HISTOLOGICAL CHANGES IN THE BRAIN AFTER UNCOMPLICATED ELECTRO-CONVULSANT TREATMENT

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THERE has been much discussion about the possible occurrence of reversible and irreversible histological changes in the brain following the convulsive treatment of mental disorder. Most investigations have been carried out either on experimental animals—with results not easily comparable to man—or in deceased patients in whom the picture is usually obscured by the presence of complications. The various causes of death following convulsive treatment have recently been reviewed by Maclay (1953).

The two cases to be described here are remarkable for the relative absence of such complications so that they are in some ways unusually suitable for the investigation of any possible effect of convulsive treatment on the histological structure of the brain.

CASE REPORTS

Case 1.—C.H., the patient, a girl, was first noticed to be behaving oddly at the age of twenty. At that time—in 1940—she became dreamy and suspicious; she would laugh to herself and wander aimlessly about the house at night. The father reported that during this period she "collapsed" three times in the street but no spontaneous attacks were observed subsequently and it is extremely unlikely that those described were epileptic in nature. She was examined at the Maudsley Hospital and was admitted to St. Ebba's Hospital with the diagnosis of early schizophrenia.

At St. Ebba's Hospital she had two electrically induced convulsions. She stayed for one month and left only slightly improved. She was then admitted to Bexley Hospital in December, 1942. The E.C.T. was continued, at first with striking success. She received during 1943 and 1944 about 85 electric shocks. In June, 1944 she was by no means well but was still able to work in the laundry and at her own request she was discharged. Within a short time however she relapsed and during the following year she was a patient in St. Crispin's Hospital, Northampton where she also received electro-convulsant treatment. Then, after a further period of improvement, she was re-admitted to Bexley Hospital in a very deteriorated condition, semi-stuporose, noisy, resistive and dirty in habits. She often had to be tube-fed. In April of the following year her physical condition was described as satisfactory but on May 13th she was found to be suffering from cystitis which was successfully treated with sulphathiazole.

On 19.v.47 intensive E.C.T. was begun with premedication of omnopon 1/3 gr., scopolamine 1/150 gr., atropine 1/100 gr. and tubocurarine 14 mg. Five shocks were given on this day within one and a half hours, the last three being accompanied by increasingly intense clonic movements especially of the upper limbs, Respiration was satisfactory throughout; the deep reflexes of the limbs were not abolished during the treatment. On 21 May another treatment was started. She had her first convulsion quite successfully but before the second was induced her respiration became weak and despite oxygen she collapsed and died.

Altogether from 1942 to 1947 about 140 seizures had been induced. The patient was 27 years old at death.

Previous History. A normal birth. The patient was the fourth of seven children, all of whom are healthy. At school she was average, leaving at the age of 14. Since that time she had held various jobs as shop assistant, munitions worker, etc.

Post-mortem Examination. This was carried out 24 hours after death by the Coroner's pathologist who found nothing abnormal except dilatation of the right ventricle of the heart and congestion of the small cerebral vessels. The sliced brain was fixed in 10 per cent. formalin

and sent to the Department of Neuropathology at the Maudsley Hospital. No additional observations were made.

Histological Examination. Sections of heart muscle, liver, spleen and adrenal gland showed mild post-mortem change. In the kidneys there were a few patches of very slight interstitial lymphocytic infiltration. The glomeruli were normal, the tubules showed post-mortem change.

The main finding in the central nervous system was that of a glial fibrosis in the marginal layer of the cortex. It was present in all cortical areas examined but was most marked in the frontal and occipital regions (Figs. 1 and 2). It was also seen around the ventricles and in the marginal areas of the brain stem. Wherever it was found it consisted of a dense network of glial fibres which stained well both with Holzer's stain and with Mallory's phosphotungstic acid haematoxylin. In cortical areas, particularly in the occipital region, the glial fibrosis often extended from the tangential layer into layers 2 and 3.

There was also a definite glial fibrosis in the white matter. It was often patchy and confined to the perivascular spaces, but both in the frontal and occipital white matter it was more extensive. Patchy fibrous gliosis was also seen in the pons.

The gliosis was so well organized in most places that its date of origin was definitely before the beginning of the intensive treatment. While it is always difficult to assess the age of glial changes it is possible that some of it may have been several years old. There were other parts however, especially in the white matter, in which the production of glial fibres was of more recent origin. This might have been caused by the intensive treatment of 19 May.

In Nissl stained sections the molecular layer of the cortex, and the white matter, were more cellular than normal. In the molecular layer the cells consisted mainly of astrocytes and a few proliferated microglial cells. There was no activation of the macro- or microglia within the cortex either in Nissl preparations or in silver impregnations.

The cytoarchitecture as a whole was preserved. There was no appreciable loss of nerve cells but these did, however, often show a loss of polarity and varying degrees of chromatolysis. The amount of lipoid material both in the nerve and glial cells was not increased.

The white matter revealed an abundance of metachromatic bodies but these were probably due to post-mortem change. There was also in places some distension of the Virchow-Robin spaces, possibly indicating terminal oedema.

The meninges showed slight patchy thickening and contained many distended blood vessels. The walls of most of the meningeal vessels and of the vessels within the brain substance showed a very mild degree of adventitial fibrosis.

Case 2.—E.S., the patient, a man, was first admitted to hospital in 1943 at the age of 32. At that time he was a private in the Army, although until he had enlisted in 1940 he had been an assistant art editor to a daily paper. In the months before his admission he had become increasingly solitary, suspicious and deluded. No further details of this episode are known but after five months he was discharged from the hospital and from the Army showing definite signs of improvement. Two months later he was admitted to Runwell Hospital with the diagnosis of schizophrenia simplex. He was mysterious, vague, and mildly grandiose. He expressed ideas of reference; he was not apparently hallucinated. There was no physical abnormality.

From this time on his mental condition fluctuated sufficiently to allow his discharge and re-admission on four occasions but his clinical history was one of gradual, but never extreme, disintegration. During the next few years of his illness he received two courses of insulin treatment (a total of 105 comas). In 1947 he underwent his first course of intensive electroconvulsant treatment and from then until his death in 1951 he had a total of 38 grand mal and 7 petit mal seizures, with two to four of the former at each sitting.

The first course finished satisfactorily in 1948, the second was given in 1949, again with good results but by 1951 his condition had deteriorated sufficiently to warrant a further series. On the first day he was given three shocks resulting in three grand mal attacks but shortly after the last he became pale and pulseless, he started sweating and then his breathing stopped. Artificial respiration was begun at once and continued for an hour and a half, interspersed with the administration of oxygen and coramine, but he did not respond. His age at the time of death was 40.

Throughout the entire series of treatments the voltage ranged from 120 to 150 and the time from 0·3 to 0·7 seconds. No relaxant drugs were used at any time.

Family History. He was the elder child. His parents and his sister showed no abnormality. His maternal grandmother and a maternal uncle committed suicide.

Post-mortem Examination. This was carried out 48 hours after death by Dr. D. C. Caldwell to whom we are very grateful for the summary of his report:

The body of a well-nourished man. Pericardium normal. Marked right sided dilatation of the heart with some dilatation of the left ventricle. The auriculo-ventricular rings were dilated. The coronary vessels were normal. Bloodstained mucus in the bronchi, the lungs were well aerated. Bloody mucus in the stomach; there was some congestion of the gastric mucosa at the cardiac end with multiple petechial haemorrhages. The liver, spleen and kidneys were greatly congested. The brain also appeared to be very congested, this being especially noticeable in the small vessels of the white matter. Other organs appeared normal. The cause of death was right ventricular heart failure occurring during electro-convulsant treatment.

Histological Examination. There was slight patchy fibrous thickening of the leptomeninges over the convexity of the brain. The meningeal blood vessels were grossly congested and in

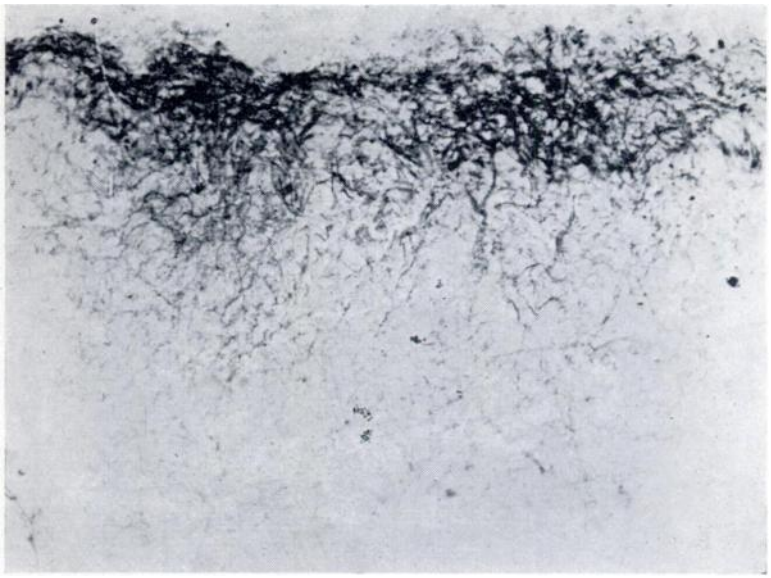

FIG. 1.—Marginal gliosis of the frontal cortex. Holzer stain. ×470.

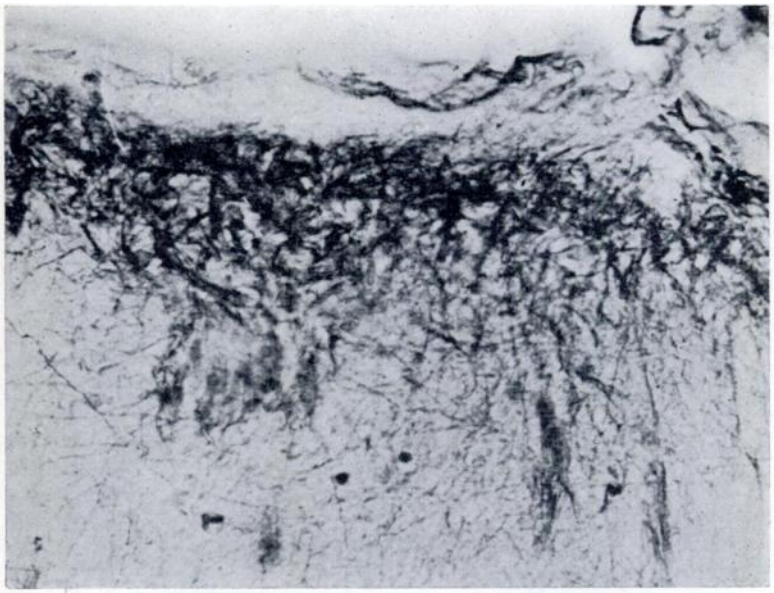

FIG. 2.—Marginal gliosis of the occipital cortex. Holzer stain. ×470.

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FIG. 3.—Marginal gliosis in the occipital cortex. Hortega's silver carbonate method for astrocytes. ×460.

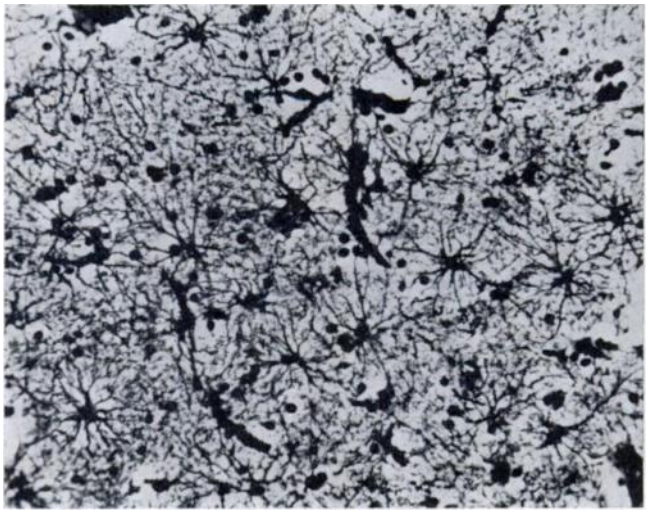

FIG. 4.—Increased number of proliferating astrocytes in the white matter of the frontal lobe. Hortega's silver carbonate method for astrocytes. ×230.

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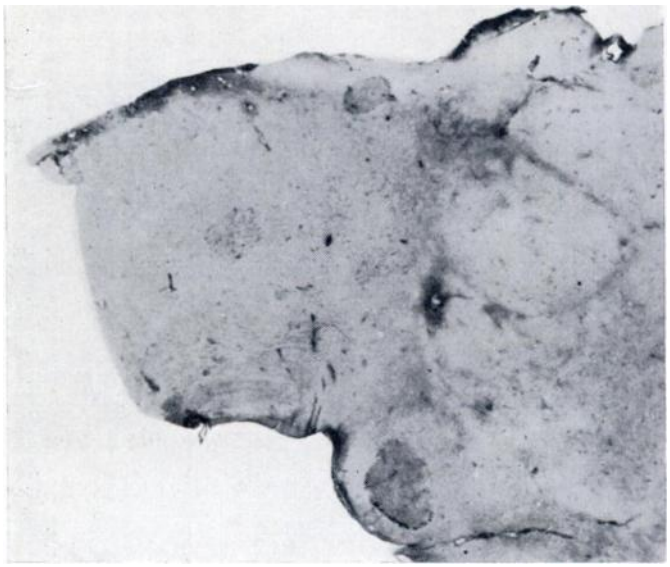

FIG. 5.—Marginal gliosis and scattered patches of gliosis in pulvinar and brain stem. Holzer stain. ×5.

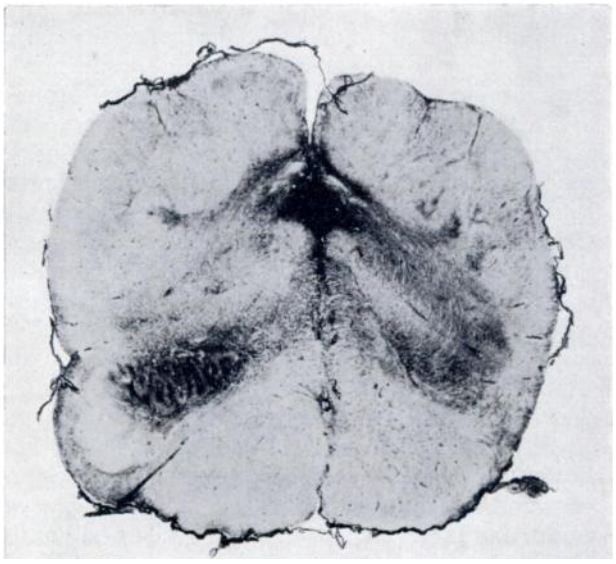

FIG. 6.—Marked glial fibrosis of the medulla. Holzer stain. ×7.

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some places, over the frontal and occipital lobes especially, there appeared to have been an occasional small haemorrhage. In the cortex and white matter there was also gross congestion of the blood vessels and occasionally the perivascular spaces were distended and contained many red cells. In van Gieson and iron haematoxylin stained sections the adventitial coats of the small vessels often were unusually thick and fibrous, especially when situated around the depth of a sulcus.

In the frontal, central, temporal and occipital regions there was some marginal proliferation of astrocytes and a fine glial fibrosis extended down into the second and third layers of the cortex (Fig. 3). At the junction of the cortex and white matter, as well as more deeply in the latter, there was also an increase both in the size and in the number of astrocytes. In cresyl violet stained sections the cell bodies often showed up faintly and contained large pale nuclei. In sections stained by Holzer's method and in silver impregnated sections there was a mild but definite glial fibrosis within the white matter but concentrated more especially around the vessels (Fig. 4).

The sub-pial surface at the base of the brain, around the optic tracts, and the laminae spreading up between the divisions of the pallidum were quite heavily gliosed (although this region is particularly susceptible). There was some patchy perivascular gliosis affecting the thalamus and brain-stem (Fig. 5). Both the sub-pial surface and the sub-ependymal zone of the mid-brain and pons were mildly affected but the gliosis in the medulla was more severe (Fig. 6). From the rostral to the caudal limits of the inferior olives a glial fibrosis was seen stretching across the floor of the fourth ventricle, through the reticular substance and into the olives themselves.

Nerve cell changes were not prominent and no areas of general or localized loss of cells were noted. There did not appear to have been any appreciable damage to the myelin sheaths and fat staining did not reveal any abnormal amounts of sudanophil material. The axis cylinders appeared normal and no microglial proliferation was observed. Both the cornu Ammonis and the cerebellum appeared normal although in the former the congestion of the blood vessels was exceptionally well-marked.

Discussion

The histological findings in the two cases described in this paper can be summarized as a mild marginal gliosis over the surface of the hemispheres and a moderate diffuse or perivascular proliferation of astrocytes in the white matter. The small blood vessels in the meninges and the substance of the brain were also slightly fibrosed. The changes were thus similar to the findings of glial proliferation which one encounters in the majority of epileptic brains. Appreciable focal or diffuse loss of neurones was, however, nowhere noted. In particular, the vulnerable Sommer sector of the cornu Ammonis and the Purkinje cell layer in the cerebellum were found intact. Since such lesions tend to occur with particular frequency in the more severe cases of idiopathic epilepsy showing a tendency to status, their absence in our two cases can be taken as an indication of the mildness of the lesions. In neither of our patients was there any clinical change which could be related to the lesions in the brain. Both patients were, however, deteriorated schizophrenics in whom it would be difficult to ascertain minor temporary or permanent psychopathological changes. In the second case there was the additional factor of insulin treatment. There is evidence to suggest however that those glial changes that may be found after such treatment are mainly dependent on the occurrence of epileptic fits (MacKeith and Meyer, 1939) and in this case none occurred.

Most of the histological changes were undoubtedly established some time before the particular convulsion which ended in death. They are not, therefore, of themselves the immediate cause of this—which in the first case was respiratory failure due to curare and in the second, right ventricular failure. It is not, however, with the cause of death that we are here concerned, but rather with the possible relation of the treatment to the histological picture. Before this relationship can be estimated it is necessary to discuss briefly other possible causative factors.

In the first place it should be remembered that mild proliferation of the glia and fibrosis of the vessel walls occur as a physiological concomitant of

higher age (Gellerstedt, 1933; Baker, 1937). However, both of these cases were below the age group in which such physiological, especially glial, changes tend to manifest themselves to any appreciable degree. Nevertheless, as the second case was 40 years old at death we investigated the brains of another ten patient aged between 40 and 50 but who had not received convulsive treatment. In none of these was comparable proliferation of glial elements encountered and it seems justifiable to conclude that the age of the patient did not materially contribute to the histological picture.

Secondly, both patients suffered from schizophrenia, a condition in which histological changes have been described by a number of workers. However, these findings have never been generally accepted as the substrate of the schizophrenic process (cf. the excellent review of the problem by Wolf and Cowan, 1952). The changes reported are not consistent and if present are more likely to be due to incidental causes including age, complicating disease or the physical effects of severe psychotic disturbances than to be the substrate of the primary disease. This was also the impression gained from personal investigations by one of us which have been communicated to the 1st International Congress of Neuropathology (Meyer).

Moreover, glial proliferation of the degree and distribution found in our two patients was not a common feature in the earlier histological research on schizophrenic brains. They were, however, a prominent finding in the brains of ten schizophrenic patients recently investigated by Winkelman and Book (1949). Closer scrutiny of this paper suggests that incidental factors may have been significant in the majority of their ten cases: their case 9 had been submitted to 111 electric shocks, case 7 had bilateral chronic pyelonephritis, case 6 suffered from several episodes of congestive heart failure; cases 2 and 3 exhibited early arteriosclerosis.

There have been a number of reports of atrophy of the brain in schizophrenics disclosed by macroscopic inspection during leucotomy (Puech, 1949; Pool, 1949) and pneumo-encephalography (Donovan, Galbraith and Jackson, 1949; Meschan and Scruggs, 1951; Huber, 1953). The significance of these findings is however not yet established; apparently no histological confirmation has been obtained in individual cases. There is some indication that the pneumo-encephalographic picture does not indicate an atrophy in the accepted sense. We may be dealing with constitutional variants of the ill-defined ratio between skull capacity and brain volume and with fluctuations of brain volume in different patients and at different times in the same patient (Meyer and McLardy, 1950).

From all this the conclusion must be drawn that in our two cases the likelihood of the glial changes being a manifestation of the schizophrenic process is slight and that consideration of their possible relation to the preceding physical treatment is therefore necessary.

There is no uniformity in the literature as regards the causation of irreversible brain changes by uncomplicated convulsive therapy. The fatalities that have been reported are in almost all instances caused by complications, particularly cardio-vascular disease. Most reviewers, including Alpers (1946), Karliner (1948) and Will, Rehfeldt and Neumann (1948) are of the opinion that irreversible damage is not likely to occur in the majority of cases in which complications are absent. Investigations of biopsy specimens is difficult owing to fixation artefacts and to the very limited material available to the histologist.

Glial proliferation has been a prominent feature in several reports on the sequelae of convulsive treatment. Weil and Liebert (1940) examined the brains

of six psychotic patients after Metrazol treatment and described findings similar to those in our cases. Ebaugh, Barnacle and Neuberger (1943) found among other abnormalities considerable stimulation of astrocytes, but as their patients were both aged 57, the age factor has to be considered. Zeman (1950) described—apart from widespread glial proliferation—necrosis of Purkinje cells in the cerebellum and of the Sommer sector in the cornu Ammonis. His cases were, however, complicated either by endocarditis or by severe lung infections, which may well have aggravated any anoxia caused by the preceding therapeutic convulsions. Wolf and Cowan (1949) described widespread astrocytosis in biopsies taken from two treated cases. The same change was however seen in a third untreated case while it was not found in a number of cases previously treated by E.C.T. Messimy and his collaborators (1951) discussed the role of previous insulin and convulsive treatment in the interpretation of glial changes which they observed in biopsy specimens taken from schizophrenic patients.

Experimental investigations have been undertaken on a fairly large scale. The results have been conflicting owing no doubt to the differences of species and experimental techniques employed by different research teams. Where experimental conditions approximated to those employed in human therapy histological findings were either negative or negligible (Cerletti and Bini, 1940; Barrera and associates, 1942; Winkelman and Moore, 1944; Alexander and Löwenbach, 1944; Siekert, Williams and Windle, 1950), or they were not severe (Neuberger and associates, 1942; Lidbeck, 1944; Ferraro and Roizin, 1949). The problem has been exhaustively discussed by Hartelius (1952). This author, after carrying out rigidly controlled investigations in cats found that significant changes in the nerve cells, blood vessels and the glia (particularly the oligodendroglia) occurred although incomparably the greater proportion of these was thought to be reversible. According to Hartelius, the direct deleterious effect of the electric current upon the tissue is negligible in therapeutic dosage. The lesions are caused by functional vascular disturbances and anoxia associated with the convulsion. Anoxia has an early effect upon the endothelial cells of the blood vessels followed by increased permeability and oedema. The occurrence of oedema in the course of epileptic convulsions is in accordance with bioptic observations (Penfield, 1936).

All Hartelius's animals (in common with those in most other experimental investigations) had only a short survival period. It is interesting that Ferraro and Roizin (1949) who investigated monkeys after a longer survival period described glial proliferation very similar in appearance and distribution to that found in our cases.

The general conclusion from this survey of the literature is that irreversible sequelae of electrically provoked convulsions are infrequent and that if they do occur they are not severe, probably even less severe than after convulsions caused by Metrazol and similar chemical substances. Their occasional occurrence cannot be denied, however, particularly if the number of electric shocks had been very large or shocks had been given (as is done in the so-called intensive treatment) in rapid succession, thus approximating to the events of status epilepticus which is well known to cause more severe sequelae than single seizures. Since frequency and intensity were both marked in our two cases the occurrence of a mild marginal gliosis and patchy astrocytosis of the white matter should not cause surprise.

This view is in complete agreement with that of Scholz (1951) who saw no reason why electrically induced convulsions, particularly if they were frequent,

should not cause the same type of histological sequelae as is observed after spontaneous epileptic convulsions.

The absence of necrosis in the grey matter particularly in the cornu Ammonis and cerebellar cortex indicates, as stated above, the mild degree of the lesions. Such slender histological findings should not, of themselves, be allowed to discredit this form of treatment nor do they provide evidence that this treatment could be the cause of atrophy of the brain.

Summary

Two cases have been described in which irreversible histological changes in the brain may have been caused by preceding heavy electro-convulsive treatment. The changes consisted mainly of a proliferation of the marginal glia and of the glia of the white matter. They were thus similar to the pathological lesions known to occur in idiopathic epilepsy but they were not accompanied by loss of nerve cells in the cornu Ammonis or in the cerebellar cortex.

The changes were mild in spite of an unusually heavy shock treatment. It is emphasized that even such slight changes are by no means common after this form of treatment.

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