ECT – brain damage – animals

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cells. In the marrow cells studied the radiosensitivity of a particular cell type appears to depend on the rate of cell division and the life span. The more frequent the cell division and the shorter the natural life span, the more sensitive is the cell type, and *vice versa*.

If the theory of inhibition of cell division is correct, certain facts must follow. There should be an upper limit of dose radiation for each cell type, beyond which increase in the amount of radiation has no further effect on the slope of the curve representing the time rate of decrease of the population, assuming of course that the doses are considerably below the excessively large doses necessary to produce direct killing of cells. This limit would correspond to the complete inhibition of cell division in all cells of that type. For example, if the life span of the lymphocyte is assumed to be 24 hours and the action of ionizing radiation is only to inhibit cell division and not to kill lymphocytes, the slope of the curve of decrease in lymphocytes could never be made more precipitous than a line drawn from the 100 per cent line at zero time to the zero line at 24 hours. This point is now under investigation. Cells incapable of division show no effect from irradiation with exposures to this order of magnitude, except those secondary to the effects on other cells which could have divided and matured to this stage. This has already been demonstrated to be true for the neutrophil lobocytes which have a natural life span in marrow cultures of 48 to 90 hours[6] and have never been observed to divide but show no significant difference from the counts in the control vials until after 72 to 96 hours.[9] Quantitative effects of irradiation could not be accurately evaluated unless the proper time were chosen. This time must be determined from the beginning of the period when conditions suitable for cell division are instituted and not from the time of irradiation, since no effects should be observed until the cells begin to divide. That this is true is shown by comparison of the curves for 400 r of radiation when incubation was begun immediately after irradiation[9] with those in Figures 2 and 3 when incubation was delayed.

Summary. Controlled quantitative studies of biologic effects of Roentgen rays produced with 1000 kv. apparatus, of Roentgen rays produced with 200 kv. apparatus, of beta rays (average 600 kv.) emitted by radioactive phosphorus, and of neutron rays were made by the technique of human marrow culture. An exposure to 200 r of 200 kv. Roentgen rays had similar effects to an exposure to 200 r of million volt Roentgen rays on lymphocytes. An exposure to 50 n of neutron rays had similar effects to an exposure to 200 r of Roentgen rays given at 200 kv. or 1 million volts. An exposure to 15 n of neutron rays had similar effects on both lymphocytes and progranulocytes to an exposure to 60 r and 400 r respectively of Roentgen rays given at 220 kv. The exposure ratio, $\frac{r}{n}$, for lymphocytes and progranulocytes in marrow cultures is approximately 4. One microcurie average of radioactive phosphorus distributed through 1 cc. of human marrow culture acting for a period of 24 hours has an effect similar to 35 r of high voltage Roentgen rays on lymphocytes and progranulocytes. These effects and the straight line character of the drop may all be explained if the major action of the ionizing radiation is to inhibit the onset of mitotic and amitotic division of the cells receiving the irradiation.

The authors are deeply indebted to Dr. J. H. Lawrence and to Dr. E. O. Lawrence for their coöperation and interest in this study.

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PATHOLOGIC CHANGES IN THE BRAINS OF DOGS GIVEN REPEATED ELECTRICAL SHOCKS.

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Numerous studies of both experimental and clinical material have shown that rather definite pathologic tissue changes result from shock therapy with insulin and with metrazol. In view of the

recent extensive use of electrical shock in the treatment of psychoses, we were led to undertake the following investigation with the object of comparing the brain changes induced by this modality with those produced by the above-mentioned convulsant agents.*

Procedure. Convulsions were repeatedly induced in a series of 12 mongrel dogs by the application of an alternating electrical current. The equipment† was the same as that used by the Department of Psychiatry in electrical shock therapy. The electrodes were applied over shaved areas of the skin superior to the zygomatic arch in the temporoparietal region, external to the motor area of the brain. Shocks were applied at a potential of 80 volts and a current strength of 200 ma.; the duration of the individual shocks was 0.15 second.‡ Shocks were administered at 3 to 5 day intervals.

The total number of shocks given each animal is shown in Table 1. For the most part the animals were given the number of shocks which are administered to patients. Individual animals varied considerably in respect to the severity of the convulsive manifestations induced by the alternating current applied. The variations are indicated in Table 1 by *slight*, *moderate* and *marked*, depending upon the degree and duration of convulsive seizures. Those rated *marked* lasted several minutes after the shock was applied and were accompanied by tonic and clonic contractions, frothing at the mouth, and involuntary defecation and micturition. *Moderate* convulsions were those which were quite marked during the application of the current but from which recovery occurred within a minute or two after the shock. *Slight* convulsions did not continue after the current was stopped.

TABLE 1.—TABULATION OF RESULTS.

Protocol No.	Dog.		Experiment.				Remarks.
	No.	Sex.	Duration, days.	No. of shocks.	Degree of severity of convulsions.	Recovery interval, days.	
1	1	F	25	14	Marked	0	
2	2	F	46	25	Marked	129	
3	3	M	31	17	Slight to moderate	26	
4	4	F	53	16	Moderate	4	
5	5	F	63	18	Marked	12	
6	6	M	53	15	Marked	42	
7	7	F	15	4	Marked	0	Killed for distemper
8	8	M	15	5	Marked	0	Very excitable
9	9	M	5	2	Marked	0	Death on 5th day (pneumonia)
10	10	M	15	5	Marked	0	Spontaneous death
11	11	F	26	8	Moderate to marked	0	Spontaneous death
12	12	F	14	5	Marked	1	

Many of the animals became quite unruly during the time the shocks were being given. A number of them even developed savage tendencies. On the other hand, dogs which were permitted to survive a number of weeks without the shock treatment did not exhibit any abnormal behavior during this recovery period.

* A paper is in preparation dealing with the brain changes in 2 human cases following electrical shock therapy.

† Manufactured by Rahm Instrument Company, 12 West Broadway, New York.

‡ Preliminary experiments showed that there was considerable variation in the susceptibility of dogs to the development of convulsions and that with a current of less than 80 volts, some of the animals failed to show convulsions at all.

Some of the animals in the series died during the experiment. The others were killed by bleeding, under nembutal anesthesia. Blocks of tissue from the various organs obtained at autopsy were fixed and prepared for histologic study by routine methods. Frontal sections were made of the brains and blocks were taken from frontal and temporoparietal cortices, basal nuclei, cerebellum, and medulla. These tissues were examined by the Nissl method; some of the tissues were prepared by the hematoxylin-eosin method and by the Loyez, Cajal, and Hortega methods.

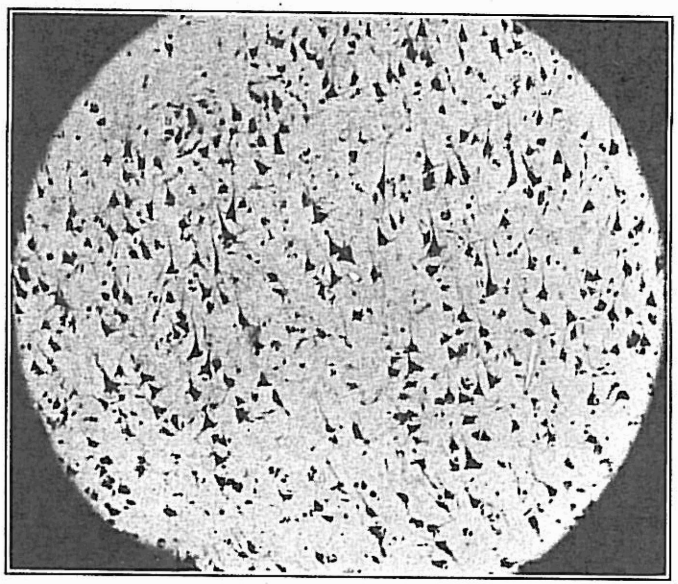

FIG. 1.—Small areas of cortical devastation from Dog 1 which had 14 marked convulsions. (Nissl, × 125.)

Protocols. DOG 1. *Brain:* Changes marked. Vascular dilatation and petechiæ. Nerve cell changes: swelling, vacuolation, extrusion of nuclei, paleness. Some satellitosis and neuronophagia. Numerous scattered shrunken elongated dark cells without clearly visible nuclei. Occasional circumscribed areas of recent necrosis with severe and ischemic changes—little glial reaction. Edema in white matter; myelin sheaths swollen and kinked; no definite demyelinization. Faintly basophilic grayish globules in white matter. Focus in subcortical white matter: small vein with round-cell infiltration, surrounded by dense area of proliferated oligodendro- and microglia. *Other organs:* Congestion.

DOG 2. *Brain:* Moderate number of swollen, vacuolated nerve cells with reticular cytoplasm. Occasional small areas of devastation, with ghost cells. Few glia stars at site of necrotic nerve cells. Slight swelling of macroglia; small numbers of fibrillary astrocytes. Swelling and kinking of occasional myelinated fibers; no definite demyelinization. Small amounts of perivascular fat in white matter. *Other organs:* Congestion; slight acute pneumonitis.

DOG 3. *Brain:* In cortex and basal ganglia: swelling and vacuolation of numerous nerve cells; delicate network of strands and granules in cytoplasm of some. Nuclei generally well preserved. Numerous dark-stained

nerve cells. Occasional severe cell changes and ghost cells. Swelling of oligodendroglia in cortex. Changes disseminated, apparently independent of circulation. Moderately increased number of glia cells, especially microglia, in molecular layer of cerebellum. Purkinje cells well preserved. *Other organs:* Congestion.

Dog 4. *Brain:* Widely scattered nerve cells with swollen and vacuolated cytoplasm and normal nuclei. Few dark-stained elongated slender nerve cells. Many nerve cells normal. Rarely minute cortical foci with ghost cells; little or no glial reaction. Vascular dilatation and petechiæ in few cortical areas. Slightly increased amounts of perivascular fat in white matter. *Other organs:* Congestion; slight acute peribronchitis.

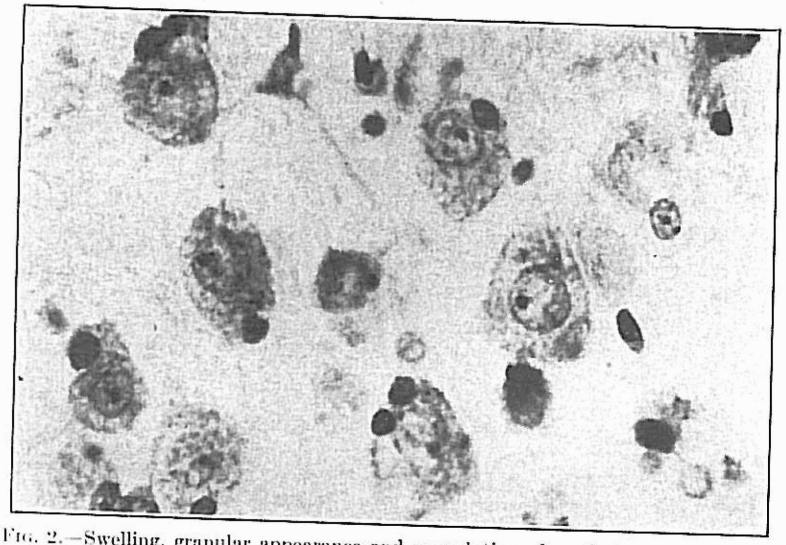

Fig. 2.—Swelling, granular appearance and vacuolation of cortical nerve cells from Dog 1 which had 14 marked convulsions. (Nissl, × 660.)

Dog 5. *Brain:* Changes less pronounced than in others: some tigrolysis and vacuolation of nerve cells. Most nerve cells essentially normal. No glial reaction. Occasional vascular dilatation and petechiæ. Almost negligible swelling and diminished tingibility in myelinated fibers. *Other organs:* Congestion; diffuse acute pneumonitis; chronic pyelitis.

Dog 6. *Brain:* Swelling and vacuolation of many nerve cells; many cells normal. Occasional satellitosis and neuronophagia, especially in basal ganglia and thalami. Vascular dilatation and recent petechiæ in several parts of cortex. *Other organs:* Congestion.

Dog 7. No autopsy.

Dog 8. *Brain:* Changes in numerous nerve cells in all areas: swelling, vacuolation, indistinct cell borders, granular cytoplasm, occasionally intranuclear granules. Occasional severe changes and ghost cells. Little or no glial reaction. *Other organs:* Congestion.

Dog 9. *Brain:* Damage rather severe: tigrolysis, swelling, vacuolation, shrinkage, granular cytoplasm. Severe and ischemic cell changes. Nuclei more damaged than in others; many hyperchromatic and distorted. Glial reaction absent or slight; some early microglial proliferation in few areas. Marked congestion and occasional hemorrhage in meninges. Thickening

of ependymal lining; some subependymal gliosis and hemorrhage. Changes not those of autolysis. *Other organs:* Congestion; pneumonia with lung abscesses and empyema. (Severe pneumonic infection: animal had had only 2 electrical shocks.)

Dog 10.—No autopsy.

Dog 11. *Brain:* Dark-stained cells with "chronic" changes numerous. In some areas: paleness of cells, severe and ischemic changes. Glial reaction little or none. Many pyknotic nuclei. Few slightly swollen nuclei. Very rarely small "gliarasen." *Other organs:* Congestion; aspiration with slight patchy pneumonia.

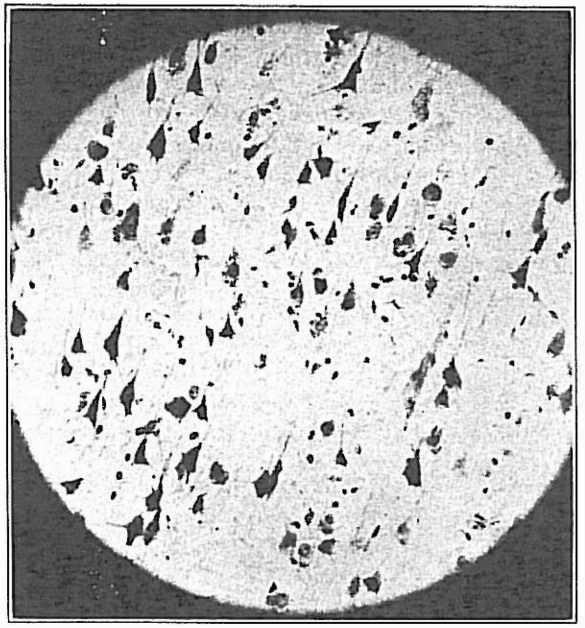

Fig. 3.—Sclerosed, ischemic, and granular cortical nerve cells from Dog 9 which had 2 marked convulsions. (Nissl, × 250.)

Dog 12. *Brain:* Changes diffuse, somewhat similar to but less marked than those of Dog 9. Occasional minute foci: paleness and ghost nerve cells. Most glial nuclei small and dark; occasional large pale nuclei and "gliarasen." Few recent petechiæ in meninges or near ependymal lining. *Other organs:* Congestion.

Results and Discussion. The most pronounced changes observed were in the brain. The cortex was more involved than the extracortical gray matter. The pathologic changes in the cortex were perhaps more noticeable in the vicinity of the pathway of the electrical current (temporoparietal cortex).

The following outstanding neuropathologic changes were observed. The nerve cells showed rather widespread damage, including tigrolysis, paleness, swelling, vacuolation, and in some instances

even ischemic and "severe" changes. Satellitosis and neuronophagia were found occasionally. In certain small circumscribed areas only pale, ischemic, ghostlike cells remained. Numerous cells exhibited "chronic" alterations: the cells appeared dark, slender and shrunken. The glia and microglia revealed slight proliferative changes. In a few of the animals some of the myelinated fibers showed slight damage, associated with a mild degree of edema in the white matter. The latter changes probably are of little significance. Vascular dilatation and minute hemorrhages were observed in the cortex, in the meninges, and around the ventricles in some of the brains. Congestion was the chief observation upon histologic examination of the other organs. The neuropathologic findings are similar in many respects to those of Morrison, Weeks, and Cobb,[3] who found a tendency to hemorrhage, shrinkage of ganglion cells, mild reaction of glia, and absence of demyelinization.

Although the changes described in the brain are definitely pathologic, they are not to be regarded as serious. Most of the nerve cell nuclei remained fairly well preserved. Many of the changes appeared to be reversible. The dogs during the recovery intervals failed to show clinical signs of brain involvement, as measured by the general behavior rather than by any specific neurologic tests. Variation in the degree of involvement may well be influenced by variation in individual susceptibility and by the degree of severity of the convulsions. In 2 dogs (Dogs 5 and 6), which had survived the experiments 12 and 42 days respectively, the findings were less pronounced than in the other dogs, although Dog 5 had 18 and Dog 6 had 15 markedly severe convulsions. On the other hand, Dog 2, which had undergone 25 markedly severe convulsions and was allowed to survive the experiment for 129 days, showed decided changes in the involved parenchyma. In 1 animal a small vein in the convolutional white matter showed lymphocytic infiltration and was surrounded by proliferated oligodendro- and microglia. Basophilic or grayish globules, observed only in the celloidin-embedded material, in the white matter of the same animal, are of questionable significance and possibly are artefacts. Similarly, the dark cells in the cortex may be artefacts, as recently pointed out by Scharrer.[4]

The investigations of several workers indicate that the brain changes induced by electrical shock are partly due to the direct effect of the current upon the brain parenchyma and partly due to the effect of the current upon the cerebral circulation (Morrison, Weeks, and Cobb, and Alexander[1]). The fact that the changes tend to be slightly more severe in the vicinity of the pathway of the current suggests the possibility that the current exerts a direct action upon the brain parenchyma distinct from any effect upon the circulation. The findings of Morrison, Weeks and Cobb, as well as those of Echlin,[2] that the current brings about a contraction of the intracranial arteries, point to an involvement of the circulation in the pathogenesis of the lesions. Petechiæ and small foci of ischemic necrosis observed in the present work also suggest circulatory effects.

For a long time it has been known that rather marked cerebral changes are to be found in patients with epilepsy. Recent use of convulsant therapy has renewed interest in the effects of convulsions upon the architecture of the brain. Shock therapy with insulin or metrazol has been shown to be accompanied by more or less marked pathologic changes in the brain.

Conclusions. The present studies indicate that some degree of neuropathologic change is to be expected in animals given electrical shocks of the same strength and duration as those employed clinically. Our results suggest that histologic changes induced by electrical shock in the brains of dogs are somewhat less severe than the changes we found following metrazol.[5]

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INTRAMUSCULAR PRESSURE.

III. The Action of Various Drugs on Patients With Normal Intramuscular and Venous Pressure.*

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The action of different drugs in various shock-like states wherein intramuscular and venous pressures fell to a low level, was reported in a previous communication.[1] It was observed that a 25% solution of Pyridine-beta-Carboxylic acid diethylamide (Coramine-Ciba) when administered intravenously raised the lowered level up to the normal range. Concomitantly, the low level of venous pressure

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