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Priorities for hydrocephalus research: report from a National Institutes of Health–sponsored workshop

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Object. Treatment for hydrocephalus has not advanced appreciably since the advent of cerebrospinal fluid (CSF) shunts more than 50 years ago. Many questions remain that clinical and basic research could address, which in turn could improve therapeutic options. To clarify the main issues facing hydrocephalus research and to identify critical advances necessary to improve outcomes for patients with hydrocephalus, the National Institutes of Health (NIH) sponsored a workshop titled "Hydrocephalus: Myths, New Facts, and Clear Directions." The purpose of this paper is to report on the recommendations that resulted from that workshop.

Methods. The workshop convened from September 29 to October 1, 2005, in Bethesda, Maryland. Among the 150 attendees was an international group of participants, including experts in pediatric and adult hydrocephalus as well as scientists working in related fields, neurosurgeons, laboratory-based neuroscientists, neurologists, patient advocates, individuals with hydrocephalus, parents, and NIH program and intramural staff. Plenary and breakout sessions covered injury and recovery mechanisms, modeling, biomechanics, diagnosis, current treatment and outcomes, complications, quality of life, future treatments, medical devices, development of research networks and information sharing, and education and career development.

Results. The conclusions were as follows: 1) current methods of diagnosis, treatment, and outcomes monitoring need improvement; 2) frequent complications, poor rate of shunt survival, and poor quality of life for patients lead to unsatisfactory outcomes; 3) investigators and caregivers need additional methods to monitor neurocognitive function and control of CSF variables such as pressure, flow, or pulsatility; 4) research warrants novel interdisciplinary approaches; 5) understanding of the pathophysiological and recovery mechanisms of neuronal function in hydrocephalus is poor, warranting further investigation; and 6) both basic and clinical aspects warrant expanded and innovative training programs.

Conclusions. The research priorities of this workshop provide critical guidance for future research in hydrocephalus, which should result in advances in knowledge, and ultimately in the treatment for this important disorder and improved outcomes in patients of all ages. *(DOI: 10.3171/PED-07/11/345)*

Key Words • **adult** • **basic biomedical research** • **children** • **clinical research** • **diagnostic criteria** • **hydrocephalus** • **infant** • **National Institutes of Health** • **neurosurgical education** • **normal pressure hydrocephalus** • **pediatric neurosurgery** • **therapeutic intervention**

Abbreviations used in this paper: CBF = cerebral blood flow; CSF = cerebrospinal fluid; CT = computed tomography; ETV = endoscopic third ventriculostomy; ICP = intracranial pressure; MR = magnetic resonance; NIH = National Institutes of Health; NINDS = National Institute of Neurological Disorders and Stroke; NPH = normal-pressure hydrocephalus; R_{out} = CSF outflow resistance.

Hydrocephalus is the abnormal primary enlargement of the cerebral ventricles that results from impaired CSF secretion, circulation, or resorption. It is distinct from "hydrocephalus ex vacuo," the abnormal secondary enlargement of the cerebral ventricles resulting from loss of cerebral tissue (for example, due to cerebral atrophy).

Most commonly recognized as a disorder of infants and children,[73,104] hydrocephalus also affects adolescents, young and middle-aged adults,[31,71,139] and the elderly.[82,118,121,126,152]

The first effective treatment for hydrocephalus, the shunt, was developed 50 years ago by John Holter, in collaboration with the neurosurgeon Eugene Spitz.[5] The shunt revolutionized the care of patients with hydrocephalus; shunt surgery is now the most common procedure pediatric neurosurgeons perform. With this dramatic success, the search for other approaches to treatment slowed.

Despite improvements in neuroimaging, shunt valve technology, and ETV, little has changed in the diagnostic and treatment approaches toward hydrocephalus in the last 50 years. Surprisingly little clinical or basic research has focused on hydrocephalus, aside from studies to test the effectiveness of new shunts (often to achieve US Food and Drug Administration approval). Frequent complications and associated morbidity often make treatment outcomes unsatisfactory.[80] The infrastructure for clinical care in the US is largely limited to pediatric neurosurgeons, and fewer than 10 centers have expertise for diagnosing and treating adult hydrocephalus. No standard mechanism exists for the smooth transition of care for individuals with hydrocephalus from pediatric to adult specialists.

Hydrocephalus is far from cured, and there is a pressing need for basic and clinical research to improve our understanding of this complex disorder. Hydrocephalus is sometimes misconstrued as a simple disorder of CSF circulation—a "plumbing problem"—when it is more properly viewed as a brain disorder. Because hydrocephalus signs and symptoms can resolve in days or weeks after existing for months or years, a novel form of reversible neuronal and glial injury may be involved. At present, the basic injury and recovery mechanisms are not adequately understood.

In recognition of the gaps in our knowledge, and the benefits that could emerge from focused research, the NIH convened a workshop titled "Hydrocephalus: Myths, New Facts, and Clear Directions" in Bethesda, Maryland, from September 29 to October 1, 2005. More than 150 neurosurgeons, neurologists, laboratory-based scientists, patient advocates, patients, parents, and program staff from five institutes and one office within the NIH assembled for a day and a half of plenary discussions that summarized the current knowledge, challenged existing dogma and mythology, and identified critical gaps in research and clinical treatment. Participants divided into three breakout groups to answer key questions (Appendices 1 and 2) with the goal of developing research priorities and collaborative opportunities.

The priorities for research (Table 1) resulting from the 2005 NIH Hydrocephalus Workshop should set in motion a broad, interdependent array of research in hydrocephalus that we hope will yield important discoveries fundamental to our understanding of brain function and CSF physiology and ultimately lead to therapeutic intervention strategies and improved outcomes for patients of all ages.

TABLE 1

Research priorities for hydrocephalus

- *Hydrocephalus Research Infrastructure*
  - Creation of research networks
    - Basic, clinical, translational, & interdisciplinary research
  - Facilitation of information sharing
    - Specimen banks: brain, CSF, genetic material, shunts, images, physiological measurements
    - Registries: clinical trials, epidemiological data, longitudinal studies
  - Education & career development for researchers
    - Scientist & clinician/scientist education
- *Basic Research*
  - Injury & recovery mechanisms in human volunteers or animal models
    - Molecular, cellular, genetic, & systems physiology
      - Role of stem cells & neural progenitor cells
      - Role of inflammation, tissue matrix, blood–brain barrier, biomarkers
    - Anatomy & physiology of CSF secretion, circulation, resorption, function
    - Development of appropriate animal models for age, acuity of onset, & mode of induction factors, including congenital & acquired hydrocephalus
      - Ex vivo models (brain slices, tissue culture)
      - Transgenic models
  - Development & validation of theoretical & biomechanical modeling
    - CBF/CSF pulsatility, compartment models, ICP gradients, & monitoring
    - Physiological effects of CSF diversion, including slit-ventricle syndrome
- *Clinical Research*
  - Diagnosis
    - Establishment & validation of diagnostic criteria at all stages of life
    - Improvement & validation of imaging & noninvasive testing techniques
  - Current treatment, outcomes, complications
    - Epidemiology & population impact
    - Surgical treatment
      - Establishment & validation of treatment criteria at all stages of life
      - Prevention of infection & device or treatment failure
      - Effects of device design, biomaterials, & technique on outcomes
    - Clinical evaluation of brain/neuronal dysfunction & recovery
      - Development & validation of clinical conventions or templates for assessing neurological & behavioral outcomes (for example, cognitive, gait, motor, continence, activities of daily living)
      - Correlation of clinical outcomes w/ imaging & noninvasive techniques
      - Effects of infection & device or treatment failure on outcomes
    - Health services research
      - Education of patients, public, physician communities
      - Determination of extent of need for centers of excellence
      - Determination of extent of need for longitudinal care for children & adults w/ chronic hydrocephalus
      - Development of age-appropriate quality of life instruments
- *Future Treatments*
  - Development of adjunctive (pharmacological) therapies
  - Development of novel medical devices & biomaterials

Clinical, Research, and Education Infrastructure

The research priorities begin with recommendations for research infrastructure (Table 1) that all three breakout groups identified independently as a need for all types of research (clinical, basic, translational, and interdisciplinary), which should facilitate the creation of research networks, data sharing, and education for future researchers.

Virtually no organized clinical, research, or educational infrastructure for hydrocephalus currently exists. Nevertheless, there is a need, given the fact that the cost of treating hydrocephalus is estimated at 1 billion dollars annually,[144] and there is evidence that treating adults with hydrocephalus who are older than 65 years of age can lower national 5-year Medicare expenditures by as much as $184.3 million.[184]

Creation of a Clinical Research Network for Hydrocephalus

Between 1996 and 2006, there were only eight publications about multicenter hydrocephalus trials (according to a search of Medline [accessed September 2006]). There is a need to establish clinical research networks such as the Children's Oncology Group, which is funded by the National Cancer Institute. Such multicenter involvement encourages pooling of data, tissue specimens, and knowledge as well as potential treatment innovation and research of clinical outcomes. Most data on the longevity of CSF shunts, for example, reside with shunt manufacturing companies. The ability to compare different shunt models across a large population would be beneficial. A multiinstitutional clinical research network could help answer basic questions, such as the outcome of treated compared with untreated hydrocephalus, or facilitate comparisons of surgical strategies and outcomes, such as shunts with or without antisiphoning devices or shunts compared with ETV. Investigators could use the research network database for the generation of hypotheses to be used in more focused research.

Creation of a Clinical Care and Research Training Infrastructure

There is currently no formal postgraduate clinical or research training program in the care of hydrocephalus. Much of the training resides within pediatric neurosurgery fellowships, not all of which have a clinical or research focus on hydrocephalus. This ad hoc system generally does not encompass adult hydrocephalus, nor does it include other specialists, such as neurologists and clinically oriented neuroscientists. Thus, the goal of reaching a "critical mass" of interdisciplinary clinical and research scientists studying hydrocephalus is a major challenge. It is plausible that the lack of critical mass or individual research mentors is a disincentive for young investigators to enter a career in hydrocephalus research.

Creation of Infrastructure to Train Basic Science Researchers

It is arguable that in the field of hydrocephalus research there may be even fewer basic scientists than there are clinicians or clinical scientists. Considering that the pathophysiological processes in this disease are diverse and poorly understood, this field is an unparalleled opportunity for clinical or basic researchers. There should be incentives for such clinicians and scientists to concentrate their career paths toward hydrocephalus research. The establishment of funded postdoctoral fellowships could provide an incentive to obtain training, as could targeted faculty positions or endowed chairs that would provide stable and productive environments for junior researchers.

Hydrocephalus Patient Advocacy

Some diseases and disorders have garnered focused federal funding for research due to the efforts of advocacy groups composed of philanthropic leaders, patients, and their families. The Hydrocephalus Association and other volunteer organizations with an interest in hydrocephalus that played an important role in the NIH workshop have filled that role in many ways. For example, the Hydrocephalus Association has made a deliberate choice to promote federal funding for hydrocephalus research rather than fund research on its own as similar organizations have done (for example, the Multiple Sclerosis Society and the Amyotrophic Lateral Sclerosis Society). Patient advocacy groups also provide information to patients and their families with regard to diagnostic and treatment options and ongoing clinical research trials. Collaboration with patient advocacy groups should be encouraged, and the emerging hydrocephalus research community should view such cooperation as a highly valuable component of any complete clinical and research program.

Priorities for Basic Research

Priorities for basic research (Table 1) focus on the injury and recovery mechanisms of hydrocephalus, ranging from the genetic and molecular levels to animal models and systems physiology approaches. Theoretical modeling of the effects of CSF, CBF, and ICP on normal and abnormal physiology is also needed.

Injury and Recovery Mechanisms

The signs and symptoms of hydrocephalus, particularly in adults (but also in children), may be present for months or years, and yet resolve in days or weeks. Consequently, they represent a unique and clinically important type of neuronal injury and recovery. There is inadequate understanding of the mechanisms that lead to the initiation, progression, and persistence of neuronal, glial, and vascular dysfunction in hydrocephalus, as well as the mechanisms by which treatment reverses this injury. The application of contemporary methods and techniques in basic neurobiology will provide critical insights into both the injury and recovery mechanisms of hydrocephalus, and we hope that this will lead to improved diagnostic, prognostic, and treatment approaches.

Hydrocephalus has many known causes, including congenital malformations, hemorrhage, infection (primarily meningitis), and trauma, among others. However, most of the available knowledge pertains to secondary injuries and responses,[41,48,123] including neuronal and glial cell death, axonal and dendritic degeneration, astroglial and microglial activation and proliferation, neurochemical alterations, decreases in CBF, and impaired cellular metabolism.[41,44–46,48,92] Animal models of hydrocephalus include natural (congenital) forms in rodents or forms induced in many species by injection of materials such as blood, kaolin, silicone, or acrylic polymers that obstruct CSF flow either through an intense subarachnoid inflammatory response or a mechanical barrier.[32,88,140]

Regardless of the cause, dilation of the lateral ventricles results in several types of brain injury. The ependymal lining is stretched and eventually lost. Cells in the subependymal zone proliferate, giving rise to reactive astrocytes. Oligodendrocyte production of myelin is retarded, and these cells eventually die. Reactive astroglial and microglial changes occur in the periventricular white matter but also in the cortical and subcortical gray matter. The extracellular fluid compartment is enlarged in the white matter but compressed in the cortical laminae. Periventricular axons are stretched and can be destroyed.[40,68,109,110] The prominent white matter damage suggests that hydrocephalus could be

considered a type of subcortical disconnection syndrome.[50] Disconnected neurons undergo atrophy of dendritic processes and synapses and may die.[19,85,86,109,110,124] Decreases in neurotransmitters and neuromodulators are common,[30,91,113,132] and reductions in energy metabolites occur within days of the onset of ventriculomegaly.[49,87,99,132] Hydrocephalus adversely affects the cerebral vasculature, CBF, and metabolism,[6,23,43,61,143,153,179,189] and there may be indirect effects on CBF via cardiac suppression.[53,58]

A number of factors modify the pathogenesis of brain injury in hydrocephalus, including the age of the individual and the state of brain maturation at onset, the rate of ventricular dilation, duration of stable ventriculomegaly, cause of hydrocephalus, and coexistence of other diseases. In the developing brain, enlargement of the ventricles and stretching of the ependymal lining raises complex questions about reduction of germinal cell proliferation, alteration of synaptic connections, and brain development.[106,133,134,142,175] There has been no systematic study of the effect of repeated episodes of ventricular dilation and contraction associated with shunt obstruction and revision. It is plausible that repeated injury to neurons and glia is cumulative, and the capacity to reverse such injury may be lost.[123] The calcium-mediated proteolytic changes in axons are similar to those in stroke and trauma.[40] In vitro neuron studies might be used to determine how changes in CSF and extracellular fluid composition are toxic to axons and neurons in hydrocephalus. Understanding the secondary role of microglial inflammation in white matter is also critical.[116,174]

Gross restoration of the brain, blood, interstitial fluid, and CSF volumes and their volume relationships can occur quickly after CSF shunting;[43] however, reduction in ventricle size is not always necessary for clinical improvement, particularly in adults. Thus, some component of the quickly reversible brain dysfunction may result from intracellular neuronal or glial changes (for example, biochemical changes or gene induction). Within a span of hours to days, CSF shunting likely corrects white matter CBF and also may divert clearance of waste products to alternate absorption sites. Relief of metabolic and physical stresses on axons may prevent injury progression. In young hydrocephalic animals, early shunt placement is associated with a "catch-up" in myelin production[47] and the restoration of axoplasmic transport in cortical connections within days.[68]

A subset of fetal or childhood-onset hydrocephalus is related to developmental anomalies that are sometimes attributed to genetic abnormalities. However, the role of genetic factors in the development of hydrocephalus overall is not well understood. The only hydrocephalus gene identified in humans, the X-linked *L1-NCAM* mutation, is associated with many brain anomalies.[69,155,167,177] Considering that a significant proportion of cases of hydrocephalus in humans occurs as part of a more widespread developmental anomaly, many defective genes may act singly or (more likely) in combination.[159] Studies of gene expression in models of either induced or genetic hydrocephalus may identify molecular mechanisms of injury and recovery.[4,131,136] A database that listed rodents with hydrocephalus, their genetic characterization, other phenotypic data, and associated publications would be an important part of the research infrastructure.

Many more hereditary forms of hydrocephalus occur in animals than in humans, including those found in the *H-Tx* rat, the *LEW/Jms* rat, and the *hy-3* mouse.[8,24,25,95–98,100,101,122,151,154,178,188] Transforming growth factor–β_1 may be involved in posthemorrhagic or postmeningitic hydrocephalus,[168,169,183] and upregulation of transforming growth factor–β_1 causes abnormal extracellular matrix in the CSF flow pathways.[72] Inducing hydrocephalus in mutant animals that do not otherwise develop this disorder can be instructive. For example, mice lacking aquaporin 4 develop hydrocephalus more rapidly after kaolin injection,[18] and rats with kaolin-induced hydrocephalus upregulate aquaporin 4.[117] The relationship of inherited abnormalities of ciliary function to hydrocephalus is not understood.[3,155,177]

There are no models with which to study the effects of chronic hydrocephalus or hydrocephalus arising across the age spectrum from brain development to senescence. Such models might provide a basis for treating the disorder in utero, or might lead to strategies to inhibit cerebral injury until treatment could be offered after birth.[57,74,130] Similarly, understanding the effects of chronic ventriculomegaly on the brain may guide decisions to treat or not treat adults with "stable" hydrocephalus.[185] Models using senescent animals might improve understanding of the interaction of hydrocephalus with hypertensive microvascular disease and Alzheimer disease, which are common in elderly patients with idiopathic NPH.[93,94,166,185]

In summary, despite progress in their identification over the past 30 years, the most important injury and recovery mechanisms in hydrocephalus remain elusive. This undoubtedly impedes the translational research necessary to advance the clinical management of hydrocephalus at all stages and ages of life. Research conducted using existing animal models should be expanded, and there is a need for new, refined, and more physiologically appropriate animal models.

Mathematical Modeling and Biomechanics

The study of the movement of CSF and interstitial fluid within the craniospinal compartment is fundamental to the understanding of hydrocephalus, and mathematical modeling has played a major role in its investigation.[171] Two tenets have guided the modeling of CSF dynamics: the Monro–Kellie doctrine and CSF bulk flow.

The Monro–Kellie doctrine[102,135] depicts the cranium as a rigid chamber with a fixed volume that contains three liquid (and therefore incompressible) components: brain, blood, and CSF. If the volume of one of the components increases, then there must be compensation by a decrease in the volume of the other components. These principles form the basis for a variety of intracranial parameters, such as compliance, elastance, and the pressure-volume index.[82,83]

The concept of bulk flow of CSF has dominated the modeling of CSF circulation and the management of CSF-related disorders[1,33–37,62,64–67,76,107,108,127–129,137,143,157,158,173,176] since 1919, when Dandy[38] demonstrated the production of CSF by the choroid plexus. The rate of CSF production is thought to be constant, and CSF flows through the ventricles, exits into the subarachnoid space, and is absorbed through the arachnoid granulations at the superior sagittal sinus or the spinal rootlets. Absorption of CSF is thought to be linearly related to the pressure gradient between the subarachnoid space and the intraluminal space of the dural venous sinuses. Consequently, hydrocephalus is often modeled as a disturbance of CSF absorption that results in a

"back-up" of fluid that increases CSF pressure and enlarges the ventricles.

Although there is little disagreement that bulk CSF flow circulation exists, its characteristics and importance are in question. For example, the net bulk flow of CSF over the cerebral convexities cannot be demonstrated by high-resolution cine MR imaging.[78,79] Cerebrospinal fluid may freely cross parenchymal capillaries and prevenules.[89,156] The concentration of radioisotope along the superior sagittal sinus and the sacral subarachnoid space may reflect a dilution effect, rather than the movement of CSF carrying the radioisotope.[79] If increased R_{out} at the arachnoid granulations causes communicating hydrocephalus, there should be an increased pressure gradient between the subarachnoid space and the sagittal sinus lumen, but currently there is no evidence of this.[61,165] In obstructive hydrocephalus in adults, there is no difference in R_{out} measured in the ventricles and the subarachnoid space.[173]

Pulsatility Biomechanics. The bulk flow model does not account for the dynamic, pulsatile movement of CSF, although Hakim[81] acknowledged its contribution. The conventional view of hydrocephalus as an imbalance of CSF production and absorption may be an oversimplification.[77–79] Newer modeling approaches consider the intracranial compartment to be highly dynamic and complex, relating the movement of CSF to CBF hemodynamics.

The cerebral arteries and choroid plexus generate intracranial pulsatility.[14–16,28,29,51,52] In fact, ventriculomegaly can be induced simply by inserting a balloon in the lateral ventricle that pulsates synchronously with arterial pulsations and increases CSF pulse pressure without changing CSF mean pressure.[51,52] Whereas obstruction of CSF flow can cause acute hydrocephalus, chronic hydrocephalus may result from increased capillary pulse pressure that causes ventricular enlargement.

The hemodynamic theory of ICP physiology posits that the dynamic movement of CSF across the foramen magnum into the distensible spinal subarachnoid space is essential for pulsatile blood flow in the intracranial compartment,[11–13] and this has been demonstrated experimentally in the venous system.[90] It has been proposed that disruption of pulsatile CSF flow should perturb CBF dynamics, leading to CBF autoregulatory and other compensatory mechanisms that result in disorders of CSF circulation.[59–61,115,179,180]

More recently, results of modeling support the suggestion that the intracranial contents oscillate at an exact "tuned" frequency, rather than passively responding to the pulsatile "hammer" of the incoming systolic blood pressure and flow. The oscillation of the intracranial contents may facilitate the "smooth" flow of blood through the intracranial compartment. There is preliminary evidence for one prediction based on the model, which is that a tuned oscillator should act as a filter, damping some flow and pressure waveform frequencies but not others.[115]

Finite Element Analysis Modeling. Finite element analysis has been used to identify brain regions that are particularly susceptible to strain and compression during progressive ventriculomegaly,[145] and results of that analysis support the suggestion that a relative reduction in intraparenchymal fluid pressure coupled with low tissue elasticity causes both ventricular enlargement and mechanical stress in the cortical mantle.[146]

Further research of mathematical modeling and biomechanical approaches may yield important new insights into the pathophysiological mechanisms of hydrocephalus.

Priorities for Clinical Research

Clinical research priorities (Table 1) include the improvement of diagnostic tests and criteria and of treatment criteria for patients at all stages of life; improvement of surgical therapy to prevent infections and treatment failure, and understanding of the impact of these adverse events on brain function and clinical outcomes; and development of clinical rating methods and correlation with other noninvasive techniques for diagnosis and outcomes research.

Diagnostic Tests

Diagnostic Criteria for Children and Adults. The goal of diagnostic and prognostic testing is to determine the need for treatment, the nature of the treatment, outcomes, and the need for treatment modification. Current diagnostic tools include the patient history and physical examination, ultrasonography in infants, CT scanning and MR imaging of the brain, and tests of CSF circulatory physiology (infusion testing for R_{out}, ICP monitoring, or symptomatic response to CSF removal).

The diagnosis of hydrocephalus is obvious when the ventricles expand on serial images and these findings are accompanied by symptoms of increased ICP. Nevertheless, the diagnosis, classification, and decision to treat are not always straightforward; for example, differentiating between progressive hydrocephalus and "compensated" hydrocephalus in apparently asymptomatic children, or distinguishing hydrocephalus from the ventriculomegaly of cerebral atrophy (ex vacuo) in the elderly.

In spite of earlier suggestions that cortical mantle thickness predicted outcome,[186] ventricular size alone cannot guide the diagnosis or the decision to treat hydrocephalus.[84] Young children with enlarged ventricles may develop normal or even superior function. In the elderly, the fact that either cerebral atrophy or normal aging can result in ventricular enlargement makes it difficult to establish reliable standards for ventriculomegaly. Even the use of CSF pressure measurement as a diagnostic criterion is limited because adult or pediatric chronic hydrocephalus may not be accompanied by an elevation in pressure.

If hydrocephalus results from a disturbance of CSF absorption, then measurement of R_{out} by using infusion methods should be a sound basis for diagnosis, as has been proposed for idiopathic NPH.[118,121,127] However, the usefulness of R_{out} measurement, especially in view of its technical difficulty and variability in techniques, is controversial as well.

The conundrum of diagnosis without a full understanding of pathophysiological mechanisms is demonstrated by decades of clinical research in which the "gold standard" for diagnosis is the response to surgical treatment itself. Guidelines for diagnosis and treatment of idiopathic NPH in the elderly have been established,[120] but there are still no guidelines for newborns, children, adolescents, and young or middle-aged adults.

Because disturbed CSF circulation contributes to hydrocephalus, detection of CSF flow abnormalities should be useful in diagnosis and treatment evaluation. Cine CSF flow MR imaging has been used to differentiate communicating

hydrocephalus (hyperdynamic aqueductal flow) from aqueductal stenosis (absent aqueductal flow).[7,179] Flow studies can show the patency of the third ventricle fenestration after ETV. Cine CSF flow MR imaging is limited by its ability to quantify flow only in specific directions, fields, and velocities.

Hydrocephalus is a chronic disorder. Thus, the assessment of treatment failure is as important as the initial diagnosis. The diagnosis of shunt or ETV failure and recurrence of hydrocephalus can be straightforward, with demonstration of expanding ventricles and symptoms of increasing ICP. The challenge is to develop diagnostic procedures that are sensitive enough to predict treatment failure before it happens or that allow intervention to be offered before permanent injury occurs. Severe morbidity and death are still seen as the result of sudden treatment failure.

Because the symptoms of shunt failure may resemble common disorders such as a viral syndrome, emergency department visits, CT or MR imaging studies, or shunt taps are often ordered to avoid harm due to "failure to diagnose." Finally, shunts may be "functioning" but still cause chronic unphysiological overdrainage of CSF. Many of these patients have headaches, nausea, and other ongoing symptoms, and yet are considered successfully treated because the ventricles are not enlarged. Improved and more sensitive diagnostic methods are needed to detect suboptimal treatment and treatment failure.

Imaging and Noninvasive Testing. Beginning with pneumoencephalography,[38] neuroimaging has been important for the diagnosis and management of hydrocephalus. Ventriculomegaly remains the sine qua non of hydrocephalus, and CT and MR imaging offer superb anatomical detail. Transependymal flow on CT scanning or MR imaging suggests the presence of increased ICP. Large ventricles without transependymal flow in the presence of normal examination results support the suggestion that the ICP is normal. Volumetric analysis to establish ventricular volume norms (especially with aging), and regional analysis comparing intra- with extraventricular CSF compartments can help distinguish idiopathic NPH from atrophy. The definition of ventriculomegaly has not been standardized, and anatomical imaging is usually insufficient as a sole diagnostic test for hydrocephalus.

Injection of contrast material or radioactive tracer into CSF (cisternography) can allow detection of CSF flow distribution and clearance. Computed tomography scanning performed after injection of contrast into the CSF can identify sites of obstruction. Although radionuclide cisternography would appear to be an excellent method for detecting abnormal CSF circulation and clearance, its utility in the diagnosis of idiopathic NPH has been disappointing.[17,20,125]

Magnetic resonance spectroscopy, functional MR imaging, positron emission tomography, and single-photon emission CT studies have been used for differential diagnosis and to assess the metabolic consequences of hydrocephalus. Although many reports implicate decreased CBF and even transient anaerobic metabolism,[143] these cannot be generalized to clinical practice.[22,163,170,181] Based on recent research, some investigators suggest that MR imaging methods can determine ICP or measure CBF responses to treatment.[75] Clearly, advances in anatomical and functional imaging have the potential to allow more efficient initial diagnosis, treatment optimization, and recognition of failure.

Invasive Testing Methods. Contemporary invasive diagnostic procedures include CSF pressure monitoring (using lumbar puncture, spinal or ventricular catheter, and intracranial sensor), CSF infusion for measurement of R_{out}, lumbar CSF drainage, and shunt tapping for diagnosis of shunt failure. Because invasive techniques carry risk, they are often reserved for complex diagnostic problems, as in the identification of idiopathic NPH, chronic shunt failure, and shunt overdrainage, where the benefit of the invasive testing offsets the associated risks and burdens.

Monitoring of CSF pressure was first advocated as a diagnostic test for idiopathic NPH more than 30 years ago.[138,141] Idiopathic NPH has the same abnormal CSF pressure waveforms originally described in brain tumor or acute injury.[21,27,138] The Lundberg A-, B-, and C-waves are slow oscillations that reveal changes in the beat-to-beat amplitude and pulsatility of CSF pressure that are thought to reflect changes in cerebral blood volume associated with normal or abnormal cerebrovascular regulation. Eide et al.[62,63,164] recently suggested that the amplitude of individual CSF pressure pulse waves may predict the response to CSF shunting in idiopathic NPH and in some children with hydrocephalus. Transfer function determination[114,148] and analysis of phase shifts[12] have led to the proposal of a link between the CSF pressure pulsation and the overall system response, linking clinical monitoring with biomechanical modeling. Ultimately, invasive measures of CSF dynamics such as pressure waves, pulsatility, CSF space compliance, and absorption resistance may be critical to the identification and optimal treatment of hydrocephalus.

Biomarkers. Researchers using animal models have used CSF markers extensively,[42,43,126] and so have investigators undertaking studies in humans.[10,152] Although trends may be apparent in relative levels of catecholamines, energy metabolites, myelin basic protein, and glial fibrillary acidic protein, to name a few, the overall results of these studies are inconclusive because of variations in models and the complex clinical origins of the disorder. Tau protein and amyloid-β are being evaluated as biomarkers in idiopathic NPH.[42,163] Although blood and CSF biomarkers based on CNS injury or metabolic or blood–brain barrier changes are unlikely to be specific to the diagnosis of hydrocephalus, they may still play an important role in determining the need to treat, the response to treatment, and also the prognosis.

Because of the difficulty in timely and sensitive identification of shunt infection, CSF markers of infection such as C-reactive protein,[160] if further developed, could play a large role in improving the treatment of shunt infection.

Neuropsychological Testing. Neuropsychological testing has long implicated problems in personality, cognition, and memory in children with hydrocephalus, and a subcortical dementia with short-term memory loss in adults with idiopathic NPH.[26,56,149,172] Although neuropsychological evaluation is not specific for hydrocephalus, it can be used to assess response to treatment and determine prognosis. Treating idiopathic NPH results in substantially better neuropsychological improvement than previously thought, surpassing the modest improvement seen with pharmacological treatment of Alzheimer disease.[172] Whether such cognitive improvement follows treatment of hydrocephalus in younger adults awaits demonstration.

Education. Because the majority of patients with hydro-

cephalus are children, most of the expertise in the diagnosis and treatment of this disorder has been among pediatric specialists. Nevertheless, there has been rapid growth in the number of adults with hydrocephalus for several reasons: children with the disorder survive to become adults; adults may experience secondary hydrocephalus from many causes; and idiopathic NPH is being recognized more frequently. Thus, if hydrocephalus continues to be perceived as "only" a pediatric disorder, it can be overlooked as a diagnostic consideration for adults.[31,185] Therefore, education about hydrocephalus should be targeted to internists, geriatricians, family physicians, and neurologists and neurosurgeons who treat adults. Patient and family-oriented education and public awareness campaigns may help bring patients to the attention of physicians.

Current Treatment, Outcomes, and Complications

The causes, presentation, course of illness, and treatment paradigms for hydrocephalus are different for children and adults. Current treatment in both groups is based on a limited number of randomized controlled trials, case-control studies, prospective observational studies, and retrospective case series. Guidelines for the most common adult form of hydrocephalus (idiopathic NPH) have been developed,[119] but paradoxically there are no guidelines for pediatric hydrocephalus, which is much more prevalent. Therefore, research needs related to treatment and outcomes of children may be broader. For example, treatment indications are not clearly defined, and there is significant variation between centers and surgeons in the decision to treat or observe. Thus, there is a need for objective methods to diagnose hydrocephalus and to select patients who will benefit from treatment.

There are no established criteria for selecting the most appropriate treatment (for example, shunt compared with ETV, type of valve, and technique of shunt insertion) for children of any age, although a randomized trial comparing shunt placement and ETV in infants (defined as children $<$ 1 year old) is under way in Europe. Shunt obstruction and malfunction occur in approximately one third of children in the 1st year after shunt surgery.[54] Two randomized trials failed to show a difference in shunt failure rates among valve types.[54,55,103]

There are few standardized outcome measures for either pediatric or adult hydrocephalus. Although shunt survival time and infection rates are commonly used, other important outcomes should be evaluated, such as neuropsychological and cognitive outcomes, which most likely are age-dependent. A Hydrocephalus Outcome Questionnaire has been developed and validated for children between 5 and 18 years of age.[111,112]

Infection complicates 8 to 10% of shunt operations in children[54,104,105,182] and may necessitate removal or externalization of the device, inpatient antibiotic therapy, and insertion of a new shunt. However, there are no standards for the diagnosis and treatment of shunt infection, and there is substantial variation in the duration of antibiotic therapy, decisions to remove or replace infected shunts, and length of hospital stay. The use of prophylactic antibiotics is generally accepted. Other strategies may reduce the risk of infection but require further study, such as antibiotic-impregnated shunt catheters,[161] double gloving,[112,147] and injection of antibiotics into the shunt lumen during surgery.[150] Reinfection is alarmingly common (25%) and does not appear to be related to the duration of antibiotic therapy.[105] Shunts impregnated with rifampicin and clindamycin reduce reinfection from *Staphylococcus epidermidis*.[9] Further studies of the effectiveness of antibiotic-impregnated external ventricular catheters and shunt catheters in the prevention and management of infection are warranted.

As discussed earlier, establishment of a hydrocephalus research infrastructure, including clinical data repositories, would facilitate longitudinal studies. The database should be broadly available to researchers and the physician community and should protect the privacy of patients, consistent with federal, local, and state regulations and laws.

Priorities for Future Treatments

The most forward-looking research priorities are for future treatments (Table 1). These include not only the development of novel medical devices, biomaterials, or surgical techniques, which represent a continuation of the first 50 years of hydrocephalus treatment research, but also the development of novel adjunctive (that is, pharmacological) therapies that should emerge from improved understanding of the basic biology of hydrocephalus and its impact on the brain.

Novel Medical Devices and Biomaterials

Shunts have been the fundamental treatment for hydrocephalus for nearly 50 years. Ironically, this may have caused many to believe that hydrocephalus was a "solved problem" that no longer required focused investigation.[114] Yet, as described earlier, shunts are often associated with side effects and complications. Despite advances in their design, shunt failure nonetheless remains a significant problem. With the exception of ETV, which is used in a minority of patients, there are no alternative treatments and no proven medical or pharmacological treatments.

Medical devices and new treatments for hydrocephalus should be designed in accordance with contemporary understanding of the pathophysiological features of hydrocephalus. The goal is to bring new technologies and research discoveries together to improve the diagnosis and treatment of hydrocephalus for patients of all ages. This should include diagnostic aids that allow treatment to be individualized and optimized. For example, the decision to change the setting of an adjustable shunt is usually guided by clinical findings, subjective impressions, or neuroimaging, resulting in variations of practice. An objective optimization parameter is needed to guide such decisions. Possibilities include the analysis of CSF pulsation amplitude or MR imaging and transcranial Doppler methods.[62,63,164]

There is no method to quantitate the pressure or flow function of shunts in real time in the outpatient setting. The development of devices that record these variables over time has the potential to improve short- and long-term treatment outcomes. Device size and inability to record ambulatory data have limited past efforts at telemetric ICP and shunt flow monitoring.[39,70,187] Microelectromechanical versions of such devices, including the development of a smart monitor to allow query of shunt performance data, could overcome these limitations.

Devices that respond to changes in the internal milieu (for example, biochemical or physiological changes) may play an important role in future therapies. For example, it is likely that the functional characteristics of a shunt that are optimal for one set of conditions (posture, activity, heart rate, blood pressure, and so on) are suboptimal in another. Antisiphoning devices, which have been used to address postural effects for many years, are rudimentary, and improved physiological understanding is the key to developing improved devices. Last, although antibiotic-impregnated shunt components already exist, further research on biomaterials is needed to create shunt catheters with less risk of cellular occlusion or more resistance to bacterial adhesion, for example.

Adjunctive Therapies

Pharmacological agents (for example, acetazolamide) have been used as temporizing strategies to treat hydrocephalus in certain situations, especially in newborns, but drugs have never been considered a mainstay of treatment, nor have they been demonstrated to be effective in adults. Improved understanding of the basic science of injury and recovery mechanisms and homeostatic mechanisms such as control of cell volume, response of endothelial cells to pulsatile shear, CSF absorption or secretion processes, and genetic regulation has great potential to lead to the development of pharmacological or biological agents to prevent or treat hydrocephalus and enhance clinical recovery. There is a need to determine the potential role of stem cell therapy, for example, to supply trophic agents or promote myelin formation. One model worth considering is the Stroke Therapy Academic Industry Roundtable, which presents recommendations for preclinical neuroprotective and restorative drug development.[2]

Human Research: Ethical Considerations

Considering that translational research in hydrocephalus represents exciting and unexplored territory, it will be vital that collaboration between basic and clinical scientists occurs to assure that promising laboratory methods transfer to humans. In addition, recognizing that hydrocephalus most often affects persons considered vulnerable human research candidates (infants, children, and adults with dementia and impaired decision-making capacity), and that neither the immediate nor long-term effects of novel pharmacological or biological agents can be predicted, it will be important to consider the ethical boundaries and safeguards of such research prospectively.

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Appendix 1

Breakout sessions and key questions

Breakout Session I: Injury Mechanisms, Neuroprotection, and Cellular Recovery in Hydrocephalus

Breakout Session II: New Insights into the Pathophysiology of CSF Circulation—-Implications of Shunt Design or Other Treatments for Hydrocephalus

Breakout Session III: Clinical Tools, Clinical Trials, and Clinical Outcomes

Key questions for all breakout sessions:

1. What is the critical information that has been missing or needs to be reconsidered to advance our understanding of the pathophysiological features of hydrocephalus, its clinical manifestations, its treatment, and its outcomes?
2. What is the best way to obtain this information?
3. How can research in related disorders be used to improve our understanding of hydrocephalus, and vice versa?
4. How can clinicians, clinical researchers, and basic scientists collaborate more effectively?
5. What are the critical differences between pediatric and adult hydrocephalus?

Appendix 2

Participants and contributors

Workshop Leadership Committee:

Chair, James P. "Pat" McAllister, Wayne State University, Detroit, Michigan; *Chair*, Marion L. "Jack" Walker, University of Utah, Salt Lake City, Utah; *Chair*, Michael A. Williams, Johns Hopkins Medical Institutions, Baltimore, Maryland; Dory Kranz, Hydrocephalus Association, San Francisco, California; Katrina Gwinn, NINDS, Bethesda, Maryland

Breakout Session 1—Injury Mechanisms, Neuroprotection, and Cellular Recovery in Hydrocephalus

Facilitators: James P. "Pat" McAllister, Wayne State University, Detroit, Michigan; Michael A. Williams, Johns Hopkins Medical Institutions, Baltimore, Maryland; Hazel Jones, University of Florida, Gainesville, Florida

Breakout Session 2—New Insights into the Pathophysiology of CSF Circulation: Implications of Shunt Design or Other Treatments for Hydrocephalus

Facilitators: Marion L. "Jack" Walker, University of Utah, Salt Lake City, Utah; Michael Egnor, State University of New York, Stony Brook, New York; Marvin L. Sussman, Miami, Florida

Breakout Session 3—Clinical Tools, Clinical Trials, and Clinical Outcomes

Facilitators: Anthony Marmarou, Virginia Commonwealth University, Richmond, Virginia; John Kestle, University of Utah, Salt Lake City, Utah; Dory Kranz, Hydrocephalus Association, San Francisco, California

Additional invited moderators and speakers:

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