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MORPHOLOGIC CHANGES IN THE BRAIN OF MONKEYS FOLLOWING CONVULSIONS ELECTRICALLY INDUCED[1]

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With the increased use of electric shock therapy several reports on histologic findings in experimental and human material have been published. However, the literature on this subject is somewhat confusing and contradictory.

To clarify possible misinterpretations in view of varying technical approaches twenty-two Maccacus rhesus monkeys were subjected to experimental electrically induced convulsions. The investigation lasted approximately two years in the course of which the monkeys were subjected to induced convulsions varying in number, duration of and intensity of the current. Two different types o electrodes, small and large, were used.

In this report we shall limit the presentation to a group of 10 monkeys, som of which were subjected to treatment which from the standpoint of the numbe of convulsions, the intensity and voltage of the current was considered closest t the therapeutic shock used in human beings.

EXPERIMENTAL PROCEDURES

Maccacus rhesus monkeys (of both sexes), weighing from 5 to 7 lbs. were used. Th details concerning the induction of convulsions with Rahm's 60 cycle apparatus are sum marized in Table 1. The same apparatus was used for E.C.T. in human beings with th exception of the electrodes, the diameter of which was reduced to approximately 2 sq. cr The monkeys were subjected to the electrically induced convulsions three times weekly ar each application was controlled with Rahm's "recording surge current meter."

The animals were sacrificed 12, 24 and 48 hours after the last induced convulsion. A the animals were sacrificed by ether and the necropsy material was fixed immediately 95% alcohol, 10% neutral formalin and formol-bromide. The standard neuropatholo techniques were used including staining for nerve cells (Nissl), staining for general stud (hematoxylin-eosin), impregnation for glia elements (Hortega's and Cajal's method staining for myelin sheaths (Roizin's combined method), impregnation for nerve fib (Bielschowsky, Bodian) and staining for fatty products of degeneration (Sudan II From each brain blocks were selected from the frontal pole, pre-central and central co volutions, parietal, occipital, temporal lobes (including Ammon's horn) and island of Re basal ganglia and hypothalamus, mesencephalon, pons, medulla oblongata, cerebellum a spinal cord (mostly cervical region). The celloidin blocks (used mostly for cytologi studies) were cut serially.

CLINICAL OBSERVATIONS

In this group of 10 monkeys the lowest potential used was 70 volts, a lower one hav resulted only in *petit mal*. With a potential of 70 v. the passage of the current had to

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increased from $\frac{1}{10}$ to $\frac{2}{10}$ of a second because the shorter duration resulted in only a *petit mal* seizure.

The so called *grand mal* convulsions consisted of a generalized tonic phase followed, after a few seconds, by a generalized clonic one with irregular breathing, ending in apnoea lasting a few seconds. During the tonic and clonic phases marked mucoserous salivation mixed often with the blood was observed; at times there was incontinence of urine and feces; marked cyanosis or marked congestion of the face was noted at other times. The pupils appeared markedly miotic or midriatic. Quite often nystagmus in vertical and horizontal direction was observed as well as conjugate deviation of the eyes in upward direction without any predominance toward right or left. After the apnoea there followed a short period of agitation which at times assumed the character of very marked excitement, at others it took the character of more localized disorderly, aimless movements. Following this stage, there appeared frequently marked muscular twitches or contractions of the body, extrem

TABLE 1

MONKEY	VOLTAGE	RESISTANCE (AVERAGE)	AMPERAGE (AVERAGE)	CURRENT FLOW TIME	NUMBER OF SHOCKS	REMARKS
A	70 v.	570 ohms	120 m.a.	.2″	12	Generalized convulsions with incontinence of urine and feces
B	80 v.	390 ohms	400 m.a.	.2″	12	" "
C	90 v.	880 ohms	102 m.a.	.1″	12	" "
D (1)	90 v.	630 ohms	115 m.a.	.2″	4	" "
D (2)	90 v.	740 ohms	120 m.a.	.2″	11	" "
D (3)	90 v.	720 ohms	125 m.a.	.2″	18	" "
E	90 v.	680 ohms	129 m.a.	.3″	13	" "
F (1)	90 v.	680 ohms	129 m.a.	.1″	6	" "
F (2)	90 v.	490 ohms	170 m.a.	.1″	12	" "
F (3)	90 v.	640 ohms	140 m.a.	.1″	18	" "

ities or the face and eyelids. In some instances, after the phase of apnoea, a second spontaneous phase of clonic convulsions lasting a minute or so was also observed. During the first tonic and clonic phases of the seizures, as well as throughout the period of apnoea and a few seconds afterwards, the animals were completely unconscious; then they gradually regained consciousness, remaining somewhat confused and disoriented for a short period. In the post-convulsive stage most of the animals appeared hyperexcitable with hyperactive deep reflexes. Through all the period of induced convulsions until the monkey regained complete consciousness the animal was properly held and protected from trauma. During the whole course of this investigation no permanent motor disability, organic defects, or behavior disorders were observed. Appetite and food intake were the same as in the control group.

NEUROPATHOLOGIC OBSERVATIONS

Macroscopic findings: Grossly the central nervous tissue appeared normal in consistence and vascularization with the exception that in some animals the pial blood vessels appeared dilated and at times markedly congested. No subarachnoid pial or intracerebral hemorrhages were grossly noticed. All other viscera appeared also normal.

Microscopic findings: The description of our findings will follow in the order indicated in Table 1.

A. Monkey subjected to 12 electrically induced convulsions, potential 70 v., duration $\frac{2}{10}$ of a second. Actual current intensity as indicated by Rahm's surge current meter

varied from 105 to 175 m.a. The animal was sacrificed four hours after the last *grand mal* seizure.

The cyto-architecture of the various regions of the brain cortex as revealed by Nissl and hematoxylin and eosin methods appeared normal. However, here and there small areas of rarefaction as well as occasional satellitosis and neurophagia were encountered. Individual neurons appeared well stained but the Nissl substance, was not always clearly outlined, particularly in nerve cells of the prefrontal region. The nerve cells of the various diencephalic nuclear formations appeared at times swollen. The cytoplasm was frequently unevenly stained and the Nissl substance, at times, condensed at the periphery of the cell body. The nuclei of the cells were at times displaced from the central location and seemed to be somewhat large.

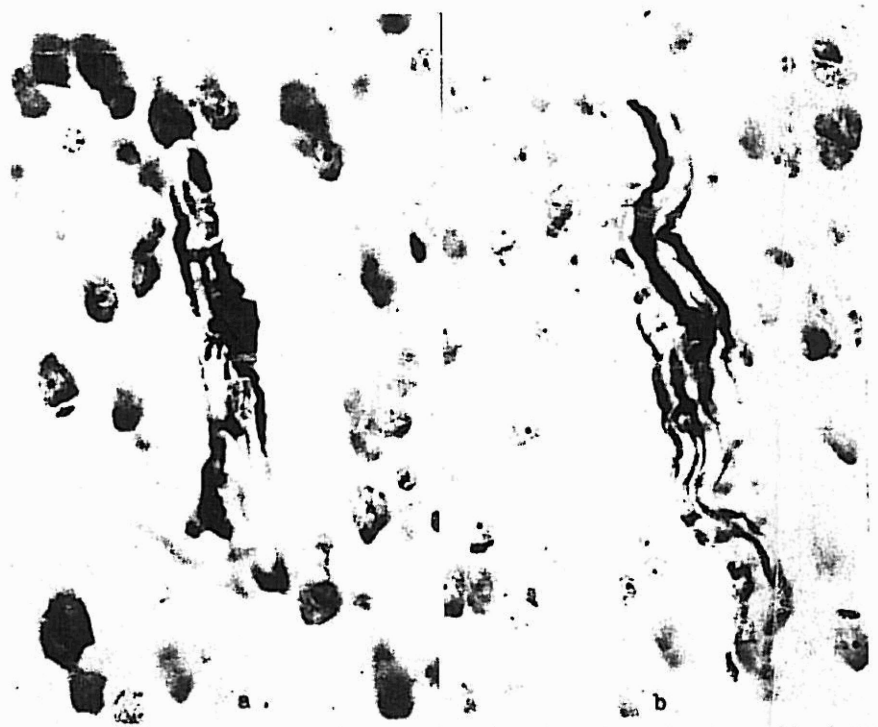

FIG. 1, a and b. Homogeneous pigment infiltrating the cellular elements of blood vesse walls, particularly the endothelial cells. Nissl stain. High power magnification.

In certain areas of the frontal and parietal lobes satellitosis and slight neurophagia were present. No significant changes were encountered in the sub-cortical nuclear formations in the mesencephalon, pons, medulla, cerebellum and spinal cord. In Nissl and hematoxylin and eosin preparations some blood vessels of the gray and white matter appeared dilated with perivascular spaces often enlarged and the surrounding elements somewhat pale.

Hortega's silver carbonate impregnation for microglia and oligodendroglia cells revealed, in areas corresponding to those where neuron changes were found, slight reactive proliferation of these cells especially along or surrounding blood vessels.

Cajal's gold sublimate impregnation for astrocytes revealed also some hypertrophy and hyperplasia of astrocytes, particularly around blood vessels and especially in the subcortical white matter. This occurrence was more often observed in the frontal, parietal and occasionally temporal lobes.

Nerve fibers and myelin sheaths did not disclose abnormalities. Only in some subcortical areas in the white matter of the frontal and temporal lobes some irregular but mostly roundish metachromatic bodies were seen in Nissl and hematoxylin and eosin preparations.

B. Monkey subjected to 12 electrically induced *grand mal* seizures, potential 80 v., duration $\frac{1}{10}$ of a second. Actual current intensity as indicated by Rahm's recording surge current meter varied from 100 to 200 m.a. The animal was sacrificed 12 hours after the last *grand mal* seizure.

The various cellular elements of the brain cortex, subcortical structures, mesencephalon, pons, medulla, cerebellum and spinal cord exhibited changes similar to those found in the previous case. However, in some blood vessels the intima and particularly the endothelial cells contained a greenish homogeneous pigment, free or embedded in some of the cellular elements (figs. 1a and b). This pigment, at times, was present also in the perivascular spaces which often appeared enlarged. This occurred more frequently in the white matter and only occasionally in the gray matter of the frontal and temporal lobes. Similar findings were also encountered in the basal ganglia.

In the subcortical white matter of the frontal and parietal lobes markedly swollen oligodendrocytes were found quite often, especially in the neighborhood of some dilated blood vessels among other somewhat more numerous glia elements.

In the white matter of the frontal and temporal lobes metachromatic bodies with a variable tinctorial appearance but mostly stained in pinkish and yellowish (Nissl stain) were present.

Methods for detecting nerve fibers, myelin sheaths and fat products did not reveal significant structural variations.

C. Monkey subjected to 12 electrically induced *grand mal* seizures, voltage 90 v., duration $\frac{1}{10}$ of a second. Actual current intensity indicated by Rahm's recording surge current meter varied from 100 to 180 m.a. The animal was sacrificed 22 hours after the last electrically induced convulsion.

Nissl and hematoxylin and eosin preparations revealed slight rarefaction of nerve cells and a few small acellular areas in the frontal and temporal lobes. The Nissl bodies were not distinctly outlined even in the large pyramidal cells. In some instances the nerve cells appeared shrunken and the cytoplasm deeply and homogeneously stained. In these cells the nucleus was undifferentiated from the rest of the cell body. Here and there satellitosis and neurophagia were apparent, particularly in the deeper layers. The nerve cells of the island of Reil appeared somewhat reduced in number but no definite changes were present in the individual elements. Some meningeal blood vessels as well as some of those passing through the underlying brain substance appeared, at times, markedly dilated. Frequently swelling, pallor and some reduction in the number of the cellular elements surrounding the blood vessels were observed. Similar findings were noticed also in the corpus striatum and diencephalon. In the latter region in some irregularly enlarged cellular elements of the blood vessels or free in the blood vessel walls granular material stained deeply green and at times slightly bluish, similar to siderophile pigments, was present (figs. 2a and b).

In the white matter of the temporal lobe, in the thalamus and the striatum some vacuoles were seen, form and dimensions of which seemed to fit the previously mentioned metachromatic bodies.

In the frontal, temporal and less frequently in the occipital lobes slight reactive hyperplasia and hypertrophy of the glia elements, particularly around, or in the neighborhood of the blood vessels was noticeable (fig. 3).

Here and there in the white matter of the frontal and parietal lobes and more seldom in the occipital and the subcortical structures acute swelling of the oligodendroglia cells was evident (fig. 4a).

D. Monkeys D1 subjected to 1 electrically induced *grand mal* seizures, D2 subjected to 11 electrically induced *grand mal* seizures and D3 subjected to 18 electrically induced

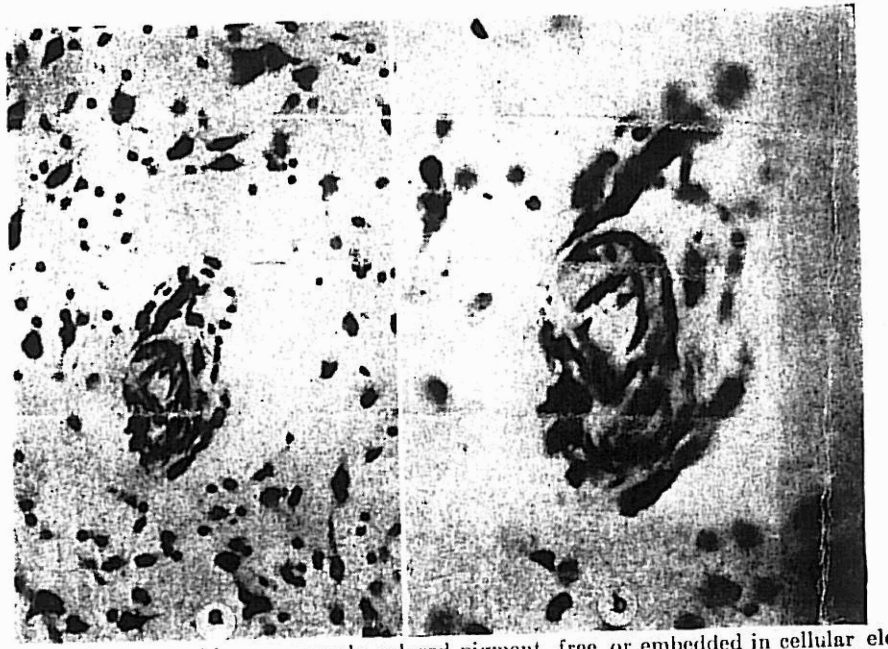

FIG. 2. Presence of homogeneously colored pigment, free or embedded in cellular elements of the blood vessel walls. Perivascular space appears dilated and pale. Nissl stain. a) Medium power magnification. b) High power magnification.

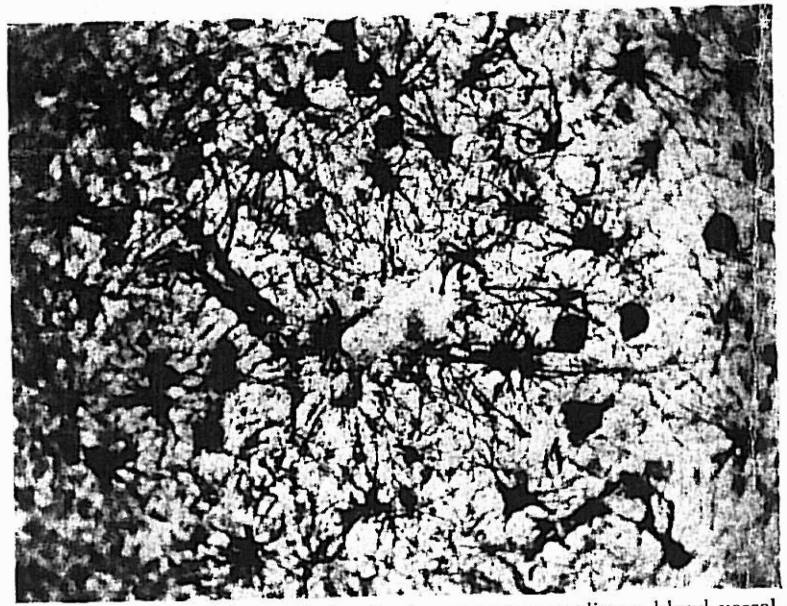

FIG. 3. Hypertrophy and hyperplasia of astrocytes surrounding a blood vessel. Cajal gold sublimate impregnation (Globus-Penfield modification). High power magnification.

grand mal seizures. In all these three monkeys the potential was 90 v., and the duration ... of a second. The actual current intensity as indicated by Rahm's surge current meter

FIG. 1. a: Acute swelling of oligodendroglia cells in the subcortical white matter. Hortega's silver carbonate impregnation. b: Nerve cells undergoing various degrees of degenerative changes. Nissl stain. High power magnification.

varied as follows: in D1 from 113 to 180 m.a., in D2 from 90 to 225 m.a. and in D3 from 82 to 180 m.a.

Monkey D1 (4 shocks) was sacrificed approximately 4½ hours after the last induced *grand mal* seizure.

Macroscopically only slight congestion of the pial blood vessels was noticed.

Microscopically here and there in the cerebral cortex there were some areas of rarefaction, otherwise, subcortical nuclear formations, diencephalon, mesencephalon, pons, medulla, cerebellum and spinal cord did not differ appreciably from the control material. At times one gained the impression that some meningeal and cortical blood vessels were slightly dilated and their perivascular spaces slightly enlarged and that some cellular elements surrounding the enlarged blood vessels were paler than usual. Here and there a greenish pigment, similar to that previously mentioned, was found in the perivascular spaces. In Nissl preparations, metachromatic bodies of bluish and pinkish color, similar in character to those previously described, were seen in the white matter of the frontal, temporal and periventricular regions.

Slight astrocytic hyperplasia and hypertrophy was evident in some subcortical areas and particularly around some blood vessels.

Monkey D2 (11 shocks) was sacrificed approximately 24 hours after the last induced *grand mal* seizure.

Throughout the frontal and temporal lobes small irregular acellular areas and occasional loss of nerve cells, tendency to satellitosis and neurophagia (particularly in the frontal region) were noticeable. Here and there nerve cells were undergoing tigrolysis associated with displacement of the nucleus and spongy appearance of the cytoplasm (fig. 4b).

The endothelial cells of some blood vessels, as well as some mononuclear cells present in the distended perivascular spaces, contained a homogeneous greenish or yellowish pigment. This was observed in a large number of sections of the frontal lobe and in a lesser degree of the temporal lobes and mostly in the cortical blood vessels. However, it was observed now and then also in the white matter and in some of the subcortical structures. In addition, in the white matter of the same regions, conglomeration of glia nuclei, mostly oligodendrogliacytes was frequently noticed often surrounding blood vessels (Nissl stain and Hortega's method) (figs. 5a, b and c). In some Nissl preparations the chromatophores of the meninges appeared intensely stained.

In scattered cortical areas the microglia elements appeared hypertrophic and increased in number, particularly in the molecular layer of the frontal and parietal lobes. In the subcortical areas acute swelling of oligodendroglia cells was present. Proliferation of the astrocytes, when encountered, was more prominent in subcortical areas and surrounding blood vessels.

Nerve fibers and myelin sheaths disclosed no appreciable changes.

Monkey D3 (18 shocks) was sacrificed 12 hours after the last shock.

The most outstanding structura changes were detected in the blood vessels. In the frontal, parietal and, less frequently, temporal lobes quite a few blood vessels appeared markedly dilated. Frequently, the perivascular spaces were also distended. Occasionally in addition to marked congestion, diapedesis of the cellular elements of the blood wa noticed (fig. 6a).

Pigments with the same tinctorial and structural appearance mentioned previously wer present in the endothelial cells of the blood vessels or frequently incorporated in larg mononuclear phagocytic cells surrounding the blood vessels (figs. 6b and c). In the fronta pole, reactive proliferation of protoplasmic glia was noticed, particularly around or in th neighborhood of dilated blood vessels (fig. 7).

Roizin's combined method for myelin sheath and lipide products of degeneration an Sudan III revealed, in certain cortical regions, surrounding markedly distended perivas cular spaces, some loss of the myelin sheaths, while others were pale, swollen and occasion ally fragmented. In these areas the endothelial cells of the affected blood vessels containe stainable fatty products. Similar fatty material was seen free and frequently included i scavenger cells (figs. 8a, b and c).

E. Monkey subjected to 13 electrically induced *grand mal* seizures, voltage 90 v., du ation $\frac{3}{10}$ of a second. Actual current intensity as indicated by Rahm's current surge met varied from 90 to 225 m.a. The animal was sacrificed 48 hours after the last induced seizur

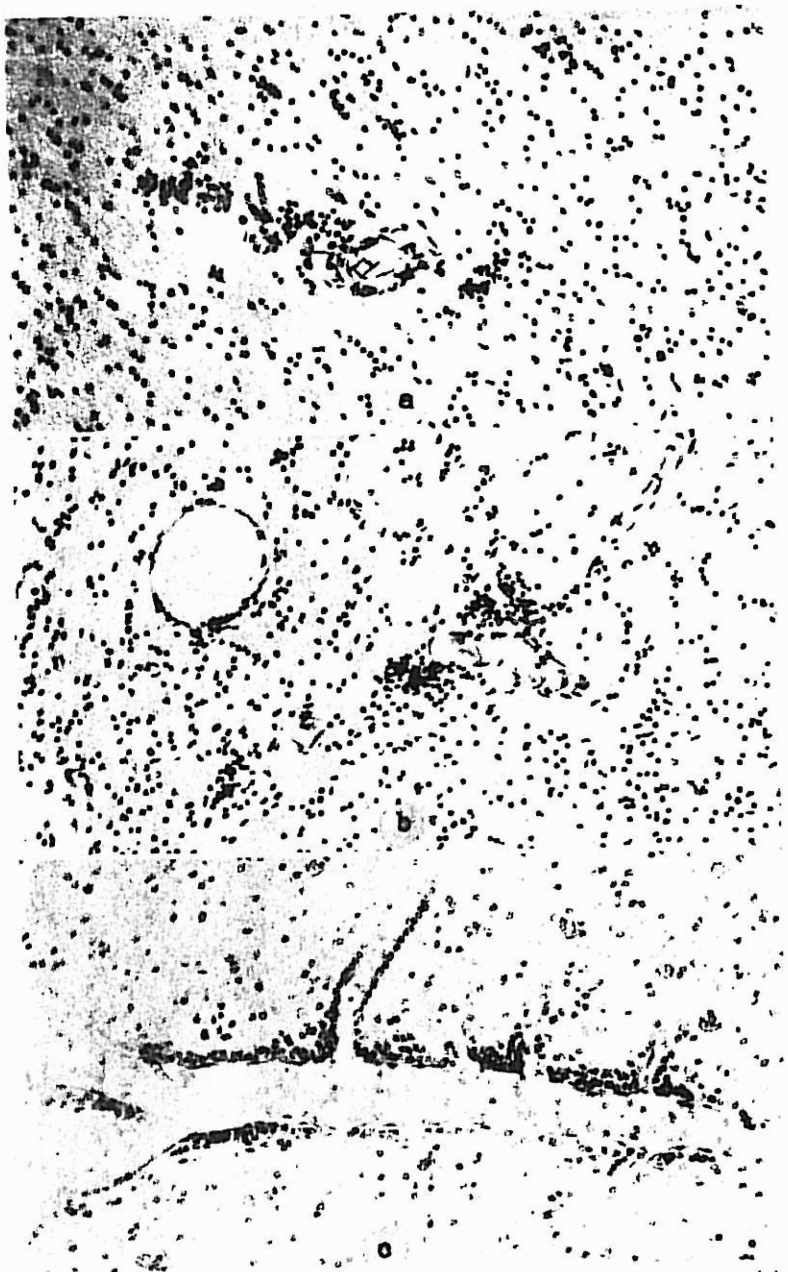

FIG. 5. Conglomeration of glia nuclei, mostly oligodendrogliocytes: a) and b) in the perivascular spaces and c) lining a blood vessel wall. Nissl stain. Medium power magnification.

In the frontal pole, tigrolysis of nerve cells was frequently encountered. At times, the nucleus seemed to be somewhat larger than usual and was stained paler. The Betz cells, however, were well stained and the Nissl substance was very clearly outlined. In some areas of the island of Reil some scattered loss or chromatolysis of nerve cells was apparent.

Nissl and hematoxylin and eosin methods revealed tortuosity and irregular enlargement of some cortical and subcortical blood vessels. Some of these blood vessels presented also,

FIG. 6. a) Vascular dilatation, enlargement of the perivascular space and blood pedesis. b) and c) Small and larger mononuclear elements in the perivascular spaces s of which contain siderophile pigment. Nissl stain. Medium power magnification.

here and there, patchy stratification of endothelial or adventitial elements. Others surrounded by small and large mononuclear elements (fig. 9a), the latter containing gr lar greenish or slightly yellowish pigment (fig. 9b). In a few instances the perivasc spaces appeared markedly dilated. In addition, some blood vessels in the white ma of the frontal lobe were surrounded by increased number of oligodendroglia nuclei.

Hortega's and Cajal's impregnations confirmed the presence of hypertrophy and hyperplasia of glia elements, particularly around the blood vessels (fig. 10).

F. Monkeys subjected to induced *grand mal* seizures with electrical current of 90 v., duration $\frac{4}{10}$ of a second.

FIG. 7. Reactive proliferation of protoplasmic glia in the neighborhood of a dilated blood vessel. Nissl stain. Medium power magnification.

Monkey F. 1 (6 shocks) was sacrificed 48 hours after the last of the six induced seizures (actual intensity varied from 150 to 257 m.a.).

Microscopically the most important findings consisted of marked vascular congestion with occasional diapedesis of the form elements of the blood. In some perivascular spaces, mononuclear phagocytic cells containing siderophil-like pigment were found. In the gray matter of the frontal pole, in a few instances, the capillaries appeared prominent and somewhat increased in number. In the basal ganglia two blood vessels were surrounded by mild perivascular infiltration, of small mononuclear elements.

Glia impregnation methods revealed increase in number and at times in size of various glia cells but particularly of micro and oligodendrogliacytes, generally around, or in the neighborhood of, the blood vessels, more so in the white matter of the frontal lobe, and occasionally in the temporal.

Sudan III preparations revealed in some nerve cells of the pons fatty products of degeneration with granular appearance and orange-reddish coloring. A few neurones of the frontal lobe (particularly of the middle layers) presented the same type of changes but to a lesser degree.

FIG. 8. Fatty products of degeneration: a) infiltrating blood vessel walls; b) and c) in the perivascular spaces. Sudan III stain. a) Medium power magnification; b) and c) high power magnification.

Metachromatic bodies were scattered in the white matter of the frontal lobe and in a lesser degree in the parietal, temporal and basal ganglia. Their structural and tinctorial appearance was similar to that described in some of the previous cases.

Monkey F. 2 was sacrificed 48 hours after the last of the eight induced seizures (actual current intensity varied from 90 to 225 m.a.).

The pial blood vessels were dilated and congested.

In the frontal lobe, particularly in the pre-central region, marked tigrolysis of the nerve cells was apparent. In some areas shrinkage of the nerve cells and corkscrew appearance of the processes were observed (fig. 11).

Some of the blood vessels of the gray and white matter were surrounded by increased number of glia nuclei.

Greenish pigment infiltrating the blood vessel walls and at times the perivascular spaces was present. In Cajal's preparations a homogeneously impregnated material, of a black color, infiltrated the walls of some of the blood vessels.

With the Hortega's silver carbonate impregnation few small petechial hemorrhages were detected in the white matter of the frontal lobe (fig. 12a). Some of them were round-

ch others slightly oval. The majority of the hemorrhagic suffusions seemed to be related particularly to capillaries and small size blood vessels (fig. 12b) and were found only in the white matter of the frontal lobe. Mostly in the immediate subcortical white matter acute swelling of oligodendroglia cells was seen.

Metachromatic bodies were distributed mostly in the white matter of the frontal and temporal lobes. Their color, in Nissl preparations, varied from pinkish and reddish to yellow. Otherwise, the histological appearance of the rest of the central nervous tissue

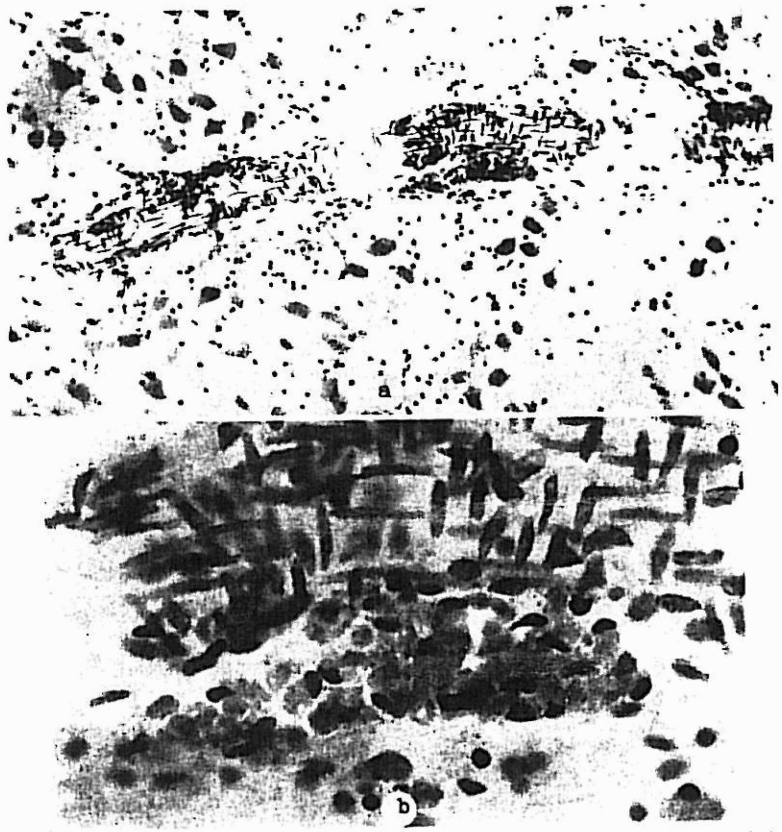

FIG. 9. Dilated blood vessel surrounded by small and large phagocytes containing granular pigment. Nissl stain. a) Medium power and b) high power magnification.

was similar to that found in the previous monkeys, with the exception that fatty products of degeneration were not observed in any of the studied sections.

Monkey F. 3 was sacrificed 12 hours after the last of the eighteen *grand mal* seizures (actual current intensity varied from 90 to 225 m.a.).

In some areas of the frontal lobe the cytoplasm of a limited number of nerve cells was homogeneously stained, the Nissl bodies being poorly outlined. More pronounced chromatolysis was occasionally present with no particular predilection for any of the cortical layers. However, satellitosis and slight neuronophagia was more apparent in the deeper layers. Pallor and some rarefaction of nerve cells was observed around some blood vessels where perivascular edema was present. Occasionally acute swelling of some nerve cells was detected (fig. 13a and b).

In the white matter of the frontal lobe several blood vessels appeared dilated; of importance was the presence of limited diapedesis or of a few small petechial hemorrhages, also roundish or oval shape and distributed in the white matter, especially along capillaries and small blood vessels (figs. 14a and b).

Cajal's gold sublimate impregnation disclosed, in certain areas, mostly in the subcortical white matter hypertrophy and hyperplasia of astrocytes, especially around blood vessels (fig. 15). A few bodies of bluish coloring (Nissl stain) were seen in the white matter of the cerebellum and pons.

No appreciable histologic changes were disclosed in the rest of the central nervous tissue.

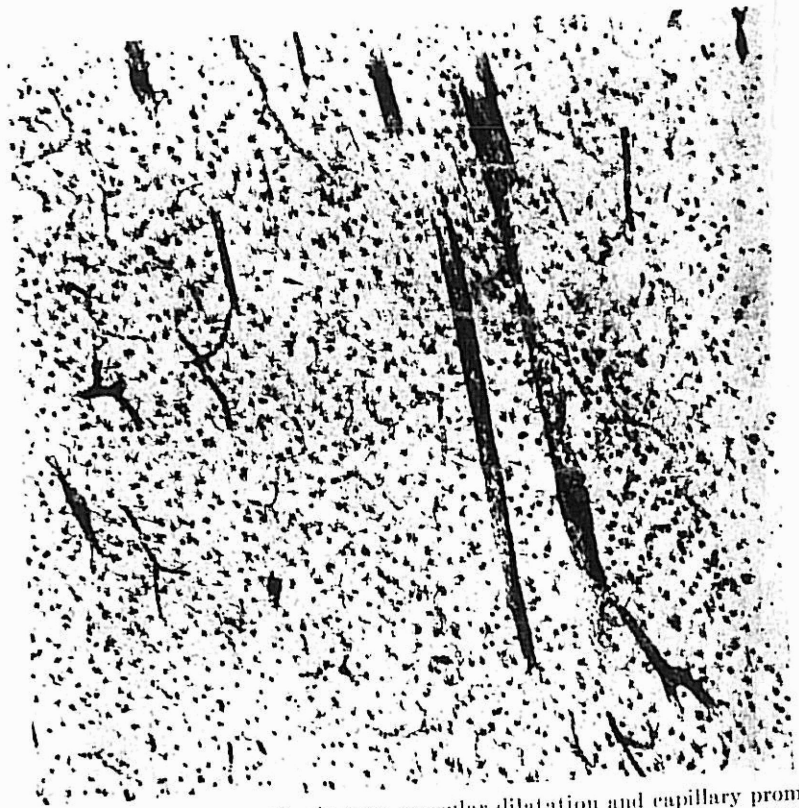

FIG. 10. Progressive astrocytic changes, vascular dilatation and capillary prominence. Cajal gold sublimate impregnation (Globus-Penfield modification). Low power magnification.

DISCUSSION

The question of neuropathologic findings in animal brains following experimental electric shock is somewhat unsettled. We feel that some of the contradictions may be due to the fact that the techniques used were not always identical and that the species of animals in the experiment used was not always the same.

In the present comments we will limit ourselves to a review and discussion of only the neuropathologic experimental findings. In subsequent papers we intend to complete our presentation with a report on the effects of electric convulsive

therapy in human cases as well as on the effect of unusually large number of electrically induced convulsions (50 to 100) in monkeys.

FIG. 11. Degenerative changes of nerve cells, mostly pyknosis. Note the corkscrew appearance of several of the processes. Nissl stain. High power magnification.

In 1940 Cerletti and Bini (1) reported neuropathologic findings in dogs subjected to electric shocks. In a first group of 12 dogs the authors induced daily one or more, seldom two, convulsions, up to an average of 24 complete seizures. The animals were sacrificed at variable lengths of time from the last seizure (from 5 days to 5 months). No macroscopic lesions were noticed in the brain or other organs. Microscopically there were found some edema, dilatation and

tortuosity of capillaries, small acellular areas around some blood vessels, vacuolization of cells of the second, third and fourth layer, pyknosis of nerve cells of

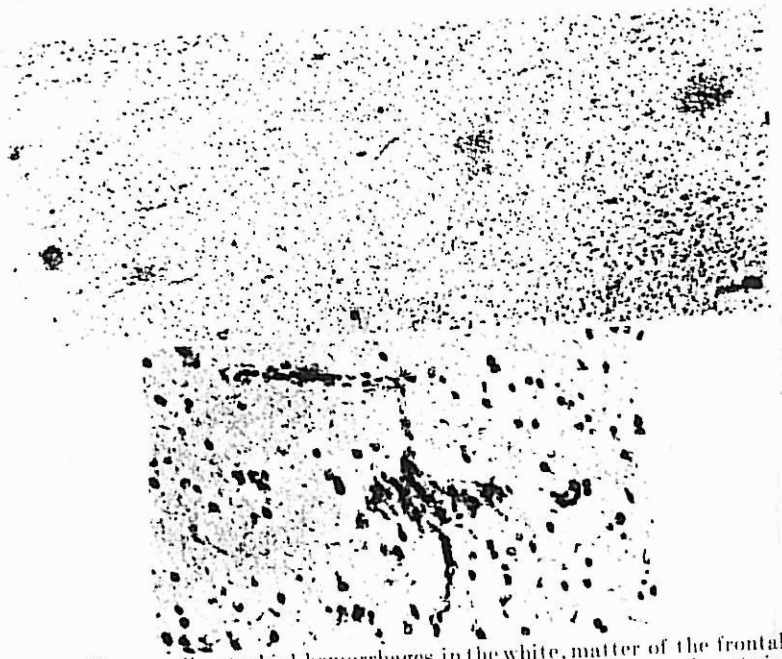

FIG. 12. a) Five small petechial hemorrhages in the white matter of the frontal lobe; b) small hemorrhagic petechia between two capillaries. Hortega's silver carbonate impregnation. a) Low power magnification; b) medium power magnification.

FIG. 13. Suffusion and swelling of nerve cells in the frontal lobe. Nissl stain. High power magnification.

the deeper layers and at times "*Cliarasen*." A second group of animals were subjected to from 20 to 70 complete seizures, 3 to 5 minutes apart from each

other. One of these animals succumbed after a series of convulsions. It disclosed the acute swelling of Nissl as well as liquefaction of nerve cell. The glia disclosed change of the "regressive" type. The vessels were dilated and congested; around the cortical vessels acellular areas were observed. The third group of dogs were subjected to electrical currents with potentials of 110, 125 and 220 volts. The intensity varied from 900 to 2500 m.a. and the duration varied from 17 to 50 seconds. The majority of the dogs died, after 2 to 8 shocks, presenting

FIG. 14. a) Marked congestion of a blood vessel and hemorrhagic suffusion. b) Petechial hemorrhage. Hortega's silver carbonate impregnation. Medium power magnification.

symptoms of asphyxia. Only two animals survived and were sacrificed after 10 and 40 days respectively. Histologically many nerve cells presented acute swelling and less frequently the severe type of change of Nissl. The glia cells showed regressive changes. The pia was thickened and the blood vessels congested. In the perivascular spaces "perivascular corpuscles," red cells and leukocytes were found only occasionally. The same changes were found in the basal ganglia and cerebellum.

Alpers and Hughes (2) used in their experimental work 30 cats. Two groups of animals were subjected to induced convulsions six times weekly for a period varying from 2 to 4 weeks. A third group of cats received shock three times weekly up to a total of 10. The potential of the 60 cycle alternating current was 110 v., the intensity varied from 150 to 200 m.a. The dimensions of the circular electrodes measured in diameter 5 mm. No data as to the exact location of electrodes and the time duration of the flow of current are given. The authors found extensive subarachnoid hemorrhages of a mild degree in 14 animals. Hemorrhages in the brain substance (cortex and white matter) mid-brain and cerebellum were found in 9 cats. In the latter they were mainly of punctate type

FIG. 15. Vascular dilatation, enlargement and pronounced glial proliferation. Caja gold sublimate impregnation (Globus-Penfield modification). Medium power magnification.

whereas in two animals they were more extensive. The distribution of the hemorrhages varied; they were not confined to the area immediately beneath the electrodes. The hemorrhages were usually fresh but in several cats disintegrated blood was also encountered. In the main, the nerve cells remained unaffected. At times, glia nodules were observed which the authors interpreted as evidence of reaction to previous hemorrhages.

In the same year, Heilbrun and Weil (3) reported similar changes in 28 rabbits and 10 rats. These animals were treated with alternating current of 50 to 60 cycles, potential 60 to 150 v., intensity varying between 65 to 300 m.a. Time duration .3 to half a second; the surface of the electrodes 2 sq. cm. It is interesting to note that 16 rabbits were paralyzed in the course of these investigations,

7 of them after the first shock. In only three of the remaining 12 rabbits no pathologic changes were found on microscopic examinations. In all the others, hemorrhages were present "within the meninges of the brain and spinal cord and within the brain stem and spinal cord. These hemorrhages were usually confined to the immediate neighborhood of capillaries and small veins and were produced by the rupture of the walls of these vessels. No generalized ganglion cell disease or generalized proliferative glia reaction was observed, except in the immediate proximity of the hemorrhages and were usually combined with a somewhat spreading edema of the surrounding tissues. Hemorrhages also were present in the lungs of 6 animals and in the kidneys of three out of 10 rats."

Barrera, Lewis, Pacella and Kalinowsky (4) subjected 12 Maccacus rhesus monkeys to electric shock under conditions "resembling as closely as possible the administration of the treatment in human beings." Seizures were induced three times weekly, voltage varying from 70 to 135 with current times of .10 to .15 of a second. The largest number of seizures administered was 30 with applied voltage of 135 and current passage time of .15 of a second. The animals usually were sacrificed 24 hours after the last shock. The common neuropathologic techniques were used. The microscopic studies did not show any significant histopathologic changes or important differences from those in supposedly normal control animals.

Neubürger and coworkers (5) described vascular dilatations and minute hemorrhages in the cortex, meninges and around the ventricles in some brains of 12 mongrel dogs. The shock was administered with a potential of 80 v., current stream of 200 m.a., duration .15 of a second at intervals of 3 to 5 days, the number of shock per animal varying from 2 to 25. The authors reported in addition shrinkage of ganglion cells, mild reaction of glia and absence of demyelination.

Similar changes were previously described by Morrison, Weeks and Cobb (6) in rabbits, guinea pigs and cats. However, these authors used four types of electric current completely different from the electro-convulsive type.

Globus, Harreveld and Wiersman (7) investigated the influence of electronarcosis upon the structure of the brain of dogs. Although electronarcosis is used with another purpose and technically is quite different from the electric convulsive shock of Cerletti and Bini we are including it in our review because the above mentioned investigators feel that "since electronarcosis may be considered, in the main, as a prolongation of the electric shock treatment, morphologic changes in the nervous system occurring from electroshock might be expected to be more out-spoken and more readily recognized in the brain of animals subjected to electronarcosis." Seven dogs were used in these experiments and in all the animals electronarcosis was started with a relatively strong current of 60 second duration. The strength of the initial current varied from 200 m.a. to 700 m.a. The voltage is not given. In all cases the current was applied through padded electrodes located over the temples. After 30 seconds of high current it was decreased to a lower level and so adjusted that respiration could take place without apparent impairment. The current of the narcosis level varied from 7

to 410 m.a. The frequency of the current varied from 60 to 10,000 per second; duration of the current flow varied from 2 to 75 minutes. The animals were sacrificed in different ways, some through injection of ether into the lungs one or more days after the electronarcosis, others by applying a very high current shortly after electronarcosis and others through a current of intermediate intensity applied for a prolonged period causing, after a considerable time, death from heart failure. The usual standard neuropathologic techniques were used. A careful gross and microscopic study of the experimental animals did not disclose pathologic changes.

Alexander and Lowenbach (8) studied the effects of electric shock in 23 cats; 19 of the animals received single shocks with currents varying from 60 to 2000 m.a. for a period ranging between 2 and 10 seconds in duration. Alternating 60 c. current was used; the potential varying from 120 to 550 v. and copper electrodes measuring 10 x 10 mm. These were placed in a way "comparable to the usual method of electroshock in man." All but 2 of these animals were killed by quick decapitation. Time of survival varied from a few minutes to 9 days following the last shock. The usual neuropathologic techniques were used including the benzidine method for vascular pattern. These authors found that a shock dose of 300 m.a. produced only for a brief period arteriolar vasoconstriction and blanching, noticeable "within the path of the current 4 minutes, but not half hour and an hour after the shock." No vascular and perivascular changes following shocks with currents of 350 to 450 m.a. were seen 1, 3 and 7 days after shock. With single shocks of 500 to 1800 m.a. arteriolar vasoconstriction with blanching of the capillary bed, was still noticeable, at times 5 minutes to 1½ hours after the shock. With shock doses of 2000 m.a. flowing for 5 seconds and more, vasoparalytic stasis could be produced within the course of the path of the current through the brain; marginal parts of the path of the current (where current density was less) showed only arteriolar vasoconstriction and blanching of the capillary bed. Early pathologic changes of the neural parenchyma could be produced only with currents of 1800 m.a. and above and only within the path of the current. With currents of 1800 m.a. flowing for 2 to 5 seconds they were of an essentially reversible type; with currents of 2000 m.a. flowing for 5 to 10 seconds they were of an essentially irreversible type. All these pathogenic currents were in amperage, time of flow and density far above the range of currents used in human E.C.T. With single shock doses no pathologic changes of the neural parenchyma could be produced which were recognizable with the common histologic methods.

Winkelman and Moore (9) also used cats in their experimental investigations. The 12 animals were divided as follows: 1) a first group of 8 cats was treated with the faradic shock modality of Berkwitz. Seven animals received 20 series of faradic shocks with break intervals of .7 of a second to 1 second; in one animal of this group (#9) the current was applied continuously for 40 seconds and a free interval of 40 seconds, followed by another shock of 28 seconds duration. The first seven animals were sacrificed at intervals varying from three days to ten weeks, following the last treatment; the last (#9) was sacrificed 24 hours subse

quent to the treatment. The second group of four cats was treated with the Cerletti and Bini method (using the Offner machine). The strength of the current was of 300–400 m.a., voltage 70 to 80 v., time 0.1 seconds. In this group of animals two received 17 convulsive treatments and were sacrificed one month after the last convulsion. A third pregnant cat received 11 treatments and after delivering normal living kittens was sacrificed four days after the last convulsive shock. The last cat received two treatments two days apart consisting of 350 m.a., 80 v. for one full second and was sacrificed three days after the second convulsion. Gross and microscopic investigations of the brain and spinal cord did not disclose any pathologic changes in the cats treated with "convulsive doses" analogous to those given in human. In one cat "receiving excessive electric shock doses a small area of precapillary hemorrhage was seen and in another congestion and prominence of the venous and capillary vessels."

Lidbeck (10) reported brain changes in three dogs subjected to shock treatment. The shock was administered with the same machine used in human cases (Offner Electronics Co., Chicago) and differed only in the "employment of smaller electrodes." The first dog was treated with a current of 250 and 350 m.a., time 0.2 of a second. The shocks were given twice weekly, total number 16. The second dog was treated with a current of 350 m.a., time 0.2 and 0.3 seconds. The shocks were given daily, total number 16. The last dog was subjected to a current of 500 m.a., time 0.7 seconds (twice) and 0.1 second (12 times), (voltage is not given) three times weekly, total number 11. Histologic studies revealed "a single perivascular hemorrhage and capillary thrombi in one animal and shrinkage and ischemia of ganglion cells near the site of the electrodes in two animals."

From this brief review of the literature on the effects of the experimental convulsions (1–13) electrically induced upon the morphology of the central nervous system, one realizes that while some authors reported marked neurohistologic changes others failed to find any appreciable alterations.

In a more detailed analysis it seems to us that some of the contradictory findings could be referred to several factors.

1) *Intensity of the electrical current used for the induction of convulsions.* Some authors have used convulsive doses in rats, guinea pigs, rabbits, cats and dogs irrespective of the size of the animal. This fact alone might explain the variation from slight findings in dogs as reported for instance by Cerletti and Bini (1) and Lidbeck (10) on the one hand, and the marked hemorrhages reported by Heilbrun and Weil (3) who used a potential of 60 to 150 volts in rats and rabbits.

2) *Flow duration of the convulsive doses current.* Some authors used only fractions of a second (for instance 0.1 of a second or 0.2 of a second); others instead prolonged the time not only to higher fractions of a second but to full seconds or several seconds and even minutes.

3) *Size of electrodes.* Quite a few authors used in small animals electrodes of such dimensions that would cover not only the precentral or prefrontal region of the frontal lobe (as used in human treatment) but at times the whole brain and possibly pons and medulla.

4) *Frequency of induction of convulsive seizures.* Some workers subjected the experimental animals to two or three shocks weekly. Other investigators applied the currents daily and in some occasions even twice daily.

5) *Total number of induced convulsions.* Some experimentors studied the brains following one or a few shocks, others instead reported findings following 10 or 20, 30 and even 40 repeated convulsions.

6) *Selection of experimental animals.* Different authors used various types of animals. It is well known from different experimental sources that not all the laboratory animals react in the same way to a given experimental investigation and that variable reactions are not observed only in different species but in the different animals of the same species. Without discussing in detail this important factor we would like only to mention that Echlin (14) for instance found that the pial vessels in cats contract vigorously on electric stimulation. The dogs are less sensitive and monkeys less so than the dogs.

7) *Careful supervision of diets.* This is essential in the course of the experimental investigations, for both the control animals and those under experimentation. Mild or subclinical vitamin B_1 (or some of the B complex group), C and, more seldom, K deficiencies (as already mentioned by Winkelman and Moore) may facilitate or accelerate the appearance of some morphologic structural changes.

It seems to us that consideration of the above mentioned seven factors might contribute to clarify to a large extent some of the contradictory experimental reports concerning the morphology of the central nervous tissue in experimentally induced convulsions. Moreover, to avoid other objections we have used as far as possible the method of serial sections in both control and experimental material. Furthermore, we have taken into consideration another important factor: the one of quantitative difference between control and experimental material. The findings of an occasional acellular area, or of a few nerve cells in a state of chromatolysis, or of a few metachromatic bodies or of a few hypertrophic glia cells is not a sufficient criterion to establish the existence of pathology in experimental investigations. But the quantitative difference between the same occurrence in the normal material as compared with the experimental one is a factor which cannot be ignored. Finding variations more frequently and more systematically in experimental material than in control material is in our opinion significant and the findings can be more justifiably related to the experimental procedure.

Some authors (4, 7, 9) have reported that some slight changes such as chromatolysis and pyknosis of nerve cells, satellitosis or neuronophagia, rarefaction and even some acellular areas may be found, in various regions of the central nervous system of the control animals. When such findings were found in the brain of animals subjected to experimental investigations there might have been an inclination on the part of the investigator to consider them as expressions of a normal occurrence. We feel, however, as mentioned above that in such a situation the element of quantitative evaluation must be added to that of a qualitative one.

Thus the study of a few slides and of only a few areas is quite inadequate and serial studies of both control and experimental material is essential.

In this light we feel that some of the milder structural alterations (figs. 1, 2, 3, 5, 7, 8 and 9), both cellular and vascular changes distributed particularly in the frontal lobes (which were mostly subject to the passage of the electrical pattern) are the effects of the experimental convulsions electrically induced.

The question as to what may cause the cerebral structural changes in experimental electric shock comes up now for consideration.

Histopathologic investigations of the effect of different types of electric current upon the central nervous tissue of mammals (15, 16, 17, 6) revealed that a shocking electric current may affect nearly all the structures of the brain tissue and, more frequently so, the blood vessels (6, 8, 11, 16, 18), a probable reason for the occurrence of hemorrhages.

The majority of investigators think that the electrical current itself and its intensity is the most important single factor. As a matter of fact, Alexander feels that 25 m.a. or more may produce permanent damage to the nerve tissue and blood vessels and that the critical level (19) for morphologic alterations in nerve tissue is 30 m.a. per 3 mm. of nerve diameter for shocks of 5 second duration. The threshold for reversible damage to brain tissue seems to l · somewhere between 15 and 18 m.a. per sq. mm. within the path of the current and the threshold for irreversible damage at 20 m.a. per sq. mm. of brain tissue within the path (8). These authors observed also that although the morphologic changes were produced only in the path of the current, these changes were not always present throughout the entire path. When found along the entire path, such as occurred in higher ranges of amperage, they varied in degree at some points in the path. They also noticed that in tissues adjacent to, but at some distance from the main path, the effective current conduction rapidly decreased, thus indicating that there was practically no diffusion of the current away or distant from its main path.

In our experiments we also observed that the morphological changes, when present, were distributed mostly in the frontal lobes, that is in the region which was subjected to the passage of the main electrical shocking current.

As for the effects of the electricity on the blood vessels it has been shown by Echlin (11) that when the current traverses arteries there is an initial constriction followed by a period of dilatation which may be severe and prolonged, and cause secondary hemolysis of the blood in the veins. However, it seems that in some fatal cases, there may be widespread engorgement of blood vessels with non-clotted "homogenized blood" which is regarded as secondary effect of prolonged disorder or paralysis of the respiratory centers. In addition Alexander (11) noticed that in "hand to hand" contacts some cerebral changes may be due not to the current directly but to "the prolonged circulatory disturbances produced by the passage of the current through the heart and the endings of the vagus nerve."

Spiegel and associates (20) studying the physico-chemical effects of electrically induced convulsions in 30 dogs, observed changes of the permeability of the vas-

cular walls and increased permeability of the blood liquor barrier. These obse vations are in accord with some of our findings, such as distention of the periva cular spaces, perivascular edema (figs. 2a and b) and, in certain instances, th presence of compound granular corpuscles containing siderophile pigments (fig 10a and b).

Concerning the duration of the morphologic changes one must consider tha most of the cellular changes being of the reversible type, a return to norm structure and function in due time is very probable. However, here and the the presence of diapedesis or petechial hemorrhages point to the fact that such damage, no matter how slight, may ultimately become permanent. The add tion of other small hemorrhages may finally influence even in a slight manne some of the mental processes.

In cases where structural damage does not occur it is conceivable that son physio-chemical change may take place in the brain structure of the animal though they may not be histologically detectable with the available technique In such cases histometabolic studies of the brain tissue may be indicated.

CONCLUSIONS

Electrical currents similar in type, intensity, duration of current flow and fr quency with that used in human electric shock therapy, may cause morpholog changes in the central nervous system of monkeys.

The nerve cell alterations are mostly of the reversible type. The changes a mostly related to circulatory disturbances and increased permeability of th blood vessel walls. The latter is shown by distention of the perivascular spac and perivascular edema (figs. 2a and b) and by some diapedesis of form blo elements. Compound granular corpuscles filled with presumably hematic pi ment and free pigment in the blood vessels seem to confirm such an occurren (figs. 10a and b).

When more intense current and of longer duration is applied, occasional n nute petechial hemorrhages result. This seems to support the contention th the severity of the lesions are proportional to the intensity of the electrical cu rent, the duration of the current flow and, to a lesser extent, to the number electric shocks.

The histopathologic changes are more pronounced in the areas of tissue tra ersed by the main path of the current.

In comparing the slight morphologic changes in experimental animals wi those encountered in control animals, it is necessary not only to evaluate the qualitatively but also quantitatively.

Reversible chemical or structural changes, and possibly some permane slight structural damage may be at the base of the temporary alterations the mental processes occurring in patients in the course of electric sho therapy.

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SPINA BIFIDA AND THE CEREBROSPINAL FLUID*

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The most dramatic manifestation of spina bifida is herniation, usua posterior region of the spinal column—a protrusion in the form of a sac f fluid or containing a solid tumor mass. Another common but less strikir is not in the region of the spinal cord but in the brain—in the nature cephalus. There are a number of other pathologic combinations, such ward replacement of the medulla oblongata and the cerebellum (Arno deformity), or defective number of cervical vertebrae (Klippel-Feil malfo and many others. Bucy (1) in his excellent review mentions twenty-t of anomalies complicating this condition, and Ingraham and associates in 232 patients (or slightly more than in half their series) 570 associated a recorded. The type of spina bifida more or less spoken of are: myelomen meningocele, myelocystocele, rachischisis (complete, incomplete, par spina bifida occulta. Some of these occur in combination. For Recklinghausen (3), Keiller (4), and others discussed at great length forms of rachischisis associated with myelomeningoceles and other spina bifida, probably unnecessarily complicating the subject. What variety, a feature common to all the types of spina bifida is a defect in t brae and the dura mater, the changes in the spinal cord itself and its ap (the roots and spinal ganglia) being less constant and for the most part se Spina bifida occulta seems to be an exception, but is not considered (Leveuf (5), for instance) as spina bifida at all. The aforementioned a were attributed to a maldevelopment of the ectodermal and mesodermal and mesoblast) embryonic layers from which the spinal cord, its append the surrounding bony structures arise. A voluminous literature exist pathologic condition under discussion, the vast references having been f gathered by Hesse (6), Ingraham and coworkers (2).

While the morphologic features of spina bifida including the emb pathologic, clinical and surgical aspects have been exhaustively inve the relationship of the bifidal changes to the spinal fluid, the cause of its accumulation resulting in the formation of a liquid tumor attracted ve if any, attention; much less than did other complications such as hydro or Arnold-Chiari malformation. Yet, it would seem proper that the cases

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