DIFFUSE TRAUMATIC DEGENERATION OF THE CEREBRAL GRAY MATTER*

JOHN DENST, M.D.
THEODORE W. RICHEY, Captain (Medical Corps), U.S.A.F.**, AND
KARL T. NEUBUERGER, M.D.
(Denver, Colorado)

Diffuse cerebral cortical degeneration, as demonstrated in the following case, appears to be an unusual if not unique reaction to trauma. Cerebral contusions, lacerations, and intracranial hemorrhages are common lesions that are related directly to external violence. Rarer focal lesions associated with head injury include delayed apoplexy, central traumatic softening, and non-hemorrhagic cortical degenerations some distance from the primary site of injury. Widespread petechial hemorrhages in the white matter constitute one form of diffuse traumatic alteration. Another type was described recently by Strich (1), who reported 5 cases of longstanding dementia and decerebration associated with extensive traumatic degeneration of the white matter without significant cortical changes. Clinically, our case somewhat resembled those of Strich. A boy, 14 years of age, survived a blow to the head for 10 months, mute, demented, and with flexion-contractures. The lesions were widespread, but conversely involved the gray matter primarily. Mechanical disruption of the cerebral parenchyma and evidence of pressure or gross hemorrhage were absent. This case appears to demonstrate the lethal effect of trauma on neurons, independent of sundering of the tissue.

CASE REPORT

History: The patient, a previously healthy 14-year-old white boy, arrived at the hospital in deep coma soon after the automobile in which he had been riding was struck by a train. The extremities were rigid, the neck was stiff, the tendon reflexes were hyperactive, and the pupils were equal and reacted slowly to light. The blood pressure was 120/80. The pulse was rapid but regular. Treatment consisted of nasal oxygen and antibiotic agents. Roentgenograms showed fractures of the right third and fourth metacarpals, but no abnormalities of the skull. The boy was restless and groaned occasionally, but most of the time he remained akinetic and mute. He never responded to verbal, and rarely to painful stimuli. He showed no volitional activity or recognition of his surroundings. His eyes roved, however, and on occasion seemed to follow the examiner. The attendants noted states of sleep and "wakefulness". Contraction-deformities developed within 2 months. His arms, hands, legs, and feet became fixed in rigid flexion. The abdominal and deep tendon reflexes were absent. Babinski reflexes were present. There were no tremors. The spinal fluid was normal. He was always incontinent of urine and feces. Feeding was accomplished with a gastric tube. An indwelling catheter was maintained in the urinary bladder. A tracheostomy was performed at 4 months. At 5 months he was fed some baby food and exhibited a normal but

* From the Department of Pathology of the University of Colorado School of Medicine.
** Resident, Department of Pathology of the University of Colorado School of Medicine, under sponsorship of United States Air Force.
slow swallowing reflex. He had continuous elevated temperature. There were repeated infections of the urinary tract. He became covered with decubital ulcers and died 10 months after the injury.

Post Mortem Findings: The body weighed 41 kg and measured 160 cm. in length. Multiple decubital ulcers marked the soft tissues over all dependent bony prominences. The lower part of the torso was rotated to the right. The extremities were moderately atrophic; the forearms, thighs, and legs were fixed in irreducible flexion. There was bronchopneumonia.
The skull showed a faint linear fracture-line, without displacement, measuring 5.5 cm. long, in the right occipital bone near the petrous process. The dura mater was intact, and the leptomeninges, although slightly opaque, were devoid of brown pigment.

**Brain:** The brain, after embalming, weighed 1110 gm. Externally, the right cerebral hemisphere appeared to be somewhat smaller than the left, with prominent atrophy of the gyri over most of the frontal lobe and to a lesser degree elsewhere (fig. 1). Sectioning showed extensive thinning of the cortex, uniformly over the top of the gyri and in the sulci, to one half or one third the normal width (fig. 2). A distinct plane of cleavage in some places was probably an artefact due to the lack of cohesion in the midzone of the atrophic cortex. Disruption of the outer cortical surface, infarction, and pigmentation were absent. The inferior surface of the right frontal lobe, and the insular and inner temporal cortex in particular, tended to disintegrate when touched. The medial surface and dorsum of the right parietal lobe were especially shrunken. Patches of the cortex of the left insula, left frontal and temporal lobes, and both occipital lobes were involved. The white matter, both convoluted and deep, appeared to be normal in color and consistency, in sharp contrast to the overlying cortex. The extracortical gray matter was symmetrical and intact grossly, and the internal capsule seemed normal. The lateral ventricles were slightly dilated, especially the right inferior horn, and contained transparent fluid. The pons was somewhat atrophic. The cerebellum, medulla, and spinal cord were not remarkable. The blood vessels were normal.

**Microscopic Examination**

**Cerebrum:** The laminar structure of the cortex in the thinned areas was lost because of total or subtotal disappearance of nerve cells, frequently accompanied by status spongiosus (fig. 3). A rather uniform gliosis was present everywhere. The glial reaction was limited mainly to evenly-spaced protoplasmic astrocytes, although fibrillary astrocytes and some rod-shaped microglial nuclei were present (fig. 4). The Holzer stain failed to reveal a noteworthy increase in fibrillary glia except in the molecular layer. Gitter cells and neutral fat were absent. The outer cortical surface was smooth, but in the sulci it showed slight irregularities due to parenchymal shrinkage. Many areas with status spongiosus showed coalescence of vacuoles in the midcortical zone. The plane of cleavage was localized to the third or fourth layers. This loosening of tissue was unaccompanied by any additional glial or mesenchymal reaction. The grossly impressive laminar dehiscence appeared to be mainly an artefact due to handling. The astrocytes encroached upon the white matter only slightly except in the right frontal pole where the degenerative process was most severe. Here, the Holzer stain revealed occasional stripe-shaped gliosis in the extremely thin cortex and a feltwork of fibers cuffing several vessels in the nearby white matter. In several sections, a band of proliferated endothelial cells and capillaries occupied the fifth and sixth cortical layers (fig. 5). In most fields, however, a mesenchymal reaction had not occurred, and the reticulum stain revealed no increase or abnormality of the small vessels. The border between the normal and abnormal cortex was usually fairly sharply demarcated. At the margin of some devastated areas, groups or bands of surviving nerve cells were obscured by glial cells. In the uninvolved areas, nerve cells were present in normal number and arrangement with only rare minute foci of outfall. In the right motor cortex, many of the Betz cells alone survived in the field of proliferated glia (fig. 6). They showed sclerosis with conglutination of the Nissl bodies and darkly-stained cytoplasm by both Nissl and hematoxylin-eosin methods. The Ammon's horn showed loss of neurons and dense plasmatic gliosis, especially in Sommer's sector; lesions were less severe in the adjacent fields of the pyramid-cell layer.

The cerebral white matter showed diffuse and focal changes. The number of oligodendroglial cells and astrocytes was increased slightly, particularly in a narrow zone of the subcortical white matter adjacent to the areas of severest cortical deterioration. The Weil stain disclosed a suggestion of paling in the central white matter with sparing of the convolutional myelin except in the right frontal lobe where the fibrillary gliosis was observed. Minute transparent spongy foci without glial reaction were rather numerous. Neutral fat
FIG. 3. Atrophic left frontal cortex, showing loss of nerve cells and status spongiosus. Hematoxylin and eosin stain; X50.

FIG. 4. Astrocytic gliosis typical of diseased cortex. Holzer stain; X250.

was demonstrated only in a few small perivascular phagocytes. Several very small patches of demyelination with gitter cells were present in the corpus callosum and basis pedunculi. Hemosiderin-laden phagocytes were present about a few vessels in the white matter, particularly in the left parietal lobe near normal cortex. The Prussian-blue reaction was negative in the cortex.

*Extracortical Gray Matter:* The most striking lesion consisted of loss of myelin
and absence of nerve cells in most of the right thalamus (fig. 7). A group of cells showed calcification. A diffuse growth of astrocytes was present. Smaller foci of devastation were observed in the opposite thalamus and in the caudate nuclei. Most of the left thalamus showed only a mild diffuse gliosis. The nerve cells of the right putamen were reduced in number, showed satellitosis, and were obscured by numerous astrocytes. The globus pallidus appeared normal on both sides. The nerve cells of the hypothalamic area and the mammillary bodies appeared to be approximately normal in number but pale. The right mammillo-thalamic tract was devoid of myelin. The basis pedunculi, particularly the ventral part on the right, was depleted of myelin, and scattered foam cells and swollen astrocytes were present. The optic tracts were normally myelinated. Most nerve cells in the peri-aqueductal region and the superior colliculi were present although pale. The oculomotor nuclei were normal. Both red nuclei were subtotally depleted of nerve cells; those that remained were pale. Myelinated fibers were fragmented, and phagocytes and gemistocytes were numerous. A minute cystic area with fibrillary gliosis and iron pigment was present in the midportion of the adjacent medial lemniscus. The substantia nigra was normal. The only significant neuronal alteration in the pons and medulla was a focal loss of cells in the locus coeruleus, with phagocytosis of pigment. The Weil stain revealed partial demyelination of many of the descending fiber-tracts in the basis pontis. The pyramids were mildly shrunken.

Fig. 5. Capillary and endothelial proliferation in lower layers of right frontal cortex. Nissl; X225.
The principal lesion consisted of severe diffuse loss of nerve cells and astrocytic gliosis in the undisrupted cerebral cortex and in selected areas of the central gray matter, mainly the thalamus, red nuclei, and putamen. Less impressive changes in the white matter consisted of mild paling of the deeper myelin, with diffuse increase of fibrillary astrocytes. The cerebellum was remarkable only for a moderate loss of cells in the Purkinje and granular layers in the vermis. The only change in the spinal cord was a slight but definite symmetrical paling of myelin in the lateral funiculi.

**DISCUSSION**

The principal lesion consisted of severe diffuse loss of nerve cells and astrocytic gliosis in the undisrupted cerebral cortex and in selected areas of the central gray matter, mainly the thalamus, red nuclei, and putamen. Less impressive changes in the white matter consisted of mild paling of the deeper myelin, with
sparing of the U-fibers, and minute vacuolar rarefactions similar to those that Strich (1) considered to be artefacts. There were a few old petechial hemorrhages in the white matter and in the medial lemniscus, several small patches of gitter cells mainly in the corpus callosum, and some atrophy of the motor tracts. The disappearance of nerve cells was more extensive on the right, the side of the fracture; fibrillary gliosis was limited almost exclusively to the right frontal pole. Definite cellular deficits were not observed in the dorsum of the midbrain, pons, or medulla.

The extensive involvement of the cortex and thalamus may explain the abnormal state of consciousness. French (2) found similarly located lesions in cases of prolonged unconsciousness although, in the majority, the lesions were located in the cephalic portion of the brain stem. He concluded that the abnormal state of consciousness “results from a deficiency of exciting influences on subcortical and cortical structures, either by destruction of the reticular activating system itself or by its isolation from higher functional areas.” This explanation would apply to both our observations and those of Strich.

The classification of this degenerative lesion of the gray matter is of major significance. There had been no external compression or laceration of the brain; the few minute hemorrhages were not of primary importance. The cortical lesions were not classical contusions although Lindenberg and Freytag (3) have stressed that all nondisruptive traumatic cerebral injuries are actually contusions. Typical contusions, as pointed out by these authors and by Moritz (4), are localized, occupy the eminences of the convolutions, show intracortical hemorrhages even in mild cases, and are accompanied by necrosis, which in time results in ulcer-like or cystic loss of tissue. Although one hemisphere was affected more than the other, the cortical atrophy was extensive and exhibited no predilection for the tops of gyri. The cortex was devoid of blood pigment, and the superficial layer was not destroyed.

The nature of the process appears to bear a close relationship to cerebral concussion. Injuries leading to the syndrome of concussion, or commotio cerebri, produce a violent shock to the brain, often without grossly visible lesions. There is no reason to doubt that this may bring about parenchymal changes of irreversible as well as reversible character. Williams and Denny-Brown (5) have reported electro-encephalographic changes that clearly indicate a more or less serious postconcussive interference with normal function. Courville (6) also concluded that concussion could lead to chronic post-traumatic neurologic disorders (on a circulatory basis). He observed that scant attention had been given to the cases with fatal outcome. In these instances, death occurred immediately or soon after cranial trauma because of paralysis of the medullary centers and without evidence of physical damage to the brain except for possible petechiae. Had our patient survived for only a brief time, the brain might have exhibited edema and petechiae at most. There was no reason to suspect that any immediate gross discontinuity of the cortex and softening, much less any pulpefaction or hemorrhage, had occurred. The absence of blood pigment and neutral fat indicates that sudden necrosis of all the tissue-elements had not been an immediate post-traumatic event.
The traumatic etiology of the lesions is beyond doubt, but the pathogenesis is debatable. The factors to be considered are: concussion, vasomotor disturbances, compression of vessels, edema, disturbance of barrier function, shock with drop in blood pressure, and anoxia. The disappearance of nerve cells could have resulted rather directly from the concussive force. The distribution of the loss of nerve cells appeared to correspond in large part to the intensity of the local disturbance of the tissue. The blow had probably exerted its impact on the skull posteriorly and to the right, with the waves of force directed forward to converge at the right frontal pole. Damaging waves also fanned toward the occiput and into the left hemisphere. The intensity of the blow had been severe enough to produce a minor fracture but was not sufficient to rupture blood vessels. The variable susceptibility of the different nerve-cell groups also was important. For example, the resistance of the cells of the substantia nigra and dorsum of the midbrain in contrast to that of the red nuclei was striking. Another interesting feature was the resistance of the motor nerve cells in an otherwise devastated area. They showed a form of alteration similar to that demonstrated by Groat, Windle, and Magoun (7) in a monkey only a few days after concussion.

Ricker and Döring (8) have stated recently that primary diffuse cell damage without disruption of the continuity of the brain-tissue is not known in human material. However, alterations of nerve cells in experimental animals subjected to concussion have been described repeatedly and have been reviewed by these authors and by Courville (6). Chromatolysis, disarrangement of cells, swelling of myelin sheaths, and breakdown of myelin demonstrable by the Marchi method have been observed directly after concussion. Groat and Simmons (9) demonstrated a considerable deficit of nerve cells in the reticular formation, lateral vestibular nucleus, and red nucleus in guinea pigs 13 months after a single blow. They noted that both the disturbance of the concussive action and the differential susceptibility of the cells were the factors that determined the final histologic picture. They subscribed to the view that the percussion wave produced transient local shearing forces in the tissue, which destroyed the nerve cells; they denied the importance of other factors such as vasoparalysis, edema, and anoxia. Strich (1), in reference to degeneration of the white matter, and Lindenberg and Freytag (3) in consideration of non-hemorrhagic necrosis in contusion, also stressed the primary etiologic importance of the mechanical factors.

Nevertheless, in our case other factors may have played a role. Interference with the barrier-function, even after slight blunt closed injuries to the skull and brain, has been demonstrated experimentally by Gerlach and Becker (10) to involve practically the whole brain. After a severe injury, as in the case under discussion, widespread edema may develop. Evans and Scheinker (11) have illustrated in detail the posttraumatic development of swelling and edema of the brain. These early changes are characterized histologically by a loosening and reticular appearance of the ground tissue, degeneration of myelin, swelling of oligodendroglia with nuclear pyknosis, and astrocytic proliferation. The nerve cells may show some swelling of the cytoplasm but are comparatively resistant to uncomplicated edema, according to Scholz (12). The severity of the neuronal damage in our case indicates that other factors were involved or played a part.
One of these is vasomotor insufficiency, the significance of which in concussion was only recently evaluated by Ricker and Döring (8), and has been emphasized in former publications by one of us (13). Ischemia, prestasis, and stasis in small intracortical vessels may produce neuronal damage of anoxic or hypoxidotic character. Lindenberg (14) has drawn attention to the fact that acutely rising intracranial pressure in cases of blunt head injury may result in compression of cerebral arteries. In our case, such compression may have been a contributing factor, especially in the lesions of the thalamus and Ammon's horn. The blood supply to the brain also may suffer as a result of shock and transient drop in blood pressure; however, these factors did not play a role in our case according to the history.

The damage in our case occurred possibly in the manner suggested by Hallervorden (15). He said that, on the basis of doctrines of colloid chemistry, protoplasm in general must be considered as a "thixotropic" system, with a labile state of gels and sols. Trauma may produce an immediate alteration of protoplasm, such as liquefaction of the gels. This alteration may or may not be reversible. If the alteration is irreversible, serious changes in the tissues or death may result. This attractive theory emphasizes both the physiologic and the histologic aspects of the problem. Parenchymal damage may manifest itself in cellular lesions and in a nondescript change of the intercellular matter. It is conceivable that such abnormalities make the brain more susceptible to circulatory disturbances that doubtless follow concussion.

The status spongiosus, as seen in our case, merits attention in this connection. Von Braunmühl (16) has stated that 2 types of status spongiosus should be distinguished. The first type, originally described by Spielmeyer (17), consists of rapid disintegration of parenchyma combined with inadequate proliferation of fibrillary glia. The second type is a "status spongiosus due to dehydration". Bound tissue-fluid is liberated, loosens the meshes of the ground substance of the cortex, and thus produces the spongy appearance. In other words, there is an unusually severe serous imbition of the ground tissue. We find it difficult to decide which of these 2 processes was pertinent in our case; perhaps a strict separation of the 2 groups is not practical. It would appear that tissue destruction, glial insufficiency, and disturbances in the water-balance of the ground substance are of major significance in all cases of status spongiosus. The assumption that repeated spells of dehydration have produced the pattern seen in our case seems plausible, especially if we attribute major significance to colloidal chemical processes. It is open to question whether serous exudations from the vessels played a role in the development of the status spongiosus.

Since we see only the final outcome, we can merely surmise what has happened during the long interval between trauma and death, and this makes the analysis difficult. The lesions must have been produced by direct force to large areas of the brain. It would seem hardly speculative that organic alterations as seen in this case would be more frequent if victims of severe concussion would live longer. We believe that there is a merging and close relationship between concussion and contusion. Similarly, Denny-Brown and Russell (18) and, more recently, Katzen-
stein (19) have pointed out that separation of *commotio* and *contusio cerebri* is unwarranted and not confirmed by pathologic findings. The mechanical and biochemical factors of trauma (if we accept the theory of thixotropy) may cause disintegration of neurons and degeneration of myelin independent of crude disruption of tissue and of hemorrhage. In addition, edema, compression of vessels, functional disturbances, and perhaps anoxia must have been significant contributory factors. There is always an inclination to overemphasize one factor in etiologic and pathogenetic considerations. We feel that in the development of the picture a "constellation" of agents (Tendeloo (20)) was operative as is true in so many other conditions.

**SUMMARY**

A diffuse degeneration of the cerebral gray matter is described in a 14-year-old boy who died 10 months after closed traumatic injury to the skull. Extensive cortical devastation and gliosis with selective involvement of the central gray matter and without evidence of crude traumatic destruction or hemorrhage were the outstanding features. The parenchymal lesions appeared to be related closely to the concussive force; a constellation of factors which included edema, thixotropy, and vasal disturbances were undoubtedly important in the pathogenesis.

**REFERENCES**