—In all the animals the cortical architecture and the structure of the ganglion cells were normal. There was no loss of cells and no disturbance of the normal lamination of the cortex. The ganglion cells not only of the motor area but of the rest of the cerebral cortex showed no evidence of damage. This is in contrast to the reaction observed in experimental insulin shock and in metrazol convulsions.

In 1 animal (cat 3) there was a small focus of microglia cells and astrocytes in the frontal cortex. In another animal (cat 4) an extensive hemorrhagic infarct was observed in the white matter under the ependyma of the lateral ventricle. The tissue in this area showed only beginning dissolution. Red cells in moderate numbers lay free in the tissue. The microglia cells, oligodendrocytes and astrocytes in this area were swollen, but there was no gliosis.

The vessels in the cortex and the white matter showed no changes. Their endothelial linings were normal, and there was none of the congestion which was seen in the pial vessels.

Studies of the microglia cells, oligodendrocytes and astrocytes failed to reveal changes in any of these glia elements, except in the case of the hemorrhagic infarct.

Brain Stem and Cerebellum.—No changes were observed in the cells of the various nuclei in the diencephalon, mesencephalon, pons and medulla. The Purkinje cells of the cerebellum failed to show changes.

Summary.—Of the 15 cats in this series, 4 showed evidence of focal subarachnoid hemorrhage and 2 of adhesive arachnoiditis; 1 had a hemorrhagic infarct in the white matter, and 1 a glial nodule in the frontal cortex.

CATS SUBJECTED TO TEN ELECTRIC SHOCKS (GROUP 2)

In this group of 15 cats the number and duration of the convulsions simulated as closely as possible the conditions of treatment of the human subject.

Meninges.—Some degree of hyperemia was found in the meninges in all the animals. It consisted of scattered dilated and congested vessels and never involved all the meningeal vessels.

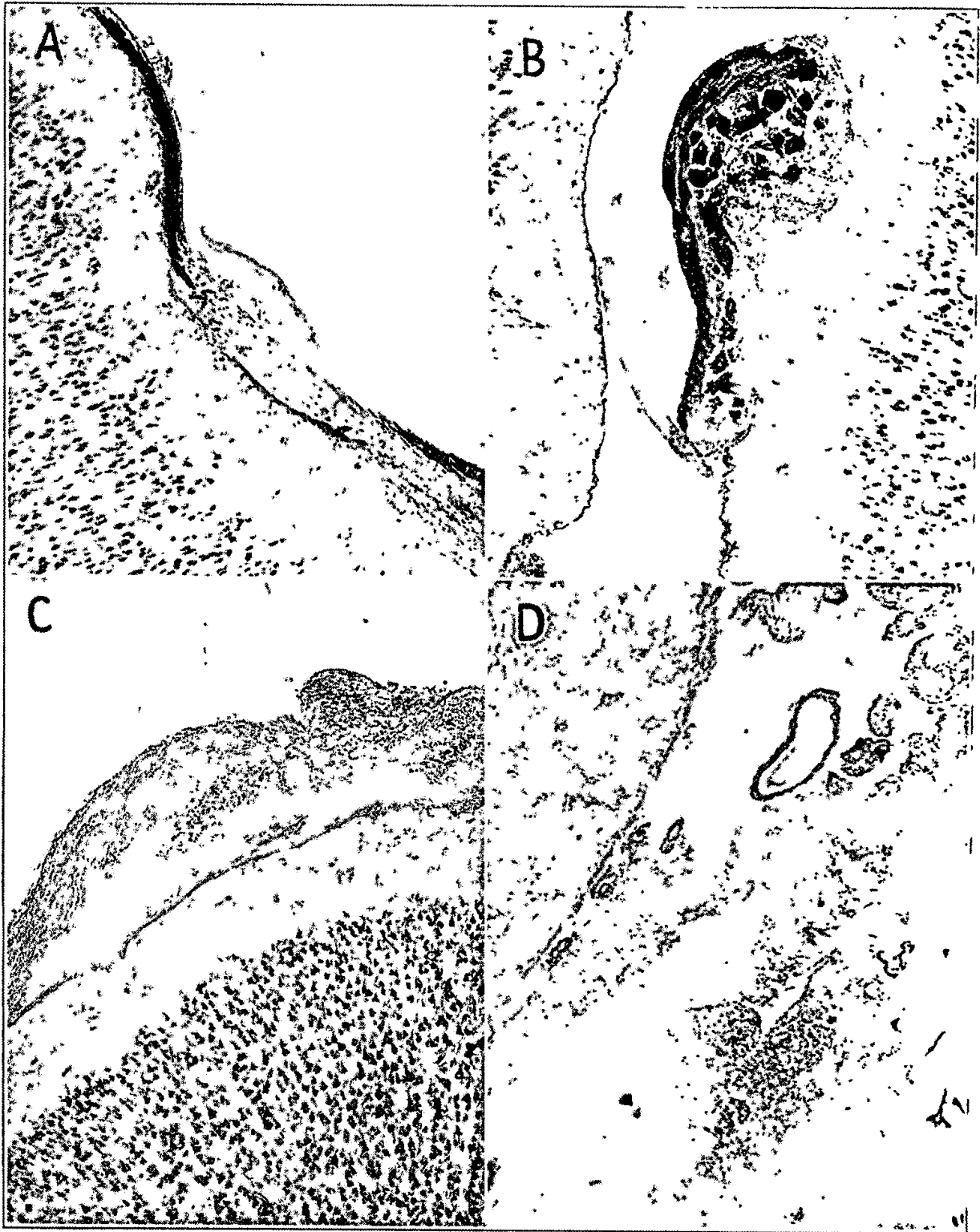


Fig. 3 (first series).—*A*, small area of subarachnoid hemorrhage over a cortical gyrus (cat 9); *B*, thrombosed vessel surrounded by hemorrhage on the mesial surface of the frontal lobe (cat 5); *C*, more extensive subarachnoid hemorrhage over a cortical gyrus (cat 1); *D*, hemorrhage in the meninges around the medulla.

In 10 of the 15 cats some degree of subarachnoid hemorrhage was observed. In 9 of these 10 cats the hemorrhage was slight and involved small areas here and there over the cortex. In 1 instance the sub-

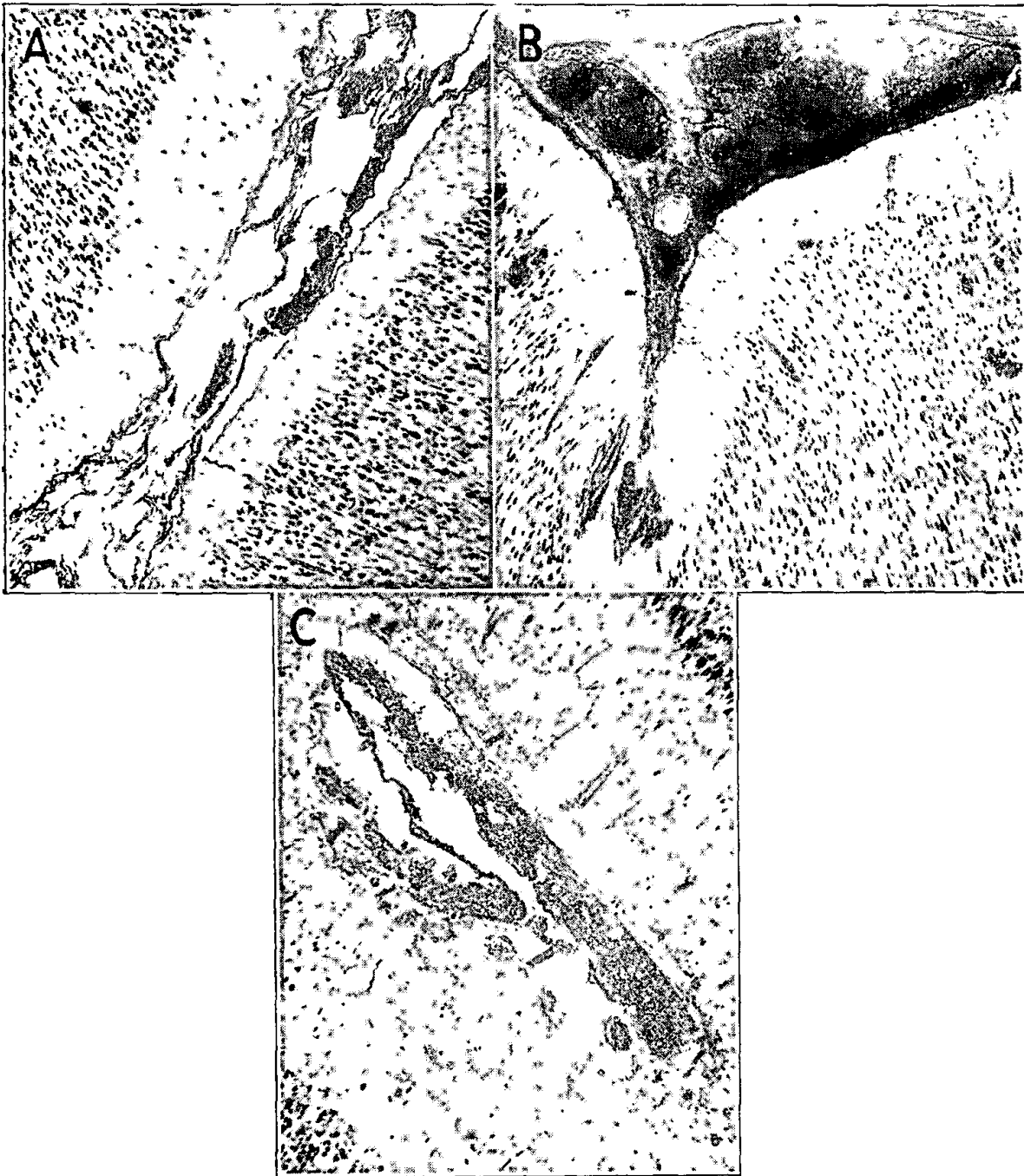


Fig. 4 (second series).—*A*, mild degree of hemorrhage in the subarachnoid space (cat 1); *B*, extensive subarachnoid hemorrhage and petechial hemorrhages in the cortex (cat 2); *C*, focal hemorrhage in the subarachnoid space (cat 6).

arachnoid hemorrhage was fairly large as to both extent and thickness. The blood in most of the cases was well preserved, but, as in the first series, areas of disintegrated red cells were seen. Slight efforts at

organization of the hemorrhage could be seen on the outskirts of the bleeding, but it was never great. There was no sign of damage to the meningeal vessels in any of the cats.

Cerebrum, Cerebellum and Brain Stem.—Punctate hemorrhages were seen in 8 of the 15 cats. These varied in number, size and distribution. They were never generalized or widespread, either in the

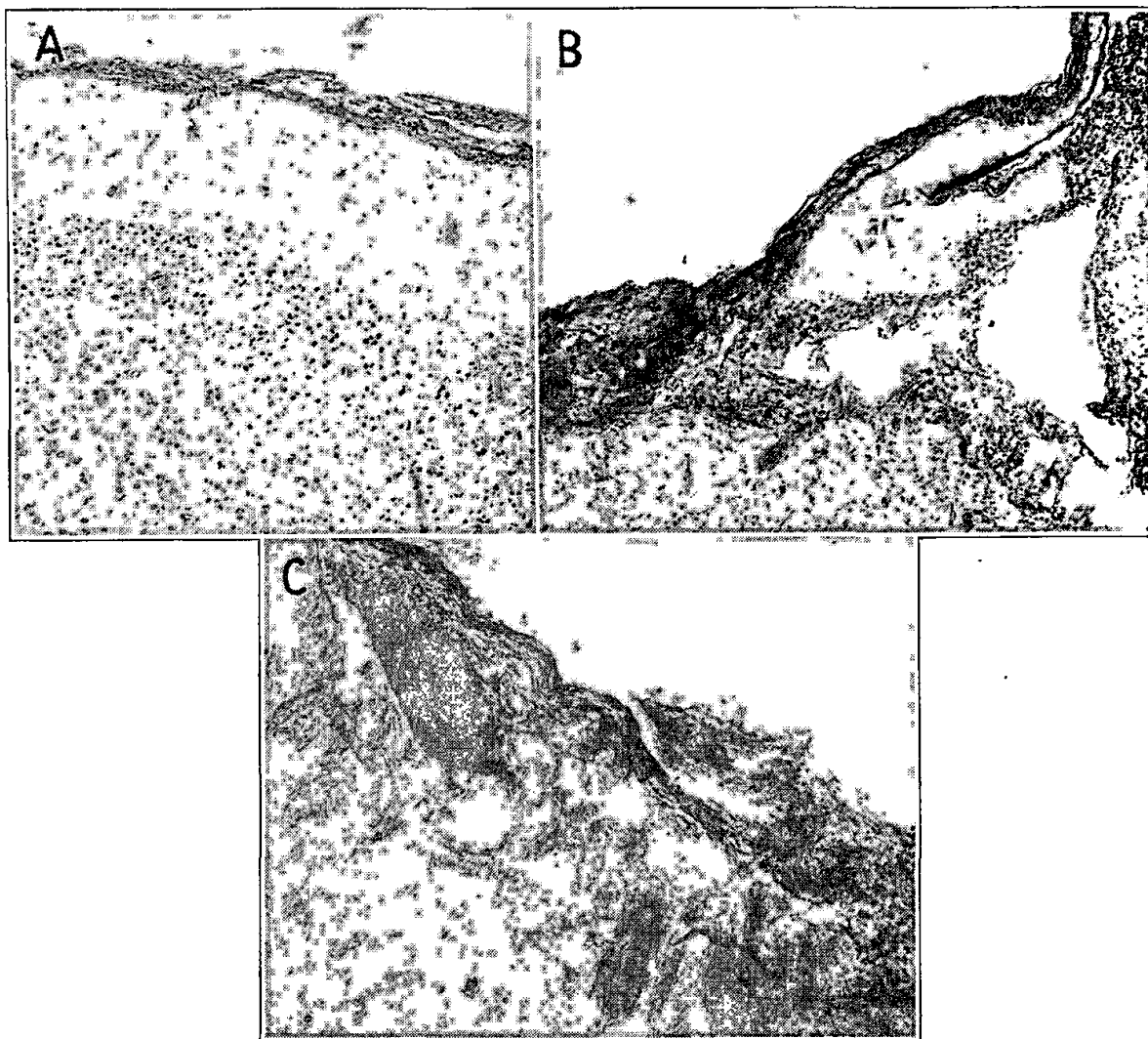


Fig. 5 (first series).—*A*, mild fibrosis of the pia-arachnoid (cat 8). *B*, marked fibrosis of the meninges over the cortex, with adhesion of the meninges to the cortex. Hemorrhage can be seen in the meninges to the left (cat 7). *C*, a similar process, showing organization of an area of subarachnoid hemorrhage, producing adhesive pia-arachnoid fibrosis (cat 8).

cerebral cortex or in the brain stem. As a rule, one found small groups of punctate hemorrhages in one part of the brain and either one or two similar groups elsewhere, or no further groups.

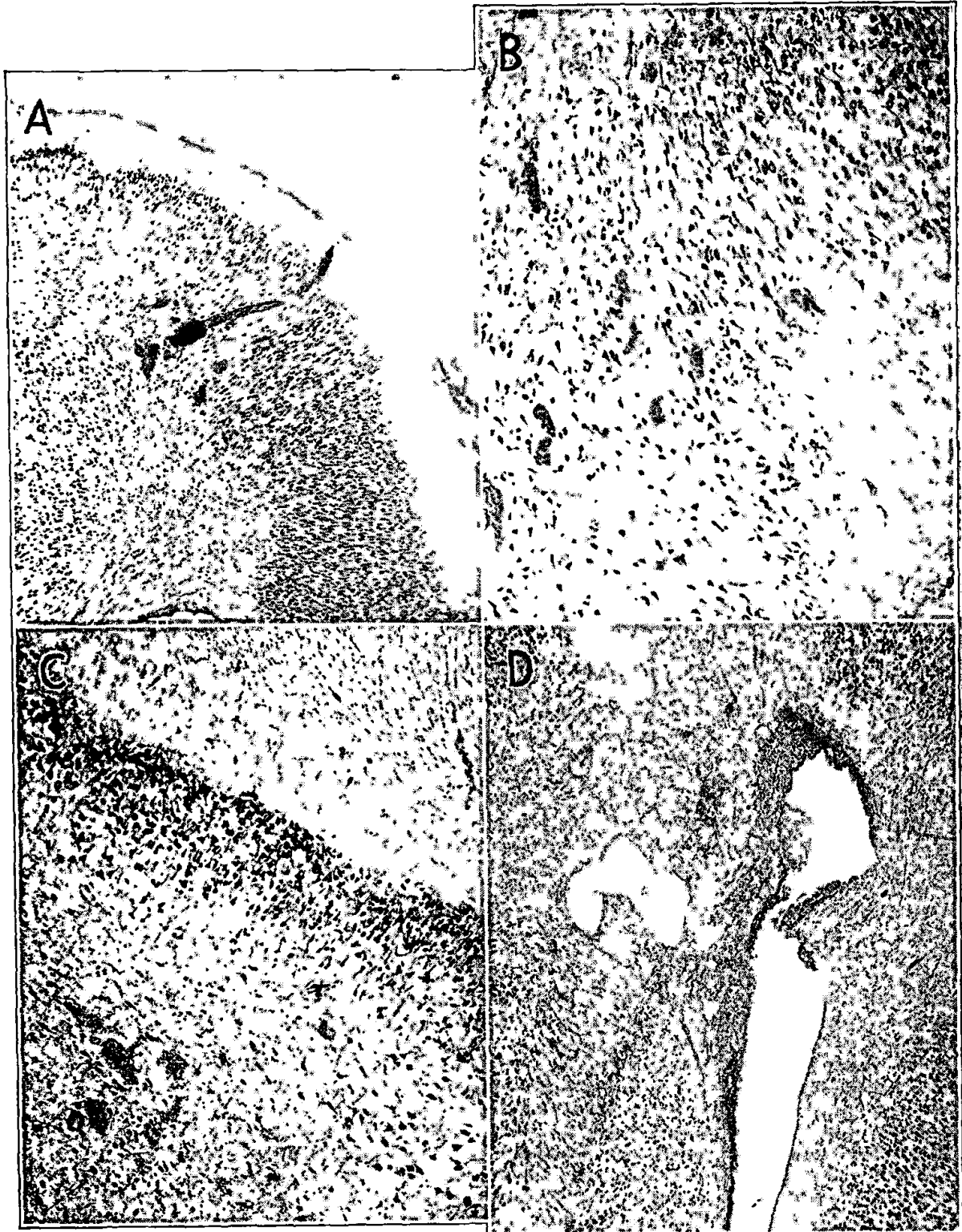


Fig. 6 (second series).—*A*, hemorrhages in the cortex, with a vessel leading down from the surface (cat 9); *B*, hemorrhages in the upper layers of the cortex (cat 2); *C*, hemorrhages in the cornu ammonis (cat 6); *D*, hemorrhage under the endyma of the lateral ventricle (cat 3).

The hemorrhages were seen in the cerebral cortex, involving chiefly the frontal and temporal areas, in the subcortical white matter, in the region of the uncus, in the walls of the third ventricle, in the cerebellum, under the ependyma of the lateral ventricles and even in the third ventricle itself. Hemorrhage in the ventricle was observed in only 1 cat, but in this instance was rather extensive. No hemorrhages were seen in the medulla or pons.

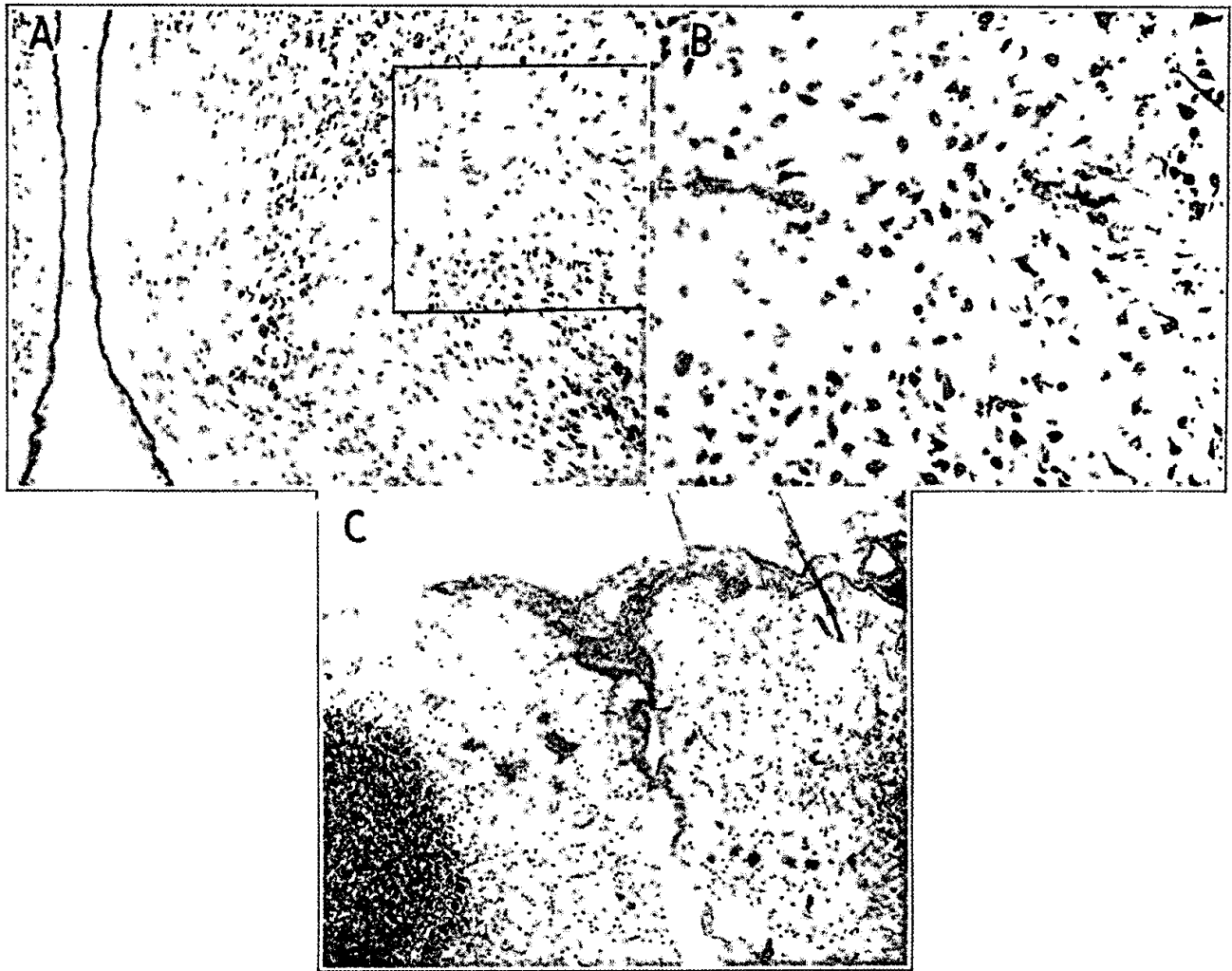


Fig. 7 (second series).—*A*, low power view, showing small hemorrhages outside the wall of the third ventricle (cat 2); *B*, high power magnification of the hemorrhages; *C*, small hemorrhages in the cerebellar cortex (cat 13).

The hemorrhages were typically punctate in 7 of the 8 cats, but in 1 (cat 2) the bleeding involved the surrounding brain substance and was rather extensive. The hemorrhages in all instances were fresh, and the red cells were well preserved. The perivascular character of the hemorrhages was easily apparent. Damage to the vessels was not found in most of the cases; in a few areas the vessel wall appeared to be torn,

but it was hard to determine whether or not this was the result of technical error. Microglial hyperplasia and hypertrophy were seen in the vicinity of some of the hemorrhages.

Myelin sheath stains revealed a breakdown of myelin and demyelination in some of the areas of more extensive hemorrhage.

The choroid plexuses of the lateral ventricles and the lateral recesses were greatly distended with blood.

In contrast to the punctate hemorrhages, the ganglion cells of the cortex, cerebellum and brain stem were remarkably well preserved. The Betz cells were fairly normal in appearance, save for a minor change in scattered cells, all of which were well within the limits of normal. Cells were, of course, destroyed in the region of the punctate hemorrhages, but apart from such areas the cells were surprisingly well preserved. Fat stains revealed no evidence of cell degeneration of a fatty nature. The basal ganglia, Purkinje cells and ganglion cells of the brain stem showed nothing. The microglia cells and astrocytes were for the most part normal except for occasional hyperplasia and hypertrophy of the microglia cells around some areas of hemorrhage. No disturbance of the cortical architecture was seen in any portion of the cortex, and no areas of cell loss were apparent.

Summary.—Of the 15 cats in this series, 10 had subarachnoid hemorrhage, and 8 showed hemorrhages of the brain, 7 of these being punctate and 1 more extensive. The ganglion cells were normal in appearance, and no damage to the vessels was apparent.

COMMENT

A survey of the observations on the 30 cats which received electric shock therapy reveals that damage to the nervous system is common in animals subjected to this form of treatment. Hemorrhage is the common lesion, particularly within the meninges and the brain substance. Of the 30 cats studied, 14 had subarachnoid hemorrhage and 9 hemorrhage within the brain substance itself. The subarachnoid hemorrhage was not as a rule extensive, except in a few instances. It was usually scattered over the cerebral hemispheres but in a few instances was found around the medulla. The hemorrhages within the brain substance were of a punctate character except in 2 instances, in 1 of which there was a hemorrhagic infarct and in the other a fairly extensive cerebral hemorrhage with hemorrhage into the ventricles. The hemorrhages varied widely in number and size from case to case. They were for the most part scattered, appearing in a single area of the cortex and nowhere else, or occurring as scattered punctate hemorrhages elsewhere in the brain or the brain stem. All parts of the brain appeared to be possible seats of the hemorrhage—the cerebral hemispheres, the cerebellum, the third ventricle and the hypothalamus.

There appears to be no apparent relation between the number of shocks and the changes in the brain. This is in agreement with the observations of Urquhart,¹ who found no relation between the severity of the shock and the presence of hemorrhage. In the second series of cats, which were subjected to many fewer electric shock treatments, there was a much greater incidence of hemorrhage within the brain than in the first series. Furthermore, there appears to be but little relation between hemorrhage and the total time of the convulsive seizures. Thus, in our first series of cats, an extensive hemorrhagic infarct was found in 1 animal (cat 4) in which the total time of convulsions was four minutes, while in another animal (cat 7) with a total of eighteen and a half minutes of convulsions only congestion of the pial and cortical vessels was noted. The same holds true for the animals in our second series. Cat 1, with a total of two and a quarter minutes of convulsions, showed rather extensive damage; cats 4 and 7, with five and six minutes of convulsions, showed less damage. It is not clear why some animals show evidence of hemorrhage in the meninges or brain while others fail to do so under similar circumstances. The possibility arises that there may be individual factors in each case which govern such reactions or that the circumstances attending the convulsions are not the same under all conditions. It seems fair to assume that while hemorrhage occurs with alarming frequency in experimental animals subjected to electric shock, it does not occur in all animals. From this it follows that if hemorrhage occurs in the human subject as a result of such treatment, it probably does not do so in every case.

The problem arises naturally as to the eventual fate of the hemorrhage. The animals studied were killed too early to answer this question definitely. In the case of the subarachnoid hemorrhage evidence was found to indicate that in the case of moderately extensive bleeding organization by fibroblasts took place, leading to adhesive arachnoiditis. This has possible clinical significance. As to the hemorrhages within the brain substance, these may in part be absorbed, or there may be replacement by glia and the formation of glial foci. Perivascular gliosis has been reported as a late sequel of electrical injury of the brain (Hassin²). Our animals were killed too soon, however, to observe the late effects of the hemorrhages. Among their more immediate effects must be mentioned the loss of the cells and fibers in the region of the extravasation.

1. Urquhart, R. W. I.: Experimental Electric Shock, *J. Indust. Hyg.* **9**:140 (April) 1927.

2. Hassin, G. B.: Changes in the Brain in Legal Electrocution, *Arch. Neurol. & Psychiat.* **30**:1046 (Nov.) 1933.

Of greatest importance, however, is the question whether similar changes in the brain may be assumed to be present in the human subject after electric shock treatment. No autopsy studies are as yet available for patients so treated. The necropsy reports on cases of human electrocution cannot be regarded as answering the problem, since the type of electrical current, usually a single severe shock of very high voltage, causes the death of the victim almost immediately. Jaffé³ and Hassin have made thorough reviews of the changes in the human nervous system. While some investigators have reported that no changes were observed in the human brain after electrocution, others have found perivascular hemorrhages, especially in the medulla and the floor of the fourth ventricle. Hassin has reported large tissue tears, as well as tears of large blood vessels.

The conditions described in our animals have apparently been found previously in experimental animals exposed to various types of electrical injury with the object in mind of determining the reaction of the nervous system to the electrical current. In a large series of rats, Langworthy⁴ observed hemorrhages in the nervous system, especially when using a high voltage (500 to 1,000 volts) alternating current, and much less frequently when using the continuous current. When voltages similar to those employed in our animals were used (110 volts) changes in the nerve cells were not prominent, but hemorrhages were still common. Similar hemorrhages have been found by Urquhart and by Morrison, Weeks and Cobb.⁵ The last-mentioned investigators observed a greater tendency to hemorrhage with the alternating current. They found hemorrhages in the pia, the ventricles and the choroid plexus and pericapillary extravasation everywhere, especially in the basal ganglia and the medulla. The changes in the ganglion cells were mild when alternating current was used. Necrotic changes in the spinal cord with electric shock have been reported by MacMahon.⁶

The experimental conditions in many of these animals paralleled those used in electric shock therapy. It remains impossible to state, however, whether petechial and meningeal hemorrhages of a similar sort occur in the human subject. It is probably fair to assume that there is some damage to the human brain, the difference being one of degree rather than of kind.

3. Jaffé, R. H.: *Electropathology*, Arch. Path. **5**:837 (May) 1928.

4. Langworthy, O. R.: *Abnormalities Produced in the Central Nervous System by Electrical Injuries*, J. Exper. Med. **51**:943 (June) 1930.

5. Morrison, L. R.; Weeks, A., and Cobb, S.: *Histopathology of Different Types of Electric Shock on Mammalian Brains*, J. Indust. Hyg. **12**:324 (Nov.); 364 (Dec.) 1930.

6. MacMahon, H. E.: *Electric Shock*, Am. J. Path. **5**:333 (July) 1929.

CONCLUSIONS

Electrically induced convulsions were produced in 30 cats.

Subarachnoid hemorrhage, usually of mild degree but sometimes extensive, was found in 14 cats.

Hemorrhage in the brain substance (cerebral cortex and white matter, cerebellum, region of the third ventricle and third ventricle) was found in 9 cats, usually of a punctate type but more extensive in 2 instances.

Whether similar changes are to be expected in human beings treated with electric shock cannot be determined from this material.

DISCUSSION

DR. M. T. MOORE, Philadelphia: The authors' presentation is not only extremely interesting but of considerable importance because of the obvious implications with regard to the future of electrocerebral shock in the treatment of psychiatric conditions. The slides show hemorrhages not only within the subarachnoid space but in the parenchyma of the brain itself. Dr. Winkelman and I, during the past year, have subjected a series of cats to electrocerebral shock treatment analogous to that given to human subjects. The current has been carefully calibrated in terms of time, volts and milliamperes so as to produce a convulsive seizure similar to that induced in human beings. Our histologic observations on the brains of the animals studied are at variance with the authors'. We found no evidence of intracerebral or subarachnoid hemorrhage. At most, there appeared pyknosis of the ganglion cells of the frontal area lying beneath the frontal electrode. The spinal cords were entirely normal.

It must be borne in mind that excessive milliamperage may produce disruptive changes in brain tissue. I should like to ask Dr. Alpers whether the current used in his experiment was similar to that advocated by Cerletti and Bini and, also, what were the size and manner of placement of the electrodes?

DR. ARMANDO FERRARO, New York: The interesting report by Dr. Alpers and Dr. Hughes and the comments by Dr. Moore confront one with contradictory results, and I feel that the time is ripe for a concerted effort on the part of neuropathologists to discuss more closely the various factors involved in experimentally induced electric shock. If the constant changes observed by the authors in cats were to be reported in human material one should be hesitant in advising such a form of therapy. On the other hand, one is aware of the fact that from a clinical standpoint no appreciable ill effects have resulted from the application of electric shocks in hundreds of patients treated to date. I am wondering whether the duration of the passage of the current might not be one of the essential factors in explaining the difference between Dr. Moore's and Dr. Alpers' results.