Development of Recent Thoughts on Intracranial Pressure and the Blood-Brain Barrier

JOHN L. FOX, M.D.*

Neurosurgical Service, George Washington University Hospital, and Department of Neurology and Neurological Surgery, George Washington University School of Medicine, Washington, D. C.

"There are works which wait, and which one does not understand for a long time; the reason is that they bring answers to questions which have not yet been raised; for the question often arrives a terribly long time after the answer."

Oscar Wilde

"It seems highly probable that only after membranes appeared could the first living things be organized from the soup brewing in the ancient seas."

J. David Robertson

What unique situation in the human body may result from capillary blood flow shearing across electrically charged semipermeable proteolipidic membranes of abutting endothelial and glial cells in the absence of adequate pericapillary interstitial space in the brain? A phenomenon known for decades as the blood-brain barrier may be the precocious answer to this question. Only after these specialized membranes appeared could the neuraxis be protected from variations in the extracellular fluid of the general body, descendant of the ancient seas.

Nearly all physicians at one time or another must deal with the phenomenon of intracranial hypertension. Neurosurgeons and anesthesiologists have been confronted at operation with a brain which suddenly and mercilessly starts billowing out under pressure. Intracranial pressure and the blood-brain barrier for some time have been thought to be closely related. Yet the clinical, physiological, biochemical and histological findings often have seemed inconsistent when one begins dealing with the blood-brain barrier, extracellular brain space, brain swelling and cerebral edema, intracranial hypertension, and even the threshold of stimulation of the central nervous system. However, reviewing the older studies and recent findings can help integrate one's thoughts towards a more meaningful perspective. Why is cerebral swelling or edema often delayed by hours or days after the brain injury? Part of the answer may lie in the often neglected pre-injury status of the brain cells, their vascular supply, and their environment: the patient himself. The neurosurgeon cannot be content with treating the brain alone. Clinical and experimental data are beginning to reveal the close dependency of the brain cell upon heart, lungs, liver, kidneys, vascular and endocrine systems, to name a few. Malfunction of any part of the whole man may adversely affect metabolism of the brain cells and consequently the success of intracranial surgery. The brain cells are complex; the succeeding paragraphs will highlight some of these complexities as well as their dynamic relationship to the blood-brain barrier and intracranial pressure. This essay evolves into a certain concept of the latter two related phenomena.

For the purposes of clarity this paper will adhere to the following definitions. The blood-brain barrier is the phenomenon or unique situation existing within the living central nervous system whereby a given molecular or ionic substance is detected to move from the blood stream into a unit quantity of brain substance at a slower rate than the identical substance in the same blood concentration at the same time will pass into an equivalent quantity of either general body tissues or injured brain substance of the same individual. The extracellular space is synonymous with interstitial or intercellular space, and in the brain it is that space existing

Received for publication August 32, 1962.
Revision received October 15, 1963.
* Present address: Veterans Administration Hospital, Washington, D. C.
outside of the cell bodies and blood vessels but not including the Virchow-Robin or cerebrospinal-fluid spaces (even though the extracellular fluid probably is cerebrospinal fluid). Brain or cerebral edema is extracellular distension by hyperhydration in brain parenchyma. Brain or cerebral swelling is intracellular distension by hyperhydration in brain parenchyma. These latter two concepts can be included under the term "increase in brain bulk"—but an increase in the vascular or cerebrospinal-fluid space may also appear to increase the bulk of the brain in vivo. Intracranial pressure is the force with which a unit area of surface of the intracranial contents and a juxtaposed unit area of its envelope oppose each other at any given instant in time. Elevated intracranial pressure (intracranial hypertension) is a result of hyperhydration of the central nervous system in the absence of adequate compartmental (e.g. vascular, cerebrospinal fluid, brain substance) buffering within a strongly elastic and resilient enclosure. Finally, the threshold of stimulation of the central nervous system refers to the level of resistance of neural elements to the formation and propagation of neural impulses. This is mentioned here, for it will become evident that irritability of the brain as well as hydration of the central nervous system seem to be intimately tied up with a concept of the "neural-glial barrier" and the "capillary-glial barrier."

Physicians have studied many physiological methods of reducing intracranial pressure. Before going behind the scenes of clinical application, it would be well to briefly list these methods. Besides the usual restrictions of intake of fluid and stimulation of diuresis, elevation of the head, drainage of cerebrospinal fluid (ventricular, cisternal, spinal), maintenance of adequate oxygenation and perfusion of brain, correction of any imbalance of electrolytes and proteins, attention to adequate functioning of body-organ systems, avoidance of coughing and straining, mechanical operative decompression, hemostasis, and limitation of iatrogenic physical and physiological brain trauma at surgery, the following have been used: controlled vascular hypotension, intravascular agents of high osmolarity, intravascular agents of hyperhydration, hypothermia, hyperventilation, cervical sympathetic block, low sodium intake, caffeine, proteolytic enzymes, antihistamines, anticholinergic agents, carbonic anhydrase inhibitors, and carbon-dioxide buffers (Fig. 1, and Table 1).

**The Circulatory System**

A discussion of the dynamic participation of intracranial capillary circulation on the blood-brain barrier will be entertained after other developments are brought to light in this essay. But at this time it should be stressed that a major factor in elevated intracranial pressure is the circulatory system (Fig. 10). After death the cerebrospinal-fluid pressure gradually drops to zero over a period of several hours (in spite of the gradually increasing brain swelling and edema) (Fig. 1). The initial drop correlates with the removal of cerebrospinal fluid from the cranial compartment and the collapse of the blood-brain barrier. The slow drop over several hours is in part due to the removal of edema fluid from the cranial compartment and the eventual collapse of the blood-brain barrier.