EXPERIMENTAL STUDIES ON ELECTRO-SHOCK TREATMENT: THE INTRACEREBRAL VASCULAR REACTION AS AN INDICATOR OF THE PATH OF THE CURRENT AND THE THRESHOLD OF EARLY CHANGES WITHIN THE BRAIN TISSUE[1]

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In a previous study by Alexander and Weeks (1), it was shown that if electric current of a magnitude sufficient to abolish irritability and conductivity of the nerve fiber was passed through a peripheral nerve, capillary and supracapillary anemia of the vascular bed of the nerve established itself in that part of the nerve through which current had been flowing. This capillary and supracapillary anemia, which was presumably due to vasoconstriction of the supplying arterioles (the capillaries probably collapsing only secondarily because of their passive contractility) lasted until shortly before irritability and conductivity of the nerve returned. After passage of far higher currents, vasoparalytic stasis in the path of the current could be observed. More recently, Echlin (2) has produced localized cerebral anemia by direct electric stimulation. While previous experimental work on electro-shock, such as used in treatment, tended to show rather diffuse cerebral and meningeal changes, not all of them of clear-cut pathological significance, observations by Weeks and Alexander (3) made it appear unlikely that electric current would distribute itself diffusely throughout the brain, but suggested the existence of a fairly clear-cut path from one electrode to the other. We, therefore, felt that it would be interesting to carry out experiments by which we could, as it were, blaze a path across the brain, clearly outlined by the above mentioned vascular reactions.

MATERIAL AND METHODS

This study is based on experiments in 23 cats. Nineteen of them received single electric shocks with currents varying from 60 to 2000 milliamperes for a period ranging between 2 and 10 seconds in duration. In some of the shocks with high amperage the current fell off after flowing for periods varying from 3 to 8 seconds; since amperage was always measured directly by means of a milliampermeter, this circumstance was recorded whenever it occurred (see table 1, animals No. 14, 17, and 19).

Alternating 60-cycle current was used in all these experiments, the voltage varying from 120 to 550 volts. The two electrodes, made of copper, were of square shape and measured 10 x 10 mm; they were placed in a way comparable to the usual method of electro-shock in man, namely, one in front of each ear, upon shaven skin treated with a jelly prepared from sodium chloride and glycerin in the usual way. The central part of the site

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of each of the two electrodes upon the skull corresponded topographically to the anterior suprasylvian gyrus of each hemisphere; this gyrus is laterally adjacent to the lateral tip of the gyrus cruciatus, and is a part of what is morphologically the frontal lobe of the cat's brain. With this arrangement the current was expected to pass from one anterior suprasylvian gyrus to the other and through the adjacent intervening parts of each fronto-cruciate lobe. In one case (Cat 16) the brain was exposed during the administration of the shock by removal of the calvarium from above, down to immediately above the point where the electrodes were applied at the temples; in all other cases, the skull was left intact in its normal enclosures until after the animal was killed.

The shock was followed by one convulsion, except in three animals which had been anesthetized by nembutal (Cats 3, 12, and 16) and in which no convulsion occurred except for the tonic contraction while the current passed. The type of the convulsion was tonic-clonic in most cases, although in three animals (Cats 1, 11, and 13) the tonic phase was much longer than the clonic one. In two cases (Cats 10 and 17) the convulsion was tonic only. The duration of the convulsion varied from 20 to 80 seconds, in the majority of the cases from 35 to 39 seconds. The immediate aftermath of the convulsion consisted in running movements in all but one of the animals, lasting for 20 seconds in most of them, with two exceptions in which they lasted 45 and 60 seconds respectively (Cats 10 and 17). Running movements were absent in Cat 13; instead, heavy breathing only occurred during the period usually occupied by the running movements. The subsequent symptoms consisted in most instances of a period of hyperactivity, attempts of righting, and incoordination lasting up to three minutes. Three animals behaved differently: in Cat 17 instead of hyperactivity unusually heavy breathing occurred for one minute, then complete flaccid paralysis for two minutes, then gradual recovery. In Cat 10 flaccidity prevailed for 150 seconds after the period of "running"; than a "rage state" manifested itself and lasted for several minutes. In Cat 15 the running period was followed by six minutes of rapid respiration, then by a "rage state" lasting one minute and fifteen seconds, then by recovery; the cat behaved normally until it was killed on the ninth day.

All but two of these animals were killed by quick decapitation; the times for which the animals were allowed to survive varied from a few minutes to nine days following the shock (table 1); the largest single group of animals (8 cats) was killed one half hour after the shock. One animal died during an intravenous injection of methylene blue immediately after the shock (Cat 12), another during intravenous injection of gentian violet 4 minutes after the shock (Cat 3).

Two animals received multiple electric shocks about one minute to half a minute apart. Cat 20 received 6 shocks, lasting two-fifths of a second each, which resulted in 6 convulsions; the first lasted 38 seconds and was tonic only; the second was clonic only; the others tonic or clonic, but never both; each subsequent one was shorter than the preceding one, the sixth lasting 4 seconds only. Cat 21 received 52 shocks, lasting three-fifths of a second each, resulting in 17 convulsions, of which 6 were tonic-clonic, 5 tonic, and 6 clonic; their duration varied from 79 seconds to 19 seconds on subsequent shocks.

Immediately after decapitation scalp and skull were opened and the brain removed and inspected. The brain was then cut into thick transverse frontal slices, in a few instances prior to fixation, in some cases after a brief period of hardening in dilute solution of formaldehyde U.S.P. (1:10), for the purpose of gross study of the cut surfaces; in most cases the brain was not cut until after three days' fixation in this solution. Then the whole brain was divided into two alternate series of thin transverse blocks. From one series of blocks frozen sections 200–300 micra thick were prepared and stained with benzidine for study of the vascular pattern. The other series of blocks was embedded in paraffin, and sections were stained with hematoxylin eosin for the general topography; with the Nissl method (cresyl violet) for nerve cells; with Masson's trichrome stain for blood vessel walls, connective tissue, glia, and myelin sheaths; and with Bodian's silver method for axis cylinders and neurofibrils. This routine was followed in all cases with the exception of one, Cat 18, in which both series of blocks were stained with benzidine.

In two animals, experiments were performed with the intention of controlling the complicating factor of heat (Cats 22 and 23; see table 1). A large number of controls of various other factors, morphological, pathological, and technical, was available in the form of a sizable collection of cats' brains sectioned and stained with benzidine and other stains, used in previous anatomical, experimental, and pathological studies by one of us.

RESULTS

Protocols of all experiments are presented in table 1, and the main findings in the single shock experiments are briefly resummarized in table 2.

Significant, morphologically recognizable tissue reactions, vascular or otherwise, were limited to that part of the brain which was within the path of the current; that is, in our experiments they were limited to the fronto-cruciate lobes or to parts of them. The exception was one animal which died after multiple shocks (Cat 21); only in this case there were, in addition to the changes within the path, diffuse changes obviously related to the general circulatory disturbance prior to the death of the animal. In all other animals those parts of the brain which were outside the path of the current, that is, those behind the anterior tips of the entolateral and ectolateral gyri, showed no morphological or histological changes, neither immediately nor at times varying from a few minutes to 9 days after the shocks. Here even temporary vascular reactions were absent, such as recognizable grossly, through a magnifying glass, or with the benzidine stain. The parietal and occipital lobes, the bulk of the temporal lobes and the brainstem from the thalami backward, showed in all these animals not only a perfectly normal picture of the neural parenchyma (nerve cells, axis cylinders, etc.), but also a perfectly normal picture of the vascular pattern (fig. 1). Within the direct path significant changes could be produced with definite regularity. But the threshold for the production of changes which were morphologically and histologically recognizable at times varying from one half hour to seven days after the shock, was rather high. No such changes were observed in animals which had received shocks varying from 60 to 450 milliamperes, for times varying from five to ten seconds; that is, in animals in which the current density within the path had not exceeded 0.6 to 4.5 milliamperes per square millimeter of the cross-section of the path through the brain (Cats 1, 2, 4, 5, 6; see tables 1 and 2). However, in one animal which had been given a 300 milliampere shock but which was killed only four minutes after the shock (Cat 3), blanching of the anterior suprasylvian gyri bilaterally within the path of the current was noted.

In those animals which had received shock currents between 500 to 1800 milliamperes, for periods varying from two to five seconds and in which the maximum current density within the path varied from 5 to 18 milliamperes per square millimeter of its diameter, "blanching" of the cerebral vascular bed manifested itself within parts of the path, when examined immediately or at times ranging from a few minutes to one and one half hours after the shock. Under "blanching" (fig. 2) we understand the picture composed of arteriolar vasoconstriction and of incomplete capillary filling, with abnormal thinness of those capillary channels which have remained filled. In those animals which were shocked with 500 to 1500 milliamperes (Cats 7, 8, 9, 10, and 11) the resulting

NO.	VOLTAGE	AMPERAGE (IN MILLI-AMPERES)	TIME OF SHOCK (IN SECONDS)	SURVIVAL TIME	LESION PRODUCED, GROSS	LESION PRODUCED, MICROSCOPIC
						Benzidine stain
1	120	60	5	½ hour	No gross changes	No———
2	520	200-300	10	½ hour	No gross changes	No———
3	520	300	3	4 mins. Was killed by injection of gentian violet.	Less intense gentian violet staining of anterior suprasylvian gyrus of left and right hemisphere, as compared to the rest of the brain. The less intensely stained anterior suprasylvian gyri and the underlying white matter appeared swollen and moist as compared to the rest of the brain.	Blanching of anterior suprasylvian gyrus of left and right hemisphere.
4	120	350	5	72 hours	No gross changes.	No———
5	120	400	5	24 hours	No gross changes.	No———
6	120	450	5	7 days	No gross changes.	No———
7	120	500	5	½ hour	Blanching, involving the anterior suprasylvian gyrus of the left and the right hemisphere.	Blanching, involving the anterior suprasylvian gyrus of the left and the right hemisphere. Blanching of the right is more intense than that of the left.
8	120	500	5	1 hour	Slight suggestive blanching involving the anterior suprasylvian gyrus of the left and the right hemisphere.	Slight blanching involving the anterior suprasylvian gyrus of left and the right hemisphere.
9	120	550	5	5 mins.	Blanching, involving the anterior suprasylvian gyrus of the left and the right hemisphere.	Blanching, involving the anterior suprasylvian gyrus of the left and the right hemisphere.
10	520	800	5	½ hour	Suggestive blanching of anterior suprasylvian gyrus of the left and the right hemisphere.	Blanching (arteriolar vasoconstriction and diminution in capillary filling) of anterior suprasylvian gyrus of the left and the right hemisphere.
11	520	1,500	4	½ hour	Blanching of anterior suprasylvian gyrus of the left and the right hemisphere.	Blanching of anterior suprasylvian gyrus of the left and the right hemisphere.
12	520	1,800	2	Killed immediately by injection of 10 cc of methylene blue intravenously.	More intense methylene blue staining of anterior suprasylvian gyrus and of the adjacent antero-lateral portion of the fronto-cruciate lobe of the left and the right hemisphere, on the left more so than on the right, with swelling of the involved cortex on the left.	Blanching of anterior suprasylvian gyrus and of adjacent parts of fronto-cruciate lobe of the left and the right hemisphere, on the left more intense than on the right.
13	520	1,800	4	½ hour	Blanching of anterior suprasylvian gyrus of the left and the right hemisphere.	Blanching of anterior suprasylvian gyrus of the left and the right hemisphere.

LESION PRODUCED, MICROSCOPIC

Nissl stain	Hematoxylin-eosin stain	Masson's trichrome stain	Bodian's silver stain
significant (Perfectly)	normal		changes appearance)
changes (Perfectly)	normal		discernible appearance)
No	significant		changes
significant			changes
significant			changes
significant			changes
No	significant		changes
No	significant		changes
No (Perfectly)	changes normal		discernible appearance)
No (Perfectly)	changes normal		discernible appearance)

Subacute encephalomyelitis identical with Cat 13, the only difference being the admixture of an occasional polymorphonuclear leukocyte to the infiltrative cells. This condition is obviously not related to the experiment.

The nerve cells of the anterior suprasylvian gyrus and of adjacent parts of the fronto-cruciate lobe of the left and the right hemisphere show numerous instances of swelling and vacuolation, on the left more than on the right. In addition, the involved cortex on the left shows also overstained, hyalinized, shrunken, pyknotic, but elongated, cells similar to those seen in Cat 17.	Confirmatory of the other stains; the Masson preparations did not reveal significant changes of the myelin sheaths.	The anterior suprasylvian gyrus, adjacent fronto-cruciate cortex and underlying white matter show, on the right and the left side of the brain, swelling and effilochement of axis cylinders; on the left in addition irregular shrinkage with bizarre deformity and overstaining, as well as fragmentation of axis cylinders. The swollen cells of the involved cortex show marginal displacement of neurofibrils, the pyknotic cells show hyalinized-homogenized appearance with abolition of the neurofibrillar pattern.

Subacute disseminated encephalomyelitis with intense microglial, histiocytic and plasmacellular infiltrative-proliferative foci, obviously not related to the experiment.

TABLE 1—

NO.	VOLTAGE	AMPERAGE (IN MILLI-AMPERES)	TIME OF SHOCK (IN SECONDS)	SURVIVAL TIME	LESION PRODUCED, GROSS	LESION PRODUCED, MICROSCOPIC
						Benzidine stain
14	520	1,800 1,200 1,000	3-4 2 5	1½ hours	Blanching of anterior suprasylvian gyrus of the left and the right hemisphere, on the right more marked than on the left.	Blanching of anterior suprasylvian gyrus and of adjacent parts of fronto-cruciate region of both hemispheres, on the right more marked than on the left.
15	500	2,000	3	9 days	No significant changes.	No significant changes.
16	520	Brain exposed by removal of calvarium, on both sides down to immediately above the point where the electrodes were applied at the temples; the amperage was not measured, presumably about 1,000-2,000.	10	4 mins.	*Intravitally,* while current passed, observation of the exposed cortex through a magnifying glass revealed that with the passage of the current the small exposed part of the anterior suprasylvian gyri and the intervening gyri cruciati turned pale. *Postmortem:* Blanching of anterior suprasylvian gyrus of the left and the right hemisphere.	Right hemisphere: The anterior suprasylvian gyrus shows marked vasoparalytic stasis with remarkably uniform dilatation of capillaries (up to 8 microns, the average being 6 microns) and of supracapillaries. However, there are no extravasations in spite of the grossly congested and hyperemic appearance of the gray matter of that gyrus. The underlying convolutional and the corresponding part of the central white matter show a relatively equal degree of universal static vasodilatation. Left hemisphere: The cortex of the anterior suprasylvian gyrus shows, in part, blanching (capillary anemia) but with perivenous extravasations about larger venules, in part, capillary and supracapillary dilatation (stasis) with perivascular hemorrhages. The underlying white matter shows, correspondingly, in part, capillary anemia with perivenous extravasations, in part, hyperemia.
17	520	2,000 1,000 500	5 3 2	½ hour	Extraordinary hyperemia of cortex of right anterior suprasylvian gyrus; pale appearance (blanching) of remainder of both frontal lobes, including the cruciate regions.	Vasoparalytic (capillary and supracapillary) stasis involving the right anterior suprasylvian gyrus and the medially subjacent convolutional and central white matter in the direction of main central core of the path of the current from temple to temple, and blanching of the remainder of both frontal lobes. A more complete description of the findings is as follows: The

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LESION PRODUCED, MICROSCOPIC			
Nissl stain	Hematoxylin-eosin stain	Masson's trichrome stain	Bodian's silver stain
Swelling and vacuolation of nerve cells of cortex of anterior suprasylvian gyrus and of adjacent parts of fronto-cruciate regions of the left and the right hemisphere. A number of encephalomyelitic lesions similar to those seen in Cats 11 and 13 were found; but in this case they were restricted to the thalamus alone.	Confirmatory of the findings with the other stains.	Swelling and decreased intensity of staining of myelin sheaths in anterior suprasylvian gyrus, adjacent parts of fronto-cruciate region and underlying white matter of the left and the right hemisphere.	Marked irregular swelling and effilochement of axis cylinders in anterior suprasylvian gyrus, in adjacent parts of fronto-cruciate region and in underlying white matter of the left and the right hemisphere.
A fairly small number of nerve cells in the anterior suprasylvian gyrus and in the adjacent lateral part of the gyrus cruciatus of the left and the right hemisphere show swelling with hyalinization of the cytoplasm; in addition there are a very few nerve cells which show pyknosis and dark homogenization of the cell body, however, with only slight increase in nuclear basichromatin.	No	significant	changes
Right hemisphere: A large number of nerve cells of the anterior suprasylvian gyrus show "elongation-pyknosis" of cell bodies and nuclei with dark staining homogenized appearance of the cell bodies. The number of cells so damaged is sufficient to make the whole cortical ribbon at the tip and the outer half of the valley of the anterior suprasylvian gyrus stand out at low magnification. Left hemisphere: The pathological findings are essentially identical to those on the right, and likewise limited to the same portion of the anterior suprasylvian gyrus. The only difference is that not all pyknotic nerve cells are elongated, but a number of them are universally shrunken. Furthermore, there is in addition to the pyknotic cells a number of swollen cells with light homogenization of the cytoplasm; and there are some intermediate forms with slightly swollen shape but with dark homogenization.	Confirmatory of the other stains.	Fluffy swelling and fragmentation of myelin sheaths in the white matter corresponding to the anterior suprasylvian gyrus of the left and the right hemispheres.	Right and left hemispheres: The axons in the convolutional white matter corresponding to the anterior suprasylvian gyrus show either swelling, or shrinkage, hyperargyrophilia, bizarre angular deflection deformity and fragmentation. The intracellular neurofibrillar pattern of the damaged nerve cells of the anterior suprasylvian gyrus is abolished by homogenization.
In the vasoparalytic static area: the nerve cells show shrinkage in the transverse diameter with appearance of elongation, similar to the morphologic change of "ischemic" cell disease; the cytoplasm appears dark and homogeneously hyalinized; the nuclei are pyknotic with irregularly elongated, occasionally triangular, frequently bizarrely irregular deformity. This change is reminiscent of the "ischemic" cell changes, except for the dark staining of the cytoplasm, and the bizarre irregular appearance of many of the nuclear deformities.	Confirmatory of the findings with the benzidine and Nissl stains.		In the vasoparalytic static area: irregular swelling, bizarre deformity with overstaining, and fragmentation of axis cylinders; hyalinized-homogenized appearance of nerve cells with abolition of neurofibrillar pattern. In the anemic blanched region: axones normal; the neurofibrillae of the swollen nerve cells show the usual effilochement and marginal displacement; the neurofibrillae of the others are normal.

TABLE 1—

NO.	VOLTAGE	AMPERAGE (IN MILLI-AMPERES)	TIME OF SHOCK (IN SECONDS)	SURVIVAL TIME	LESION PRODUCED, GROSS	LESION PRODUCED, MICROSCOPIC
						Benzidine stain
17 (Cont'd)						gray cortical ribbon of the right anterior suprasylvian gyrus, corresponding to an area measuring 5 mm in diameter on its outer lateral surface shows marked localized hyperemia, with dense filling, rounding, and distension of capillary loops which are enlarged to an average caliber of 5.3 microns, and with venous congestion and some perivenous extravasations. The convolutional and central white matter medially adjacent, i.e., the white matter in immediate prolongation of the path of the current shows hyperemia with numerous nodular perivascular extravasations down to a depth of 5–6 mm below the cortex. The gray matter of the remainder of both frontal lobes shows blanching, namely, constriction of arterioles and poor incomplete capillary filling with thinness of the capillary channels which have remained filled; the average diameter of these capillaries is 3.6 microns. The prolongation of the vasoparalytic (congestive-hemorrhagic) lesion into the white matter is essentially wedge-shaped, present only on the right side and attenuates itself medially to a point. The vascular bed of the remainder of the white matter of the frontal lobes is relatively better filled than that of the "blanched" gray matter of the non-vasoparalytic parts of the frontal lobes, although it shows definite evidence of anemia, particularly severe in the deep parts of the right hemisphere. The paraventricular capillaries and veins are very well filled, in fact, congested, and so are medioventral parts of the heads of both caudate nuclei. The remainder of the brain, including the parietal, temporal, and occipital lobes as well as the cornua ammonis, the thalami, hypothalami, geniculate bodies, midbrain and medulla oblongata show complete and normal vascular filling. The average capillary diameter of the parietal and occipital cortex is normal, namely, 4.2 microns.

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LESION PRODUCED, MICROSCOPIC			
Nissl stain	Hematoxylin-eosin stain	Masson's trichrome stain	Bodian's silver stain
In the anemic blanched region: a significant number of nerve cells show acute swelling of the cytoplasm.			

NO.	VOLTAGE	AMPERAGE (IN MILLI-AMPERES)	TIME OF SHOCK (IN SECONDS)	SURVIVAL TIME	LESION PRODUCED, GROSS	LESION PRODUCED, MICROSCOPIC
						Benzidine stain
18	500	2,000	7	9 days	Extraordinary red congestion of sharply outlined areas at the antero-lateral aspects of the left and the right hemispheres. The congested areas are on the left: the convexity of the anterior suprasylvian gyrus and of an adjacent small anterior part of the ecto-lateral gyrus comprising an area measuring 8 x 4 mm on the surface; the convexity of the lateral tip and of the adjacent lateral part of the posterior limb of the gyrus cruciatus over an area measuring 8 x 4½ mm on the surface. These two congested areas are separated by the valley of the sulcus which runs latero-posteriorly to the gyrus cruciatus; this noncongested separating ribbon appears on the surface to be 1 mm wide. The total congested area on the left antero-lateral aspect of the brain including the non-congested band between the two main congested areas measures 14 x 8 mm on the surface and is surrounded by an anemic rim 3 mm wide. The congested area on the right is limited to the lateral convexity of the anterior suprasylvian gyrus; it measures 5 x 5 mm and is surrounded by an anemic rim which measures 2 mm in width.	Vasoparalytic stasis with beac deformities of dilated vascular channels of all sizes and with hemorrhagic extravasations, involving those parts of the cortex within the path of the current which had shown congestion on gross inspection such as described in the preceding column and medially adjacent parts of the convolutional and central white matter. The remainder of the brain shows normal vascular filling.
19	500	2,000 1,000	8 2	½ hour	The anterior suprasylvian gyrus, the lateral part of the gyrus cruciatus, and the anterior part of the ecto- and entolateral gyri of the left hemisphere, and the anterior part of the entolateral gyrus of the right hemisphere show large roundish sharply outlined areas of extraordinary red congestion which are limited to the summits of these convolutions where they touch the skull and which resemble areas of mechanical traumatic contusion; they measure 4–6 mm in diameter. The skin and the subcutaneous tissue underneath the electrode on the right shows a deep burn hole; but the underlying bone of the skull is intact and uninjured.	Vasoparalytic (capillary and supracapillary) stasis in the path of the current, that is, involving on the left the anterior suprasylvian gyrus, the lateral part of the cruciate gyrus and the anterior part of the ecto- and entolateral gyri; on the right the anterior part of the entolateral gyrus. In these regions all vessels are extraordinarily dilated, the capillaries up to 8 microns in width; the majority of the dilated capillaries measures 6 microns in width. The vasodilatation in the gray matter of the involved cortex is regular and uniform. The cortex immediately adjacent to the area with vasoparalytic stasis shows a zone of blanching which is 1-3 mm wide. There are only very few perivenous extravasations, in many of the involved areas none. The underlying white matter shows vasodilatation with bead deformities of venules.

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LESION PRODUCED, MICROSCOPIC			
Nissl stain	Hematoxylin-eosin stain	Masson's trichrome stain	Bodian's silver stain
Not done: the entire specimen was cut in series and stained with benzidine.			
The involved cortical areas as enumerated in the preceding columns show pyknosis of nerve cells and of their nuclei similar to that in ischemic cell disease, except for darker staining of the homogenized cytoplasm. In addition, the involved cortex shows also a number of cell shadows in this case, with only the nucleolus preserved in its original dark shade of staining. The involved areas of the cortex stand out sharply against the adjacent essentially normal areas of the cortex. The intercellular tissue of the involved areas appears swollen, with corresponding increase of intercellular distances; therefore, the involved areas stand out light on inspection with the naked eye, similar to ischemic foci.	Confirmatory of the other stains.	The involved cortex of the left and the right hemispheres and the convolutional white matter adjacent to it in the path of the current shows swelling and disintegration of myelin sheaths, with low power appearance of demyelination due to lessened intensity of staining.	The axis cylinders in the involved cortex and in the underlying involved convolutional white matter show shrinkage and hyperargyrophilia with occasional bizarre deformities, and fragmentation. The intracellular picture of the involved nerve cells shows homogenization with abolition of the neurofibrillar pattern.

TABLE 1—

NO.	VOLTAGE	AMPERAGE (IN MILLI-AMPERES)	TIME OF SHOCK (IN SECONDS)	SURVIVAL TIME	LESION PRODUCED, GROSS	LESION PRODUCED, MICROSCOPIC — Benzidine stain
20	550	1,500	6 shocks were administered lasting $\frac{2}{5}$ of a second each, the second one minute after the first, subsequent ones $\frac{1}{2}$ minute apart. The time occupied by shocks totaled 1.4 seconds.	$\frac{1}{2}$ hour	No significant changes.	Throughout the fronto-cruciate regions numerous areas of congestion (with capillaries dilated up to 6 microns) alternate with areas of reduced vascular filling (slight blanching) and of normal filling.
21	550	1,400	52 shocks were administered lasting $\frac{1}{4}$ of a second each, distributed over a period of 29 mins.; the total time of all shocks together being 33.2 seconds, the intervals varying from $2\frac{1}{2}$ mins. to 15 seconds.	$\frac{1}{2}$ hour; the cat died one minute after the 52nd shock in a state of flaccid paralysis.	Generalized congestion.	The anterior suprasylvian gyrus and the adjacent anterior part of the ecto-lateral gyrus on the right, and the anterior part of the ecto-lateral gyrus on the left, as well as the underlying convolutional and central white matter, and, to a slightly lesser extent than the anterior suprasylvian and ecto-lateral cortex, the parts of the cortex of the gyrus cinguli of the left and the right hemisphere, which correspond to the transverse level of the anterior suprasylvian gyrus, show marked vasoparalytic dilatation of capillaries and supracapillaries, with bead deformities of capillaries and venules and pericapillary and perivenular extravasations. However, the vasoparalytic stasis and the allied phenomena do not involve the entire vascular bed within the involved areas as completely as in the other cases with vasoparalytic stasis. The remainder of the brain, including the parietal, occipital and temporal lobes of the hemispheres, the brain stem, and the medulla oblongata, shows diffuse congestion without the extreme vasoparalytic dilatation of the capillaries, however, with a significant number of perivenous extravasations and of bead deformities of venules, obviously secondary to general circulatory factors.
22	Under nembutal anesthesia, a red-hot soldering iron of a size identical with that of the electrodes in the electrical experiments (10 x 10 mm) was applied instead of electrical current to the identical place of the skull as in the electrical experiments, but on the left side only.		Time of application in seconds: 10	$\frac{1}{2}$ hour. (Died due to nembutal intoxication).	Slight blanching of left anterior suprasylvian gyrus, less intense than that observed in most of the electrical experiments which resulted in blanching.	Slight blanching of left anterior suprasylvian gyrus, less intense than that observed in most of the electrical experiments which resulted in blanching.

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LESION PRODUCED, MICROSCOPIC			
Nissl stain	Hematoxylin-eosin stain	Masson's trichrome stain	Bodian's silver stain
No	significant		changes
In the anterior suprasylvian gyrus, the adjacent part of the ecto-lateral gyrus and the upper lip of the gyrus cinguli on the right, and in the anterior part of the ecto-lateral gyrus and in the upper lip of the gyrus cinguli on the left, a significant number of nerve cells show marked pyknosis with cell deformities similar to those in ischemic cell disease but with dark staining of the cytoplasm as well as of the nuclei. The involvement is more severe on the right than on the left, but on both sides numerous normal nerve cells have remained preserved within the most severely involved areas.	Confirmatory of the benzidine and Nissl stains; no significant changes of the myelin sheaths could be made out.		The pyknotic nerve cells within the involved cortical regions (see Nissl stain) show homogenization with uniformly dark staining and with abolition of the neurofibrillar pattern. No significant changes of the axones.
Swelling and vacuolation of nerve cells of left anterior suprasylvian gyrus and of large adjacent ventrolateral aspects of left hemisphere. The right hemisphere appears perfectly normal.	Confirmatory of the other stains; no changes of myelin sheaths recognizable.		Confirmatory of the Nissl stain findings concerning the nerve cells; no pathological changes of axones.

TABLE 1

NO.	VOLTAGE	AMPERAGE (IN MILLI-AMPERES)	TIME OF SHOCK (IN SECONDS)	SURVIVAL TIME	LESION PRODUCED, GROSS	LESION PRODUCED, MICROSCOPIC: Benzidine stain
23	Under nembutal anesthesia, a red-hot soldering iron of a size identical with that of the electrodes in the electrical experiments (10 x 10 mm) was applied instead of electrical current to the identical place of the skull as in the electrical experiments, but on the left side only.		Time of application in seconds: 10	½ hour	No significant changes.	Slight suggestive blanching of anterior suprasylvian gyrus and of neighboring parts of adjacent convolutions of the left hemisphere.

"blanching" of the brain tissue within the path was limited to those lateral parts of the central core of the current path which were closest to the points of entrance and exit of the current into and from the brain, namely, to the cortex and the medially subjacent convolutional white matter of the anterior suprasylvian gyrus of both hemispheres. In those animals which had received shocks of 1800 milliamperes (Cats 12, 13, and 14) the resulting blanched area was wider and deeper, i.e., it included adjacent orbital cortical areas and lateral parts of the gyrus cruciatus, and protruded deeper, into the central white matter of both hemispheres; in other words, it included the marginal parts and more of the medial parts of the current path. Frequently the involvement was not quite symmetric, but slightly more severe or extensive on one or the other side of the brain. Blanching was also present in marginal parts of the current path when the shock current had been higher than 1800 milliamperes. Here the current density presumably fell within the limits of 5 to 18 milliamperes per square millimeter of the cross-section of the path. An example is the marginal part of the current path of an animal shocked with 2000 milliampere current (fig. 2).

The presence of blanching was best demonstrated with the benzidine stain, although it could usually be recognized with the unaided eye in the fresh unfixed and unstained specimen. In one case blanching of the exposed cortex was observed through a magnifying glass during and after the shock (Cat 16); in one other case it was demonstrated by intravenous injection of gentian violet (Cat 3). In one animal, after intravital intravenous injection of methylene blue the blanched areas were stained more deeply than the remainder of the brain (Cat 12). Freshly sectioned, the blanched regions usually appeared somewhat moist and edematous.

In those animals which were shocked with currents of 2000 milliamperes for 5 to 10 seconds with a maximum current density of 20 milliamperes per square

Concluded

LESION PRODUCED, MICROSCOPIC			
Nissl stain	Hematoxylin-eosin stain	Masson's trichrome stain	Bodian's silver stain
Predominantly pyknosis, but in many instances swelling and vacuolation of nerve cells of the cortical ribbon of the left anterior suprasylvian gyrus.	Confirmatory of the other stains.	Swelling and disintegration of myelin sheaths within the cortex and the immediately subjacent convolutional white matter of the left anterior suprasylvian, gyrus, with low power appearance of demyelination, due to lessened intensity of staining, limited to the cortical ribbon of the left anterior suprasylvian gyrus.	Homogenization with loss of the neurofibrillar pattern of the involved nerve cells of the left anterior suprasylvian gyrus; however, remarkably normal appearance of axis cylinders throughout the entire cortex and white matter of the brain, including the left anterior suprasylvian gyrus.

millimeter of the cross-section through the path of the current, vasoparalytic stasis (fig. 3) manifested itself within lateral parts of the core of the path of the current across the brain (figs. 4 and 5). "Vasoparalytic stasis" we call the picture of congestion and extreme dilatation of capillaries, arteries, and veins, with or without, but usually with, some perivenous hemorrhages. The animals with these findings (Cats 16, 17, 18, and 19) had been allowed to survive the shock for 4 minutes, one half hour and 9 days respectively (see table 1). The vasoparalytic stasis within the lateral parts of the core of the path of the current was never quite symmetric; usually it was more extensive and severe on one or the other side of the brain (Cats 16, 18, and 19; see fig. 4); in one case (Cat 17) the lateral part of the core of the path of the current showed vasoparalytic stasis only on the right side of the brain, while the corresponding part of the core of the current path on the left showed merely a particularly severe degree of blanching. The lateral part of the core of the path of the current through the brain which showed vasoparalytic stasis always included the whole width of the cortical ribbon at the convexity of the involved convolution or convolutions, the whole length of the medially subjacent convolutional white matter and a further medially adjacent part of the central white matter. The cortical area thus involved was either limited to the anterior suprasylvian gyrus, (such as in four of the eight hemispheres included in this group), or included in addition a lateral part of the cruciate gyrus and the anterior tip or tips of the ectolateral gyrus or of the ecto- and entolateral gyri; in one instance the involvement was on one side limited to the anterior tip of the entolateral gyrus alone. This occurred on the right side of Cat 19, where melting of, and sparking and burning about the electrode occurred, which probably caused the current to short-circuit through the entolateral gyrus instead of proceeding lateral to the usual point of exit at and about the anterior suprasylvian gyrus. The involvement of the convolutional subcortical white matter was always in medial direction from the over-

TABLE 2

The changes found within the path of the current through the brain, in the single shock experiments (Cats 1-19)

Summarized from table 1

CAT NO.	AMPERAGE OF TOTAL CURRENT, IN MILLIAMPERES	AMPERAGE PER MM^2 OF DIAMETER OF PATH OF CURRENT, IN MILLIAMPERES	TIME OF SHOCK, IN SECONDS	SURVIVAL TIME	INTRACEREBRAL VASCULAR BED	NERVE CELLS	AXIS CYLINDERS	MYELIN SHEATHS
1	60	0.6	5	½ hr.	No change	No change	No change	No change
2	200-300	2-3	10	½ hr.	No change	No change	No change	No change
3	300	3	3	4 mins.	Blanching	No change	No change	No change
4	350	3.5	5	72 hrs.	No change	No change	No change	No change
5	400	4	5	24 hrs.	No change	No change	No change	No change
6	450	4.5	5	7 days	No change	No change	No change	No change
7	500	5	5	½ hr.	Blanching	No change	No change	No change
8	500	5	5	1 hr.	Blanching (slight)	No change	No change	No change
9	550	5.5	5	5 mins.	Blanching	No change	No change	No change
10	800	8	5	½ hr.	Blanching	No change	No change	No change
11	1500	15	4	½ hr.	Blanching	No change	No change	No change
12	1800	18	2	Immediately	Blanching	Swelling and vacuolation; some pyknosis	Swelling and effilochement, and some hyperargyrophilia, bizarre deformities and fragmentation.	No change
13	1800	18	4	½ hr.	Blanching	No change	No change	No change
14	1800 1200 1000	18 12 10	3-4 2 5	1½ hrs.	Blanching	Swelling and vacuolation	Swelling and effilochement	Swelling and decreased intensity of staining
15	2000	20	3	9 days	No change	Swelling; few pyknosis	No change	No change
16	1000-2000	10-20	10	4 mins.	Vasoparalytic stasis	Pyknosis	Swelling, effilochement, hyperargyrophilia, bizarre deformities, fragmentation.	Fluffy swelling and fragmentation
17	2000 1000 500	20 10 5	5 3 2	½ hr.	Vasoparalytic stasis (surrounded by blanching)	Pyknosis (swelling in the blanched region)	Irregular swelling, hyperargyrophilia, bizarre deformities, fragmentation.	No change
18	2000	20	7	9 days	Vasoparalytic stasis			
19	2000 1500	20 15	8 2	½ hr.	Vasoparalytic stasis	Pyknosis; few cell shadows	Shrinkage, hyperargyrophilia, bizarre deformities, fragmentation.	Swelling, fragmentation and disintegration, with low power appearance of demyelination.

lying cortical area or areas, that is, clearly in the direction of the path of the current. The further medially adjacent part of the central white matter which was included in the region of vasoparalytic stasis varied somewhat in length. While in the majority of instances the vasoparalytic lateral part of the core of the current path never exceeded in total length that of the external third of the transverse diameter of either hemisphere, in one instance, on the right

FIG. 1. Cat 17: Shock with current of 2000 milliamperes for 5 seconds, falling off to 1000 milliamperes for an additional 3 seconds, then to 500 milliamperes for an additional 2 seconds, administered from temple to temple. Cortex and subcortical white matter of the brain from the parieto-occipital region which was outside the path of the current. Benzidine stain. × 53. Note perfectly normal vascular pattern and perfectly normal degree of filling of capillary and supracapillary channels.

hemisphere of Cat 16 the vasoparalytic central core of the current path extended medially almost to the convolutional white matter of the gyrus cinguli. However, the convolutional white matter of the gyrus cinguli and the gyrus cinguli itself did not show vasoparalytic stasis, neither in this animal nor in any other animals in which single shocks were applied. In other words, the median part of the core of the path of the current never showed vasoparalytic stasis in any of these animals. However, the entire central core of the path of the current

including its median part, namely, the anterior part of the gyrus cinguli of both hemispheres, did show vasoparalytic stasis in an animal which had received multiple shocks of a total of 33 seconds' duration, although of lesser amperage

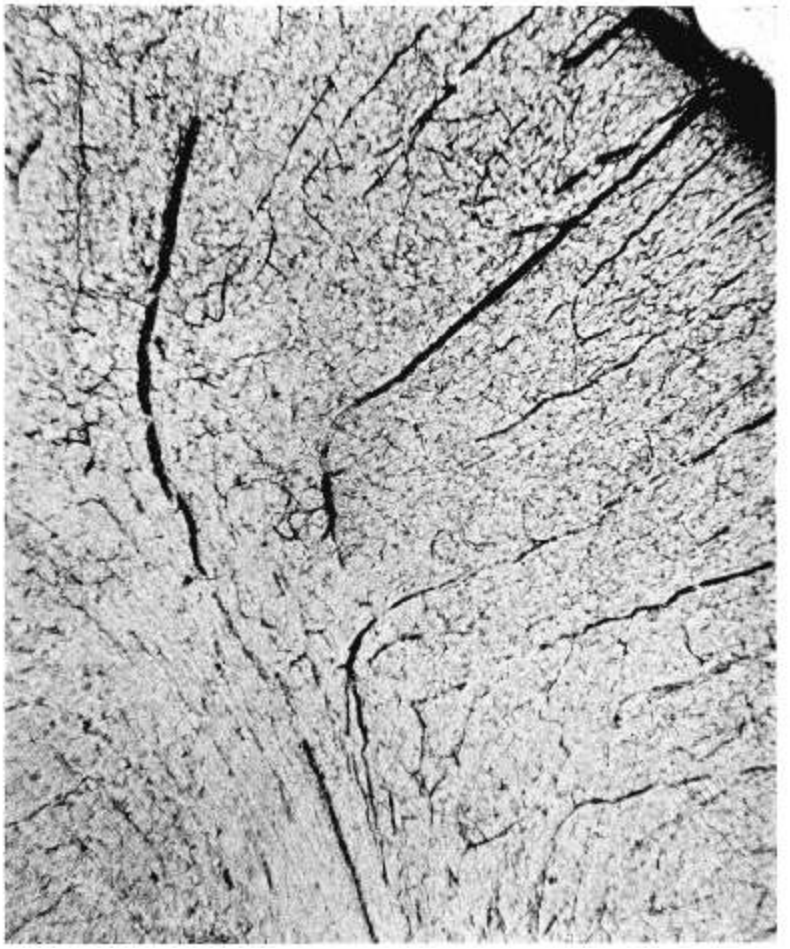

FIG. 2. Cat 17: Shock with current of 2000 milliamperes for 5 seconds, falling off to 1000 milliamperes for an additional 3 seconds, then to 500 milliamperes for an additional 2 seconds, administered from temple to temple. Cortex and subcortical white matter from the anterior tip of the right entolateral gyrus (seen at lower enlargement at the upper tip of figure 5) which was within the marginal part of the path of the current, where current density was estimated to have been about 10 milliamperes per square millimeter of the cross-section of the path through the brain tissue. Benzidine stain. × 53. Note characteristic "blanching" of the vascular bed: constriction of arterioles, poor incomplete filling of capillaries with abnormal thinness of those capillary channels which have remained filled, and moderate congestion of some of the larger venules.

(Cat 21). The relatively greater depth, as compared to the other single shock experiments, of the vasoparalytic part of the core of the current path, although only on the right side in Cat 16, may be due to the fact that the current was in

part relatively more concentrated than in the other animals because of the removal of the calvarium, the dura, and the surrounding layer of spinal fluid in this animal. Correspondingly, a surrounding zone of blanching was likewise absent in the more severely involved right hemisphere of this animal.

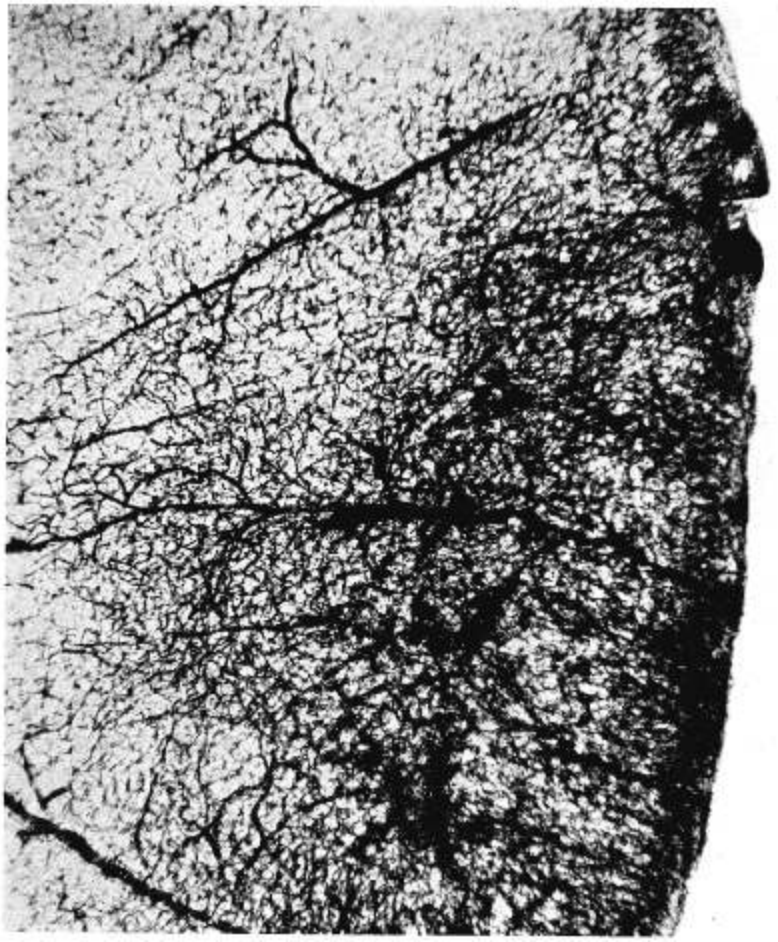

FIG. 3. Cat 17: Shock with current of 2000 milliamperes for 5 seconds, falling off to 1000 milliamperes for an additional 3 seconds, then to 500 milliamperes for an additional 2 seconds, administered from temple to temple. Cortex and subcortical white matter of the right anterior suprasylvian gyrus, which was within the lateral part of the central core of the path of the current, where current density was 20 milliamperes per square millimeter of the diameter of the path through the brain tissue. Benzidine stain. × 53. Note vasoparalytic stasis, namely, congestion and extreme dilatation of capillaries, arteries and veins, with some perivenous hemorrhages.

The marginal parts of the current path through the fronto-cruciate lobes of both hemispheres showed blanching in Cats 17 and 19. These parts were extensive in Cat 17 (fig. 5), fairly narrow in Cat 19 (see table 1). There was an anemic rim about the vasoparalytic areas in Cat 18, but this animal was

allowed to survive for 9 days following the shock, and this anemic rim could, therefore, not necessarily be regarded as a residue of an early blanching in the

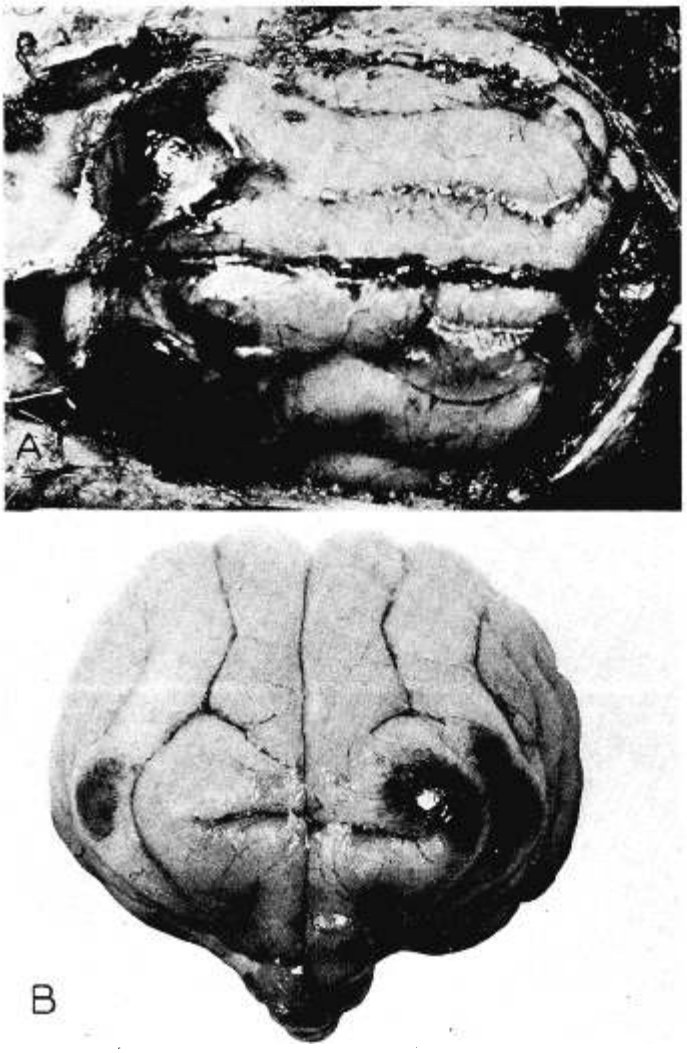

FIG. 4. Cat 18: Shock with current of 2000 milliamperes for 7 seconds from temple to temple. A. The brain in situ in the skull (forehead to the left, occiput to the right) viewed from above, after removal of the calvarium. Note congestive-hemorrhagic appearance of meninges and parts of cortex across fronto-cruciate regions of both hemispheres. B. The brain after removal from skull and dural sac. Anterior view. Note congestive-hemorrhagic discoloration of cortex at points of entrance and exit of core of current. (For complete description see table 1.)

marginal parts of the path but may have more likely, at this stage, been due to circulatory difficulties in the vicinity of the congestive hemorrhagic lesions at the sites of basoparalytic stasis.

The median part of the central core of the path of the current showed intensive blanching in Cat 17 (fig. 5), while it showed approximately normal vascular filling in Cat 19. In Cat 18 blanching was likewise absent within the median part of the central core of the path. In contrast to the other three cats in this group which were killed 4 minutes (Cat 16) and one half hour (Cats 17 and 19)

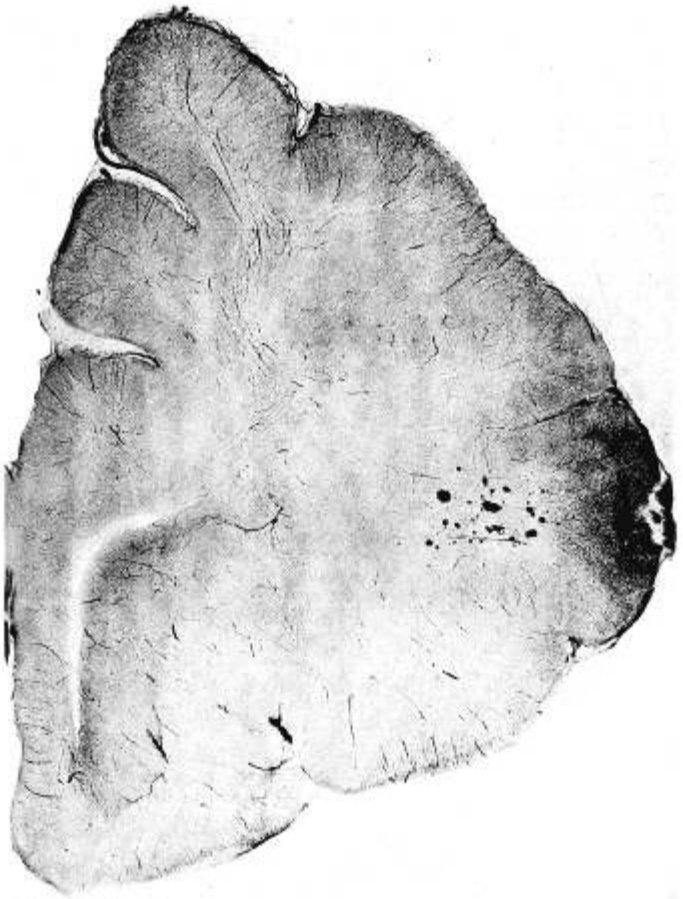

FIG. 5. Cat 17: Shock with current of 2000 milliamperes for 5 seconds, falling off to 1000 milliamperes for an additional 3 seconds, then to 500 milliamperes for an additional 2 seconds, administered from temple to temple. Section through right fronto-cruciate lobe. Benzidine stain. × 7. Note congestive-hemorrhagic involvement (vasoparalytic stasis) of the right anterior suprasylvian gyrus (seen at the extreme right of the section) and of the medially subjacent parts of the convolutional and the central white matter; blanching of the remainder of the lobe. (For complete description see table 1.)

after the shock respectively, this animal was killed 9 days after the shock; and blanching, which may have been present originally within the marginal and the median parts of the current path in this animal, may have had time to recover during the 9-day period for which this animal was allowed to survive.

Even in this group of animals, which received shocks of 2000 milliamperes

flowing for 5 to 10 seconds, the parts of the brain outside the path of the current, namely, the parietal lobes, the occipital lobes, the bulk of the temporal lobes of the hemispheres and the brain stem from the thalami backwards, showed no vascular reactions of any kind. Here the vascular pattern was perfectly normal, with a normal degree of filling of capillary and supracapillary vascular channels (figs. 6 and 1).

One animal (Cat 15) whose shock of 2000 milliamperes lasted for only 3 seconds, showed when killed on the ninth day following the shock, no changes of

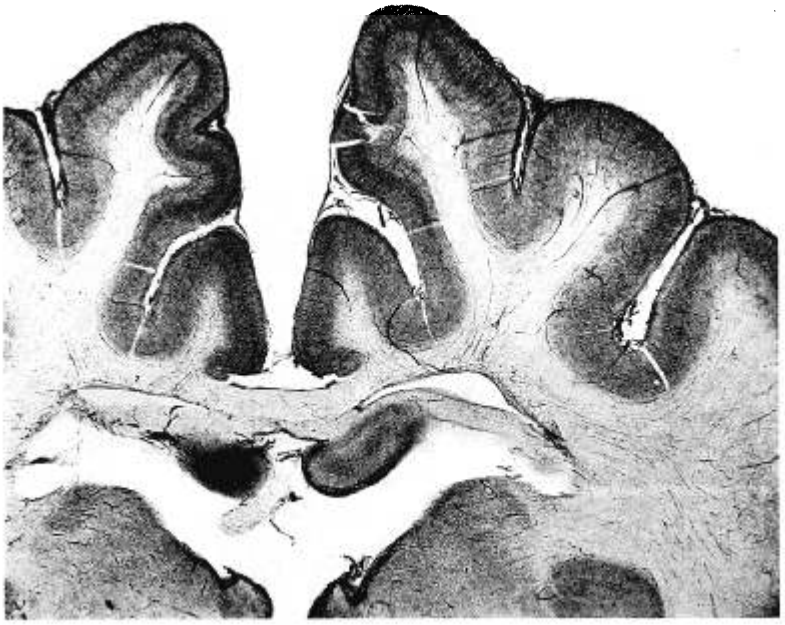

FIG. 6. Cat 17: Shock with current of 2000 milliamperes for 5 seconds, falling off to 1000 milliamperes for an additional 3 seconds, then to 500 milliamperes for an additional 2 seconds, administered from temple to temple. Section through parieto-occipital region. Benzidine stain. × 7. Note perfectly normal vascular filling of parieto-occipital lobes which were outside the path of the current.

the vascular pattern. Probably there had been blanching only, which had recovered within the interval.

The threshold for changes of the cerebral parenchyma (nerve cells, axis cylinders, and myelin sheaths) was still higher than that for morphologically recognizable vascular reactions. No changes of nerve cells, axis cylinders and myelin sheaths were present in the brains of those animals which had been given single shocks varying from 60 to 1500 milliamperes of three to ten seconds' duration and which had survived for periods varying from four minutes to seven days. Neither were any significant changes of the cerebral parenchyma observed in an animal which received six shocks of 1500 milliamperes, each of which lasted two-fifths of a second (Cat 20).

With single shocks of higher amperage significant changes of the cerebral parenchyma could be produced. Like the vascular reactions these were strictly limited to the direct path of the current. Changes of nerve cells of predominantly reversible type (swelling and vacuolation, with only a few instances of pyknosis) appeared in those animals which had received single shocks of 1800 milliamperes for two to four seconds (see table 2: Cats 12, 13, and 14). After single shocks with currents of 2000 milliamperes for 5 seconds and more, irreversible types of nerve-cell changes, predominantly severe degrees of pyknosis with bizarre deformities and homogenization, were found in those cortical areas which showed vasoparalytic stasis and where current density must have been 20 milliamperes per square millimeter of diameter of the current path. In the marginal parts of the current path, where density was less and where the benzidine preparations had shown blanching only, the nerve cells showed milder and reversible changes, predominantly swelling (see table 1, Cat 17).

The threshold for changes of the axis cylinders was likewise found at the 1800 milliampere level (18 milliamperes per square millimeter of cross-section of path of current). The changes found in these animals were also predominantly reversible, consisting of swelling and unravelling of the fibrillae with a few instances of hyperargyrophilia, bizarre deformity and fragmentation present in only one of the animals on the side of more severe involvement (Cat 12, table 1). The animals which had been shocked with 2000 milliamperes showed predominantly irreversible changes of the axis cylinders in those parts of the path of the current where current density was 20 milliamperes per square millimeter and where vasoparalytic stasis had been noted in benzidine stained preparations. These irreversible changes consisted mainly in hyperargyrophilia, bizarre deformities in addition to irregular swelling or shrinkage, and fragmentation.

The changes of the myelin sheaths followed similar rules. However, they did not occur with equal constancy, probably because they were secondary to the axonal changes. Only one of the animals shocked with 1800 milliamperes showed swelling and decreased intensity of staining of myelin sheaths within the core of the path of the current; two of the animals shocked with current of 2000 milliamperes showed in addition to fluffy swelling, fragmentation and disintegration of myelin sheaths within the core of the path.

In one animal which received 52 shocks of 1400 milliamperes for a total time of 33 seconds, severe pyknosis of nerve cells was produced in the anterior suprasylvian gyrus, the adjacent anterior part of the ectolateral gyrus, and the upper lip of the gyrus cinguli on the right, and in the anterior part of the ecto-lateral gyrus and in the upper lip of the gyrus cinguli on the left. Thus this change was strictly limited to the central core of the path of the current. However, there were no changes of axis cylinders or myelin sheaths.

DISCUSSION

It is interesting to note that the thresholds of significant reversible and irreversible tissue damage which we found for the brains of these animals were of a

similar order of magnitude as those which had been found for the sciatic nerve in studies by Alexander and Weeks (1). Both experimental studies were carried out in the cat. For the sciatic nerve Alexander and Weeks had found that the threshold for reversible, morphologically demonstrable damage was 10 milliamperes per square millimeter of the diameter of the nerve through which the current flowed; for irreversible damage it was 14 milliamperes per square millimeter of nerve diameter. In the present experiments we found the threshold for reversible damage of brain tissue to be somewhere between 15 and 18 milliamperes per square millimeter of brain tissue within the path of the current, and the threshold for irreversible damage at 20 milliamperes per square millimeter of brain tissue within the path. The slight difference between these thresholds for sciatic nerve and brain is not necessarily significant: in the sciatic nerve experiments the density within the path of the current could be exactly determined by measurement of the diameter of the nerve, all marginal side paths having been eliminated by packing the nerve into insulating sheets of dental rubber film; in the experiments on the brain, current was applied to the skull and the exact width of the path of the current could be determined with less accuracy.

It emerges from these findings that changes were produced only within the path of the current, but that these changes were not always present throughout the entire path. When present throughout the entire path such as occurred in higher ranges of amperage, they did not occur in an equal degree throughout the entire path. This is due both to electric and neuro-anatomical factors.

Certain differences in degree of intensity of blanching, as well as in degree of intensity of vasoparalytic stasis between gray and white matter are obviously due to differences in the anatomy of the cerebral vascular bed in the gray and white matter respectively. The vascular network of the white matter is normally less dense than that of the gray, its ramifications are farther removed from the larger, more contractile, arteriolar channels at and near the surface of the brain. Hence the picture of blanching is always slightly less striking in the white matter than in the corresponding gray. The same is true for the picture of congestion and perivascular extravasation resulting from vasoparalytic stasis due to localized circulatory disturbance. In a study of this particular problem Campbell, Alexander, and Putnam (4) have concluded as follows: "When the circulatory disturbance is localized, as in pial venous thromboses and in some red infarcts resulting from arterial occlusion, such hemorrhages are most frequent in the gray matter." "On the other hand, when the circulatory disturbance is generalized throughout the brain, the hemorrhages are most frequent in the white matter." "This difference in the incidence of diapedesis in the gray and in the white matter according to whether the vascular disturbance is localized or general may be explained tentatively by the assumption (a) that, *ceteris paribus*, diapedesis occurs more easily in capillaries of the white than in those of the gray matter and (b) that in an area of stasis resulting from localized vascular occlusion collateral circulation will occur into the gray matter of the affected area to a greater extent than into the white matter. The first hypothesis explains

the predominance of diapedesis in the white matter in general disturbances in which there is no question of collateral inflow from a neighboring unaffected vascular bed. The second hypothesis, which is supported anatomically by the much richer capillary circulation of the gray matter, explains the predominance of hemorrhages in the gray matter in local infarcts; stasis in the white matter is too complete for diapedesis to occur, while the more active, though still sluggish, flow ("*prestasis*" of Ricker) in the gray matter allows of diapedesis, and, of course, of a relatively greater amount of congestion."

The lesser severity of involvement in the marginal parts of the path of the current through the brain is explained by electric factors. Weeks and Alexander (3) have shown that electric current passes through the animal body as though it were passing through a structureless gel, always choosing the shortest path from contact to contact without deflection by anatomical landmarks. However, when electric current passes through a conductor which exceeds in width that of the shortest current path from one electrode to the other on all sides, such as in our experiments, the outer boundaries of the current path will not be straight lines, but elliptic or sometimes paraboloid curves (see figures 5 and 6 in Weeks and Alexander (3)). The density of the current diminishes along the margins of the curved outer boundaries of the path, while the maximum density of the current travels only through the core of the path along the shortest possible line from one electrode to the other. This diminution in density is greatest along the crest of the curve of the margin of the path. This explains the lesser intensity of the vascular as well as of the parenchymal reaction along the marginal parts of the path (see fig. 5). However, it does not explain the lesser intensity of reaction within the median parts of the core of the path which we found in the brains of our animals, unless we assume that there may also be a slight spread and diminution in density of the current within those median parts of the central core of the path which correspond to the crest of the elliptic curve of marginal spread and corresponding marginal diminution in density of current. However, this appears unlikely on the basis of previous experimental work (Weeks and Alexander (3)). It is more likely that the lesser intensity of change in the median part of the central core of the path is also explained by anatomical factors. In the lateral parts of the core of the path the current travels along the entire length of the larger supplying arterioles as they come in from the meningeal surface and distribute themselves within the medially adjacent gray and white matter; and the wedge-shaped outlines of the extensions of the areas of vasoparalytic stasis into the medially subjacent white matter are indeed more representative of the manner of distribution of these vessels than of the actual outlines of the core of the path of the current (fig. 5). In the median parts of the core of the path, the current only crosses the finer ramifications of arterioles, the main contractile stems of which arise outside of the path of the current.

The possible complicating factor of electric energy converted into heat had to be investigated in connection with these findings. In the one case in which melting of one of the electrodes occurred (Cat 19), the vasoparalytic

lesion was found not on that side but on the other. This finding was not suggestive of the possibility that Joule's heat played an important role in the production of these lesions. Furthermore, in two control animals heat only was used (Cats 22 and 23) and areas of vasoparalytic stasis were absent. There was blanching at the cortical surface, but less intense than in those electric experiments which had resulted in blanching; and although one animal showed pyknosis of cells within the underlying anterior suprasylvian gyrus, the other animal showed only mild changes consisting in swelling and vacuolation of nerve cells spread over a larger area of the antero-ventro-lateral aspects of the underlying hemisphere.

Applied to the theory and practice of electro-shock treatment, the most significant finding is that morphological changes recognizable with our present day histologic methods within the brain tissue of our experimental animals at the times at which they were sacrificed, could be produced only with shocks which in amperage, duration of flow and density of current by far exceeded those used in electro-shock treatment in man. In electro-shock treatment in man, currents varying from 300 to 900 milliamperes flowing for periods varying from 1/10 to 3/10 of a second through electrodes measuring 2000 to 3000 mm^2 are usually employed. The sole exception was a fleeting period of vasoconstriction and blanching of the capillary bed within the path of the current, which occurred within the range of amperage employed in treatment in man. This finding does not agree with some of the reports on the neuropathologic sequelae of electro-shock treatment. Before we discuss the findings of the authors who obtained results which on the surface appear to be so fundamentally different from ours, we should like to discuss the theoretical possibilities for production of any types of cerebral lesions under conditions of electro-shock.

There are three factors which are conceivably the source of pathological changes in the brain:

(1) *Direct action of the electric current upon the brain tissue through which it passes.* The changes attributed to the direct action of the current should be limited to the path of the current, i.e., to the area circumscribed by the slightly outwardly rounded, elliptic or paraboloid lines from the outer circumference of one electrode to that of the other. Only pathological changes restricted to the region within these boundary lines of the direct path of the current, can be accepted as caused directly by the current. The changes described above fulfilled this condition. Other examples of direct electric influence upon neural tissue are found in some of the electric accidents in which currents passed through parts of the brain or spinal cord (Hassin (5), Alexander (6)), the severity of the damage being correlated to amperage and the duration of flow. Other examples are the spinal cord changes produced experimentally by Langworthy (7), and some of the changes found in the brain after legal electrocution (Spitzka and Radasch (8), Langworthy (9), Hassin (10)). Under the usual conditions of legal electrocution the complicating factor of Joule's heat is considerable, and the picture may sometimes be furthermore obscured by the results of the circulatory effects of passage of current through the medullary centers, because

the hindbrain is included in the path of the current. In legal electrocution, of course, only the earliest changes are seen.

(2) *Excessive stimulation of the vago-vasomotor centers of the medulla oblongata by the passing electric current, followed by disturbance of the activity of these centers causing generalized cardio-circulatory disturbance, which then interferes with the integrity of the brain tissue.* Prevost and Battelli (11) discovered that currents of high intensity produce bulbar respiratory paralysis, while currents of low intensity produce disturbances of heart action. This disturbance of heart action occurs irrespective of whether the low intensity current (which is the general type of current used in electro-shock) passes through the medulla oblongata and the origins of the vagus nerve, or through its endings in the heart (Ferris, King, Spence and Williams (12), Urquhart (13), Hooker (14), Langworthy and Kouwenhoven (15), Jellinek (16), MacMahon (17)).

(3) *Generalized disturbances in an impaired cardio-circulatory-respiratory system under the strain of the excessive demands upon its efficiency imposed by a convulsion.* Every convulsion causes an upheaval of circulation and respiration, and electroshock treatment certainly creates a great deal of demand on the efficiency of the circulation and internal respiration throughout the body; but so does a 500 yard dash too, in an equally unspecific way. In patients with diseased or otherwise imperfect cardio-circulatory mechanisms the efficiency of vascular supply and oxygenation of the brain tissue may break down and become inadequate under either strain.

In our experiments we have eliminated the second factor by applying the electrodes far enough forward to leave the hindbrain outside of the path of the current. The third factor was eliminated by using healthy animals. Thus we were dealing with the first factor only as the source of changes in the cerebral tissue.

We have limited our material to single shock experiments with longer duration of flow of current than used therapeutically in man. The two animals which were given multiple shocks, received these within one half hour. We limited our study to the question of early changes; and the longest period for which we allowed any of our animals to survive was 9 days.

Moore and Winkelman (18) and Barrera, Lewis, Pacella and Kalinowsky (19) have carried out experiments with repeated shocks comparable to the therapeutic use in man, and they, too, excluded the second and third factors in their experiments. Moore and Winkelman (18), like ourselves, applied the electrodes to the frontal lobes, and, with shocks repeated at the usual intervals, failed to produce significant morpho-histological changes. Barrera, Lewis, Pacella, and Kalinowsky (19) have administered to macacus rhesus monkeys series of up to 30 electro-shocks, distributed over periods of up to ten weeks. Administration, shock doses, and duration of flow of current in each instance were patterned after the methods used in treatment in man. When the animals were killed, usually 24 hours after the last shock of the series, their brains failed to show any significant histopathological changes or significant differences from the brains of not-shocked control animals. Like our own study, this study does

not settle the question of late changes; but early changes, and the operation of factors two and three, were excluded.

As the first in the series of authors who published positive early findings, Alpers and Hughes (20) found generalized disseminated, subarachnoid and perivascular intracerebral hemorrhages in cats which received 10 to 23 shocks with currents of about 150 to 200 milliamperes, flowing through disc electrodes measuring 5 millimeter in diameter. No data as to exact location of electrodes or as to time of flow of current are given. Description of the changes is suggestive of the fact that the hindbrain was within the path of the current; Alpers and Hughes themselves described their results as similar to those of Urquhart (13) and MacMahon (17), who produced their changes by shocks through the medullary centers and the heart respectively. The fact that the pathologic changes which they describe are not due to the direct action of the current upon the brain tissue but due to indirect action by means of vago-vasomotor mechanisms which do not come into play in electro-shock treatment in man at all, is furthermore supported by Alpers' and Hughes' statement that neither the number nor the duration of the treatments appeared to influence the degree of damage to the brain. Primary electric damage to brain tissue is always perfectly correlated to the duration and number of shocks; vagus disturbance, on the other hand, is not significantly influenced by the duration and number of shocks, once the amperage and the duration fall into the general rather wide category of shocks which will elicit the vagus disturbance.

Heilbrunn and Weil (21) described early cerebral lesions produced in rabbits and rats by electro-shock doses comparable to those used in treatment in man. They applied the electrodes to both temporo-occipital regions and were quite aware that they elicited profound vago-vasomotor disturbances in their animals. However they seem not to have appreciated the fact that similar disturbances do not occur in the customary electro-shock treatment in man (Löwenbach (22)). Their findings are quite similar to those of one of us (Alexander (6)) in human beings killed accidentally by electrocution through the heart region. After 1 to 13 shocks through electrodes measuring 20 x 20 mm in diameter with currents varying from 65 to 300 milliamperes, Heilbrunn and Weil (21) found no histological changes which could be ascribed to the direct action of the current upon the brain tissue, but only generalized, disseminated, perivascular cerebral changes, predominantly petechiae, which were not present in all animals and which they attributed to the cardio-circulatory upheaval incidental to the convulsion. The changes were similar to those found in the lungs and the kidneys.

Neubuerger, Whitehead, Rutledge and Ebaugh (23) produced essentially similar early changes in the brains of dogs which had been shocked with currents of 200 milliamperes, flowing for 0.15 seconds, through the temporo-parietal region. They found "widely scattered" changes of the nerve cells, congestion, edema, petechiae and focal areas of ischemic necrosis throughout the brains of their animals, as well as congestion of other organs. "The pathologic changes in the cortex were perhaps more noticeable in the vicinity of the pathway of the electrical current (temporoparietal cortex)." However, this appears to

be an afterthought based on theoretical considerations rather than a conclusion based on their own findings such as described in the body of their paper. The fact that they, too, dealt with vago-vasomotor disturbance rather than with direct action of the current on the brain or the local cerebral vessels, but unlike Heilbrunn and Weil unknowingly, is not only suggested by the position of their electrodes, but also by the facts that some of their animals died during the experiment and that they noted significant variations in "individual susceptibility."

The types of histopathologic changes described in the brains of human beings who had been treated with electro-shock appear to be in their entirety due to factor three. Alpers and Hughes (24) described two such cases. The first was a woman aged 45 who died after 62 electro-shock treatments. Her brain showed numerous punctate hemorrhages in the cerebral cortex, medulla, cerebellum and basal ganglia, as well as areas of perivascular edema and necrosis. The second case concerned a woman aged 79 who died 5 months after the administration of the last of 6 electro-shock treatments. Autopsy showed generalized arteriosclerosis, arterio-sclerotic heart disease and mesenteric thrombosis. The brain showed cortical atrophy in both frontal areas, thickening of the vessels at the base of the brain, scattered areas of old perivascular hemorrhage, gliosis, fibrosis, rarefaction chiefly in the white matter, and fresh hemorrhages in the brain stem; the latter, in this case, were regarded as agonal. Ebaugh, Barnacle, and Neubuerger (25) likewise described two cases. The first of these was a man aged 57; he received a series of 13 electro-shock treatments, (12 with generalized convulsion, 1 with a "minor" reaction). After the last generalized convulsion he complained of pain suggesting angina pectoris and died within $1\frac{1}{2}$ hours. Autopsy revealed coronary sclerosis and thrombosis; the brain showed small disseminated ischemic cortical lesions and occasional accumulations of perivascular pigment in the white matter. The second case was a man aged 57 who had received three electro-shock treatments at weekly intervals. After the first two which were "minor" reactions, the patient had experienced respiratory difficulties after the seizure. It was thought that these reactions were due to curare given before the treatment. After the third treatment which elicited his first "major" reaction, he died. The brain showed ischemic lesions scattered throughout the cortex, including Sommer's sector of the cornu ammonis, which were most marked throughout the fronto-parietal regions. There were additional similar lesions in the striatum, the thalamus, and in the dorsal nucleus of the vagus on the left.

All these changes appear to us to be representative of the type which can be commonly found in the brains of individuals who have been exposed to periodic or even single incidents of circulatory-respiratory embarrassment, irrespective of whether this embarrassment was due to shock therapy, coronary heart disease, an episode of asphyxiation under anesthesia, a period of respiratory embarrassment incidental to the ingestion of other toxic substances, or an episode of collapse following physical overexertion in an individual with cardio-vascular disease. We are certain that the 79-year-old woman, or the man with coronary heart disease, or the man with the history of respiratory embarrassment incidental to

curarization, would have shown similar changes in their brains even if they had not been exposed to the additional rigors of convulsive electro-shock. It is also possible that the circulatory system of a 45-year-old psychotic woman might not stand up under the repeated exertions of 62 electro-shocks. In other words, the findings in the brains of these patients are representative of what can sometimes happen in electro-shock therapy; they are probably representative of the findings in the 2 per cent of the cases in Bellet, Kershbaum, and Furst's (26) series; they teach us what precautions to take, both in the selection of patients and in the administration of the shocks. But they are not representative of the organic changes which must take place in the brains of the vast majority of the patients whom we treat with electro-shock. That early organic changes, physiological and physico-chemical, must take place in the brain during electro-shock treatment, of that there can be no doubt. The electroencephalographic changes are clear-cut evidence, and the resulting clinical phenomena, the changes and improvements in the clinical picture of treated patients cannot be explained on the basis of the associated psychological factors alone. What these early organic changes are, we do not know. We do not know at all whether or not there are late changes like those which follow certain electric accidents (see literature in Alexander (6)) and X-ray irradiation (Lyman, Kupalov, and Scholz (27)); neither treated human beings, nor experimental animals have yet been followed up for a sufficient length of time in order to decide that point. As to the early changes, we know that there is a strong excitation of all neurons within the path of the current, and that this excitation transmits itself to other parts of the brain. What we have learned from the present experiments is that there may be a brief period of arteriolar vasoconstriction and blanching of the capillary bed, limited to the direct path of the current through the brain. But no changes of the cerebral parenchyma, including nerve cells, axis cylinders and myelin sheaths establish themselves which are of the order demonstrable with present-day histologic methods and within the limits of time for which our animals were allowed to survive. With currents far higher and of far longer duration than those used in treatment, significant early changes of the neural parenchyma can be produced which are strictly limited to the path of the current. No such changes were found with shocks of a range of amperage within and even quite considerably and significantly above the range of those used in electro-shock treatment in man. Still we know that there must be such changes, although their physiological and physico-chemical nature is yet unknown. The first step in the direction of their exploration has been made by Spiegel, Spiegel-Adolf and Henny (28). The preliminary account of their studies described changes of conductance and of permeability. In our experiments, the occasional observation of edematous transsudation and the observation of increased methylene blue staining within the path of the current were suggestive leads in the direction of an early change in permeability.

SUMMARY

1. Electric shocks varying from 60 to 2000 milliamperes flowing for times varying from two-fifths of one second to ten seconds were administered to cats,

through electrodes measuring 100 mm², applied to the temples. The site of the electrodes upon the skull corresponded to the anterior suprasylvian gyrus and small adjacent parts of the remainder of the fronto-cruciate lobe of the left and the right hemisphere.

2. With single shock doses of 500 to 1800 milliamperes, arteriolar vasoconstriction with blanching of the capillary bed, still noticeable at times varying from 5 minutes to 1½ hours after the shock, could be produced within the path of the current through the brain, where the maximum current density was 5 to 18 milliamperes per square millimeter of the diameter of the path. A shock dose of 300 milliamperes produced only a brief period of arteriolar vasoconstriction and blanching, noticeable within the path of the current four minutes, but not one-half hour after the shock. No vascular and perivascular changes following shocks with similar currents (350–450 milliamperes) were seen one, three and seven days after the shock.

3. With shock doses of 2000 milliamperes, flowing for 5 seconds and more, vasoparalytic stasis could be produced within the core of the path of the current through the brain, where the maximum current density was at least 20 milliamperes per square millimeter of the diameter of the path. Marginal parts of the path of the current, where current density was less, showed arteriolar vasoconstriction and blanching of the capillary bed.

4. Early pathological changes of the neural parenchyma could be produced only with currents of 1800 milliamperes and above, and only within the path of the current. With currents of 1800 milliamperes, flowing for 2 to 5 seconds, where current density was 18 milliamperes per square millimeter of the diameter of the path, they were of an essentially reversible type. With currents of 2000 milliamperes flowing for 5 to 10 seconds, where current density was 20 milliamperes per square millimeter of the diameter of the path within the core of the path of the current, 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 electro-shock treatment in man, in which currents of 300–900 milliamperes flowing for periods varying from $\frac{1}{10}$ to $\frac{3}{10}$ of a second through electrodes measuring 2000–3000 mm² are usually employed.

5. With single shock doses within the range of amperage used in electro-shock treatment in man, no pathological changes of the neural parenchyma could be produced which were recognizable with present-day histological methods at times varying from 4 minutes to 7 days after the shock. It is concluded that early organic physiological and physico-chemical changes of the neural parenchyma must nevertheless exist, but that they are of an order not yet demonstrable morphologically. The nature of these early physiological and physico-chemical changes awaits future investigation. The question of late changes is likewise uninvestigated and open to future study.

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