CEREBRAL SWELLING
HISTOPATHOLOGY, CLASSIFICATION AND CLINICAL SIGNIFICANCE OF BRAIN EDEMA*

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(Received for publication January 20, 1947)

The appalling frequency of cerebral swelling in neurosurgical practice dealing with brain injuries, cerebral neoplasms or brain abscesses gives special significance to the study of this condition. Neurosurgeons have long realized that swelling often is the greatest obstacle to the exact localization of brain tumors. The operability of a cerebral neoplasm cannot always be determined with certainty from its histopathologic structure alone. The presence of swelling may at times be of greater significance for postoperative prognosis than is the structural character of the tumor itself. Clear understanding of the histopathology and physiology of brain swelling is of paramount importance, for postoperative prognosis frequently depends upon it more than upon any other single factor.

The paucity of histopathologic studies concerning the problem of cerebral swelling is surprising. Moreover, the terms cerebral swelling and cerebral edema are used by both clinicians and pathologists with quite different connotations. There is great diversity of opinion as to what histologic changes characterize cerebral swelling, and any attempt to group such descriptions as available results in apparent confusion. Until relatively stable histopathologic definitions are established, this confusion will persist. This presentation is based on a study of 125 cases of cerebral swelling caused by space-consuming lesions (brain tumor and brain abscess), cerebral injury and by circulatory disturbances such as massive intracerebral hemorrhage or thrombosis of larger blood vessels.

HISTORY

The term cerebral edema is one of long usage. Local edema of the brain has long been recognized as occurring in the vicinity of cerebral neoplasms and abscesses. Diffuse cerebral edema, on the other hand, has been reported in such diverse conditions as cerebral vascular accidents, uremia, severe intoxications and in status epilepticus.

Reichardt¹⁸ (1905) was the first to introduce the concept of cerebral swelling ("Hirnschwellung") as a specific reaction of nerve tissue. He defined it as an increase in brain volume, not due to hyperemia or to excess of free fluid. According to Reichardt, the brain is considered swollen when the difference between brain volume and skull capacity is less than 8 per cent. (The normal correlation between brain volume and skull capacity was first established by Rieger in 1885.)

The relation between brain tumor and cerebral swelling and edema has been the subject

* The findings and conclusions incorporated in this paper will be elaborated in chapter I of the author's forthcoming book, Neurosurgical Pathology, scheduled for publication in 1947 by Charles C Thomas, Springfield, Ill.
of many papers, most of which are in German (Stengel,25 Spatz,27 Fünfgeld,6 Jaburek,9 and Scheinker).26,27 Spatz came to the conclusion that true swelling of the brain is of common occurrence in cases of cerebral neoplasm, and is the direct cause of increased intracranial pressure. He also expressed the opinion that a distinction should be drawn between cerebral swelling and cerebral edema. It must be noted that in English and American literature the concept of cerebral swelling, as distinct from cerebral edema, does not exist; in fact, cerebral edema is the only term in common use. In French articles the two terms appear to have been employed indiscriminately, and Le Beau25 was of the opinion that it was not possible to make a distinction between them. His conclusions, however, were based entirely upon a gross study of the brain.

Until recently, cerebral swelling was considered as a pathologic reaction of the brain without any evident histologic changes.

In a series of cases of cerebral swelling the only abnormal finding noted by Wohllwill (1914) was the presence of Alzheimer's ameoboid glial cells. Spatz,27 too, was unable to find any definite histologic alterations characteristic of brain swelling. Only in some of his cases did he observe swelling of the processes of the astrocytes in the white matter and signs of clasmatodendrosis. In a clinical review of the subject Pette16 stated that, to date, investigations into the problem of the histopathology of cerebral swelling have proved unsuccessful.

The first attempt to outline the characteristic histopathologic features of brain swelling was made in 1938 (Scheinker25,27). In subsequent papers5,22 the author repeatedly emphasized that, despite the histologic difference between cerebral swelling and cerebral edema, the two conditions are actually two stages of the same biologic process. Both pathologic conditions include morphologic signs of vascular alterations with increase in permeability of the vessel walls. It was concluded that circulatory disturbances are essential to the pathogenesis of both cerebral swelling and edema.

In cases of cerebral edema associated with brain tumors, Greenfield7 described degeneration of myelin sheaths and varicosities of axis-cylinders, swelling of astrocytes and slight proliferation of microglia. Perret and Kernohan15 came to the conclusion that increased intracranial pressure is the direct result of edema which, in cases of brain tumor, may either remain local or be generalized throughout the whole brain. He accepted the view that edema is caused by circulatory disturbances resulting in hypoxia and acidosis of the brain tissue.

Histologic study has been supplemented by relatively few physiochemical and experimental investigations. The relationship between the wet and dry weight of the brain tissue was studied by Alexander and Looney4. They concluded that edema is confined almost entirely to the white matter of the brain. The gray matter of edematous brain disclosed the normal ratio between wet and dry weight.

Very significant contributions to improved understanding of both the histopathology and the physiology of cerebral edema are the experimental studies by White, Brooks, Goldthwait and Adams39 and the recently reported study made by Prados, Strowger and Feindel.17

**DEFINITION AND TERMINOLOGY**

A thorough study of a large number of cases seems necessary to bring order out of the chaotic diversity of opinions and findings relating to the pathology and pathogenesis of cerebral swelling and edema. After many years of systematic investigation of the problem, the author reached the following conclusions:

“Cerebral swelling” is the term with which the author proposes to denote the gross appearance of a brain characterized by a local or diffuse increase in bulk of one or both hemispheres, **regardless of the underlying histopathologic findings**.

The gross findings of “cerebral swelling” are characterized by: (1) in-
crese in brain volume; (2) flattening of the gyri and narrowing or obliteration of the sulci; (3) considerable enlargement of the central and subcortical white matter with consequent narrowing and compression of the cortical gray; (4) loss of demarcation between white and gray matter; (5) decrease in size or complete obliteration of one or both lateral ventricles; and (6) shift of the midline structures and of the third ventricle from the side of the cerebral swelling toward the opposite hemisphere when the swelling is unilateral (Fig. 1).

It is the author’s belief that the condition referred to grossly as “cerebral swelling” is represented microscopically by three underlying histopathologic syndromes which the author proposes to designate as (1) tumefaction, (2) edema, and (3) liquefaction.

Despite discrepancies in the histopathologic features of the syndromes of cerebral tumefaction, edema and liquefaction, it is quite evident that fundamentally they represent three different stages of the same biologic process; occasionally these stages may merge insensibly with one another.

The three conditions can be differentiated histologically. Criteria for their recognition will be given in detail together with illustrations from representative cases.

I. Cerebral Tumefaction

Microscopic findings characteristic of cerebral tumefaction may easily be overlooked in routine sections stained with hematoxylin and eosin. They are best noted with careful study of silver impregnations, such as Bodian or Bielschowsky stains.

Pertinent histologic findings characteristic of cerebral tumefaction may be summarized thus: (1) parenchymatous changes with evidence of swelling of the nerve fibers, myelin sheaths, glia and particularly of the oligodendroglia; (2) vascular alterations confined to the small veins and capillaries, characterized by (a) congestion and stasis, and (b) swelling and degeneration of
the endothelial cells. These changes are predominant in the white matter; seldom do they extend into the gray substance.

Preparations stained with hematoxylin and eosin fail, as a rule, to reveal any abnormalities other than a slight degree of tissue rarefaction and congestion, and stasis of the small veins and capillaries with occasional peri-vascular hemorrhages. Careful analysis of sections impregnated with silver (Bodian stain), however, discloses a tremendous swelling of most of the nerve fibers of the white matter (Fig. 2). More advanced changes are in-

![Image]

**Fig. 2.** Cerebral tumefaction. Tremendous swelling of the nerve fibers of the white matter. Bodian silver impregnation; ×280.

dicated by irregular, ragged outlines of some of the larger axis-cylinders and by the formation of numerous varicosities and end-bulbs. The most obvious swelling of the nerve fibers is noted in sections taken from the central white matter. In most sections from the subcortical white matter the degree of nerve fiber swelling gradually recedes in the vicinity of the cortex; the "u" fibers are spared, for the most part, and of normal appearance.

Changes in the myelin sheaths were studied in sections stained by the
Loyez and Spielmeyer methods. Less obvious than those in the axis-cylinders, they consist of diffuse, irregular swelling and beading of the large majority of myelin sheaths. Occasionally, within some of the myelin sheaths, there are fusiform enlargements and end-globules, together with black-staining, granular masses. In sections taken from the centrum semiovale there is diffuse pallor of the tissue, with many sheaths unstained and widely separated from each other.

In preparations stained with cresyl violet there is occasional swelling or loss of stainability of some of the nerve cells. Any stage of ischemic degeneration, beginning with swelling and chromatolysis and ending with shrinkage, homogenization or complete loss of stainability and formation of “ghost cells” may be present.

Changes of the glia are less conspicuous. There is, however, a moderate degree of swelling of most of the oligodendroglia cells. Some of the cells have a large oval, swollen nucleus and rounded cytoplasm harboring numerous fine granules. The astrocytes appear to be little affected. There are no signs of microglial proliferation.

The distended capillaries and small veins show signs of congestion and
I. MARK SCHEINKER

stasis. Many of the small vessels are surrounded by small accumulations of extravasated red blood cells.

Striking are the hypertrophic and hyperplastic changes of the capillary endothelium (Fig. 3). The nuclei of the endothelial cells are markedly swollen and the surrounding cell protoplasm occasionally contains a few vacuoles. Many of the capillaries are conspicuous for the increased cellularity of their walls. Actual infiltration with hematogenous cells, however, is not present. Definite signs of degenerative alterations of the capillary endothelium are seldom seen.

II. Cerebral Edema

Whereas parenchymal changes in the early stage of cerebral tumefaction may be easily overlooked unless analyzed with special staining methods for nerve fibers and myelin sheaths, the more advanced changes of cerebral edema are quite conspicuous in preparations stained with the routine hematoxylin eosin stain.

Histologic differentiation between the two conditions is relatively simple.

Fig. 4. Cerebral edema. Spongy appearance of the nervous parenchyma caused by distention of perivascular and pericellular spaces and by numerous round or oval spaces filled with serous fluid. Loyez myelin sheath stain; ×280.
Essential criteria for the histopathology of cerebral edema are specified as follows (Scheinker): (a) alveolar or sieve-like appearance of the nervous tissue; (b) maximal distention of the perivascular and pericellular spaces; (c) signs of venous congestion and stasis; and (d) evidence of degeneration and necrosis of the endothelium of the capillaries.

There is little doubt that cerebral edema is to be considered as an advanced stage of cerebral tumefaction. The histopathologic process characterizing cerebral tumefaction apparently is the result of an intracellular hydration with consequent swelling of the individual cells and fibers. This process of physicochemical hydration is histologically apparent only when it has attained a certain degree of intensity (which may explain the absence of structural findings, as reported by many workers). The initial stage of intracellular hydration, however, is soon followed by extracellular fluid accumulation together with a tremendous increase of tissue fluid within the interstitial, pericellular and perivascular spaces, resulting in the histopathologic changes characteristic of cerebral edema.

Sections taken from different portions of the centrum semiovale and from the subcortical white matter of the swollen hemisphere in a typical case of cerebral edema disclose both diffuse alterations of the nervous parenchyma and vascular changes. Fig. 4 illustrates the characteristic spongy appearance of the tissue caused by tremendous distention of the pericellular and perivascular spaces and by numerous large, oval spaces filled with serous fluid. The latter contain neither cellular elements nor stainable substance.

In preparations stained by the Bodian silver method the widely separated nerve fibers display advanced degenerative changes, such as irregularity of contour, beading and final loss of stainability.

The Loyez staining method for myelin sheaths reveals a striking, diffuse pallor. The lack of stainability is due partly to separation of the myelinated fibers and partly to the considerable degree of myelin sheath degeneration, as characterized by pronounced irregularity of contour and occasional disintegration into numerous darkly stained globules and granules.

The glia shows only minor alterations. Some of the astrocytes disclose various degenerative changes of their nuclei. There is no appreciable increase in number of the neuroglial fibers. The oligodendroglial cells are moderately swollen and show partial loss of stainability; in some of their nuclei the chromatin is broken up into fine granules. The microglial cells are little affected. A few microglial phagocytes are seen near the walls of some of the blood vessels.

The axons and myelin sheaths of the overlying cortical gray matter are relatively well preserved. The nerve cells, however, show various stages of ischemic degeneration as a result of tissue hypoxia, secondary to circulatory disturbances.

The vascular alterations, which are conspicuous, consist of pronounced congestion, stasis and morphologic signs of vasoparalysis. Most of the veins and capillaries exhibit distention of their lumina and varying degrees of
I. MARK SCHEINKER

degeneration of the walls, associated with increased permeability for serous fluid. The perivascular spaces are tremendously distended with fluid.

It is of interest to note that in some areas there is an accumulation of fluid between the pia and underlying cortical gray, thus forming an artificial “subpial space.”

III. Cerebral Liquefaction

This last, most advanced stage of cerebral swelling is characterized by: (1) large accumulations of serous fluid within the central white matter; (2)

![Image](https://via.placeholder.com/150)

Fig. 5. Cerebral liquefaction. Large accumulations of serous fluid throughout the liquefied parenchyma. Hematoxylin eosin; X180.

diffuse and almost complete disintegration of the nerve fibers and myelin sheaths; (3) regressive glial changes (Alzheimer’s ameboid glia); and (4) degenerative alterations of the vessel walls.

Sections taken from the white matter of the swollen hemisphere in a typical case disclose an extreme degree of tissue liquefaction. Large accumulations of serous fluid are seen throughout the liquefied parenchyma and within the extremely distended perivascular spaces (Fig. 5).

Preparations impregnated by the Bodian silver method reveal an almost complete destruction of the nerve fibers or disintegration into small fragments. The remaining axons, separated from one another by large spaces,
CEREBRAL SWELLING

exhibit various degrees of degeneration ranging from tortuosity and diffuse or varicose swelling to complete disappearance.

Sections stained by the Loyez method for myelin sheaths reveal diffuse pallor of the white matter as a result of widespread disintegration of most of the myelin sheaths.

The glia shows far advanced regressive changes characteristic of Alzheimer’s type of ameboid glial degeneration (Fig. 6). The individual glial nuclei appear shrunken and pyknotic, and are surrounded by scanty, irregularly shaped cytoplasm.

The majority of small veins show necrosis and homogenization of their walls (Fig. 7).

Sections taken from the cortical ribbon disclose signs of compression and diffuse ischemic changes of the nerve cells.

GENERAL PATHOLOGIC CONSIDERATIONS

Among the histologic findings characteristic of all three stages of cerebral swelling (cerebral tumefaction, cerebral edema and cerebral liquefaction), circulatory changes are uniformly essential and predominant.
The earliest stage of vascular alterations, found in cerebral tumefaction, consists of a striking swelling of the endothelial cells of the capillaries.

A more advanced type, seen in cerebral edema, reveals circulatory disturbances characterized by an extreme degree of congestion and stasis in frequent association with signs of vasoparalysis. These vascular changes, confined chiefly to small veins and capillaries, are manifested by signs of increased permeability for serous fluid of the vessel walls.

Finally, in cerebral liquefaction, the smaller veins and capillaries disclose frank signs of degeneration and necrosis.

Alterations of the nervous tissue proper, secondary to the circulatory disturbances, are briefly summarized as follows: In cerebral tumefaction, diffuse swelling of all constituents of the nervous parenchyma is the predominant, characteristic feature. Such changes are observed only rarely in cases of cerebral edema. The findings in cerebral edema feature an alveolar or sieve-like appearance of the nervous tissue, together with maximal distention of the perivascular and pericellular spaces.

Whereas the myelin sheaths and nerve fibers in cerebral edema disclose only a relatively moderate degree of degeneration, in cerebral liquefaction the bulk of the nervous parenchyma shows severe damage or complete destruction. Even the glia, which seems to withstand the process of tumefac-
tion and edema quite well, succumbs to the process of liquefaction, disclosing widespread regressive signs in the form of Alzheimer's ameboid glial degeneration.

From these points of differentiation, it seems proper to conclude that cerebral liquefaction is a late sequela of cerebral tumefaction and cerebral edema. There is little doubt that the three histopathologic syndromes are varieties of the same morbid process. Differences in their morphology may be explained by differences in the duration and severity of the causative agent. Whereas the pathologic process in the early stage of cerebral tumefaction may be interpreted as intracellular accumulation of fluid with consequent swelling of the individual cells and fibers, the more advanced changes of cerebral edema and cerebral liquefaction are probably caused by an extracellular increase of tissue fluid within the interstitial spaces. And it is to this condition that the differences among the histologic pictures of the three stages of cerebral swelling are to be attributed. Needless to say, the borderline between one stage and the next is not always well defined. In many cases there is gradual transition or partial overlapping from one to another of the three stages.

It should be stressed that the relatively minor lesions observed in cerebral tumefaction indicate the possibility of a reversible process, whereas the more advanced lesions seen in cerebral edema and cerebral liquefaction appear irreversible.

Regardless of the histopathologic varieties of the morbid process, the gross appearance of the brain always manifests a considerable increase in bulk (actual swelling) of one or both hemispheres. The most appropriate common designation of the gross appearance of all three varieties of the morbid process, therefore, would seem to be "cerebral swelling."

Predominant localization of cerebral swelling. The white matter is predominantly involved in all cases of brain swelling. The cerebral gray matter (cortical gray and basal ganglia) is less vulnerable. Although pathologic lesions of the cortical ribbon are frequently seen, they differ considerably from those of the white matter. Even grossly there is a striking discrepancy between the two. In contrast to the tremendously swollen white matter, the cortical gray substance is considerably decreased in size and may appear narrowed and compressed.

Microscopically the change most commonly observed within the cortical gray matter in all three stages is early chromatolysis of the nerve cells. Only occasionally are encountered more advanced changes, such as pyknosis or ischemic nerve cell degeneration. The latter is characterized by loss of stainability of the cell cytoplasm, shrinkage of the nucleus, and irregularity and eccentricity of the nucleolus. The affected cells are frequently surrounded by an increased number of satellites (oligodendroglia nuclei).

It is the author's opinion that the cellular changes of the cortical ribbon are secondary to the swelling of the underlying white matter and may readily be interpreted as the result of pressure and ischemia.
Widening of the pericellular and perivascular spaces of the gray matter, described by many observers as characteristic for cerebral edema, is too frequently seen as the result of formalin fixation or of embedding in paraffin to be considered as a reliable sign. According to the author's experience, such changes are to be evaluated only in association with other, more reliable signs, such as vascular alterations, swelling of the nerve fibers and glial changes.

The accumulation of fluid, however, in the distended subpial space may constitute a fairly reliable sign of edema; it cannot be interpreted as an artifact resulting from poor fixation or embedding, because it is seldom observed under those conditions.

*What mechanism is responsible for the selective vulnerability of the white matter for cerebral swelling?* Different regions of the cerebrum are characterized by different patterns of blood supply. It has been demonstrated in an extensive series of pathologic conditions (Scheinker24) that the type and distribution of cerebral lesions are influenced primarily by local structure and, in particular, by local vascular supply. The selective vulnerability of the white matter for cerebral swelling can best be explained by the peculiar-}
CEREBRAL SWELLING

The same changes are frequently observable in vascular accidents resulting in sudden occlusion of a major blood vessel. It is generally known that, in the early stage of cerebral infarction, there may be a pronounced degree of associated swelling confined chiefly to the white matter. It is quite evident that the causative factor of edema in these cases must be ascribed to circulatory disturbances.

EXPERIMENTAL STUDIES

In their recent experimental work on brain edema, Prados, Strowger and Feindel17 found changes similar to those described by the author in human brains. In the earliest phase of the experimentally produced edema, vasodilatation of the venules and capillaries occurs. About two hours after the outset of the experiment, a certain degree of brain swelling may be noticeable. By means of intravenous injections of trypan dyes, the authors demonstrated a definite increase in the permeability of the blood vessels as evidenced by diffuse leakage of the dye through the capillary endothelium into the adjacent tissue, resulting in diffuse staining of the nervous parenchyma. It has been established by numerous investigators that, except under pathologic conditions, ectodermal elements of the brain have no affinity for trypan blue.

Histopathologic examination of the brains of the experimental animals disclosed pronounced morphologic changes in the small blood vessels, as characterized by engorgement and aneurysmal dilatation of the capillaries and occasional extravasation of blood into the perivascular spaces. Some of the capillaries, however, were emptied and collapsed; with benzidine stain, areas of ischemia were occasionally demonstrated. Neuronal changes, which were observable early, were characterized either by swelling, chromatolysis and liquefaction or by shrinkage and homogenization of the cells associated with dilatation of the perineural spaces. There was a moderate degree of microglial proliferation. After 48 hours the pathologic tissue alterations began to revert to normal, and at the end of the third or fourth day normal, preoperative conditions were restored.

In their study the authors arrived at the following conclusion: "Our experiments show that the vessels of the brain undergo an increase of permeability and certain morphologic changes, which would lead us to agree with Scheinker's point of view that the circulatory changes are essential to explain the excess of fluid in the tissue spaces which is the fundamental feature in any edematous condition." In summarizing the histopathologic findings, the authors concluded that "the whole picture could be considered as a mild, edema-like reaction due to a primary alteration, both functional and anatomic, of the integrity of the circulation, the cellular alterations being secondary to the circulatory changes." [italicized by the writer]

Although the aforementioned experiment is of great value, many more studies are needed to fill in all the gaps in present-day knowledge of the intricate problem of cerebral swelling.
In the vast majority of cases of space-consuming lesions, increased intracranial pressure is the direct result of cerebral swelling. General brain tumor symptoms, such as headache, vomiting, dizzy spells, associated with general signs of increased intracranial pressure (papilledema and slow pulse rate), are probably in part the result of cerebral swelling.

In 1920 Meyer\textsuperscript{15} called attention to medial displacement and herniation of the hippocampal gyrus into the tentorial incisura in cases of space-consuming intracranial lesions. The subject was later elaborated by van Gehuchten,\textsuperscript{29} Jefferson,\textsuperscript{10} Moore and Stern,\textsuperscript{14} Smyth and Henderson,\textsuperscript{26} Reid and Cone,\textsuperscript{19} and Schwarz and Rosner.\textsuperscript{25} All these contributors have amply demonstrated that space-consuming lesions may cause appreciable herniation of the hippocampal gyrus of the temporal lobe into the potential space lying between the free edges of the tentorium and the brain stem.

The same studies have shown that a series of clinical signs and symptoms may be associated with this type of herniation. The most frequently observed symptoms are: anisocoria, with or without dysfunction of the pupillary light reflexes; imbalance of extra-ocular muscles; cardiorespiratory and thermoregulatory disturbances; paradoxical and shifting signs of involvement of the pyramidal tracts; decerebrate rigidity and stiffness of the neck.

In a recent study (Scheinker\textsuperscript{23}), it was demonstrated that herniation of a relatively small portion of compressible tissue (hippocampal herniation) is not the real cause of the gravity of the clinical syndrome.

A histopathologic analysis of 55 cases revealed that most of the clinical symptoms and the frequent sudden deaths are to be ascribed to a frank herniation of the rostral portion of the brain stem into the tentorial opening, followed by swelling and/or hemorrhages within the vitally important midbrain centers. The syndrome, previously designated by several investigators as “hippocampal herniation” or “temporal pressure cone,” was described by this author as “transtentorial herniation of the brain stem.”

Of the numerous points that emerged from the study of transtentorial herniation of the brain stem, the following are briefly summarized:

\textit{Unilateral cerebral swelling as a frequent cause of brain stem herniation through the tentorial opening.} In all cases of brain stem herniation associated with cerebral trauma, brain tumor, brain abscess or massive intracerebral hemorrhage, there is pronounced unilateral swelling of the affected hemisphere with shift and compression of the ventricular system toward the opposite side. The shift and compression of the ventricles are readily explained by the unilateral swelling of the brain, in some instances sufficient to cause displacement of the affected hemisphere across the midline under the free edge of the rigid falx. Inasmuch as the falx in the adult is an immobile structure, it is obvious that there must be a tendency to displacement of the swollen hemisphere specifically beneath the free edge of the falx, causing herniation of the supracallosal gyrus.

In all cases under study by the author, there was a herniation of the
rostral portion of the midbrain through the tentorial opening. The homolateral side of the brain stem was considerably swollen. The aqueduct of Sylvius appeared displaced and compressed.

It is evident that, as a result of the swelling of the entire hemisphere, including the temporal lobe, the mesial portion of the latter lying immediately above the tentorial ring is the first to be displaced downward through the tentorial opening. With increased duration and severity of the brain swelling, a downward displacement and frank herniation, together with distortion and compression, of the midbrain take place.

![Fig. 8. Transtentorial brain stem herniation.](image)

Pathologic lesions produced by the transtentorial brain stem herniation. On gross examination the midbrain appears swollen, as a rule, and reveals large numbers of small, coalescent hemorrhagic effusions (Fig. 8). No part of the brain stem appears immune from hemorrhage, though most of the hemorrhages are observed in the rostral portion of the brain stem and only relatively few are detected in the caudal portion. The great majority of hemorrhagic lesions are situated in the tegmental portion of the midbrain, chiefly in the periaqueductal region and in the median raphe. However, it should be emphasized that the brain stem lesions may occasionally be of such
minimal degree that they may easily be overlooked on gross examination. Almost all cases of brain stem herniation which came to the author’s attention as grossly normal disclosed, on microscopic examination, various stages of swelling and far advanced degenerative neuronal changes.

*Origin and pathogenesis of hemorrhages of the brain stem.* In published reports on midbrain hemorrhages, stress has always been placed upon their arterial origin (Moore and Stern,14 and others). However, there has recently been brought forth evidence that hemorrhages of the brain stem are, irrespective of their etiology (cerebral trauma, brain tumor, brain abscess or intracerebral massive hemorrhages), *venous* in origin and related to medium-sized and small veins (Scheinker). Often the hemorrhages may occur in the form of narrow bands, enclosing the extremely congested veins like a sleeve, either occupying the perivascular spaces or lying free in the adjacent nerve tissue. In many instances the small perivenous hemorrhages tend to fuse, thus giving rise to larger hemorrhages. Only in those relatively few instances when the hemorrhagic lesions are more extensive, may it be difficult or impossible to be sure of the source of the hemorrhage; and this is mainly because of complete disintegration of the tissue and abundance of blood. Within the great majority of the smaller hemorrhagic lesions, however, there may be seen one or several tremendously congested veins with walls displaying advanced disorganization, but not real rupture. In some instances the veins are represented by mere outlines of their walls. These have undergone almost complete degeneration and the content of the veins merges with the extravasated blood surrounding the blood vessels. The perivascular spaces, maximally distended as a rule, are filled with large masses of serous fluid and red blood cells.

*Swelling of the herniated brain stem.* In many of those cases in which the gross appearance of the herniated brain stem is normal or shows a moderate degree of increase in bulk, the microscopic examination discloses findings characteristic of tumefaction, edema or liquefaction. As a rule, these changes are associated with congestion of the smaller veins and capillaries. Only occasionally are there small petechial hemorrhages within the distended perivascular spaces of some of the congested veins.

*Pathophysiologic mechanism responsible for herniation and hemorrhages of the brain stem.* The following theory of the mechanism responsible for the development of edema and hemorrhage in the brain stem is proposed for consideration: The author’s own observations afford evidence that a sudden increase in bulk of one of the cerebral hemispheres, caused by swelling of the brain, leads to an acute increase in the supratentorial pressure. In the earlier stages the affected cerebral hemisphere displaces cerebrospinal fluid from the subarachnoid space and from the cisterns. At a later stage the ever increasing demand for space leads to profound shifts of cerebral substance; the initial formation of a temporal pressure cone (as described by Meyer,13 van Gehuchten,29 Jefferson,10 Reid and Cone,19 and others) is followed by downward displacement and herniation of the brain stem with subsequent
CEREBRAL SWELLING

plugging of the tentorial hiatus, producing a bottleneck for both the subarachnoid and the ventricular fluid. At the same time, the shifting cerebral substance may compress or occlude the narrow aqueduct of Sylvius, and the intraventricular fluid becomes trapped in the lateral and third ventricles. This leads to a steadily progressing disparity between the intracranial pressure above and that below the tentorium. With the constant increase of the intraventricular pressure, the herniated portion of the brain stem is pushed deeper into the tentorial opening. As it progresses, it leads to compression and stretching of the superficial blood vessels, especially the veins, with considerable obstruction of the venous circulation and a resultant severe degree of congestion and stasis. The thin-walled, smaller veins, composed of simple endothelial tubes, are most likely to be vulnerable to compression and to hypoxic degenerative changes in their walls resulting from stasis. Thus, in the earlier stages, compression of thin-walled veins between the impinging uncus and the brain stem is believed to occur. In the later stages the possibility of interference with free venous outflow is even greater because the cerebral substance and the intervening veins are jammed against rigid dural reflections. This is believed to result in a severe degree of congestion and stasis, local venous hypoxia due to the stasis and, possibly, degenerative changes in the walls of the veins. Finally, if complete block of cerebrospinal fluid occurs, resulting in increased supratentorial pressure with complete herniation of the brain stem, the smaller veins are ready to give way and numerous perivenous extravasations take place. The small veins of the periaqueductal region evidently are poorly supported by the loose tissue of the gray substance, as compared with those of the white matter; which theory may explain the predilection of the perivenous hemorrhages for this region. The fixation of a certain number of the larger superficial veins of the brain stem for a long distance parallel to a bony surface makes them more exposed to the increased pressure.

The anatomic observations in support of this theory of mechanism may be listed as follows: (1) the gross and histopathologic evidence of swelling of the brain present in the affected hemisphere; (2) transtentorial herniation of the rostral portion of the brain stem; and, finally (3) the predominantly perivenous character of the hemorrhages in the midbrain associated with far advanced venous congestion and stasis.

Correlations between ventricular and lumbar pressures. In the past the pressure within the cerebral ventricles was considered always to be in equilibrium with the pressure throughout the spinal subarachnoid space. The observations of Hodgson and Smyth and Henderson give strong support to the belief that the lumbar and the ventricular pressures are not of necessity always equal. Hodgson reported a series of 49 cases of intracranial tumor in which he studied the ventricular and lumbar pressures. He concluded that partial block might result from herniation of the cerebellar tonsils, and that under such conditions the initial lumbar pressure might be lower than the pressure in the ventricles. The relation between the lumbar and the ventricu-
lar cerebrospinal fluid was studied by Smyth and Henderson in 39 patients, the majority of whom had intracranial tumor. Their observations proved that the ventricular pressure exceeded the lumbar pressure in all cases in which the tumor was above the tentorium and in which there was post-mortem evidence of herniation of the ipsilateral temporal lobe through the incisura tentorii. On the other hand, in cases in which the tumor was situated subtentorially the lumbar and ventricular pressures were equal. It is of interest that in the latter group of cases there was pronounced, and in some cases extreme, tonsillar herniation. On the basis of these extremely important observations, Smyth and Henderson came to the conclusion that the disparity between the ventricular and the lumbar pressures is due mainly to herniation of the medial border of the temporal lobes into the incisura tentorii, with subsequent compression or obliteration of the iter of Sylvius.

Moore and Stern\textsuperscript{14} collected 10 cases of hemorrhages of the brain stem out of 130 cases of intracranial tumor. The presence or absence of herniation of the hippocampal gyrus was not stated in every case, but the lesion was present in the majority. In spite of this observation, the authors came to the conclusion that the hemorrhages in the brain stem "are finally brought on by reflex increase in the systemic blood pressure."

Experimental observations. The relation between the ventricular and lumbar cerebrospinal fluid pressures has been studied experimentally by Kahn.\textsuperscript{11} An extreme degree of edema of the brain was produced by the perfusion of distilled water in the common carotid artery of animals. During the experiments the cisternal and intraventricular pressures were recorded simultaneously.

High intraventricular and relatively low cisternal pressures were constantly observed. This disparity was interpreted as probably due to herniation of the brain stem into the foramen magnum or through the incisura tentorii, with the creation of a resulting partial block between the lateral ventricles and the cisterna magna. The circulatory and respiratory embarrassment associated with high levels of intraventricular pressure could be relieved by ventricular drainage. No circulatory or respiratory embarrassment occurred when both the cisternal and the intraventricular pressures were at high levels; medullary embarrassment appeared soon after the cisternal pressure was lowered, the intraventricular pressure alone remaining high.

Clinical conclusions. What additional therapeutic conclusions are to be derived from the pathologic observations described? The following significant clinical points should be stressed:

Transtentorial herniation of the brain stem presents a grave hazard for the clinician and the neurosurgeon. It is evident that lumbar puncture and pneumoencephalography must be interdicted if the existence of the herniation of the brain stem has been clinically recognized or suspected.

Transtentorial herniation of the brain stem explains in some instances
the fact that lumbar pressures are not always a true index of intraventricular pressures.

Patients with lesions of the temporal lobe appear to be graver clinical risks, probably because of the possible tendency toward development of transtentorial herniation of the brain stem. Therefore such manipulative procedures as lumbar puncture or pneumoencephalography are attended by greater risks.

It has been assumed, in cases of supratentorial tumor in which death followed lumbar puncture, that cerebellar herniation into the foramen magnum was responsible. However, it has not been explained how the intraventricular pressure could be transmitted to the posterior fossa. There is little doubt that transtentorial herniation of the brain stem is the important factor. The frequent absence of cerebellar pressure cone corroborates these conclusions.

It is quite evident, however, that in some cases of subtentorial lesions, such as cerebellar neoplasms, the cerebellar herniation into the foramen magnum may be responsible for death following lumbar puncture.

Clinical and pathophysiologic evidence has been accumulated to prove that the hypothalamic nuclei contain the higher regulatory centers for respiratory and cardiac control. It appears that transtentorial herniation of the brain stem might result in an interruption of the cardiorespiratory pathways between the diencephalic and the medullary centers, and might be responsible for the so-called neurovegetative disturbances: namely, irregularities in respiration and pulse, hyperthermia and sudden cessation of respiration, with a rapid, bounding and often irregular pulse.

Attempts to release the temporal pressure cone by removal of the herniated portion of the gyrus hippocampus have been suggested by Jefferson.10 The author's own observations suggest that section of the free edge of the rigid tentorium should be undertaken in an effort to distribute pressure more evenly. In many cases, and particularly in those of tumor of the temporal lobe, this is technically possible.

It is conceivable that in certain cases the establishment of ventricular drainage might prove to be a life-saving measure, pending a more definite operative attack.

SUMMARY

The gross and histopathologic findings of cerebral swelling in 125 cases have been studied.

Regardless of the primary cause of the cerebral swelling (brain tumor, cerebral abscess, massive hemorrhage or cerebral infarction), the findings in all cases were identical.

Attention is called to the incompleteness of understanding of cerebral swelling on the part of both clinicians and pathologists, and to the prevalence of contradictory concepts relative to the condition.
“Cerebral swelling” is the term proposed to denote the gross appearance of a brain characterized by a local or diffuse increase in bulk of one or both hemispheres.

The condition referred to grossly as “cerebral swelling” is represented microscopically by three types of histopathologic change, described as tumefaction, edema and liquefaction. The characteristic histologic criteria for recognition of, and differentiation among, the three types of lesions are given in detail.

Despite discrepancies in their histopathologic features, it is assumed that fundamentally the three conditions represent different stages of the same biologic process; occasionally they may merge insensibly one with another. Attention is drawn to the significance of unilateral cerebral swelling in the production of transtentorial brain stem herniation.

The rôle of cerebral swelling in the production of midbrain hemorrhages is emphasized. These are believed to be perivenous in origin, and to be caused by an extreme degree of venous congestion resulting from compression and strangulation of the veins of the herniated midbrain.

In view of the gravity of the clinical symptoms resulting from transtentorial herniation of the brain stem, an attempt to distribute pressure more evenly by means of the establishment of ventricular drainage or by means of section of the free edge of the rigid tentorium may be a life-saving measure, pending final and more radical treatment.

REFERENCES
CEREBRAL SWELLING


