HISTOLOGIC STUDIES OF THE BRAIN FOLLOWING HEAD TRAUMA
I. POST-TRAUMATIC CEREBRAL SWELLING AND EDEMA

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The terms cerebral concussion, edema, and contusion are familiar to both the clinician and the pathologist. Often, however, the words have different connotations for them, and until relatively stable definitions are established, confusion will persist. It is our purpose to review in several papers some of the changes associated with injury to various parts of the central nervous system in an effort to clarify terms and to correlate more closely clinical and pathologic findings, in the hope that thereby a broader basis may be laid for therapy.

In these papers we propose to stress the occurrence of vascular alterations, and to interpret their effects on nervous tissue, because we believe that exploitation of this rather neglected line of approach is promising, even though it may well prove but a partial answer to the problem of nervous system trauma.

We define as cerebral concussion that state of altered consciousness that occurs in association with sudden acceleration or deceleration of the brain, and we regard it as a disturbed physiologic state for which there can be found with our present methods no definite anatomical substratum or, at most, minimum cellular alterations. However, it seems likely that altered activity in the brain stem reflexes with resultant respiratory, blood pressure, and vasomotor changes may contribute to the circulatory disturbances to be discussed in this and subsequent papers.

In the literature dealing with the clinical aspect of "head injury," frequent reference is made to the occurrence of cerebral edema. The term appears to be employed to designate a clinical state that is thought to be due to an increase in tissue fluids within the brain. The correlation between the clinical and the pathologic condition is still indefinite, and as indicated by Pilcher, and by White and his co-workers, much information is needed in order to arrive at a satisfactory explanation of the morbid physiology.

It is our belief that the condition referred to loosely by clinicians as cerebral edema is represented pathologically by two states, one of which merges rather insensibly into the other, edema and its precursor, brain swelling.

Macroscopically in the fixed brain, there is rather little to differentiate the two conditions, which are characterized by an increase in brain volume, some convolutional flattening, and by increased volume of the white substance which results in narrowing and compression of the gray matter. In addition the ventricles are apt to be compressed, and, in unilateral swelling or edema, to be shifted.
The differentiation between the two conditions is made histologically, and the criteria of recognition, as already specified by one of us in cases of brain tumor,\textsuperscript{10,11,12,13} have been found in this study to apply in instances of brain injury also. There are in edema the alveolar and sieve-like appearance of the nervous tissue and distention of the perivascular and pericellular spaces, the resultant liquefaction of nervous tissue, amoeboid degeneration of the astrocytes, and significantly, in the more advanced stages, signs of vascular stasis: congestion and engorgement of the capillaries and veins, perivascular accumulations of fluid and even of cellular elements, and occasionally evidence of endothelial necrosis.

In post-traumatic brain swelling the changes are of lesser degree. The parenchymal changes are less striking and consist chiefly of hydration and swelling of the axis cylinders, myelin sheaths, and glial cells. These changes, particularly those of the nerve fiber and medullary sheath, are easily overlooked in hematoxylin and eosin preparations, but are evident on careful study of silver impregnations, such as the Bodian, or with the Loyez stain.

The present report is based on a review of the accumulated material of seven years from a large and active "head injury" service, and an intensive study of the material derived in the past three years.

A typical instance of each condition, swelling and edema, will be cited.

A. BRAIN SWELLING


D.G., a 30-year-old bartender and chronic alcoholic, had suffered a severe head injury three years previously, when a sharp object was driven into the skull over the left eye. He was unconscious for a few hours, was hospitalized for about two months, and then apparently made an uneventful recovery.

On the night before his final admission he was assaulted and fell striking the back of his head resoundingly on the pavement. He was unconscious for a few minutes, but thereafter walked home, where he was found unconscious the following morning. On admission to the hospital he was thought to be intoxicated. That evening he was seen by a neurologic consultant. Examination showed him to be stuporous. He responded to painful stimuli by vigorous movement of the right arm and leg. The optic discs were not remarkable, the pupils were fixed bilaterally at 4 mm., and there were a left facial paresis, weakness of the left extremities with increased tone, hyperreflexia, and a positive Babinski response on the left side. There were strong and purposeful movements of the right arm and right leg; the right plantar response was also extensor.

Lumbar puncture showed a pressure of 200 mm. of water; the fluid contained 24,000 red blood cells per c.mm. Roentgenograms of the skull revealed no fracture.

He was taken to the operating room and a right subtemporal opening was made. There was a transverse fracture line running across the temporal bone and an extradural clot, 4 cm. in depth at its greatest thickness, extended from the frontal to the occipital region. This was evacuated, but the brain showed no tendency to fill out. Respirations ceased before the operation was terminated, the pulse became rapid and thready, and the blood pressure fell. Death occurred on the operating table approximately 28 to 30 hours following his injury.

Necropsy. The residuals of an extradural clot, measuring 10 cm. in diameter, were present over the occipito-parietal region. The underlying brain was flattened. Inspection of the median cleft revealed a displacement of the cingulate gyrus under the free edge of the falx.
The undersurfaces of the frontal lobes showed signs of the old injury, with considerable loss of substance and replacement gliosis, which were more evident on the left. As a manifestation of the recent injury there was a well defined herniation of the uncal portion of the right temporal lobe, measuring 2.5 cm. in length and 1.3 cm. in width. The pons and optic chiasm were shifted to the left by the herniation.

Coronal sections (Figs. 1 and 2) showed definite increase in bulk of the right hemisphere, more evident in the white matter than in the gray. There was a shift of the ventricular system to the left. The right basal ganglia appeared swollen, and the right lateral ventricle was compressed.

In association with the uncal herniation on the right there was a displacement of the right hypothalamic region downward and mesially into the incisural notch (Fig. 2). There was also displacement of the substantia nigra and of the peduncle of this side. A few scattered hemorrhages were to be seen at the level of the inferior colliculi and the gray matter of the tegmen. In addition there were scattered petechial hemorrhages in the lower lip of the Sylvian fissure on the right and in the right temporal lobe, particularly in the herniated portion of the right uncus. The white matter of the right hemisphere showed a moderate degree of congestion with occasional perivascular extravasations of lymphocytes.

The cerebellum and medulla appeared grossly normal. The blood vessels at the base were normally distributed and were of normal appearance.
**Microscopic Observations.** Survey sections from the white and gray substance of both hemispheres, from the hypothalamus, and the midbrain were stained with hematoxylin and eosin and with cresyl violet, and were also prepared by the Loyez and Bodian methods.

The white matter of the right hemisphere showed swelling of all the constituent elements, both parenchymal and interstitial. These changes were not evident in the hematoxylin and eosin preparations, but careful analysis of the Bodian and Loyez sections disclosed findings ranging from hydropic swelling of the axis cylinders and the myelin sheaths to more severe alterations indicated by ragged outlines and signs of gradual disintegration of the nerve fibers. The myelin sheaths disclosed irregularities in contour with many large globules and granules of lipid. The axis cylinders showed not only diffuse swelling, but many small fusiform varicosities, throughout their course and at their termination (Fig. 3).

![Fig. 3. Case 1. Diffuse swelling of the nerve fibers associated with formation of small fusiform varicosities throughout their course and at their fragmented ends. Bodian silver impregnation, ×240.](image)

In all of the sections from the right hemisphere there was rarefaction of the tissue indicated by a loose reticular appearance, which was most evident in the white matter of the centrum semiovale and which was less intense near the cortex. The subcortical U fibers were comparatively well preserved.

Glial changes consisted chiefly in hydropic swelling of the oligodendroglia, occasionally by evidence of disintegration of the cell bodies. There were also associated clasmatodendrosis and occasional amoeboid degeneration of the astrocytes.

No definite vascular abnormalities were detected except for a moderate degree of dilatation of the smaller blood vessels and occasional distention of the perivascular spaces, which were sometimes filled with transuded serous fluid. Here and there were present areas of perivascular hemorrhage and in these zones the typical signs of vasoparalysis could be found.

The cortical ribbon appeared normal.
B. CEREBRAL EDEMA


R.R., a white male of 53, was admitted to the hospital on January 20, 1939. Some twelve to eighteen hours earlier, he had been repeatedly beaten over the head with a shotgun and left for dead. Subsequently he regained consciousness and after some hours was brought to the hospital from a physician's office.

On admission he was deeply cyanotic and gasping for breath. The difficulty was promptly relieved by elevation of the chin and establishment of a proper airway (one can only speculate what the effect of the prolonged cyanosis may have been on the outcome of the case). Further examination showed him to be deeply comatose, flaccid, and unresponsive to painful stimuli. The temperature was 99, pulse 92, respirations 26, and the blood pressure 130/40.

The head displayed diffuse edema and four scattered lacerations, bilateral Battle's signs, a huge hematoma of the right eye with subconjunctival hemorrhage, and dried blood in the auditory canals, in the nose, and in the mouth. General examination was otherwise negative. Neurologic examination revealed no localizing signs.

Lumbar puncture on admission showed an initial pressure of 300 mm. of water; the fluid contained 350,000 red blood cells per c.mm. Skull films revealed a questionable fracture in the external orbital wall on the right, and another beneath the anterior clinoid processes. Shortly after admission the patient began to be very restless and continued so for the remaining 32
hours of his life, despite sedation. Lumbar puncture 40 to 48 hours after the assault and four hours prior to death showed an initial pressure of only 30 mm.; presumably the low pressure was due to relative dehydration, or possibly to cerebrospinal fluid block at the tentorium or foramen magnum. He was found dead in bed four hours after the lumbar puncture was performed.

Necropsy. In addition to a terminal bronchopneumonia, there were linear fractures of both temporo-parietal regions, and bilateral extradural hemorrhages, that on the left being insignificant, that on the right measuring 5×2 cm. in circumference and up to 1 cm. in thickness.

There was a minimal subdural hemorrhage on the left overlying a superficially contused temporal lobe. There was diffuse subarachnoid hemorrhage.

Cross sections of the brain showed the ventricles to be of normal size and to be in normal position. Throughout the brain there was a very moderate vascular congestion, particularly in the white matter.

Microscopic Observations. Sections were taken from different parts of the centrum semiovale and from the cortical gray matter. Those of the white matter revealed both vascular changes and diffuse changes in the parenchyma. Fig. 4 illustrates an advanced degree of vascular alteration. Most of the vessels exhibited distention of their lumina and varying degrees of degeneration of the walls, associated with an increased permeability for serous fluid and, at times, for red blood cells. The perivascular spaces were tremendously distended with fluid.

The changes in the parenchyma consisted of reticular appearance of the tissue due to the distention of the pericellular and perivascular spaces (Fig. 5), and necrobiosis of the ganglion cells. Most of the neurones showed signs of ischemic degeneration: shrunken cytoplasm, dis-
appearance of the Nissi bodies, and darkly staining nuclei. Cells of this type were scattered diffusely. In some areas, almost every neurone was affected in this manner. The nerve fibers, separated by the accumulations of serous exudate in the interspaces, revealed no signs of destruction. Only a few of the axones were thickened and showed irregular varicosities and end bulbs. Myelin sheath preparations revealed a diffuse pallor and also irregular thickening and degeneration of a few of the myelin sheaths. Diffuse changes in the macroglia were observed, ranging from irregular increase in size of cell bodies and granular appearance of the cell processes to advanced changes typical of clasmatoendrosis. The meninges appeared distended.

COMMENT

Case 1 presents the histologic findings of a condition that we regard as the precursor of cerebral edema, namely cerebral swelling. Its existence is characterized by the histologic evidence of swelling of the nerve fibers, the myelin sheaths, and the glia, particularly the oligodendroglia. These changes are not evident in the usual hematoxylin and eosin preparations, but may be clearly identified in silver preparations where they are predominant in the central white matter.

In this stage the reaction presumably is a reversible one, but if the circumstances are unfavorable it appears to progress insensibly from a stage of increased intracellular fluid accumulation into that of cerebral edema, characterized microscopically by distention of the perivascular and pericellular spaces, transudation of serous fluid into the nervous tissue about the blood vessels with resultant liquefaction of the tissues, and the production of an alveolar and sieve-like appearance of the tissue. Amoeboid degeneration of astrocytes also occurs.

What is the origin and physiopathologic mechanism of post-traumatic swelling and edema?

We believe that the histologic changes described in and about the blood vessels in our cases provide the important clue to the mechanism. We consider both the increased amount of tissue fluid and the tissue changes to be secondary to local circulatory disturbances. On the basis of these observations, we suggest the following theory of the mechanism: As the result of trauma obvious superficial damage with cortical bruising and laceration may occur. But in addition there are alterations in the deeper structures of the brain which likewise demand explanation, particularly the often striking changes in the white matter.

We believe that there occurs transmission of the energy accompanying the traumatic insult to the deeper portions of the brain, and that the transmitted force causes vasoparalysis of the capillaries and venules of a degree sufficient to cause actual slowing of the blood stream. With the swelling of the tissue there presumably occurs an increased venous pressure, and it is even conceivable that there may occur actual reversal of the normal direction of fluid exchange. Local accumulation of carbon dioxide, because of less effective circulation, leads to further vascular dilatation and to increased permeability of the vessel wall. If these alterations be sufficiently severe, actual structural changes may occur in the capillaries and veins. The
developing edema of the tissue then serves in turn further to retard circulation and contribute to hypoxia, and no doubt these physiologic changes interfere with proper oxygen and carbon-dioxide exchange, so that the normal cycle becomes more and more disturbed and incompatible with the maintenance of local function. Should this local function be of vital importance, e.g., that of the respiration or of temperature control, and should the impairment of activity become sufficiently severe, death will result. Should, on the other hand, the changes occur in a non-vital region, loss of function, temporary or permanent, may result in a clinical deficit depending on the specific circumstances of site, severity, and duration of impairment.

Such an hypothesis need not suppose the activation of a neurovascular network, which has not yet been demonstrated except for the larger cerebral vessels. The experimental work of Echlin, though limited to vasoconstriction produced in the pial arteries of animals by electrical and mechanical stimulation, confirms and amplifies the work of other authors, including Florey. That similar mechanical changes may occur in the deeper vessels supplying both the gray and the white matter seems not too gross an assumption for our working hypothesis.

From the clinical point of view one must accept the reality of cerebral swelling and edema. Their recognition in the patient may actually be difficult and the differentiation from other post-traumatic states associated with increased intracranial pressure may present a problem. From this limited clinico-pathologic study, nothing positive can be said concerning clinical recognition.

SUMMARY

1. Post-traumatic brain swelling and cerebral edema are described in detail clinically and histologically.

2. The histologic changes described as accompanying cerebral edema are interpreted in terms of functional vascular disturbance. Cerebral swelling is believed to be a precursor of edema and the mechanism responsible for its occurrence is regarded as the same, but of lesser degree.

3. The changes characterizing edema consist in pericellular and perivascular accumulations of fluid, but there are to be emphasized the signs of functional vascular disturbance: congestion, stasis, dilatation of capillaries and veins, and occasional evidence of endothelial necrosis.

4. The changes characterizing brain swelling consist chiefly of swelling of the axis cylinders, myelin sheaths, and glial cells. These changes are poorly shown in routine stains, but are evident in the silver impregnations.

REFERENCES


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