Three Steps Forward and 2 Steps Back: The Echternach Procession Toward Optimal Hydrocephalus Treatment

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The dancing procession in Echternach, a small town in Luxembourg, is a centuries-old religious procession to the shrine of St. Willibrord that has taken various forms over time. At one point in history, the celebrants took 3 steps forward and 2 steps backward, thus taking 5 steps to make 1 step of progress. This, I think, provides a good analogy for the last 100 years of progress in our understanding and treatment of hydrocephalus.

I joined this procession when my family and I moved to Uganda in 2000 to work with CURE International, a non-profit Christian organization, in founding a pediatric neurosurgery hospital for the region. When the hospital was opened, it quickly became apparent that infant hydrocephalus was the most overwhelming problem, and we subsequently found that the majority (60%) of these cases were secondary to neonatal ventriculitis.[1] We have subsequently reported the enormous burden of infant hydrocephalus in sub-Saharan Africa[2] and the long-term outcome for these postinfectious hydrocephalus cases.[3] We were soon treating >500 new infants for hydrocephalus at the CURE Children's Hospital of Uganda each year.

Creating shunt dependence was more problematic in sub-Saharan Africa than in developed countries and begged the question as to what the best treatment for hydrocephalus would be in that particular context. However, I suggest that we do not yet know the correct answer to that question for this or any other context because we have an incomplete understanding of both cerebrospinal fluid (CSF) physiology and hydrocephalus. The problem is compounded by often not recognizing our unfounded assumptions.

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THE CLASSIC "BULK FLOW" MODEL OF CSF

The classic conception is of CSF flowing like a river from its origin at the choroid plexus to its terminus in the arachnoid villi. Hydrocephalus is thought to arise when a dam obstructs the river at some point along the way. The CSF then backs up under pressure in the ventricles, which dilate in response to the resulting pressure gradient. Much of this classic model originated with Walter Dandy's dog experiments in which he created hydrocephalus and drew conclusions about CSF physiology from his observations.[4] In 1 of these experiments, he occluded 1 foramen of Monro, which caused dilation of that lateral ventricle. When the experiment was repeated after removal of the choroid plexus from the ventricle, the ventricle failed to dilate. From this, he concluded: "This is absolute evidence that the choroid plexus secretes cerebrospinal fluid and that ependyma takes no part in its formation" and that "there are no collateral channels that assume the function of the iter when it is occluded." [4]

THE EVOLUTION OF HYDROCEPHALUS TREATMENT IN THE 20TH CENTURY

From the 1920s to 1940s, using this model, Dandy and then later Putnam and Scarff very logically explored treating so-called communicating hydrocephalus by extirpation of the choroid plexus to reduce CSF production (Figure 1).[5-8] It has largely been forgotten that this was reasonably effective, with Scarff reporting success in 68% of infants <1 year of age. However, with the operative and anesthesia techniques of the day, the operative mortality was >10%.

Similarly, and in the same time period, open third ventriculostomy was performed to treat obstructive hydrocephalus, as in aqueduct stenosis, first by Dandy and then with modifications by Stookey and Scarff.[9-11] Like Dandy, Scarff initially fenestrated the lamina terminalis through

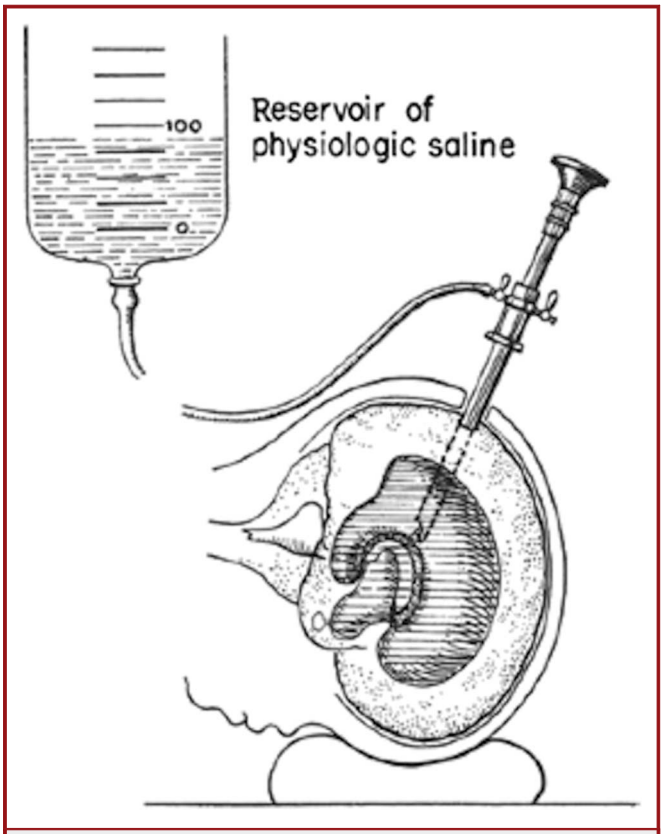

FIGURE 1. *Illustration of the Scarff technique for endoscopic cauterization of choroid plexus.*[8]

a subfrontal approach; he then extended this to include a blind perforation of the third ventricular floor (Figure 2). With either method, the reported overall success for aqueduct stenosis was 62%, with 57% success in children <1 year of age. Again, however, given the techniques available, there was a high operative mortality of >20%.

In the 1940s through 1960s, the focus of hydrocephalus treatment became shunting, many variations of which were attempted. Third ventriculostomy and plexus cauterization were largely abandoned. With the invention of Silastic tubing, a biologically inert material became available that allowed successful shunting to the peritoneal cavity, as reported by Ames[12] in 1967. With few meaningful variations, shunting has remained the standard of hydrocephalus treatment for the last half-century. However, by most standards, this is not a very successful operation, and shunts have among the highest failure rates of any implanted medical device. Half will have failed at least once within 2 years, with an average of about 3 shunt revisions per patient. Some patients have dozens or even scores of operations, with failures sometimes being a life-threatening emergency.[13,14] This places an enormous burden of suffering on the patients and families, accounting for about 400 000 inpatient hospital days and up to $2 billion in healthcare costs per year in the United States alone.[15]

THE EVOLUTION OF HYDROCEPHALUS TREATMENT AT CURE CHILDREN'S HOSPITAL OF UGANDA

At CURE Children's Hospital of Uganda in 2001, we began treating infant hydrocephalus by placing shunts. However, it was immediately apparent that creating shunt dependence in large numbers of children who would not have ready access to treatment for their malfunctions was of questionable value. Endoscopic third ventriculostomy (ETV) had been reported by Vries[16] in 1978, but this is the only citation in the English literature before 1990. When I finished my pediatric neurosurgery fellowship at Boston Children's Hospital in 1992, I had never seen an ETV, but it seemed worth pursuing more aggressively in the context of rural sub-Saharan Africa because, when successful, late failures were typically rare and failure for infants was typically a visible and non—life-threatening diagnosis. ETV became an option for us when we

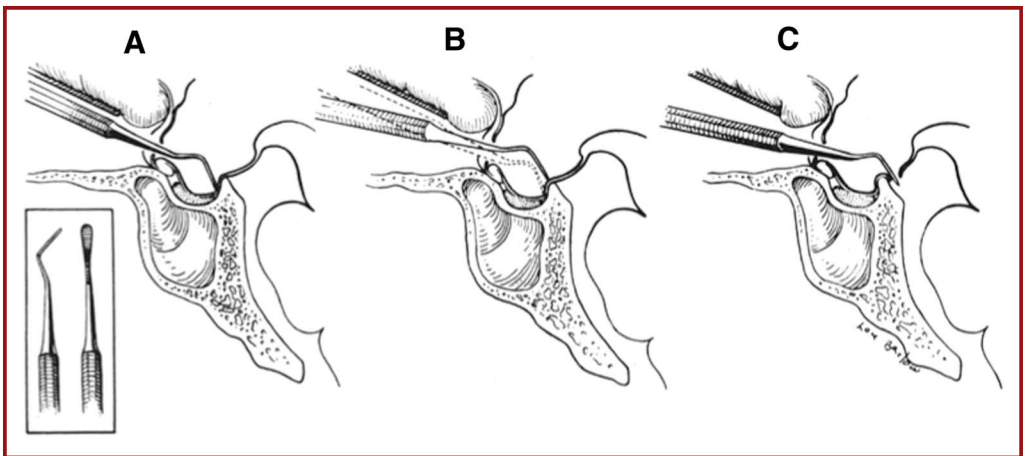

FIGURE 2. *Illustration of the Scarff technique for open third ventriculostomy.*[11]

acquired a flexible ventriculoscope as a donation. However, we found, like others, that ETV was not as successful for infants <1 year of age.[1] Interestingly, the flexible endoscope allowed us to fenestrate the lamina terminalis, as Dandy and Scarff had in the open operation but from within the third ventricle, for use as an alternative to the floor when that location was technically inadequate.

My assumption then, based on the classic bulk flow model of hydrocephalus, was that ETV was less successful for infants because their ability to absorb CSF was less developed and that their hydrocephalus might often have both obstructive and communicating components. With the flexible ventriculoscope, it was apparent that the entirety of the choroid plexus in both lateral ventricles could readily be accessed, and I decided to resurrect the Scarff technique of plexus cauterization, but now with the ability to do this bilaterally through a single frontal approach and in conjunction with the ETV. We reported in 2005, in a series of 550 children, that the combined ETV/choroid plexus cauterization (CPC) procedure did indeed have a significantly higher success rate than ETV alone for infants <1 year of age (Figures 3 and 4).[17] As it turns out, however, I may have begun doing the right thing for the wrong reason.

OUR UNDERSTANDING OF HYDROCEPHALUS: TIME FOR A REVOLUTION

In 1961, Edgar Bering[18] at Boston Children's Hospital reported on his expansion of Dandy's original experiments. He found that when he removed the choroid plexus from 1 lateral ventricle while leaving the foramen of Monro open and created communicating hydrocephalus by injection of kaolin into the cisterna magna, the ventricle without plexus expanded little, despite being in communication with the other ventricles, which progressively enlarged as expected. Furthermore, he showed that the amplitude of the CSF pulsations was dramatically reduced in that ventricle compared with its contralateral counterpart. Charles Wilson,[19] then at the University of Kentucky, showed a similar result in 1967 when he unilaterally occluded the choroidal artery. These observations suggested that plexus pulsations played an important role in producing ventriculomegaly.

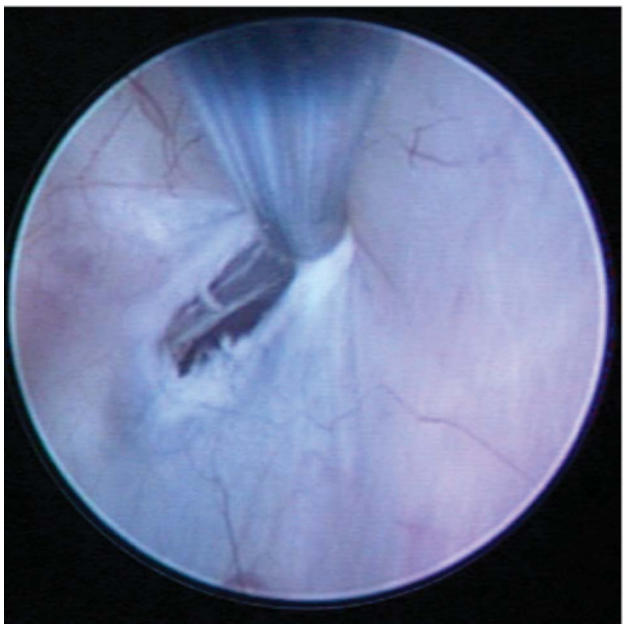

FIGURE 3. *Performing third ventriculostomy with Bugby wire and 3.7-mm flexible steerable ventriculoscope (anterior is to the left).*

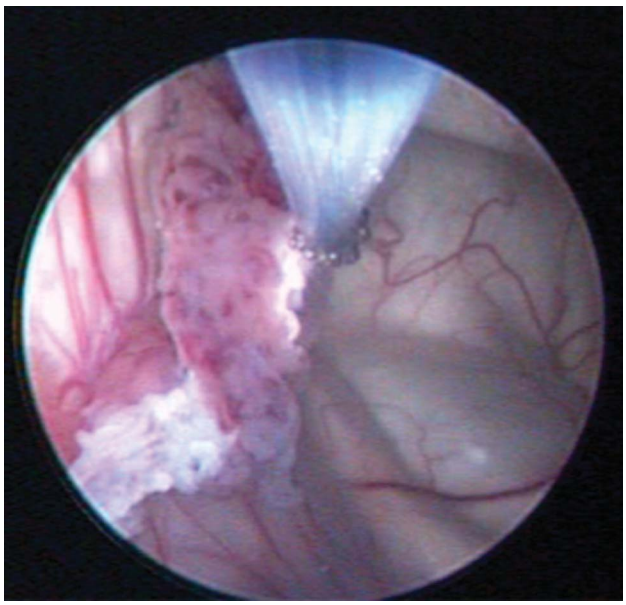

FIGURE 4. *Performing choroid plexus cauterization in the atrium of the right lateral ventricle with Bugby wire and 3.7-mm flexible steerable ventriculoscope (anterior is to the left).*

In contrast to the findings of both Dandy and Bering, Thomas Milhorat[20] observed ventriculomegaly after foramen of Monro obstruction even after removing the choroid plexus. He concluded that plexus was not the main source of CSF production, nor was it essential to ventriculomegaly.

In 1978, DiRocco and colleagues[21] created hydrocephalus in dogs simply by implanting a pulsating intraventricular balloon catheter that augmented the intraventricular pulsations in synchrony with the cardiac cycle with no alteration in CSF production, mean pressure, or circulation. This provided more evidence for the importance of pulsations in the development of hydrocephalus. Others, including colleagues in neurosurgery,[22,23] have continued to support a hydrodynamic model of hydrocephalus in which pulsations play a key role.

Researchers in recent decades have provided these and other observations that challenge the classic model of hydrocephalus. For

instance, (1) arachnoid granulations, the presumed point of CSF absorption, are not present in children <2 years of age[24]; (2) as noted, choroid plexus is not the chief source of CSF[20]; (3) water is exchanged freely between the brain and the ventricles across the ependyma,[25] and hydrocephalus can be produced by increasing CSF osmolality[26]; (4) no pressure gradient to expand the ventricles has been found in hydrocephalus[27]; and (5) fluid pulsation amplitude in the ventricles is increased in hydrocephalus,[28] and as described above, artificially increasing the fluid pulsations alone produces hydrocephalus.[21]

Of likely importance to the response of the brain to pulsations, there is evidence that brain compliance changes over the life span, being greatest in the youngest and the oldest.[29] This has led to the suggestion that idiopathic communicating hydrocephalus in infants, idiopathic intracranial hypertension in younger adults, and normal-pressure hydrocephalus in the aged might all be manifestations of the same underlying origin, likely decreased venous compliance.[30]

Interestingly, however, many have maintained the classic model of hydrocephalus as the underlying assumption of their patient management and their conversations with patients and their families, students, and colleagues alike. In his classic work *The Structure of Scientific Revolutions*, Thomas Kuhn[31] made the observation that "[phenomena] that will not fit the box are often not seen at all." Furthermore, he explained that historically, "Discovery commences with the awareness of anomaly. . .it closes only when the paradigm theory has been adjusted so that the anomalous has become the expected."[31]

We must consider whether we have been working in the wrong box. Perhaps the CSF compartment is more like a reservoir than a river, a reservoir that is pliable (with compliance that changes with age or pathology), permeable (as water is exchanged across its boundaries), and pulsatile, with each parameter offering potential opportunities for treatment. One can envision CSF dysfunction as being primarily a vascular problem at the level of venous compliance, capillary permeability, or arterial pulsations, with variance in the clinical presentation according to the underlying brain compliance.

The hydrodynamic model envisions the intracranial compartment as distributing and buffering incoming systolic arterial pressure waves.[22,23] The subarachnoid space is considered an initial buffer, absorbing pressure waves via the Windkessel phenomenon before their entrance into the smaller arteries of the brain parenchyma. The systolic pulse wave moves into the choroid plexus and is distributed to the ventricular CSF with pulsation absorption through the ventricular outlet foramina and the aqueduct. The veins absorb pulsations as dynamic capacitance vessels. All the while, water appears to be in equilibrium between the interstitial fluid of the brain and the intraventricular CSF, as determined by Starling forces.[25] Recently, evidence for a complex "glymphatic" extravascular circulation of brain interstitial fluid and CSF involving the perivascular spaces and astrocytes has been reported.[32]

Increased intraventricular pulsation amplitudes that lead to progressive ventriculomegaly can result from decreased pulsation absorption elsewhere in the system such as with decreased venous compliance, as has been demonstrated in congenital idiopathic hydrocephalus[30]; dysfunctional subarachnoid spaces, as from meningitis or subarachnoid hemorrhage; or obstructed ventricular outlets such as in aqueduct stenosis or fourth ventricular outlet obstruction.

This paradigm theory can help explain 3 enigmas better than the classic model. First, why should ETV work in so-called "communicating" hydrocephalus? Recent reports have demonstrated the efficacy of ETV in adult communicating hydrocephalus.[33-35] In a hydrodynamic model, ETV, rather than creating a bypass to an obstruction, may provide an additional pulsation absorber, thus reducing the net intraventricular pulsation amplitude. Next, why should ETV not work well in newborns? Given the relatively high brain compliance in newborns, the ventricles may be so easily distended that the additional pulsation absorption provided by an ETV is less likely to reduce the pulsation amplitude sufficiently to arrest ventricular expansion. Increased brain compliance in the elderly may possibly contribute to ventriculomegaly in normal-pressure hydrocephalus and a similarly reduced likelihood for ETV to be effective in those patients. Finally, why should CPC enhance the effectiveness of ETV for infants? We have reported that the addition of CPC increases the 5-year success rate for ETV in congenital idiopathic communicating hydrocephalus of infancy from 21% to 65%.[36] We similarly reported that CPC increased the 5-year success rate of ETV for infants with aqueduct stenosis from 48% to >80%.[37] I propose that, as Bering[18] demonstrated decreased intraventricular pulsation amplitude with the removal of choroid plexus and subsequent abatement of progressive ventriculomegaly, CPC acts to primarily reduce pulsation amplitude and in this way augments the pulsation absorber function of ETV, the combination of which leads to a greater net decrease in pulsation amplitude that increases the likelihood of success in the more compliant infant brain above either technique alone.

Over the years, we have demonstrated the efficacy of combined ETV/CPC for a number of different causes of hydrocephalus in infants with an overall success rate of roughly 2 out of 3 when there is no significant scarring of the prepontine cistern.[17,36-41] In addition, in our American patient population at Boston Children's Hospital where the major causes are post-hemorrhagic hydrocephalus, aqueduct stenosis, and myelomeningocele, the effectiveness of ETV/CPC is proving to be very similar.

CONCLUSION

The Echternach Procession of hydrocephalus treatment proceeded from plexus cauterization and third ventriculostomy as separate procedures for communicating and obstructive hydrocephalus, respectively, and was based on the classic bulk flow paradigm of CSF physiology. These treatment approaches saw reasonable success but significant operative mortality. The procession continued through 50 years of troublesome shunting and the acceptance of very high treatment failure rates. Technical

advances allowing the far less invasive endoscopic method of creating a third ventriculostomy revived the use of this technique for cases of aqueduct obstruction, but it was far less successful in young infants. On the basis of continuing assumptions of the bulk flow model, the procession then led to combining ETV with the largely abandoned idea of CPC for significantly enhancing the success for infants. A re-evaluation of clinical observations and research data in recent decades now suggests that alternative models may better explain the efficacy of combined ETV and CPC and supports expanding the use of ETV to cases of so-called communicating hydrocephalus. Before getting to the shrine of optimal treatment, we will undoubtedly progress through new models and better methods of treatment.

It is now possible to successfully avoid shunt dependence in more than half of all infants from the beginning, avoiding an average of 2 to 3 anticipated additional shunt operations for each of these patients in the future. But why, for the same type of hydrocephalus, does ETV/CPC work for 1 infant and not for another? What we need now are better preoperative parameters for selecting treatment and biomarkers that tell us when hydrocephalus has been optimally managed. We also need a better model for hydrocephalus and new strategies for treatment. If the reservoir model is basically correct, innovative treatment strategies may lie in manipulation of brain compliance or control of water passage into the ventricles (which may be nonoperative approaches), in addition to the reduction of intraventricular pulsations.

Thomas Kuhn wrote, "Confronted with anomaly or with crisis, scientists take a different attitude toward existing paradigms, and the nature of their research changes accordingly."[42] There is much we do not know, and some of what we think we know, we do not. So we must be willing to challenge our assumptions, stepping backward to proceed forward, as we labor to improve our care of these patients.

Disclosure

The author has no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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