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# Periventricular White-Matter Cysts in a Murine Model of Gram-Negative Ventriculitis

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Hydrocephalic patients with shunt infections frequently develop multiple cerebrospinal-fluid-density cysts that cause midline shift and life-threatening intracranial hypertension and respond poorly, if at all, to shunt diversion of cerebrospinal fluid. These cysts have been considered to represent multiloculation of the ventricular system by ependymal adhesions and veils resulting from ventriculitis. Studies using an experimental model of *E. coli* meningitis/ventriculitis in the hy-3 mouse suggest these cysts: (1) develop by the coalescence of lakes of white-matter edema, (2) grow to large size entirely within the periventricular white matter, and (3) cause pseudoloculation of the ventricle by compression from without. The so-called intraventricular septa or "veils" are the ependyma displaced inward by subependymal cysts or sheets of residual pericystic white matter. This finding permits better interpretation of computed tomographic images depicting persistent enlargement of the so-called multiloculations despite functioning ventricular shunt catheters, the multiplicity of cysts, and the white-matter location of these cysts.

Hydrocephalic children with shunt infection, choroiditis, and ventriculitis frequently suffer: (1) reduced cerebrospinal fluid (CSF) production, (2) poor ventricular CSF turnover, (3) elevated CSF protein concentration, (4) isolation of individual ventricles by paraventricular abscesses or cysts that compress the exit foramina, and (5) so-called multiloculation of the ventricular system by broad sheets of tissue designated "intraventricular septations," "septae," or "ventricular veils" [1–10]. Such children frequently require organism-specific antibiotics, immediate placement of external ventricular drains, multiple revisions of obstructed shunts, placement of long multihole catheters to attempt drainage of multiple "loculations," and eventual laser fenestration of the multiple "septae" to achieve adequate decompression of the hydrocephalus [2, 5].

Clinical experience has shown: (1) that mental retardation in hydrocephalic children is directly related to the development of shunt infection [11, 12], (2) that the most severe infections occur with Gram-negative organisms [2, 13–15], (3) that younger children with immature brains suffer the most severe sequelae, and (4) that the so-called multilocular ventricles are refractory to routine shunt decompression [1, 2, 5–9, 15.] The following study was undertaken to increase our understanding of the pathophysiology of Gram-negative bacterial infection in the immature nervous system and to

serve as a guide to improved management of the infant with shunt infection.

## Rationale for the Experimental Model

The hy-3 mouse is an inbred strain with a significantly depressed immune system and a genetic form of hydrocephalus transmitted as a mendelian recessive trait [15–19]. Litters of hy-3 mice thus provide hydrocephalic study subjects with otherwise similar but nonhydrocephalic litter-mates for controls. Because hydrocephalus in these mice is genetically determined, the model is free from artifact introduced by a destructive procedure undertaken to create hydrocephalus. Prior detailed descriptions of the histological and ultrastructural features of the normal and hydrocephalic hy-3 mouse brain provide an adequate basis for distinguishing between pathological changes caused by ventriculitis and those associated with hydrocephalus alone [15–19]. Prior work has documented that the extracellular space of the hy-3 mouse does not reach full maturity and hydrocephalus is not fully expressed until age 21 days [17].

## Materials and Methods

In the protocol designed and implemented by D. G. M. and Y. Y., the study group of 133 hy-3 mice was divided into three age groups simulating different degrees of brain maturity: 5-day-old mice ( $n = 39$ ), 10-day-old mice ( $n = 48$ ), and 15-day-old mice ( $n = 46$ ). Of this group, seven 10-day-old mice and three 15-day-old mice were hydrocephalic. Twelve normal and six hydrocephalic hy-3 mice of various ages underwent insertion of sterile catheters to serve as controls. A virulent K1 strain of *E. coli* was isolated from a documented human case of shunt infection and maintained by serial transfers in our laboratory [20]. Inocula were prepared from well shaken broth suspensions diluted in normal saline to concentrations of  $10^3$ – $10^7$  microorganisms/ml.

A 20 gauge trocar and polyethylene tubing (outer diameter 0.61 mm) were inserted under sterile conditions through skull and frontal lobe into one lateral ventricle; 5  $\mu$ l of inoculum or control solution was injected, and the trocar was removed. The tubing was then cut and left in situ, covered by skin, to simulate a contaminated shunt system.

Animals surviving for 5 days were sacrificed and studied by light microscopy, electron microscopy, and photomicrography of the

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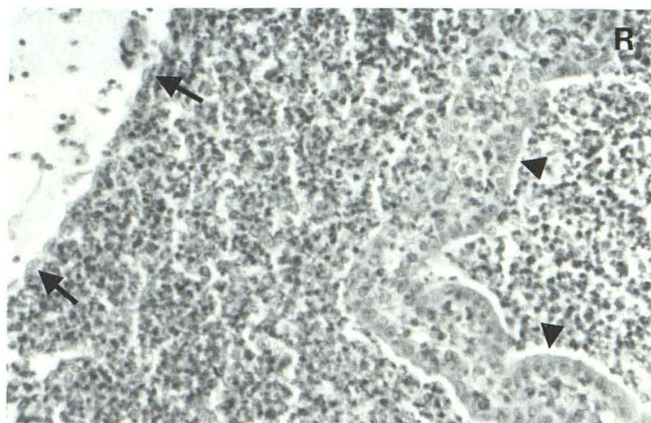


Fig. 1.—Primary *E. coli* pyocephalus in hydrocephalic hy-3 mouse (H and E stain). Leukocytes pack inoculated ventricle (R), surround choroid plexus (arrowheads), and infiltrate its stroma. Choroidal epithelium and ependymal layer (arrows) are well preserved. There is little subependymal edema.

meninges, subarachnoid spaces, ventricles, corpus callosum, catheter, catheter tract, and ventriculostomy site. Animals dying of infection within 5 days were used to assess infection rates and mortality. Animals in whom technical complications such as puncture-induced hemorrhage obscured the pathologic findings were excluded from analysis. Additional details of the experimental procedures are reported elsewhere [15; other unpublished data].

## Results

None of 18 control animals contracted infection. The overall infection rate in the study group of 133 was 89.4%. Five of the 10 hydrocephalic mice failed to contract infection and survived. All five hydrocephalic mice in whom infection was successfully introduced died. Linear regression analyses indicated independent, statistically significant increases in mortality with increase in numbers of organisms injected; increasing immaturity of the mouse; and presence of hydrocephalus.

### Postmortem Findings

Strikingly consistent anatomic and histologic changes are described below. Ultrastructural changes will be discussed in a separate report. The polyethylene tube punctured the ipsilateral ventricle in all cases. In some animals, particularly those in the 5-day-old group, the tip of the tube lay only partly within the ventricle, suggesting that inoculation was partly intraventricular and partly extraventricular.

An abscess was usually present at the shunt tip. Depending on the location of the tip, the abscess was a focal paraventricular abscess and/or a localized primary pyocephalus. When the inoculum produced primary pyocephalus, the infection remained largely confined to the ventricle and did not transgress ependyma to infect the paraventricular region (fig. 1). In such cases, the ependymal layer appeared intact on light microscopy and the subependymal zone showed little evidence of edema or inflammation.

When the inoculum produced a paraventricular abscess, the abscess frequently spread along the extraluminal surface of the ventricular wall and extended into the choroid plexus via the tela choroidea. The ependymal layer appeared intact on light microscopy. In the main, the infection did not transgress the intact ependyma; only limited amounts of purulent material could be observed in the ventricle in such cases (figs. 2–4). Paraventricular abscesses

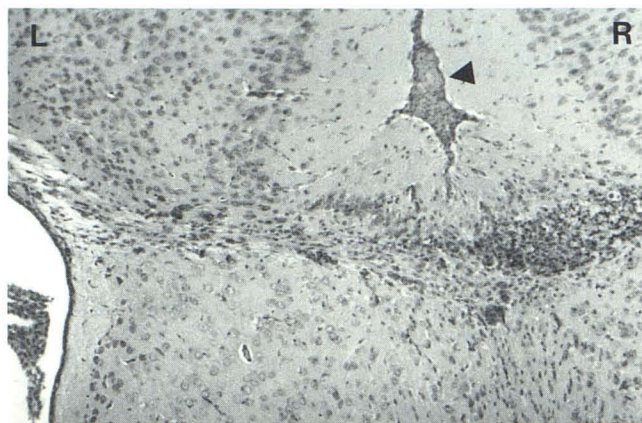


Fig. 2.—Paraventricular inflammation in hydrocephalic hy-3 mouse with *E. coli* ventriculitis (H and E stain). Coronal section through inoculated hemisphere (R), contralateral hemisphere (L), and pus-filled interhemispheric fissure (arrowhead). Hemorrhage, edema, and inflammatory cells penetrate corpus callosum to contralateral paraventricular region. Contralateral ventricle shows little pus, normal choroid plexus, intact ependymal layer, and moderate edema of subependyma.

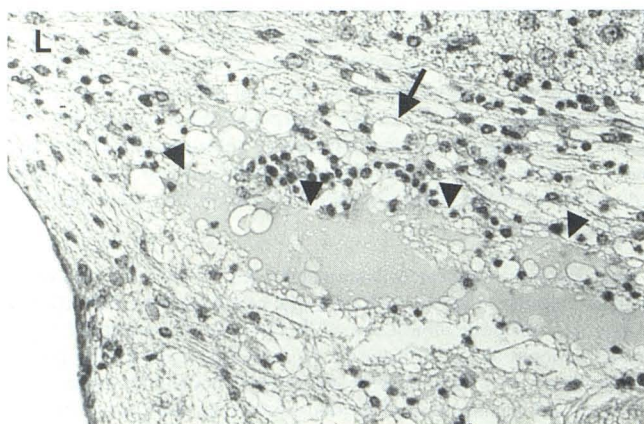


Fig. 3.—Paraventricular inflammation in hydrocephalic hy-3 mouse with *E. coli* ventriculitis (H and E stain). Marked inflammatory edema has expanded extracellular space and penetrated corpus callosum from inoculated side (not seen) to contralateral paraventricular region (L). Edematous spaces appear as small cysts (arrow) or larger coalescent cavities (arrowheads) filled with homogeneously staining fluid. Cavities vary widely in size.

frequently compressed the subjacent ventricle and occasionally isolated the lateral ventricles by occluding the foramina of Monro, causing substantial ventricular dilatation. Paraventricular abscess extended retrograde along the catheter tract in some mice, but the degree of infection was usually milder than at the shunt tip. In the younger animals, particularly the 5-day-old group, the infection spread diffusely throughout the parenchyma and was often associated with focal necrosis in the paraventricular tissue.

Spread of infection in either direction across the ependyma was observed in three situations: (1) when the ependymal lining had been disrupted mechanically by the trocar; (2) when the infected mice were hydrocephalic (even if the infection at the primary site was mild); and (3) when the infected mice were very immature. When paraventricular infection transgressed the ependyma to cause secondary pyocephalus, the inflammatory cells generally remained attached to the ventricular wall locally and to the choroid plexus. They filled the ventricular cavity only in severe cases.



Infection commonly spread to the cortical subarachnoid space via either the CSF pathways or (less frequently) the catheter tract. Subarachnoid accumulations of purulent material were most prominent in the basal cisterns. In severely infected animals, particularly those in the 5-day-old group, small subcortical abscesses appeared to develop by direct extension of subarachnoid infections along the Virchow-Robin spaces.

#### Choroid Plexus

The choroid plexus was often totally surrounded by purulent material (fig. 1). The inflammatory cells coated the choroid plexus and extended into the stroma. The choroidal cells rested on an intact basal lamina. However, the underlying connective tissue

stroma and fenestrated capillary network were involved in the inflammatory process.

#### Extracellular Space and Subependymal Region

The extracellular space was markedly increased in many animals, especially in the subependymal region. This increase was more dramatic in the hydrocephalic animals and in the youngest animals, particularly the 5-day-old group. In most animals, inflammatory cells were concentrated in the subependymal region despite the absence of identifiable organisms in this region. Only in the very immature 5-day-old group were organisms consistently observed. Inflammatory cells and edema consistently spread from the paraventricular region to the contralateral hemisphere along the enlarged extracellular spaces of the corpus callosum and other commissures, spreading to distant sites of the inoculated hemisphere along the enlarged extracellular spaces of the longitudinal nerve bundles (fig. 2). Inflammation nearly always reached the opposite paraventricular region more rapidly via the extracellular spaces of these fiber bundles than by the CSF pathways of the ventricles (figs. 2 and 3). Inflammation also involved the extreme capsules prominently.

The enlarged, edema-filled extracellular spaces appeared to form small cavities or cysts in the white matter, particularly in the paraventricular region (fig. 4). These cysts separated the cellular elements of the white matter and, in places, caused the intact ependymal layer to detach from the brain parenchyma (fig. 4). The smaller cysts appeared to coalesce into larger cysts, producing some edema cavities as large as the ventricles themselves. Such cavities may be designated pseudovertricles. When two large edema cavities abutted each other, the intervening residual white matter had the appearance of a thin septum (fig. 4). When a juxtaventricular edema cavity compressed the ventricle and displaced the intact, detached ependyma inward, the combined cavities of the ventricle and the pseudovertricle resembled a single dilated ventricle loculated by a thin intraventricular septum or veil (fig. 4). Where abutting cyst walls began to diverge from the ventricle or from each other, the remaining brain tissue typically assumed the shape of a small triangle or wedge whose apex gave rise to the septum (fig. 4).

#### Neuropil

The neuronal elements and myelin of the brain appeared relatively resistant to the inflammatory process. Glial astrocytic processes,

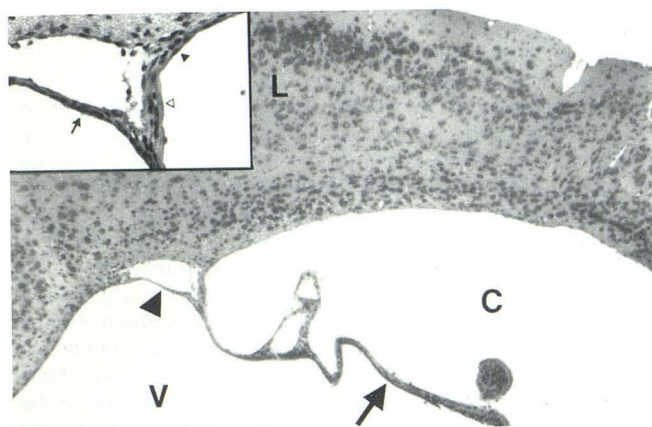
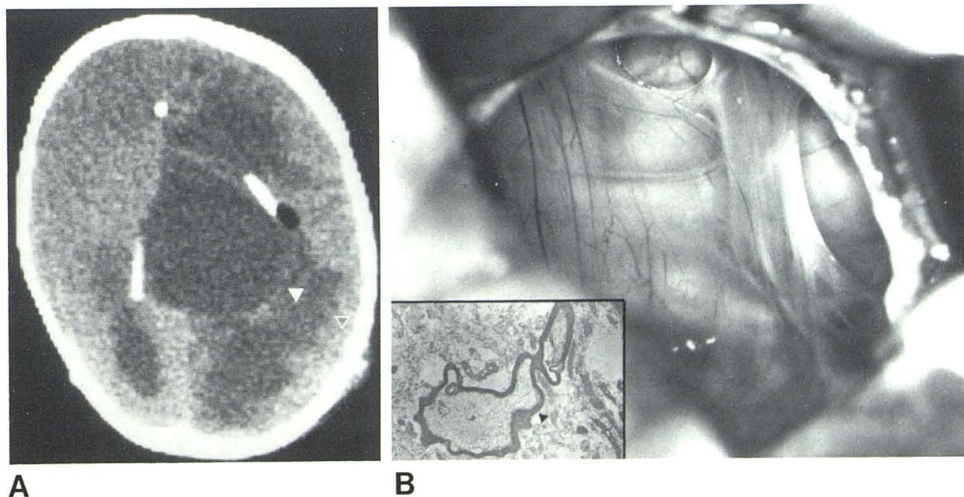


Fig. 4.—Paraventricular pseudovertricles with "multiloculation" in hydrocephalic hy-3 mouse with *E. coli* ventriculitis (H and E stain). Coronal section through cortex and white matter of uninoculated contralateral hemisphere (L) shows uninoculated ventricle (V); equally large, juxtaventricular edematous cavity (C); and several small subependymal cysts (arrowhead). Pseudovertricular edematous cavity (C) and small cysts shear ependyma (arrow) from brain and displace it inward. True ventricle (V) and abutting pseudovertricle (C) may be misinterpreted as single ventricle loculated by intraventricular septations. Inset: High-power magnification of junctional region. Ventricular wall is formed by smooth, intact ciliated ependyma (arrow), while equally smooth cyst wall is formed by compacted white matter (closed arrowhead) denuded of ependyma. "Septations" may be formed by white matter alone (open arrowhead) or by intact ependyma plus residual subependymal white matter (arrow).

Fig. 5.—*E. coli* ventriculitis in hydrocephalic 3-year-old boy. A, Unenhanced axial CT. Appearance of loculation and septation is simulated by large, noncommunicating callosal and juxtaventricular white-matter cyst (closed arrowhead) that compresses lateral ventricles and displaces intraventricular shunt catheters inferolaterally. Additional white-matter cysts in parietooccipital region (open arrowhead). B, Intraoperative photograph of apparent intraventricular septum at point indicated by closed arrowhead in A. Laser fenestration of this thin, translucent outer wall afforded exit of cyst fluid. Inset: Electron micrograph of "septum." Intact axons (arrowhead) show "septum" is residual white matter, not inflammatory membrane or glial scar.





however, appeared very sensitive to the infection. The perivascular glial foot processes appeared retracted from the endothelial cells, leaving definite clear spaces between. Large areas of edema were almost devoid of astrocytic processes, leaving neurons and synaptic complexes devoid of glial investment. This shrinkage and loss of the glial component of the brain was a dramatic feature of the pathology of ventriculitis.

## Discussion

In mice and man, ventriculitis causes the greatest damage to the brain in younger animals, hydrocephalic animals, and those with disruption of the ependymal layer. One anatomic feature common to both young animals and hydrocephalic animals is an unusually large extracellular space [15–19]. Our study shows that severe ventriculitis is associated with substantial extracellular edema and with spread of inflammation along the dilated extracellular spaces of the commissural and longitudinal fiber tracts to distant sites in the inoculated and contralateral hemispheres. If the extracellular space is already large at the time of inoculation, as in immature and in hydrocephalic animals, then the spread of infection is likely to be more rapid and the infection more severe. In animals with depressed immune response, such spread may overwhelm the animal before its immune system is able to respond. These factors probably explain the greater severity of ventriculitis in hydrocephalic animals and the early deaths of all infected hydrocephalic mice. They may also shed light on the greater severity of Gram-negative ventriculitis in very young human infants.

In this and previous studies [10], the intact ependyma seemed to be a significant barrier to the spread of infection into or out of the ventricle. The greater severity of ventriculitis and paraventricular infection in the hydrocephalic animal may also be related to the separation of ependymal cells and the deterioration in the ependymal "barrier" that occur with hydrocephalus. By all three risk factors, premature infants with hydrocephalus, prior disruption of the ependyma by rupture of subependymal hemorrhage into the ventricle, and later disruption of the ependyma by shunting would be expected to suffer the most severe sequelae of shunt infection and ventriculitis. In our clinical experience, this has proved true.

The hy-3 mice with sterile hydrocephalus show little change in the corpus callosum [16–19]. The dramatic spread of inflammatory edema along the corpus callosum and the formation of coalescent callosal and paraventricular edematous cavities appear to be specific features of ventriculitis in these animals. The marked reduction in the glial astrocytic processes also appears to be specific to ventriculitis. Loss of the astrocytic processes probably reduces the structural integrity of the white matter and contributes to the formation of the large edematous cavities.

In our opinion, processes akin to those demonstrated in this murine model may explain some instances, perhaps most instances, of the so-called multiloculation and septation of the ventricles in human Gram-negative ventriculitis (fig. 5A). Certainly the coalescent edematous cavities may grow large, may compress the ventricles, may abut each other (thus leaving thin walls of intervening white matter), may abut and compress the ventricles, and may displace the intact ependymal layer inward as an intervening sheet of tissue (fig. 4). The edematous cavities appear smooth-walled although they are not lined by ependyma, and they are filled with fluid of a density very similar to that of the stagnant CSF. The wedges of tissue remaining between abutting cavities bear striking resemblance to the glial tufts described by Schultz and Leeds [7]. These authors' descriptions of inflammatory cells; subependymal gliosis; small areas of denuded ependyma; glial tufts, which extended through the denuded ependyma into the ventricular lumen; and

apparent origin of filmy, translucent fibroglial membranes from the glial tufts [7] might well be applied to the changes observed in the hy-3 mouse (figs. 1–4). Documentation that axons traverse such membranes in human *E. coli* ventriculitis (fig. 5B) is strong support for the theory we advance. The common locations of the noncommunicating cysts in the corpus callosum and paraventricular regions; the failure to drain these spaces by intraventricular catheters; and the common observation that intraventricular catheters are usually displaced centrally by the undrained spaces also favor our theory.

Gilles et al. [21] have documented that injection of sterile *E. coli* endotoxin into the peritoneal cavities of neonatal kittens (but not adult cats) produces severe paraventricular leukoencephalopathy and cavitation. In these kittens, a rim of tissue is preserved between the cyst and the ventricle and resembles a septum in some cases [21]. These findings could help explain the increased incidence of "multiloculation" and "septation" in patients with Gram-negative ventriculitis, especially *E. coli* ventriculitis.

We acknowledge that inflammation may scar the ventricular foramina to cause hydrocephalus with multiple, isolated ventricular chambers. This is not the process we discuss. True intraventricular septa and consequent ventricular loculation may occur in some cases. However, we have not observed these to date. The experimental data from the hy-3 mouse model of *E. coli* ventriculitis do not support the concept that a subependymal gliotic process disrupts the ependyma and produces glial tufts that act as niduses for the organization of intraventricular exudate and debris into filmy fibroglial membranes. In our experience, it is difficult to grow glial cells even under optimal laboratory conditions. It is correspondingly unlikely that such glial or fibrous tissue would grow down through a pus-filled cavity to form a septum across the ventricle. Rather, the experimental and clinical data are consistent with the conclusions that: (1) so-called multiloculation represents compression of the true ventricles by multiple, juxtaventricular white-matter cysts, and (2) the septa themselves represent displaced ependyma and residual sheets of white matter traversed by axons. If this is true, then wide fenestration and disruption of the septa may be contraindicated, lest they disrupt functional pathways.

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