HYDROCEPHALUS TREATMENT IN UGANDA: LEADING THE WAY TO HELP CHILDREN

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AND HUMAN RIGHTS
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Subcommittee on Africa, Global Health, and Human Rights

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HYDROCEPHALUS TREATMENT IN UGANDA: LEADING THE WAY TO HELP CHILDREN

TUESDAY, AUGUST 2, 2011

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON AFRICA, GLOBAL HEALTH, AND HUMAN RIGHTS
COMMITTEE ON FOREIGN AFFAIRS,
Washington, DC.

The subcommittee met, pursuant to notice, at 2 o'clock p.m., in room 2172, Rayburn House Office Building, Hon. Christopher H. Smith (chairman of the subcommittee) presiding.

Mr. SMITH. The subcommittee will come to order. I want to thank you for joining us this afternoon for this hearing on this serious and seriously neglected health condition and a relatively inexpensive, technologically sophisticated advancement for curing it, created, designed, and perfected by one of our distinguished witnesses, Dr. Benjamin Warf.

I had the opportunity to learn more about hydrocephalus when I was traveling in Africa last March. Children who suffer from hydrocephalus characteristically have heads that are far out of proportion to the size of their small bodies. I was horrified to learn that in Africa, where superstitions still are widespread, hydrocephalus is commonly perceived as a curse, or caused through witchcraft. A child may be subjected to horrific abuse and even killed as a result. It was, therefore, a real eye-opener for me to see the cultural context of hydrocephalus in Africa and the extraordinary efforts of a number of courageous, compassionate individuals who are addressing it.

The human brain normally produces cerebrospinal fluid which surrounds and cushions it. The fluid also delivers nutrients to and removes waste away from the brain. This fluid is drained away from the brain and absorbed into blood vessels as a new fluid is produced. Hydrocephalus occurs when this draining process no longer functions properly. The fluid levels inside the skull rise, causing increased pressure that compresses the brain and potentially enlarges the head. Symptoms include headaches, vomiting, blurred vision, cognitive difficulties in balance, convulsions, brain damage, and ultimately death. Hydrocephalus can occur in adults but most commonly is present at birth.

Our witnesses will testify that there are believed to be more than 4,000 new cases of infant hydrocephalus in Uganda and 100,000 to 375,000 new cases in sub-Saharan Africa each year. By comparison, in the United States, hydrocephalus occurs in 1 out of every 500 births. Another 6,000 children under the age of 2 develop hy-
drocephalus annually. The U.S. National Institutes of Health estimates that 700,000 Americans have hydrocephalus, and it is the leading cause of brain surgery for children in this country. A major difference between the United States and sub-Saharan Africa is the number of neurosurgeons available to treat this condition. The United States has 3,500 neurosurgeons, whereas Uganda, for example, has only 4. Dr. Warf said earlier today, and will say in his testimony, the number is about 1 per 10 million Africans. There is just such a dearth of this very important and needed specialty.

Another major difference between the United States and sub-Saharan Africa is the methodology employed to treat hydrocephalus. In the Western world, doctors surgically insert a shunt into the brain in order to drain the fluid through the neck and into another part of the body where the fluid can be absorbed.

A shunt is only a temporary solution, and there is always a danger that any one of a number of things may go wrong. For example, the tube may become blocked, an infection may develop, catheters may break or malfunction due to calcification, or the valve may drain too much or too little fluid. In almost half of all cases, shunts fail within the first 2 years, and when they do, the patient must have immediate access to a medical facility and a doctor who can correct the problem.

This precarious situation must be a constant source of concern and stress for people in the United States who suffer from hydrocephalus and for their families. However, in a place like sub-Saharan Africa, a shunt is fundamentally impractical. Trained neurosurgeons, as I noted earlier, are extremely few in Africa, as are properly equipped hospitals; and roads and transportation systems on the African continent make travel arduous and long for the vast majority of people, even under the best of circumstances.

A hydrocephalic child in a place like Uganda, even if he or she could be treated with a shunt, would have little hope of living for more than a couple of years.

In March of this year, I had the privilege of meeting with Dr. John Mugamba, one of the four neurosurgeons in Uganda. With the help of a video such as we will be viewing during this hearing, Dr. Mugamba explained the fascinating surgical procedure, again developed by Dr. Warf, that he is performing several times daily in Uganda to cure small children of hydrocephalus. This treatment is being provided at CURE Children’s Hospital of Uganda and is not only overcoming a medical barrier that children inflicted with the condition face, it is also serving to educate Ugandan communities that the condition is not the result of a curse and is not a reason to kill a child.

Parents whose children have been cured are helping other parents to identify the condition early in an infant’s life and know where to go for treatment. As I said, one of our witnesses, Dr. Benjamin Warf, was the first to identify neonatal infection as the chief cause of pediatric hydrocephalus in a developing country. He also developed a new surgical technique, ETV/CPC, which holds great promise not only for the children of Africa but potentially for children in developed countries as well. As Dr. Warf will soon testify, hydrocephalus has never been a public health priority in developing countries. Most infants in Africa do not receive treatment.
And even when treated, they often succumb to premature death or suffer severe disabilities. Therefore, it is imperative that we find the causes in order to develop a public prevention health strategy.

I am very pleased to welcome our distinguished witnesses who will explain these innovative procedures, efforts being undertaken to determine the causes of hydrocephalus, and initiatives to end the suffering caused by this life-threatening condition. I would plead that all stakeholders who care about the children of Africa, including African ministries of health, nongovernmental organizations, and our own U.S. Agency for International Development, urgently provide tangible support for these efforts and for these initiatives.

I would like to now yield to my good friend and colleague, Mr. Payne, for his opening.

Mr. PAYNE. Thank you very much. Let me begin by thanking Chairman Smith for calling this hearing, helping us to shine a light on the terrible condition that we have heard him describe and that we will be discussing today. We certainly appreciate the experts who have given their time to come here today to enlighten us on this situation.

As Chairman Smith has mentioned, hydrocephalus is an excessive accumulation of the cerebrospinal fluid in the brain, and can be congenital or acquired. Congenital hydrocephalus may be caused by parental factors or genetic abnormalities caused by infections, tumors, or head injuries. The disease can be fatal if left untreated.

I am hopeful that by providing prenatal care to mothers, the President's Global Health Initiative can help prevent the infection that causes the disease.

The prevalence rate of hydrocephalus is not well known or not well documented. However, CURE International estimates that there were roughly 400,000 new cases in 2010. I believe that the numbers of cases in east Africa and the developing world is much greater due to a high rate of neonatal infections. In east Africa, as a region, it is estimated that 6,500 new cases occur each year and more than 45,000 in sub-Saharan Africa. The actual number of hydrocephalus cases in Uganda is unknown. Conservative estimates have the number at 1,000 to 2,000 cases occurring each year. Roughly 60 percent of these are reportedly attributed to neonatal infections.

While Dr. Warf, CURE International, and others are making an impact in Uganda, it is clear that these innovative interventions are needed throughout Africa. The resources available to combat this disease are severely lacking in Africa and the developing world. In addition to the lack of funding and access to health facilities, the expertise needed to combat such a disease is rare. There is an estimated one neurosurgeon for every 10 million people in east Africa; and as has been noted, the number in Uganda is one trained neurosurgeon per 8.6 million. So, believe it or not, it is a little bit better in Uganda than other east African countries.

And really, if you take other countries in Africa, it is even worse because it is documented that there are no trained neurosurgeons in a number of countries in Africa—zero, not one. So we see that we have a very serious situation where in the U.S., we have 2.67 physicians per every 1,000 people; and for the neurosurgeons, we
have 1 neurosurgeon for every 88,000 people in America. So if you see where we have 1 per 88,000 in the U.S., and 1 for 10 million, or zero for millions, we see why we have such a serious problem.

Of course the resources available to combat this disease are severely lacking, as we can see by the number of physicians. And in addition to the lack of funding and access to health facilities, the expertise needed to combat the disease is rare, as we mentioned, with the lack of trained people to deal with this.

I am interested in hearing from our experts here today about how the U.S. Global Health Initiative can best promote the training of specialized doctors and surgeons to combat this disease and ones like it. I am also interested in learning about what measure can be taken to prevent the disease altogether.

So I think we need to really try to work on prevention. It is going to be difficult to get people in to treat and to care for, but if we can deal with an overall prevention, I think that our dollars will go much further and really keep a lot of agony from people.

So I certainly look forward to hearing the witnesses. And actually kind of the fact that we lack the training, I just want to mention that I am cosponsoring a bill on African higher education. We call it the African Higher Education Advancement and Development, we call it the AHEAD Act for 2011, where we are really trying to deal with higher education in Africa, regardless of whether it is medicine, whether it is just basic education, whether it is teacher training.

As we see Africa moving more to universal elementary education, most countries now have decided that there is universal elementary free education, although there are still school fees but they are minimal. And now that the girl child has finally been recognized as an entity that ought to be included in elementary and secondary education, at least we are seeing a move for girls in elementary education, and hopefully we will see it in secondary education.

And of course, finally, getting into higher ed, I think that we need to try to move forward assistance in higher education so that doctors and neurosurgeons and people that we need to have positioned in Africa, Africans themselves, will be able to have the training so that we can deal with this issue. So, Mr. Chairman, I yield back the balance of my time.

Mr. SMITH. Mr. Payne, thank you very much.

We are joined by the chairman of the Commerce, Justice, Science, and Related Agencies Subcommittee of the Appropriations Committee, Congressman Frank Wolf.

Mr. WOLF. Thank you. I want to welcome the witnesses. I will thank Mr. Smith for having the hearings. We were talking about this issue on the floor. I don't serve on this committee. I have to go to another place soon, but I just wanted to come by to hear your testimony. Thank you for the invitation, Mr. Smith.

Mr. SMITH. Chairman Wolf, thank you very much.

I would like to now introduce our very distinguished panel, beginning with Dr. Benjamin Warf who began his career in pediatric neurosurgery at Children's Hospital Boston in 1991 as the first pediatric fellow in neurological surgery. In 2000, he and his family moved to Uganda to help found a hospital for pediatric neurosurgery with CURE International, a nonprofit Christian medical
mission organization. While at CURE, Dr. Warf served as medical director and established the only pediatric neurosurgery hospital in sub-Saharan Africa.

Dr. Warf was the first to identify neonatal infection as the chief cause of pediatric hydrocephalus in a developing country, and remains involved in working to uncover its pathogenesis in order to ultimately construct prevention strategies. He developed a novel surgical technique for treating hydrocephalus in infants, known as ETV/CPC. Since returning to the U.S., Dr. Warf has investigated the role of ETV/CPC in North American instances and also continues to work in international neurosurgery development.

He rejoined the team at Children’s Hospital in Boston in 2009, and was appointed director of Neonatal and Congenital Anomaly Neurosurgery. He is associate professor of surgery at Harvard Medical School and has an affiliate appointment with the Program for Global Surgery and Social Change in the Department of Global Health and Social Medicine.

We will then hear from Dr. Steven J. Schiff, Brush chair professor of engineering and director of the Penn State Center for Neural Engineering. He is a faculty member in the departments of neurosurgery, engineering science, and mechanics and physics. A pediatric neurosurgeon with a particular interest in epilepsy, hydrocephalus, and Parkinson’s disease, Dr. Schiff holds a Ph.D. in physiology and an M.D. from Duke University School of Medicine, and trained in adult and pediatric neurosurgery at Duke and Children’s Hospital in Philadelphia. He is perhaps the only fellow of both the American Physical Society and the American College of Surgeons, and he serves as a divisional associate editor of Physical Review Letters. He has been listed in the Consumers Research Council of America’s guide to top physicians and surgeons, and he plays the viola with the Nittany Valley Symphony. There is no time for that today, though.

We will then hear from James Cohick who has served as a health care executive in the fields of specialty medicine and surgery since 1983. For 16 years, he served in field and in corporate administration with U.S.-based specialty hospital networks. And for the past dozen-plus years, he has been a part of internationally focused pediatric specialty hospitals and organizations.

In 1997, Mr. Cohick and his family moved to Kenya to start and run the first CURE International hospital, the first of its kind on the African continent. In addition to serving as executive director of the hospital, he directed regional operations for east Africa for CURE, which involved the creation of the two other facilities.

Returning stateside in 2000, he continued to provide oversight of CURE International’s growing network of hospitals and initiated a CURE global clubfoot program. After completing his MBA and studies at the Kellogg School of Management, he served as hospital administrator at the Shriners Hospital for Children in Chicago and was elected to the board of directors for Metropolitan Chicago Healthcare Council, a number of committees for Illinois Hospital Association, and continues to be a fellow with the American College of Healthcare Executives.
Now, as senior vice president of specialty programs at CURE International, Mr. Cohick provides executive leadership to CURE Clubfoot Worldwide and CURE hydrocephalus.

Dr. Warf, if you could proceed.

STATEMENT OF BENJAMIN WARF, M.D., DIRECTOR, NEONATAL AND CONGENITAL ANOMALIES NEUROSURGERY, DEPARTMENT OF NEUROSURGERY, CHILDREN’S HOSPITAL BOSTON

Dr. Warf. Thank you very much, Chairman Smith, Congressman Payne, members of the committee. It is a great honor to be here today, and I appreciate the opportunity to testify about this devastating condition affecting ultimately millions of babies in Africa and across the developing world. I am currently at Children’s Hospital Boston and am an associate professor of surgery at Harvard Medical School. But from 2000 to 2006, my family and I lived in Uganda as medical missionaries to help start a specialty hospital for pediatric neurosurgery, CURE Children’s Hospital of Uganda.

From its opening, our hospital was inundated with a steady stream of mothers seeking treatment for their infants with hydrocephalus, a condition in which the fluid is unable to circulate out of the brain and be absorbed normally. This leads to mounting pressure, rapid expansion of the infant’s head, progressive damage to the developing brain, and usually death, if untreated.

Astonished by the staggering volume of patients, we were presented with two questions: One, what were the chief causes and burden of disease in this part of the world? And two, what was the best way to treat this condition in the context of rural sub-Saharan Africa?

The burden of hydrocephalus in Africa is arresting. We estimate there are between 100,000 and 375,000 new cases of infant hydrocephalus each year in sub-Saharan Africa, with an annual economic burden of untreated hydrocephalus from $1 billion to tens of billions of dollars, depending on the type of economic analysis used.

This economic burden is comparable to published estimates of other common surgical conditions in Africa, such as malignancies, perinatal conditions, congenital anomalies, cataracts, and glaucoma. Yet we are the first to highlight infant hydrocephalus as a serious health burden in any region of the developing world.

In the U.S., most infant hydrocephalus is either congenital or related to brain hemorrhage in very premature babies. We discovered that in marked contrast to developed countries, 60 percent of the Ugandan cases were caused by infections, mostly within the first month of life, the neonatal period. The infections were characterized by a febrile illness, usually accompanied by seizures, which was followed by rapid enlargement of the infant’s head. In addition to the resulting hydrocephalus, the brains of these children contained frank pus and blood and substantial destruction of tissue. We could successfully save the vast majority of these children by treating the hydrocephalus. But the primary brain injury from the original infection was often devastating. In a study now in press, we found that a third of these children had died by 5 years and a third of the survivors had severe disabilities. The importance of prevention or early treatment of these infections was obvious. But...
we were unable to isolate any bacteria from the fluid at the time of the surgical treatment.

This is where my valuable colleague Dr. Schiff here and his team at Penn State have come to the rescue, as he will give testimony. Infant hydrocephalus is almost always treated by implanting a tube, called a shunt, which drains the fluid from the brain into the abdomen. In the U.S., the average patient requires two to three operations per shunt failure during their childhood. Shunt failure is a life-threatening emergency in children. But in rural Africa, accessing emergency neurosurgical care is impossible. We developed a novel way to treat hydrocephalus using a scope that avoided shunt dependence in more than half these babies overall, including those with postinfectious hydrocephalus. The operation makes a new pathway for the fluid to escape the spaces in the brain and cauterizes the tissue that makes the fluid, thus decreasing its rate of production. We have since learned to predict which patients are most likely to be treated successfully in this way, and have trained and equipped other surgeons in the technique which will be demonstrated shortly in a brief video.

Detailed economic analysis estimates a lifetime treatment cost of around $90 per disability-adjusted life-year averted using the treatment paradigm we developed at CURE Children’s Hospital of Uganda. This cost compares very favorably to the few other surgical interventions that have been studied in developing countries. Hydrocephalus has never been a public health priority in the developing countries. Most infants in Africa receive no treatment. Training and equipping centers in an evidence-based treatment paradigm is essential, and it is imperative that we identify the causes of infection in these babies so that public health strategies for prevention can be constructed and millions of lives saved. These are the challenges that lie before us. Thank you very much.

And we have a video now that I would like to show. The man you will hear, Dr. Mugamba, a Ugandan neurosurgeon whom I trained in the technique and worked with me for a couple of years in Uganda before I came back to the U.S.

[Video was played.]

Dr. WARF. This is a scene in our operating room in Uganda. It just takes about 1½ minutes or so to demonstrate the setup in the operating theater. There is Dr. Mugamba making the small incision in the infant’s scalp just over the soft spot, the anterior fontanelle. And in a few moments, he will insert a small flexible fiberoptic endoscope into the cavity in the brain, the ventricle of the brain. And you will see, as I will point out, where he makes the opening to allow the fluid to escape.

That is a view from inside the brain. On the left side of the screen is actually where the pituitary gland is. To the right, just off screen, is the brainstem. This is the floor of the third ventricle. He is making an opening in the floor of the third ventricle where the fluid is trapped. And now the fluid will be able to exit this new opening which bypasses levels of obstruction and allows the fluid to escape to the outside of the brain into the spaces where it can normally circulate and be absorbed. This part of the procedure is called the choroid plexus cauterization. This is the tissue that is being cauterized, the tissue that makes the spinal fluid. We found
that in infants, the endoscopic third ventriculostomy success rate
was greatly increased by addition of this procedure at the time of
the surgery. The innovation here was combining the two techniques
which hadn't been tried before.

Thank you very much.
Mr. SMITH. Dr. Warf, thank you so very much.
[The prepared statement of Dr. Warf follows:]

Statement of Benjamin C. Warf

Director, Neonatal and Congenital Anomalies Neurosurgery
Children’s Hospital Boston
Associate Professor of Surgery
Harvard Medical School

August 2, 2011

House Committee on Foreign
Affairs, Subcommittee on Africa, Global Health, and Human
Rights

Chairman Smith, Congressman Payne, and members of the committee it is an honor to be
here today. Thank you for the opportunity to testify about a devastating condition
affecting millions of babies in Africa and across the developing world.

I am currently the Director of Neonatal and Congenital Anomalies Neurosurgery at
Children's Hospital Boston, and Associate Professor of Surgery at Harvard Medical
School, with an Affiliate appointment in the Harvard Medical School Department of
Global Health and Social Medicine.

In 2000, my family and I moved to Uganda as medical missionaries to help start a
specialty hospital for pediatric neurosurgery, the CURE Children’s Hospital of Uganda.
From its opening, our hospital was inundated with a steady stream of mothers seeking
treatment for their infants with hydrocephalus: a condition in which the cerebrospinal
fluid made in the cavities of the brain is unable to circulate out of the brain and be
absorbed normally. This leads to mounting pressure, rapid expansion of the infant’s head,
progressive damage to the developing brain, and usually death if untreated. Astonished
by the staggering volume of patients, we were presented with two questions: 1) what
were the chief causes and burden of disease in this part of the world; and, 2) what was the
best way to treat this condition in the context of rural sub-Saharan Africa?

The burden of hydrocephalus in Africa is arresting. We conservatively estimate there are
100,000 to 375,000 new cases of infant hydrocephalus each year in sub-Saharan Africa.
Our recent work has demonstrated an annual economic burden of hydrocephalus in sub-
Saharan Africa from $930 million to $1.6 billion using a human capital approach, and $1.4 billion to $56 billion using the value of a statistical life approach. This economic burden is comparable to published estimates of other, more common medical conditions in Africa such as malignancies, perinatal conditions, congenital anomalies, and cataracts and glaucoma. Yet, we are the first to highlight infant hydrocephalus as a serious health burden in any region of the developing world.

In the US, most infant hydrocephalus is either congenital or related to brain hemorrhage in very premature newborns. We discovered that, in marked contrast to developed countries, 60% of the Ugandan cases were caused by infections – mostly within the first month of life. The infections were characterized by a febrile illness, usually accompanied by seizures, which was followed by rapid enlargement of the infant’s head. In addition to the hydrocephalus caused from infection the brains of these children contained frank pus and blood and substantial destruction of tissue. We could successfully save the vast majority of these children by treating the hydrocephalus, but the primary brain injury from the original infection was often devastating. In a study now in press, we found that 1/3 of these treated children had died by 5 years, and 1/3 of the survivors had severe disabilities. The importance of prevention or early treatment of these infections was obvious; but, we were unable to isolate any bacteria from the fluid at the time of surgical treatment. This is where my invaluable colleague Dr. Schiff and the team of scientists he assembled at Penn State have come to the rescue, as he will explain.

Infant hydrocephalus is almost always treated by implanting a tube, called a shunt, which drains the fluid from the brain into the abdomen. In the US, half of these fail and need revision within 2 years and 80-90% fail at least once in the first decade, with the average patient requiring 2-3 operations for shunt failure during their childhood. Shunt failure is a life-threatening emergency in children, but in rural Africa accessing emergency neurosurgical care is impossible. We developed a novel way to treat hydrocephalus using a scope (endoscopically) that avoided shunt dependence in more than half of these babies overall, including those with post-infectious hydrocephalus. The operation combines endoscopic third ventriculostomy (ETV), which makes a new pathway for the fluid to escape the cavities (ventricles) of the brain, and endoscopic choroid plexus cauterization (CPC) which cauterizes the tissue that makes the fluid thus decreasing its rate of production. We have since learned to predict which patients are most likely to be treated successfully in this way, and have trained and equipped other surgeons in the technique, which will be demonstrated momentarily in a brief video. Detailed economic analysis estimates a life-time treatment cost of around $90 per disability adjusted life year (DALY) averted, with a minimum benefit to cost ratio of 7:1, using the treatment paradigm we developed at CURE Children’s Hospital of Uganda. This cost compares
very favorably to the few other surgical interventions that have been studied in
developing countries.

Hydrocephalus has never been a public health priority in developing countries. Most
infants in Africa receive no treatment. Training and equipping centers in an evidence
based treatment paradigm is essential. Post-infectious hydrocephalus, even when treated,
leads to premature death or severe disability in the majority. It is absolutely imperative
that we identify the underlying organisms that infect these babies so that public health
strategies for prevention can be constructed and millions of lives saved. These are the
challenges that lie before us. Thank you.
STATEMENT OF STEVEN J. SCHIFF, M.D., DIRECTOR, CENTER FOR NEURAL ENGINEERING, PENNSYLVANIA STATE UNIVERSITY

Mr. SMITH. Dr. Schiff.

Dr. SCHIFF. Chairman Smith and Congressman Payne, thank you very much for the invitation to testify today.

I am a pediatric neurosurgeon who started my career practicing at the Children's Hospital here in Washington, DC. I now direct the Center for Neural Engineering at Penn State University, seeking solutions to problems that lie at the intersection of medicine, engineering, and science.

I have known Dr. Warf for many years. And hearing of his efforts to address childhood illnesses in Uganda, I visited him in 2006 to see how our engineering center might help his patients. It was readily apparent that he and his colleague, Dr. Mugamba, were inundated with cases of postinfectious hydrocephalus. At that time they had treated over 1,000 patients without being able to culture any of the causative organisms in their laboratory.

I asked Dr. Warf what the single most important problem was that he faced at the hospital, and he said, Finding out what causes these cases. I have since devoted much of my professional effort toward seeking those answers.

We began by bringing specimens from Ugandan infants back to Penn State and we threw the book at them in terms of advanced ways of growing organisms. We grew nothing. We then turned to DNA collection tools police use at crime scenes and set up a little forensics lab at CURE Hospital. We gathered DNA from the brain fluid of infants at the time of surgery to sequence the bacterial genes that might be present.

My Penn State colleagues, Vivek Kapur, Mary Poss, and I found evidence of bacteria within the brain fluid in nearly every one of these children. The bacterial types appeared consistent with those found on a farm, with animals. The bacterial spectrum also was noted to change with the various seasons and with the rainy seasons in Uganda. The most prevalent bacteria was called Acinetobacter, a notorious organism that has caused terrible wound infections in our military personnel in both Vietnam and the Iraq-Afghanistan conflicts. We then undertook field work to track down the infants in which we had found evidence of Acinetobacter infection.

Environmental samples from huts, dung, and water supplies yielded very close genetic matches for the organisms that we had previously retrieved from these infants' brains. Our findings were significant, but did not determine what initially made the infants sick. Most of them developed serious infections within the first month of life, called neonatal sepsis.

The World Health Organization estimates that infections lead to the death of 1.6 million infants each year, the majority in sub-Saharan Africa and southern Asia. The causal bacteria in the developing world appear different from those we see in the U.S. And most of the culture results from septic African neonates have failed to grow out organisms in any laboratory.
We began a study last year of neonatal sepsis at one of Uganda’s major referral hospitals at the Mbarara University of Science and Technology. Last year we recruited 80 mother/infant pairs, and in partnership with their head pediatrician, Dr. Julius Kiwanuka, collected spinal fluid and blood from the babies and birth canal specimens from the mothers. We are now collaborating with the J. Craig Venter Institute in Washington, DC, to perform an exhaustive sequencing of the bacterial and viral content of these samples.

Since CURE treats all the hydrocephalus that develops in Mbarara patients, once we have studied a sufficient number of patients with neonatal sepsis from Mbarara, we will know which infections lead to hydrocephalus, treated at CURE Hospital.

Recently, by fusing Dr. Warf’s case data with U.S. NOAA satellite data, we demonstrated a strong link between climate and post-infectious hydrocephalus. Infants get sick at intermediate levels of rainfall, emphasizing the role of the environment in this condition. Our work demonstrates that we are benefiting from the United States’ technology in ways we had never anticipated.

We are committed to optimally surgically treat the large numbers of children who have hydrocephalus. However, we will never operate our way out of this problem. A critical long-term goal is more effective treatment for children with neonatal sepsis to decrease the brain complications in the survivors. And most importantly, once we understand the root causes, we need public health measures to prevent these infections.

Hydrocephalus is thus a global health issue well beyond the specifics raised by a small, very fine African hospital, a great U.S. charitable organization that brings the highest-quality medical care and compassion to children around the world, and the finest physician I have ever met, Dr. Warf.

Of the 130 million children born around the world each year, we are inadequately addressing the 1.5 million who die of preventable newborn infection. As a physician and scientist and as a father, I am struck by how much we don’t know about newborn infections in developing countries. I am concerned that one reason is that the newborn infants who die there have no political voice.

I will offer three conclusions in closing: First, we have not paid sufficient attention to the massive loss of human life from newborn infections in the developing world; second, we now have the technology to shed new light on the causes of a substantial fraction of these deaths; and third, we can now develop sustainable strategies and scalable technologies to more effectively prevent the deaths and tragic survivals from these devastating illnesses. The fate of millions of lives depends on our actions. Thank you.

Mr. SMITH. Dr. Schiff, thank you so very much.

[The prepared statement of Dr. Schiff follows:]
Statement of Steven J. Schiff

Director, Center for Neural Engineering
Brush Chair Professor of Engineering
Penn State University

August 2, 2011

House Committee on Foreign Affairs, Subcommittee on Africa, Global Health, and Human Rights

Chairman Smith and Congressman Payne, thank you for the invitation to testify today.

I am a pediatric neurosurgeon who started my career practicing at the Children's hospital here in Washington, DC. I now direct the Center for Neural Engineering at Penn State University, seeking solutions to problems that lie at the intersection of medicine, engineering, and science.

I have known Dr. Warf for many years, and hearing of his efforts to address childhood illnesses in Uganda, I visited him in 2006 to see how our engineering center might help his patients. It was readily apparent that he and his colleague Dr. Mugamba were inundated with cases of postinfectious hydrocephalus. At that time, they had treated over 1000 patients, without being able to culture any of the causative organisms in their laboratory. I asked Dr. Warf what the single most important problem was that he faced at the hospital, and he said finding out what causes these cases of postinfectious hydrocephalus. I have since devoted much of my professional effort towards seeking those answers.

We began by bringing specimens from Ugandan infants back to Penn State and 'threw the book at them' in terms of advanced ways of growing organisms. We grew nothing.
We then turned to DNA collection tools police use at crime scenes and set up a small forensics lab at the CURE hospital. We gathered DNA from the brain fluid of infants at the time of surgery to sequence the bacterial genes that might be present. My Penn State colleagues, Vivek Kapur and Mary Poss, and I found evidence of bacteria within the brain fluid in nearly all of the children. The bacterial types appeared consistent with those found on a farm with animals. The bacterial spectrum changed during rainy seasons.

The most prevalent bacteria was Acinetobacter, a notorious organism that has caused terrible wound infections in our military personnel in both the Vietnam and the Iraq-Afghanistan conflicts.

We then undertook fieldwork to track down the infants in which we found evidence of Acinetobacter infection. Environmental samples from huts, dung and water supplies yielded very close genetic matches for the organisms that we had previously retrieved from the infants’ brains.*

Our findings were significant but did not determine what initially made the infants sick. Most of them developed serious infections within the first month of life, called neonatal sepsis. The World Health Organization estimates that infections lead to the death of 1.6 million infants each year, the majority in sub-Saharan Africa and southern Asia. The causal bacteria in the developing world appear different from those we see in the US. And most of the culture results from septic African neonates have failed to grow out organisms in any laboratory.

With funding from the Penn State Clinical and Translational Sciences Institute, and the endowment funds of Harvey F. Brush, we began a study of neonatal sepsis at one of Uganda’s major referral hospitals at the Mbarara University of Science and Technology. Last year we recruited 80 mother-infant pairs, and in partnership with their head pediatrician Dr. Julius Kiwanuka, collecting spinal fluid and blood from the babies and birth canal specimens from the mothers.

We cultured the specimens on site at Mbarara and shipped the DNA samples to the U.S. We also collected specimens for viral RNA analysis, to ensure that we did not overlook any important viral role in this syndrome.
We were able to culture bacteria from the blood and spinal fluid of only a minority of the infants, and we found no evidence of significant transmission of maternal bacteria to them or any relationship to HIV infection in the mothers.

We are now collaborating with the J. Craig Venter Institute near Washington, DC, to perform an exhaustive sequencing of the bacterial and viral content of these samples. We have further received clearance from the Mbarara hospital, and the government agency that oversees human research in Uganda, along with Penn State and Harvard human investigations oversight committees, to proceed with extensive additional sampling.

Since CURE treats all of the hydrocephalus that develops in Mbarara patients, once we have studied a sufficient number of infants with neonatal sepsis from Mbarara, we will know which infections lead to hydrocephalus treated at the CURE hospital. Once we have identified the organisms, we can determine the routes of infection.

Recently, by fusing Dr. Warf's case data with US NOAA satellite data, we demonstrated a strong link between climate and postinfectious hydrocephalus. Infants get sick at intermediate levels of rainfall, emphasizing the role of the environment and consistent with our bacterial DNA findings. Our work demonstrates that in fully unraveling the mystery of postinfectious hydrocephalus we are benefitting from US technology in ways we had not anticipated.

We are committed to optimally surgically treat the large numbers of children who have hydrocephalus. However, we will never operate our way out of this problem. A critical long-term goal is more effective treatment of children with neonatal sepsis to decrease the brain complications in the survivors. And most importantly, once we understand the root causes, we need public health measures to prevent these infections.

Hydrocephalus is a thus global health issue well beyond the specifics raised by a small, very fine African hospital, a great U.S. charitable organization that brings the highest quality medical care to children around the world, and the finest physician I have ever met, Dr. Warf. Of the 130 million children born around the world each year, we are inadequately addressing the million and a half who die of preventable newborn infection.
As a physician and scientist, I am struck by how much we do not know about newborn infections in developing countries. I am concerned that one reason is that the newborn infants who die there have no political voice.

What we learn in Uganda needs to be replicated in other countries, such as Kenya, Tanzania, Rwanda, Zambia, Sudan and South Africa. All of them have similar cases.

We need to create inexpensive technologies that can be used indigenously to reduce the costs of identifying the microorganisms, determining their resistance to drugs and developing environmental and public health strategies.

I offer 3 conclusions:

1) We have not paid sufficient attention to the massive loss of human life from newborn infections in the developing world;
2) We now have the technology to shed new light on the causes of a substantial fraction of these deaths; and
3) We can now develop sustainable strategies and scalable technologies to more effectively prevent the deaths and tragic survivals from these devastating illnesses.

The fate of millions of lives depends upon our actions.

Thank you.

STATEMENT OF MR. JIM COHICK, SENIOR VICE PRESIDENT OF SPECIALTY PROGRAMS, CURE INTERNATIONAL

Mr. COHICK. Chairman Smith, Congressman Payne, and members of the committee, thank you for inviting me to discuss the problem of hydrocephalus in the developing world and what CURE International is doing to heal children suffering from this devastating condition. It is an honor to be here with Doctors Warf and Schiff, who have contributed enormously to the understanding of this condition and innovative new treatment techniques which make possible the healing of infants in the world’s poorest countries.

Fifteen years ago, as the executive director of the first CURE International hospital in Kenya, I opened and then ran the hospital for a number of years. I now serve as the senior vice president of specialty programs for CURE International, an American-based nonprofit organization. Our mission is to heal disabled children. We operate hospitals throughout the developing world, from Afghanistan to Zambia. CURE Hydrocephalus is perhaps our most ambitious and innovative initiative.

Our unique work at CURE Children’s Hospital of Uganda is the endoscopic treatment of children with hydrocephalus—that condition is more commonly known as water on the brain—which can be present at birth or caused later by infection.

The CURE Hydrocephalus Initiative was born at the CURE Uganda Hospital because of the work of Dr. Warf during his tenure as medical director there. While there, he also trained Dr. John Mugamba, the current medical director, and over a dozen other surgeons from both the first and developing world arenas.

More than 650 surgical procedures are performed annually at the CURE Uganda Hospital to treat hydrocephalus, more than any other hospital in the world. We estimate that in 2010, there were more than 4,000 new cases of infant hydrocephalus in Uganda and nearly 300,000 in the developing world, using a ratio of 3 per 1,000 births. Virtually all these children, if left untreated, die. Over the next 5 years, that means as many as 1.5 million infants in the developing world could die from hydrocephalus.

The majority of hydrocephalus cases treated at our hospitals, when medically appropriate, involve the novel combination of two surgical procedures described by Dr. Warf, commonly known as ETV/CPC. The ETV/CPC technique truly is a cure for children suffering from hydrocephalus, as it eliminates the need for a shunt in the brain, the standard hydrocephalus treatment, which can need a replacement two to three times, even up to five times over a child’s lifetime. As you can imagine, this is a huge logistical and economic challenge in developing-world locations like Uganda. Too many children with hydrocephalus are never treated and die. And many treated with a shunt live only a short time before their shunt fails and their families are unable to access further medical care.

Mr. Chairman, hydrocephalus is a global concern that is widespread in poor countries and vastly underreported. With new techniques like ETV/CPC, we have the opportunity to save thousands of children and to end the suffering of their families. What is need-
ed is to scale-up proven treatment by increasing training of national surgeons and creating the proper infrastructure to support their ongoing work.

To give you a sense of the scale of this problem, there are four trained neurosurgeons in Uganda, a country of 33.6 million people. There is approximately one neurosurgeon for every 10 million people in east Africa, as was mentioned before. In the United States, we have 3,500 board-certified neurosurgeons, which means we have 110 times the access to treatment than that of the people living in east Africa.

Our effort to address this problem is summed up in four initiatives that make up CURE Hydrocephalus: First, strengthening national health systems through training and equipping national surgeons from the developing world in advanced surgical treatment methods for hydrocephalus. Second, enabling those surgeons to use their new skills by providing them the appropriate operative equipment. Third, developing the IT infrastructure to capture patient care data to facilitate research with our strategic partners to advance the understanding of causes, the understanding of best practices, and the effective methods of prevention of postinfectious hydrocephalus.

And, finally, demonstrating compassionate care and concern for the world’s most vulnerable children, their parents and their families by ongoing follow-up.

Training, treatment, research, prevention, and compassionate care will change how hydrocephalus is treated. It will translate into significant cost savings for fragile, developing world-health systems.

Mr. Chairman, thank you again for your personal interest in this life-threatening medical condition and your leadership in helping to establish creative and effective ways to save more lives and end the suffering of many thousands of children. My colleagues and I at CURE International and our partners are excited and stand confident to go forward as we are called upon to do so.

Mr. Chairman, this may have already been handled but I do have a document to submit as part of the record, if that would be permitted.

Mr. SMITH. Without objection, it will be made a part of the record. And any additional materials from any of our three distinguished witnesses will likewise be added.

Mr. COHICK. Thank you.

Mr. SMITH. Mr. Cohick, thank you very much for your testimony. [The prepared statement of Mr. Cohick follows:]}
U.S. House Committee on Foreign Affairs
Subcommittee on Africa, Global Health and Human Rights

"Hydrocephalus Treatment in Uganda: Leading the Way to Help Children"

Prepared Statement by
Jim Cohick
Senior Vice President for Specialty Programs
CURE International
Lemoyne, Pennsylvania
Tuesday, August 2, 2011

Chairman Smith and Congressman Payne, thank you for inviting me to discuss the problem of hydrocephalus in the developing world and what CURE International is doing to help children suffering from this devastating condition. It's an honor to be here with Drs. Warf and Schiff -- who have contributed enormously to the understanding of this condition, and innovative new treatment techniques which make possible the healing of infants in the world's poorest countries.

Fifteen years ago as the first Executive Director of the first CURE International hospital in Kenya, I opened and then ran that hospital for a number of years. I now serve as Senior Vice President of Specialty Programs for CURE International, an American-based non-profit. Our mission is to heal disabled children. We operate hospitals throughout the developing world, from Afghanistan to Zambia. CURE Hydrocephalus is perhaps our most ambitious and innovative initiative.

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More than 650 surgical procedures are performed annually at CURE Uganda to treat hydrocephalus, more than any other hospital in the world. We estimate that in 2010, there were more than 4,000 new cases of infant hydrocephalus in Uganda, and nearly 300,000 in the developing world (3 per 1,000 births). Virtually all of these children, if left untreated, die. Over the next 5 years, as many as 1.5 million infants in the developing world will die from hydrocephalus.

The majority of hydrocephalus cases treated at our hospitals, when medically appropriate, involve the novel combination of two surgical procedures, endoscopic third ventriculostomy and choroid plexus cauterization (ETV/CPC), developed in Uganda by Dr. Warf. The ETV/CPC technique truly is a cure for children suffering from hydrocephalus as it eliminates the need for a shunt in the brain -- the standard hydrocephalus treatment, which must be replaced 3-5 times over a child's lifetime. As you can imagine, this is a huge logistical and economic challenge in developing world locations like Uganda. Too many children with hydrocephalus are never
treated and die, and many treated with a shunt live only a short time before their shunt fails and their families are unable to access further medical care.

Mr. Chairman, hydrocephalus is a global health concern that is widespread in poor countries, and vastly underreported. With new techniques like ETV/CPC we have the opportunity to save thousands of children, and to end the suffering of their families. What's needed is to scale up the proven treatment by increasing training of national surgeons and creating the proper infrastructure to support their on-going work. To give you a sense of the scale of the problem, there are 4 trained neurosurgeons in Uganda, a country of 33.6 million people. There is approximately one neurosurgeon for every ten million people in East Africa. In the United States, we have 3,500 board certified neurosurgeons, which means that we have 110 times the access to treatment than that of people living in East Africa.

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Mr. SMITH. Mr. Wolf, do you have any questions?

Mr. WOLF. No. Thank you, Chairman.

Mr. SMITH. Let me begin with opening questions. First of all, I think it needs to be shouted from the rooftops that hydrocephalus is a preventable tragedy. And the solutions that you have pioneered, and have done so for over a decade, remain the best-kept secret, I think, in Washington. There are many people, Africans, who have been working health issues—and I have seen it myself and I have raised and handed out some of the materials that you have provided to my office and to me and they are shocked—they had no idea the prevalence—up to 375,000 as, Dr. Warf, you testified—new cases per year. And no idea, frankly, that there is an ongoing and very, very effective, efficacious solution that you are employing every day, but you need more people and more resources to expand the solution.

So again, on behalf of—I know Mr. Payne and I, all members of our subcommittee, we thank you for the pioneering humanitarian work that you have done. It is absolutely extraordinary.

If you could perhaps, Dr. Warf, describe the life cycle of a child with hydrocephalus. You know, as the pressure builds, the pain perhaps that he or she may experience, and what is the ultimate consequence if untreated?

Dr. WARF. Yes, sir. Well, as the fluid is trapped in the spaces in the brain and as the brain continues to make more fluid at the rate of about an ounce every hour, the head begins to expand, sometimes to enormous sizes. The soft spot on the baby's head begins to bulge. The veins on the scalp begun to bulge. The eyes begin to be deviated downward in something called a sunset sign. The children become listless. They feed poorly. They are irritable. They are in pain. They vomit. About half of them will be dead by the age of 2; the other half will be severely devastated.

Sometimes hydrocephalus, after it becomes quite advanced, can sort of accommodate or spontaneously arrest itself, and that is why some of them survive. The bad news is that they all virtually either die or are badly disabled. The good news is that it is an imminently treatable condition.

If hydrocephalus is the only problem—for instance, a congenital cause of hydrocephalus—and you treat the hydrocephalus early, those children can be quite normal. In a case where the hydrocephalus is secondary to another event, such as an infection or a hemorrhage, there is sometimes varying degrees of primary brain injury, like we described in the children with postinfectious hydrocephalus.

I would also add that children that are shunt-dependent—even in developed countries, in our own practices here in the U.S.—are fortunate to have access to a safety net, such that when their shunt malfunctions, they almost always have emergency access to neurosurgical care, and we fix those shunts at 2 o'clock in the morning, or whatever it takes, because it is an emergency.

But one of the things that drove me to look for other solutions and to push the envelope a little bit on the endoscopic kinds of treatments was knowing that when I put a shunt in one of these children and they went back into the bush, that when the shunt failed later in their life, when the soft spots of the skull had closed
up, that they would almost certainly die before they could find their way to a hospital where anybody could do anything about it.

Mr. SMITH. Thank you. Dr. Schiff, you talked about the discovery of—you said the most prevalent bacteria was Acinetobacter, a notorious organism that has caused the deaths or wound infections to our military personnel in Vietnam and Iraq and Afghanistan.

Is that the only one? Were there other bugs, if you will, or infections? And secondly, Dr. Mugamba—and you implied this as well—when we met with him in Africa, he said that a likely major cause of hydrocephalus—and I think it is based on the work that you have done as well, the breakthrough work in Uganda—is the use of cow dung, which is cheap and plentiful, to cauterize the umbilical cord following birth, which normally occurs at the mother’s home. And I am wondering if that is one way that some of these children are contracting hydrocephalus, infection—you know, born—and whether or not the ministries of health, for example, of Uganda have shown any interest in better birthing practices to mitigate the passage of this terrible infection?

Dr. SCHIFF. I hope that in a few years we can come back and be very clear that we truly have worked all of these mysteries out. We find a great deal of evidence for Acinetobacter and related organisms in the brains of these children. That doesn't tell us, though, what caused the initial devastating infection that may often have destroyed a great deal of brain and leaving them in a devastated state.

So we are conducting several different clinical trials, trying to untangle this. We have a trial at the CURE Hospital where we are comparing children with hydrocephalus, who have a history of serious newborn infection, with those who don’t. It is entirely possible. You and I brush our teeth in the morning. We shower our bodies with bacteria. It may be that these children are exhibiting for us a great deal of the environmental bacteria that they encounter as newborn infants.

In field work, I must say, it is rather an eye-opener for one of us to go to the rural settings and understand the conditions in which these newborn infants need to survive. The huts are actually lined with dung, purposefully. It is a very good insulator against both rain, and it keeps out ants, which are unpleasant. The patios around the huts are stripped of vegetation, and dung is pounded in to keep the dust down and the vegetation away. Granaries are lined with dung for ants and rain. So there is tremendous exposure, in addition to cultural practices of certain Nilotic peoples and the Maasai, for instance, of using dung on umbilical stumps. So infants are exposed to a great deal of this.

One of the other things we need to do is to nail down what causes the very common scenario that Dr. Warf mentioned, not just high fevers and a serious infection in the newborn period, but almost all of these children have had epileptic seizures to go along with it. And we have what appears to be organisms that have a predilection to get into the brain. Are they bacteria or viruses, one or more, early in life, that opens things up so that they are very able to show you what they are exposed to in the environment, because we then sequence it from the CURE Hospital. This is an ex-
ample of the kind of complexity that we face. And being able to work all this out now is straightforward.

We fortunately have the ability to go—even in burned-out infections, go back, find the fragments of the organisms, use new techniques to do this. And I think one of our challenges will be how do we bring this to the next country. You can’t have the major science institutes in the United States running very expensive sequencing and sampling on every site in the developing world. But I really do think that in the coming years, being able to understand how to go into another country, whether it is east Africa, southern Asia, and the other sites that seem to have many, many of these cases, learn how to uncover the organisms, learn how to keep surveillance in those countries so we can do two things: Learn how to better treat the infants when they are sick and, most important, be able to institute rational public health strategies to cut down the numbers of these infections. Thank you.

Mr. Smith. Goal number four obviously seeks to drastically reduce the number of children who die, childhood mortality, and, I would add, morbidity as well. Has UNICEF and other U.N. agencies, NGOs in general that deal with health issues, including the USAID, the European Union and its health initiatives, particularly in Africa, have they addressed the hydrocephalus epidemic that is occurring, which is a preventable and very treatable—preventable, if you stop the infection in the first place, obviously the children don’t get sick, but you also have a solution if they do get sick. Are they addressing this?

Dr. Warf. To my knowledge, no, sir. There has not been much of a focus on this at all. I mean there are many overwhelming problems obviously, and I think hydrocephalus has been below the radar screen. I recently attended the World Health Organization rollout of their report on disability. And many things were mentioned in that report. But hydrocephalus and the infection of these children were not among the things that are talked about in that report. So I think it is something that just needs to be brought to the attention of the kind of bodies that are able to fund work in this area.

Mr. Smith. Which is precisely what you are doing. So I think you are doing an enormous service for those children and their parents and siblings.

If I could, has the Gates Foundation or the ONE Campaign or any of the other very laudable and noble charities, have they joined in as far as you know?

Dr. Warf. Not yet.

Mr. Smith. Not yet. Let me just ask, with regards to ETV/CPC, what is the acceptance of that domestically here in the United States, could you compare the costs of shunt interventions versus that procedure that you have created and perfected?

Dr. Warf. Well, yes. That is sort of a multianswer here. So first of all, I should make it clear that ETV has been done for quite some time. It was found to be not very successful in babies under 1 year of age, or even under 2 years of age, and it was rarely done and still isn’t done that often. In an effort to find a way to make it more successful and to be able to avoid shunt dependence in babies from the beginning, what we did was we added an old idea
which had been practiced a number of years ago, before shunts actually, as an idea of how to treat hydrocephalus, and that was to reduce the tissue that makes the fluid. But that had been largely abandoned. It was not effective by itself. The idea of combining the two procedures was to address both the obstructive problems with the hydrocephalus, bypassing the fluid obstruction to getting it out of the brain and allowing an exit for that, and also addressing what some people call a communicating hydrocephalus which is left over sometimes in babies after the ETV. They can't handle absorbing the fluid once it gets out. So by reducing the tissue somewhat and reducing the rate of production, we found in a fairly large study that there was a significantly increased success rate with the ETV.

There is a growing acceptance of this in the U.S. It is our preferred primary treatment of infant hydrocephalus at Children's Hospital in Boston. There are others that have begun to use the technique. And I think the main shift in culture has been a shift away from simply placing a shunt in a baby, to thinking could this be avoided by a bit more sophisticated of a technique that takes some different skills but it is very often well worth doing.

For instance, a common cause of hydrocephalus in the U.S. is that which is associated with spina bifida. About two-thirds of those children have hydrocephalus that needs to be treated. Those children were all treated with shunts up until fairly recently. What we had found was that the ETV by itself was only successful in 35 percent of those babies. But with the combined procedure, it is successful more than 75 percent of the time. That is not only the Ugandan data but is now, as the numbers grow, we are matching those same success rates in the U.S. There is a growing interest in that, especially in the spina bifida community. So it is a matter of practice change and those things can happen fairly slowly.

Mr. Smith. Dr. Schiff, you talked about how the data from Dr. Warf's cases and NOAA satellite data demonstrated strongly a link between climate and postinfectious hydrocephalus. And you pointed out that infants get sick at intermediate levels of rainfall. Why is that? Do we know?

Dr. Schiff. We don't know for sure yet. But it is very substantial and it points to an environmental component to this, which we will need to understand and then take into account, to know how to rationally reduce the numbers of infections. There are other serious infections in the world where this type of rainfall link has been shown. The one that is most famous is called melioidosis. It is a terrible skin infection in southeast Asia and northern Australia. The bacteria is so nasty, it is on our select agent list now. But in speaking to the doctors who have worked that out, they had to learn how the soil temperature and the soil moisture allowed that bacteria to get to the surface at certain times of year and then infect people directly.

Those are the kinds of things that, if we need to do that here, then it is straightforward and it will give us the answers to design good preventive measures.

Mr. Smith. Has the CDC worked with you on that? Because it seems to me this is the beginning of a prevention strategy that will drastically—potentially—reduce the number of hydrocephalic children suffering from hydrocephalus.
Dr. SCHIFF. Not yet. But this is all relatively new findings and we will now be in the process of raising the resources that we need to get to the bottom of this.

Mr. SMITH. Thank you, Mr. Payne.

Mr. PAYNE. Thank you very much. I certainly appreciate your testimony. And just sort of on this whole question of water-borne diseases, even though it is kind of off the specific topic here, in your opinions, how much preventable diseases are actually caused by impure water, you know, water-borne diseases, things like diarrhea, just diseases in general, and especially for newborns and infants and children?

In your opinion, investment in clean water—do you think that that probably would be one of the greatest preventative methods to preventing many childhood diseases and even in particular what you are talking about, although you are talking about rainfall, which is a little bit different than the question of clean water and things of that nature. Would any of you like to tackle that?

Dr. SCHIFF. Congressman Payne, there is nothing I think I have seen more shocking in my work than unprotected wells in rural villages in Africa, and what people need to drink and to bathe their children in. And there is no question that you are right; that the availability of potable drinking water that is safe is an enormous factor in public health around the world.

When I started this work, I thought that was going to be the likely answer to these children. But we see these cases in villages with excellent government-drilled boreholes, very good water supplies, and in villages with terrible water supplies. I am not going to discount that there may not be an important role from water supplies; and if that is what we find, then the answers are going to be straightforward. But my suspicion is that it is going to be, as with everything else in this story, more complicated than we had hoped.

Mr. PAYNE. Thank you. Although it is not well documented, general estimates note that the developing world has a significantly higher prevalence of hydrocephalus than the developed world. Is there one form of hydrocephalus that is more common in the developed world versus the developing world? And in your opinion, what accounts for such differences?

Dr. WARF. I can answer that, Congressman Payne.

There is a huge difference. So what we showed in Uganda was that 60 percent of our cases—and this has continued on as we have gone into the thousands of cases and we keep looking back, it persists—60 percent of cases that we see of infant hydrocephalus are secondary to these infections.

We rarely see hydrocephalus from that cause in North America, for instance. A common cause of hydrocephalus here is one that we never see in Africa and that is hydrocephalus secondary to hemorrhage in the brain of prematurely born infants, which obviously don’t survive in Africa because they don’t have neonatal intensive care units to keep them alive.

So I like to say that post-infectious hydrocephalus is a disease of poverty, and post-hemorrhagic hydrocephalus is a disease of prosperity. There are other causes in the U.S. which are common, congenital causes, congenital obstruction of one of the pathways that
the fluid has to get out, the hydrocephalus associated with spina bifida and so forth.

But what we don’t see very much of ever are these post-infectious cases. So what I suspect is that with the high birth rates in Africa, we probably see the same incidents of the other causes of hydrocephalus that we see in developed countries and then, on top of that, another 60 percent from the infections that we don’t see at all here.

Mr. PAYNE. Actually, with the sort of health care costs say in Uganda and throughout the developing world—of course, we know it is much higher than in other places, due to lack of the resources and the ability of the average income of people, the level of consumer income—what does the U.S. and the international community need to do to make treatment more accessible for patients and families in the developing world? Are what are the differences in terms of costs and technical barriers in using stints versus the ETV or the combined ETV/CPC? Can more be done to prevent the disease, and would preventable measures be more cost-effective?

Dr. WARF. I think preventable measures are certainly more cost-effective, if we can eliminate the neonatal infection that causes not quite two-thirds of the cases, that would be almost certainly more cost-effective. However, there will always be hydrocephalus and fairly large numbers of it in populations that have high birth rates because it is not an uncommon disease of childhood from congenital causes.

In regard to the endoscopic treatment versus shunting, we have actually done fairly detailed—well, people I worked with that are economists, I should say, have done fairly detailed analysis of costs. And what we found is that the more patients, hydrocephalus patients, that you have in your population with shunts, the less cost-effective the treatment, the more cost burden there is because those shunts require maintenance.

The numbers that we used for determining this was based on the type of shunt we were using in Uganda, which was a very inexpensive shunt that cost about $35 that is made in India. I did a prospective randomized trial that was published in 2005 that showed that the outcomes for a year of using that shunt were no different than the outcomes for using one of the commonly used American shunts, which costs $650. And the shunts that we typically use now in my practice cost around $1,000, which is impossible for children in Africa. So even at the cheap shunt numbers, the more children that you can spare shunt dependence and treat endoscopically, the more cost-effective it is.

We also looked at the initial cost of treatment in our hospital, including everything, keeping the lights on, salaries, depreciations, all those kinds of things, including the cost of the shunt and the cost of the endoscopy equipment. And we found the upfront cost of treatment to be almost the same, so the cost benefit is there.

Mr. PAYNE. Actually, what happens to an infant, I mean, that goes untreated in some remote village in a country where there is just no care? What happens? Does it grow? Does the child have excruciating pain? Do they die after a certain number of years? What is the life of an untreated person?
Dr. WARF. I can give you about three different scenarios. In Uganda at least, a baby with a growing head like that is often thought to be the result of a curse, and sometimes those babies are killed. So they die in that way. We know that to be true.

The second scenario is the child who has the progressive head growth, the mother does the best she can. The head gets very heavy, and the child gets hard to handle. It eventually dies either directly from the elevation of pressure in the head or dies from failure to thrive, because of poor feeding and vomiting and the general effects of being so debilitated.

And the third scenario is the child that actually survives the early childhood hydrocephalus. The course arrests itself, but the patient, the person has a very large head is, is quite cognitively disabled, usually or often blind and spastic, much like a person that you might see that is severely involved with cerebral palsy.

I never will forget visiting one village when I first moved to Uganda and before we opened the hospital, I was trying to get a feel for how things were, and I visited an area where I was told there was a patient with hydrocephalus. This was a teenage girl with a head about the size of a basketball, whose mother dragged her out and put her on a mat under a tree every day and gave her a mango to chew on. Her mother took very good care of her, but she was totally disabled and unable to communicate or do anything. So there is death, and then there is tragedy beyond death.

Mr. PAYNE. Thank you.

Mr. SMITH. I recognize Ann Marie Buerkle, who, just by way of background to our witnesses, combines a unique background. She is former Assistant New York State Attorney General, so she is a lawyer, but she is also a registered nurse.

Ms. Buerkle. Thank you, Mr. Chairman, and thank you for organizing and hosting this extremely important hearing today. I am much prouder of my background in nursing; I often lead with that. But in my profession as an attorney, I represented a hospital so I have spent my life in health care, so this is certainly of importance to me.

I have a couple of questions, and Mr. Cohick this is for you, but anyone else who might have an answer to it. We hear that our country is a very generous country, and we fund HIV/AIDS, malaria, many other diseases throughout the world. As you all know and you have suffered through these debt negotiations and all that has been going on here in Washington, money is becoming much more of a premium. Help us to justify this cause in funding for hydrocephalus.

Mr. COHICK. Well, I think I personally and we all recognize we are in that situation, and it is a difficult time to indeed bring this type of scenario to you and what can be done.

Somewhat germane to one of the questions and answers given before, this is very cost-effective. The comparison between what we do in Uganda and what is done in the U.S. is roughly at 5 percent, our cost, looking at surgery, one surgery done in Uganda versus one surgery in the U.S., is roughly 5 percent of what it costs in the U.S. When you take into account the surgeries or the subset of those that can be helped by the ETV–CPC, where it may be one
and done, versus the shunts that are two or three or four revisions, that 5 percent grows—or I should say shrinks down to close to 1 percent. So it is very cost-effective to go forward.

We have found the partnerships to allow us to go forward with training when Dr. Warf was there, and it continues on with Dr. John Mugamba, who is his successor as well. We are eager to do what is the most effective and efficacious manner going forward.

It is a difficult thing to ask for a substantial amount of money at this point in time, but we think, and we believe, and we feel it is strong evidence that it is as well spent and it brings value beyond its numbers.

We also concur with those who have come out earlier this year that have noted the public health emphasis on prevention, which is absolutely needed, needs to be balanced with those efforts to create better abilities, better capacity, I should say, for technology and for surgery that is wanting in areas because that is a hard price to pay no matter what the economy is.

Ms. Buerkle. Thank you.

Dr. Warf.

Dr. Warf. Yes, thank you very much. I can actually give a few comparative numbers that might help put things into perspective a little bit. This is from a study that is in press through our Harvard Medical School, Department of Global Health and Social Medicine, and we have been looking at the cost-effectiveness of treatment of hydrocephalus in Uganda, partly based on our data from Uganda and extrapolating that. Depending on what kind of economic analysis you use, we have reported that in sub-Saharan Africa, if you use one economic model, human capital approach, the cost of hydrocephalus is around $1 billion. And if one uses the value of a statistical life approach, which is that which I think is used by certain government organizations like the EPA, it is on the order of tens of billions of dollars, $1.4 billion to $56 billion in economic burden to Sub-Saharan Africa.

The other way that we gauge burden of disease and cost-effectiveness, as I am sure you know, is the daily adjusted—disability adjusted life year, the DALY so called, and that is 1 year of healthy life lost. And you can compare the gravity of different diseases by these kinds of assessments using the disability adjusted life year. So, for instance, when we look at treating hydrocephalus and the cost of treatment, it costs us about $37 to $80 per disability adjusted life year averted with the initial treatment. That is compared to about $75 per DALY averted for treating a person with AIDS. That is not prevention. Prevention is always much more cheaper. You can prevent AIDS with a dollar for disability adjusted life year.

There have few examples of surgeries done in developing countries where these kinds of analyses have been done. One is with trauma surgery. In Nigeria, the published number is $172 per DALY averted; in Haiti, it is $223 per DALY averted for taking care of a trauma patient. This is verus $58 per DALY for treating hydrocephalus.

So we do have some hard numbers, as hard as they can get when working with an economist. And it seems to be there is an enormous burden, and the cost-benefit ratio we have determined to be
a minimum of 7–1, or the other way around cost-to-benefit, 1–7, but potentially as high as 1–50 in terms of economic benefit to the society. So I think those kinds of things need to be taken into perspective when you are comparing them with the high-profile diseases.

Ms. Buerkle. Dr. Schiff, did you have anything to add?

Dr. Schiff. I couldn’t, no.

Ms. Buerkle. Thank you all very much.

Thank you for being here. I yield back.

Mr. Smith. Ms. Buerkle, thank you.

Dr. Cohick, if I could just ask you, did you run into any problems with CURE International’s effort on hydrocephalus children in Uganda, for example? Was there a disbelief or lack of buy-in from the government, or were they pretty open to the idea when you sited your hospital there?

Mr. Cohick. Well, our hospital began in 2000, and actually, we were—there was a lot of, as you can imagine, preparation done before the site was selected, and actually all those arrangements were made for where we would build and the fund as well. I guess to answer your question, Dr. Warf was there at the beginning, and I participated with him as well as the other leadership in overseeing the hospital.

And our first goal was to be part of the medical community and the continuum of medical education. We realize that we were bringing something new and different. I think that became more evident as discussions were held with district and other officers of the medical system and others, but if I could allow a segue to Dr. Warf to probably explain better. His focus on making sure that—his presence and his desire to be part of the community, not only in rendering care, but teaching and education, I think was well received. They might have been a little skeptical at first because of others who may have promised similar things, but with his genuine and consistent manner in staying there and doing what he had promised and to share his expertise with those of us that were part of the hospital and hospital system, as well as those in the medical teaching community were well received. Our efforts certainly were much more than what were inside of our hospital walls.

Mr. Smith. Let me briefly ask you, Ministries of Health, do they show profound interest in what you are doing? Do they just allow you operate or do they embrace it? When we talk about the number of physicians, there is clearly a capacity problem. I think you have said, at least previously in previous conversations, obviously, the skills that a newer surgeon will acquire are applicable to a host of other trauma and head injuries that might occur, again desperately lacking in Africa, so not only are hydrocephalic children going to get lifesaving and enhancing treatment, others will benefit as well. I hope that is appreciated, both in our Government, which has yet to act, and NGOs that could be philanthropic, NGOs that could be helpful.

This is a whole area of health care that has been ignored. You have paved the way. You have done the hard work of proving the model, particularly in Uganda. Now the bugs are out of it so to speak, and it seems to be “replication” should be the action word,
let’s grow this everywhere. But if you could, how many doctors, the applicability of the skills to other trauma and problems.

Dr. WARF. So to address your first question about the Ministry of Health, we started from the beginning in Uganda with a memorandum of understanding with the Ministry of Health and worked with them. We worked with them on education and referral from district and regional hospitals. After about 4 years, it was recognized that we were sort of the national referral center for hydrocephalus and other neurosurgical problems in children. And in recognition of that, the Parliament included us in their budget, which amounted to about 1 month of running costs, but it was quite gratifying, not so much just from the financial end of it, but the fact they had embraced us as part of their—acknowledged part of their medical service.

But we always did, and I was the only non-Ugandan physician there. We had an all-Ugandan nursing staff, except for some people who came for training. We hired people out of medical school and internships to come and work with us and train. And we fostered their training as we go forward.

So I think that that was—we became a sort of integral part of that. Other Ministries of Health are interested in what we are doing. We are currently in some conversations with the Government of Rwanda, and I met with their Minister of Health and so forth. So I think Ministers of Health generally do value what we are doing as part of the bigger picture.

Mr. SMITH. Would anybody else like to add anything?

Mr. PAYNE. Only that I certainly command you for the outstanding work that you all were doing. I do know that you are in the right country to move forward in medical attention. As you know, 30, 40, 50 years ago or even longer, Uganda was known for having an outstanding medical school. I guess the Makerere Medical School, where doctors or potential doctors from, in particular East African communities, would go there to study. I first visited there about 40 years ago and did hear about the medical school, and other East African countries. I think Kenya had the school where you wound up to be a good lawyer and you would go there, but Uganda was the place to go for good medical attention.

Dr. WARF. That is right.

Mr. PAYNE. So I am glad that they have continued and at least tried to give the support. I also have some appreciation about what Uganda’s—of course, it has nothing to do with this in particular, but they have provided about 8,000 000 troops to Somalia, where the Ugandan forces are assisting the transitional Federal Government of Somalia, which is weak. And without the U.N. support for the Ugandan and Burundian troops, I think that the al-Qaeda forces of Al Shabaab would probably have taken over Somalia, which would just wreak havoc on the whole Horn of Africa. So as a matter of fact, as you may recall, there was a bombing during the World Cup at a restaurant in Uganda, and that was primarily because the Ugandan troops were there in Somalia, much of it supported by the U.S. through peacekeeping through the U.N., and so it is a long stretch. But the al-Qaeda people felt that they should do harm, and about 20 or 30 people were killed because the Ugan-
dans were supporting the Government of Somalia, which we support, and therefore directly should be penalized.

So I do appreciate work there in Uganda. Have to work a little bit with president for life, but you know, we are doing something. I tell him sometimes—he is a farmer, and I tell him, why don’t you go back to the farm? He said, well, I still visit the farm on the weekends. I say, why don’t you just visit it all the time?

I really do commend you for the great work you are doing, thank you.

Mr. SMITH. Ms. Buerkle.

Ms. BUERKLE. Thank you, Mr. Chairman.

I just have one question, in these developing nations, how many centers do you think would it take to address this problem adequately?

Dr. WARF. I would probably have to do a little bit of arithmetic, but I would say probably two per country, depending on the size of the country, a place like Congo would need more, more like half a dozen; smaller countries, maybe one, but it depends on the size of the country, the population density, and how bad the infrastructure is for transportation obviously.

But I think that a huge impact would be made by starting with the goal of one center per country and more in the bigger countries, like Congo.

Mr. COHICK. Part of our plan is to continue to expand the training we have where there are treatment centers in place because of those surgeons that have been trained. As we have the capacity to allow those that have the desire, willingness and abilities to become trainers themselves obviously helping that whole scenario is somewhat akin to what Dr. Warf has said.

Dr. WARF. What we are not envisioning is building more centers. What we want to do is to come into existing government hospitals with what you might call a vertical program, and you train and equip the people that are there who have a commitment to taking care of these children anyway and just don’t have the tools. And we have done some of that and hope to do more of that.

Ms. BUERKLE. Sure.

Dr. Schiff.

Dr. SCHIFF. I also might add we also envision a very similar sustainable way of allowing countries to do the appropriate discovery of their organisms, surveillance and institute both better treatment of the sick infants as well as prevention strategies without having to rely on what is a very large scale at present effort to do that. And I think that is very doable. One could attack both the children who need surgery and simultaneously and parallel with that address the root causes.

Ms. BUERKLE. Thank you. If you did what you are talking about and you found existing centers and you dropped in the vertical program, have we talked about how much that costs?

Mr. COHICK. As part of record, we have submitted a plan that is scalable. The plan itself as it is presented is multi-year and multi-millions of dollars, but results in over 100 surgeons being trained and going on and over that course of time close to 27,000 surgeries having been done, but having a ongoing rate of at least 10,000 and obviously growing more if it were to continue on its
course. That is at least the plan that is in consideration. Again, it is scalable to become the right size as needed.

Ms. Buerkle. Thank you.

I just want to echo my colleague, Mr. Payne, in thanking all of you for your efforts and your hard work and for paving the way in giving these children a chance, an opportunity to survive and to live normal lives. So thank you very much. Thanks for being here today as well.

I yield back.

Mr. Smith. Thank you.

Let me just ask, finally, the ranking of the countries of Africa, do you have a sense of what countries have the most compelling need that goes unmet?

Dr. Worf. Yes, sir. The DRC to my knowledge has one neurosurgeon that I have met who told me he is the only one. I know of two mission hospitals in Congo that see a stream of these children and don’t have the wherewithal to treat them. So that is one place.

Mr. Smith. What do they do when a child presents?

Dr. Worf. Well, send them away, say there is nothing to do.

Mr. Smith. So, obviously, we have a huge challenge of capacity building.

Dr. Worf. Yes, sir.

Mr. Smith. And prioritization within our own Government and the NGO community, which, again, you have provided extraordinary leadership on for years, which has gone under-recognized, I would say, by Congress and by the White House and by the State Department, no matter who is at the helm.

I think you wanted to say something further.

Mr. Payne. Not, of course, once again, not anything to do with the hearing here, but I would like to certainly commend you all for your testimony.

But I was just looking at a Ugandan Little League team that was qualified for playing in Williamsport, and they defeated a Saudi Arabian team, and they played in Poland on July 16th, which is my birthday, kids supposed to be 11 to 13 and they won. Our State Department just declined to allow them to come to play in the World Series. It is a real World Series. Of course, now they bring in Taiwanese kids usually win the championships when we watch these games. I am going to dash off a letter to the State Department to ask them why are they denying these young kids from Uganda. If there is a question about AIDS, sometimes that becomes an issue, but they won’t disclose what the issues are. And they come from the Reverend John Foundation, so it can’t be any better than that. Whoever Reverend John is, it sounds good to me.

So I am going to follow up to try to find out why are these Little Leaguers, I think it would be great to finally have an African baseball team to go back to their country. Also, I think it is a great experience for Third World kids to get an opportunity to visit our country, because sometimes that is the greatest ambassador for democracy. And when they get back and see how it is here, then they can be ambassadors in their country. Once again, thank you, Mr. Chairman, for calling this important hearing.

Mr. Smith. Thank you very much.
Anything you would like to add before we conclude?

Dr. WARF. Well, I would like to say how much we all appreciate this. It is the kind of thing that I never thought I would have a chance to do, so I am very honored and humbled by the whole thing and just want to thank you.

Dr. SCHIFF. I would certainly like to echo Dr. Warf's sentiments.

Mr. COHICK. I add my thanks, thank you so much.

Mr. SMITH. Again, you are pathfinders. You are saving lives each and every day, and we need to expand capacity. I know this subcommittee stands ready to leave no stone unturned in trying to help kids suffering from this debilitating but preventable and treatable condition known as hydrocephalus.

So thank you so much. The hearing is adjourned.

[Whereupon, at 3:33 p.m. The subcommittee was adjourned.]
APPENDIX

MATERIAL SUBMITTED FOR THE HEARING RECORD
SUBCOMMITTEE HEARING NOTICE
COMMITTEE ON FOREIGN AFFAIRS
U.S. HOUSE OF REPRESENTATIVES
WASHINGTON, D.C. 20515-0128

SUBCOMMITTEE ON AFRICA, GLOBAL HEALTH, AND HUMAN RIGHTS
Christopher H. Smith (R-NJ), Chairman

July 26, 2011

You are respectfully requested to attend an OPEN hearing of the Committee on Foreign Affairs, to be held by the Subcommittee on Africa, Global Health, and Human Rights, to be held in Room 2127 of the Rayburn House Office Building (and available live via the WEBCAST link on the Committee website at http://www.house.gov):

DATE: Tuesday, August 2, 2011
TIME: 2:00 p.m.

SUBJECT: Hydrocephalus Treatment in Uganda: Leading the Way to Help Children

WITNESSES:
Benjamin Wat, M.D.
Director
Neonatal and Congenital Anomalies Neurosurgery
Department of Neurosurgery
Children's Hospital Boston

Steven J. Schiff, M.D.
Director
Center for Neural Engineering
Pennsylvania State University

Mr. Jim Cohick
Senior Vice President of Specialty Programs
CURE International

By Direction of the Chairman

The Committee on Foreign Affairs seeks to make its facilities accessible to persons with disabilities. If you are in need of special accommodations, please call 202-225-9922 at least five business days in advance of the event, whenever practicable. Questions or requests for special accommodations in general (including availability of Committee materials in alternative formats and assistive listening devices) may be directed to the Committee.
COMMITTEE ON FOREIGN AFFAIRS

MINUTES OF SUBCOMMITTEE ON  Africa, Global Health, and, Human Rights  HEARING

Day  Tuesday  Date  August 2, 2011  Room  2172 Rayburn

Starting Time  2:40 p.m.  Ending Time  3:32 p.m.

Recesses  0  (to ) (to ) (to ) (to ) (to ) (to ) (to )

Presiding Member(s)
Rep. Chris Smith

Check all of the following that apply:
Open Session  Yes  Electronically Recorded (taped)  Yes
Executive (closed) Session  No  Stenographic Record  Yes
Televised  Yes

TITLE OF HEARING:
Hydrocephalus Treatment in Uganda: Leading the Way to Help Children

SUBCOMMITTEE MEMBERS PRESENT:

NON-SUBCOMMITTEE MEMBERS PRESENT: (Mark with an * if they are not members of full committee.)
Rep. Frank Wolf*

HEARING WITNESSES: Same as meeting notice attached? Yes  No  
(If "no", please list below and include title, agency, department, or organization)

STATEMENTS FOR THE RECORD: (List any statements submitted for the record)
Prepared statement from Rep. Carnahan
Information requested by Rep. Buerkle
CURE International Global Impact Strategy
Article on Hydrocephalus in Uganda
Selected papers written by Dr. Werf

TIME SCHEDULED TO RECONVENE  
TIME ADJOURNED  3:33 p.m.

Subcommittee Staff Director
OPENING STATEMENT OF
THE HONORABLE RUSS CARNAHAN (MO-03)
SUBCOMMITTEE ON AFRICA, GLOBAL HEALTH, AND HUMAN RIGHTS
U.S. HOUSE COMMITTEE ON FOREIGN AFFAIRS

Hearing on
Hydrocephalus Treatment in Uganda: Leading the Way to Help Children
Tuesday, August 2, 2011, 2:00 P.M.
2172 Rayburn House Office Building

Chairman Smith and Ranking Member Payne, thank you for holding this hearing on hydrocephalus, an underreported global health concern that disproportionately impacts the developing world. Today, I hope our dialogue promotes ways to combat hydrocephalus and other global health challenges.

The incidence of hydrocephalus in Sub-Saharan, and particularly East Africa, is significantly higher than the developed world, with such trends characterized by a far higher percentage of cases caused by neonatal infections. Insufficient logistical and public health infrastructures in countries like Uganda further compound the debilitating impacts of hydrocephalus—resulting in high probability of severe disability or loss of life even among those who receive treatment. I want to commend the work of our panelists here today to shed light on this disease and advance causes that save the lives of children in Africa and throughout the developing world.

Your work to advance research of root causes and cost-effective treatment methods reflects the importance of U.S. technology and innovation. In fact, my district in the St. Louis region is widely recognized as an important hub for healthcare research and education. At Washington University and St. Louis Children’s Hospital, neurological experts are also working to advance biomarker diagnostics and early treatment of hydrocephalus.

While working to implement important technological advancements in the developing world, CURE International also prioritizes training local nationals to promote sustained access to health care. This core principle—capacity building through health systems strengthening—is also a tenet of the U.S. government’s Global Health Initiative. Through an emphasis on local ownership, we seek to address some of the most dire public health challenges in Africa, from malaria and neglected tropical diseases to HIV/AIDS. We must continue to work with our international partners to improve weak health systems, poor infrastructure, and powerful social stigmas that continue to perpetuate epidemics in Africa.

The world’s poor continue to face stark health crises, and I’m grateful to the witnesses for their leadership on this issue. Thank you for your presence here today, and I look forward to hearing your testimony.
Information from Mr. Jim Cohick, in response to a question from Rep. Buerkle regarding cost of addressing hydrocephalus globally.

As discussed in the hearing, it is conservatively estimated that this year alone over 300,000 newborns will suffer from congenital or acquired hydrocephalus in the developing world where access to life-saving surgical treatment is virtually nonexistent. The vast majority of these children will not be treated and therefore will die or suffer devastating lifelong physical and mental disabilities.

Training local doctors and medical professionals in the “shunt-less” surgical technique (ETV/CPC) along with the treatment process for successfully addressing hydrocephalus and conducting ongoing research on the causes of hydrocephalus in order to help prevent a portion of new cases, is a sustainable, long-term solution for addressing this global health concern head on. The only such initiative, begun by Dr. Benjamin Warf and continuing at the CURE Children’s Hospital of Uganda through the CURE Hydrocephalus Surgeon Training Program (CHSTP), is currently being scaled up.

A five-year $75 million effort for emergency surgical treatment and training additional surgeons from the developing world would be the beginnings of a much needed effort to address such a global health concern. Such a global hydrocephalus treatment and training program would begin by targeting training for more than 100 surgeons from the developing world and creating on-going annual capacity for over 11,000 life-saving surgeries. As more local surgeons are trained, and they in turn train other developing world medical professionals, the number of cases treated will grow exponentially. More investment would mean a greater number of surgeries provided and doctors trained, thus reaching a larger percentage of children suffering from hydrocephalus.

The value of this life-saving effort is realized both individually and aggregate. A child is healed and her life expectancy is extended well beyond her second birthday. More broadly, using the DALYs and statistical economic value of life (accepted public health measurements) referenced by Dr. Warf, provides strong evidence that the cost per hydrocephalic child treated with the ETV/CPC technique rivals the cost of many low-cost immunization programs in that many thousands of children are immunized who may actually never need it in order to save the few who do.

A 2011 Harvard University study citing 2 billion of the world’s population not having access to proper surgical care motivates CURE International to pursue this effort. And yet the effect of training surgeons in developing world settings goes well beyond the treatment of hydrocephalus patients. It has a broader and deeper impact on building the capacity of fragile developing world health systems, which is a major objective of the U.S. Government. Surgeons are equipped to leverage high quality care and patient safety in other aspects of their work. A cadre of trained medical professionals is created across nations for on-going medical education, clinical research, and other collaboration. Goodwill is strengthened or created at the grass roots and at government ministries between developing world nations and the United States.

Executive Summary

Infant Hydrocephalus: A Global Health Concern

Infant hydrocephalus is one of the most common congenital abnormalities affecting the nervous system of children around the globe. Commonly referred to as “water on the brain,” infant hydrocephalus can be congenital (existing from birth) or acquired. Hydrocephalus is an abnormal medical condition that develops when the normal flow and absorption of cerebrospinal fluid (CSF) in the brain is hindered or blocked resulting in excessive accumulation of fluid in the ventricles of the brain. This excessive accumulation of CSF creates severe and harmful pressure on the brain and eventual swelling of the head. Left untreated, in addition to pain and suffering, infant hydrocephalus leads to significant brain damage, severe developmental delays, blindness, and ultimately death.

Hydrocephalus is a life-threatening medical condition that goes vastly untreated in developing countries because neurosurgical care is simply not available. This year alone, it is conservatively estimated that nearly 400,000 newborns (1/1,000 births1-3) will suffer from congenital or acquired hydrocephalus around the globe and over 310,000 (79%) of these children will be born in the developing world with limited or no access to critical life-saving care. Over the next five years, as many as 1.5 million infants in the developing world will die from hydrocephalus.

Children suffering from hydrocephalus in the developing world have not been a significant priority for resource-poor nations’ Ministries of Health, major international actors in global health, or other international development groups to date. With this in mind, CURE International, an international health network dedicated to healing children with correctable physical disabilities, has launched a global initiative, CURE Hydrocephalus, to address the needs of these underserved children and expand the medical infrastructure necessary for addressing this significant global health concern.

CURE Hydrocephalus: A Global Response

Over the past ten years, CURE has become a global leader in the efforts to save the lives of children with hydrocephalus in the developing world by providing surgical treatment to infants and training programs for neurosurgeons. In December 2008, CURE officially opened the CURE Children’s Hospital of Uganda (CURE Uganda), the first pediatric neurosurgical hospital in Sub-Saharan Africa. CURE Uganda began under the leadership of Benjamin C. Warf, M.D., Dr. Warf, a pioneering neurosurgeon from the U.S., relocated his family to Uganda and served as the hospital’s first medical director for six years while establishing the neurosurgical practice and training programs at the hospital.

Since inception, CURE Uganda has provided surgical care to over 4,000 children suffering with hydrocephalus and trained 11 neurosurgeons from ten developing countries. CURE Uganda’s leadership as a center of excellence for the treatment and management of children with hydrocephalus has resulted in the hospital treating more children with hydrocephalus than any other hospital in the world over the last decade.

CURE Uganda also leads the way in the endoscopic treatment of hydrocephalus. During Dr. Warf’s tenure as medical director of the hospital, he pioneered a novel surgical procedure (endoscopic third ventriculostomy combined with a choroid plexus cauterization, or ETVCPC) to effectively treat infant hydrocephalus without shunt dependency. In developing countries where shunt dependence is life-threatening due to limited access to emergency care, this innovative ETVCPC procedure offers significant advantages for treating hydrocephalus. Published in numerous peer-reviewed medical journals, Dr. Warf has proven the superiority of the ETVCPC procedure over traditional shunting through his treatment results for the largest volumes of hydrocephalus patients in the world. His work continues to expand through the training program he established for surgeons at CURE Uganda. One of Dr. Warf’s first successful trainees, Dr. John Mugamba, became his successor at CURE Uganda.

Dr. Mugamba, CURE Uganda’s current Medical Director, has now surpassed Dr. Warf in performing more ETVCPC procedures than any other surgeon in the world.

More recently, the Beit-CURE Hospital of Zambia (CURE Zambia) established a similar neurosurgical practice and has completed over 1,000 hydrocephalus surgeries in its first three years of implementation. Dr. Kadzonga Siyaba, another graduate of CURE Uganda’s initial training program, is the current head of neurosurgery at CURE Zambia.
Building on over a decade of experience in delivering hydrocephalus treatment and surgical training, CURE International launched CURE Hydrocephalus (CH) in 2011. CH is focused on building global health systems' capacities for treatment, training, research, and prevention to address infant hydrocephalus in the developing world. The mission of CURE Hydrocephalus is to save lives through the elimination of untreated hydrocephalus and its preventable causes.

As a division of CURE, CH has been launched to develop a world-class network of Hydrocephalus Treatment Centers (HTCs) in the developing world that target the following primary program pillars:

- **Treatment** – Expanding access to life-saving surgical treatment for children with hydrocephalus;
- **Training** – Strengthening national health systems by training and equipping national surgeons from the developing world to provide advanced surgical treatment methods for hydrocephalus;
- **Research and Prevention** – Developing the IT infrastructure to capture patient data to facilitate research with CH's strategic partners in an effort to advance the understanding of the causes, best treatment practices, and effective methods of prevention of post-infectious hydrocephalus; and
- **Compassionate Care** – Demonstrating compassionate care and concern for the world's most vulnerable children.

**Implementation**

CH's primary strategy is to train, develop, and expand a fully functioning network of surgeons in the developing world skilled at treating children with hydrocephalus. By doing so, the ultimate goal of saving the lives of thousands of vulnerable hydrocephalic children every year will be achieved. This strategic plan includes the following goals and strategic elements for implementation over the next five years which will be further outlined in the 'Program Description & Implementation' section of this document:

1. **Global HTC Network** – Establish a network of as many as 100 HTCs in the developing world over the next five years.
2. **Life-Saving Surgical Treatment** – Expand global access to life-saving surgical treatment through the HTC network by achieving surgical volumes of as many as 11,300 infant hydrocephalus cases annually by year five and 26,900 cumulative cases over the first five years (Appendix II).
3. **CH Surgeon Training Program** – Recruit, train, and equip qualified surgeons in the ENVPC procedure, sharpeplication procedure, and the Uganda Score Methodology, through the following structure:
   a. **CURE Pediatric Neurosurgical Hospitals (CNHs)** – Utilize 4 CURE hospitals (CURE Uganda, CURE Zambia, CURE Ethiopia, and CURE Hospital TB) as centers of excellence for training and equipping as many as 100 surgeons (neurosurgeons and general surgeons) from the developing world over the next five years.
   b. **Annual Training Cycles** – Facilitate the training of 30 new surgeons annually by year five (10 surgeons per three-month training cycle/three cycles annually).
   c. **Hydrocephalus Treatment and Training Centers (HTTCs)** – Expand the number of new treaters through the creation of additional training locations in the future.
4. **Leadership Team and Staff** – Initiate and implement CH goals and strategies through the key leadership team, including the Executive Director, Senior Medical Director, Medical Faculty Director, Operations Director, Medical Advisory Board, CH Affiliate Surgeons, Patient Care Coordinators, and Regional Program Directors.
5. **Patient Care Coordination Program** – Initiate the social work program under the lead of Patient Care Coordinators (PCC) as an essential component to the delivery of effective, holistic care to children and families suffering from hydrocephalus.

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4 The Uganda Score is a success prediction tool developed by Dr. Walt at CURE Children's Hospital of Uganda which prescribes the surgeon to follow a logical sequence of assessments of certain co-morbidity issues. The methodology includes among other things, factoring the cause for the onset of the condition, the age of the patient, and other contributing aspects such as the presence of infection, the extent of swelling, and the appearance of key anisoc in the brain cavity surrounding the third ventricle and aqueduct.
6. **IT Infrastructure, Clinical Data Tracking System, Quality Assurance, and Collaborative Research Initiatives** — In collaboration with Dr. Benjamin Warf, establish uniform evidence-based treatment protocols across the HTC network, as well as the protocols for capturing and reporting clinical data. This will entail developing the necessary IT infrastructure to enable high quality data feedback from the network.

**Financial Summary**

Over the next five years alone, as many as 1.5 million children will be born with or acquire hydrocephalus in the developing world, a fatal condition in this setting. CURE Hydrocephalus has an extremely ambitious mission of eliminating untreated hydrocephalus and its preventable causes. Transforming this program into a global health initiative will require significant strategic partnerships and leadership level financial investments from major players. In order to rapidly scale up the CURE Hydrocephalus program model over the next five years, in order to accomplish these goals and develop the capacity of global health systems to effectively address infant hydrocephalus in the developing world, a total funding investment of $75.6 million will be necessary over the next five years (see “Financials”). With these financial resources, the CURE Hydrocephalus model will be expanded to achieve significant measurable results on a global scale:

- As many as 100 trained surgeons from the developing world will be operating within a global network of HTCs.
- As many as 100 HTCs will be established.
- As many as 27,000 children’s lives will be saved through surgical intervention over the next five years.
- The global health systems’ capacity will be expanded to provide life-saving surgery to over 20,000 children with hydrocephalus each year.
- A fully-trained CURE Affiliate Surgeon working in a typical developing world government hospital will be equipped to perform a life-saving surgical treatment for hydrocephalus for less than $175.
- Critical clinical data continue to be gathered and utilized for research aimed at breakthroughs in reducing preventable hydrocephalus.

Since 2006, CURE has utilized the underlying program of CURE Hydrocephalus to provide life-saving surgery for over 5,000 children, effectively proving the success of our model. It is our hope that over the next decade, hundreds of thousands of infant deaths from hydrocephalus will be prevented through the establishment of treatment and training centers, breakthroughs in research, and implementation of effective prevention methods as this global health concern is broadly recognized and addressed.
About CURE International

Founded in 1996, CURE International’s mission is to provide healing to disabled children in the developing world that suffer from correctable conditions such as clubfoot, cleft lip and palate, hydrocephalus, and other physical deformities. We truly believe that curing a child’s disability eliminates a major obstacle to overcoming the challenges of growing up in resource-poor countries and contributes to the alleviation of poverty for the family of that child. It is estimated that as many as 80 million children in the developing world have a physical disability; CURE focuses on those children whose physical condition can be corrected through medical care or surgery, so they can have a chance at a normal life.

Currently, CURE operates surgical teaching hospitals in 11 nations (Afghanistan, China, Dominican Republic, Ethiopia, Honduras, Kenya, Malawi, Niger, Uganda, the United Arab Emirates, and Zambia), and has also begun a pediatric orthopedic surgical program serving disabled children in Egypt.

In addition to the wide range of disabling conditions treated at our hospitals, CURE has also initiated CURE Clubfoot Worldwide (CCW), a community-based, non-surgical clubfoot program that impacts a total of 15 countries, including Afghanistan, Cambodia, the Democratic Republic of Congo, Dominican Republic, El Salvador, Ethiopia, Guatemala, Ghana, Haiti, Honduras, India, Kenya, Malawi, Niger, Rwanda, and Zambia. A recent grant from the U.S. Agency for International Development (USAID) will expand this program to include Burundi, Liberia, Mozambique, Sierra Leone, and Togo.

Since inception, CURE International has provided medical care during more than 1,200,000 patient visits, while performing more than 84,000 life-changing surgeries and training over 800 national medical practitioners.
Financials

CURE International projects the following revenues and expenses for all CURE Hydrocephalus program and administrative activities:

<table>
<thead>
<tr>
<th>Operating Expense Projections (US$)</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>SYR - Totals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Program Personnel</td>
<td>$ 625,000</td>
<td>$ 1,018,750</td>
<td>$ 1,586,969</td>
<td>$ 2,348,808</td>
<td>$ 3,246,672</td>
<td>$ 8,665,178</td>
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<td>Surgical Training Program</td>
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<td>$ 938,529</td>
<td>$ 1,354,855</td>
<td>$ 1,683,685</td>
<td>$ 1,932,080</td>
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<td>ETV Equipment &amp; Setup</td>
<td>$ 348,000</td>
<td>$ 1,122,300</td>
<td>$ 1,608,630</td>
<td>$ 2,017,493</td>
<td>$ 2,322,716</td>
<td>$ 7,420,136</td>
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| Treatment Program & Patient Care   |        |        |        |        |        |              |
| Patient Care Support - Hospital Treatment Fees | $ 1,914,063 | $ 3,383,898 | $ 4,995,189 | $ 7,549,283 | $ 10,020,192 | $ 27,962,625 |
| ETV Scope Replacement Expenses     | $ 82,400 | $ 129,000 | $ 246,842 | $ 468,282 | $ 724,358 | $ 1,900,897 |
| Shunt Systems Expenses             | $ 262,000 | $ 537,500 | $ 1,028,506 | $ 1,626,176 | $ 3,018,160 | $ 6,670,343 |
| CH Training Centers Capital Expansion | $ 2,252,700 | $ - | $ - | $ 1,750,000 | $ 1,200,000 | $ 5,202,700 |
| Information Technology             | $ 236,200 | $ 218,678 | $ 323,666 | $ 323,693 | $ 439,156 | $ 1,441,794 |
| Travel                             | $ 75,000 | $ 80,625 | $ 86,672 | $ 93,472 | $ 100,160 | $ 425,629 |
| International Program Administration Expense | $ 910,907 | $ 1,114,422 | $ 1,669,728 | $ 2,704,588 | $ 3,456,633 | $ 9,856,348 |

Total Expenses: $ 6,083,620 | $ 8,543,902 | $ 12,801,259 | $ 20,735,178 | $ 26,501,157 | $ 75,555,116 |

Total Annual Surgery Volumes

<table>
<thead>
<tr>
<th></th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>SYR - Totals</th>
</tr>
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<td>Cumulative Surgeries</td>
<td>1,300</td>
<td>2,500</td>
<td>4,450</td>
<td>7,350</td>
<td>11,300</td>
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<td></td>
<td>1,300</td>
<td>3,800</td>
<td>8,250</td>
<td>15,600</td>
<td>26,900</td>
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The following assumptions have been used in the financial projections for CH operating expenses above:

1. Total CH employees by year: 136
2. Total surgeons in training: Two (2) per training cycle per trainer / three (3) cycles per year.
   a. Year 1: 1 location, 1 trainer, 6 trainees
   b. Year 5: 3 locations, 5 trainers, 30 trainees
3. Total calculated training costs per surgeon: $45,725
4. Total ETV equipment and setup costs per new HFC: $58,000
5. Case load distribution: 60% ETV procedures vs. 40% shunt placements, based on 4,500 completed cases to date
6. ETV scope replacement required every 100 cases: $8,000 (scope Storz flexible endoscope – German manufactured)
7. Shunt cost per unit: $360 (Cedexo Biocompatible Universal Shunt system – U.S. manufactured)
8. Average annual inflation rate – 7.5%
9. Patient care support: 40% of cases in Government-hospital treatment model by Year 5 (shunts and scopes provided, no patient care subsidy)
10. International program administration expense rate: 15%
<table>
<thead>
<tr>
<th>Country</th>
<th>Region</th>
<th>Population: 2010</th>
<th>Total New Cases of Infant Hydrocephalus (2 per 1000 births)</th>
<th>Total New Cases of Infant Hydrocephalus (1 per 1000 births)</th>
<th>Total New Cases of Infant Hydrocephalus (5 per 1000 births)</th>
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Appendix 1: Estimated New Infant Hydrocephalus Cases - 2010 (Developing World)
<table>
<thead>
<tr>
<th>Country</th>
<th>Region</th>
<th>Population: 2010(^{10})</th>
<th>Total New Cases of Infant Hydrocephalus (2 per 1000 births)(^{10})</th>
<th>Total New Cases of Infant Hydrocephalus (3 per 1000 births)(^{10})</th>
<th>Total New Cases of Infant Hydrocephalus (5 per 1000 births)(^{10})</th>
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<tr>
<td>India</td>
<td>Latin America &amp; Caribbean</td>
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<td>732</td>
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<td>Total New Cases of Infant Hydrocephalus ($) per 1000 births**</td>
<td>Total New Cases of Infant Hydrocephalus ($) per 1000 births**</td>
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**Annual Totals (Developing World)**

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<th>Country</th>
<th>Region</th>
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Notes:
* World Bank defines low-income and middle-income economies as developing economies.
* Incidence of congenital hydrocephalus in the developed world:
  * 0.5 case per 1000 live births
* Overall incidence of total neonatal hydrocephalus in the developing world:
  * 5 to 10 cases per 1000 live births
* CURE indicates rate of 1 per 1000 neonatal live births for hydrocephalus (57%).

References:
5. World Bank list of economies (April 2010). http://data.worldbank.org. For operational and analytical purposes, the World Bank divides economies into income groups according to 2005 gross national income (GNI) per capita, calculated using the World Economic Classification and data reported for geographic regions are for low-income and middle-income economies only. Classification by income does not necessarily reflect development status.
Association of bacteria with hydrocephalus in Ugandan infants

Clinical article


Departments of Veterinary and Biomedical Sciences, Biology, Engineering Science and Mechanics, Neurosurgery, and Physics; Center for Neural Engineering, The Pennsylvania State University, University Park, Pennsylvania; Department of Neurosurgery, Children's Hospital Boston, Massachusetts; CURE, Children's Hospital of Uganda, Mbale, Uganda; and Uptown International Center, National Institutes of Health, Bethesda, Maryland

Object. Infantsile hydrocephalus in East Africa is predominantly postinfectious. The microbial etiology remains unclear, since most patients present with postinfectious hydrocephalus after antenatal neonatal sepsis (NS) has resolved.

Methods. To characterize this syndrome in Ugandan infants, we conducted polymerase chain reaction targeting bacterial 16S ribosomal DNA from CSF to determine if bacterial etiology of ventriculitis were detectable. Bacteria were identified based on the relationship of genetic sequences obtained from reference bacteria in public databases. The authors examined samples from patients presenting during dry and rainy seasons and performed environmental sampling in the villages of patients.

Results. Bacterial DNA was recovered from 34% of patients. Gram-negative bacteria in the phylum Proteobacteria were the most commonly detected. Within this phylum, gamma-proteobacteria dominated in patients presenting after the rainy season. During the dry season, Flavobacteriaceae was most common, following infections during the dry season. Acinetobacter species were isolated in 25% of patients identified after rainy season infections.

Conclusions. Postinfectious hydrocephalus in Ugandan infants appears associated with predominantly gram-negative bacteria. These findings highlight the need for linking these cases with antecedent NS to develop more effective treatment and preventive strategies.

DOI: 10.3171/2011.6.PEDS10167

Keywords: hydrocephalus • central nervous system infection • tropical medicine • pediatrics • developing country

W ords Health Organization estimates suggest a worldwide yearly toll near 1.6 million neonatal deaths from infection. Neontal mortality disparity ranges from 5 cases per thousand five births in developed countries to 42 cases per thousand in some African countries. There are 2 classes of NS: early onset, within the first week of life from intrauterine organism transmission; and late onset, within weeks 2-4 of life from community and nosocomial sources.

Abbreviations used in this paper: NS = neonatal sepsis; PCR = polymerase chain reaction; HIV = human immunodeficiency virus; CSF = cerebrospinal fluid.

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The occurrence of hydrocephalus in survivors of neonatal meningitis was well described by the 1960s, with incidences in developed countries as high as 30%. By the 1970s, pneumencephalography demonstrated that in such patients, there were intraventricular septa and loculations, which appeared to be related to a progressive ependymal inflammatory process. Ventriculostomy has recently provided direct observation of ependymal and choroid plexus scarring, postinflammatory ependymal obstruction, and intraventricular deposits of pus and hemorrhoids. The latter finding appears to be the pneumencephalographic descriptor of such cases by Handler and Wright, who reported that PIH accounted for 30%–40% of cases in a South African population of infants with hydrocephalus.
with a disproportionate percentage of these patients represented in the nonwhite peoples they treated.

It has recently been reported that most cases (60-65%) of infantile hydrocephalus in East Africa may be postinfectious. Hydrocephalus is estimated to develop in between 1000 and 2000 0.3-4 year infants each year. The microbial origins of these infections remain elusive, since the majority of patients present with PTH after antibiotic NS has resolved and CSF cultures have been consistently negative.

The spectrum of bacteria causing NS in the developed countries is well known and relatively homogeneous in North America, Europe, Australia, and South Africa group B Streptococcus, Escherichia coli, and Listeria monocytogenes. When gram-negative enteric bacteria cause NS in industrialized countries, risk factors typically include neural tube defects and urinary tract anomalies. In contrast, the spectrum of bacteria infecting neonates in the developing world is biased toward gram-negative organisms and appears to differ at each site from which high-quality (fetal or postnatal) data are available. There is a striking absence of group B Streptococcus in many studies in the developing world despite the fact that maternal carriage rates of this organism may be similar. In Handler and Wright's cases, the meningococcal organisms were found to be gram-negative enteric bacteria (Escherichia coli, Aeromonas, and Enterobacter cloacae).

The advent of modern molecular techniques permits us to identify the presence of microorganisms by the amplification of their genetic material through PCR. The amplified gene can then be used to establish a taxonomic relationship among microbes. For bacteria, the 16S rRNA gene has become a standard for identifying bacteria, often to the level of individual species. This new approach to bacterial identification has provided a significant clinical breakthrough, it provides a means of identifying bacteria that are not easily distinguishable based on biochemical properties and, most significantly, it allows for the detection of bacteria that cannot be cultured. In this study, faced with a large patient population with clinical infection resistant to antibiotics without successful bacterial culture results, we used amplification and sequencing of the bacterial 16S rRNA gene to further study these patients.

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We performed the following cohort study to delineate the nature of PTH in a Ugandan infant population presenting weeks to months after NS for neurosurgical treatment of their hydrocephalus.

Methods

All research was performed with institutional review board approval from the UCHF Children's Hospital of Uganda and Penn State University.

Our criteria for PTH in infants presenting with hydrocephalus under 1 year of age were as follows: no history of hydrocephalus at birth and either a history of febrile illness and/or seizures preceding the onset of hydrocephalus, or endovascular imaging findings indicative of prior ventriculitis such as scarring, dilatation, thickened white matter, or purulent intraventricular debris (Fig. 1). In the overwhelming majority of infants presenting with PTH, their antecedent serious febrile illness had developed within the 1st month of life, demonstrating that PTH very likely derives from preceding NS. One of the key motivations for our work is that CSF sampled at the time of endoscopic third ventriculostomy or shunt insertion has been consistently culture negative in more than 1000 such children treated at the UCHF Children's Hospital of Uganda since the year 2000.

At the time of endoscopic third ventriculostomy or shunt insertion, we collected samples of CSF from 3 cohorts of infants meeting the above criteria for PTH: Cohort 1, specimens from 25 consecutive patients collected in January 2008 for DNA analysis; Cohort 2, specimens from 25 consecutive patients obtained in July 2008 for culture; and Cohort 3, specimens from 25 consecutive patients obtained in October 2008 for DNA analysis. Each specimen was obtained from an individual patient. There were 2 rainy seasons in Uganda, generally April–May and October–December. Cerebrospinal fluid samples from Cohort 1 were collected during the dry season in January 2008, and those from Cohort 2 were collected at the beginning of the rainy season. Because the infants were ages 1–6 months and the mean median time from illness to the onset of PTH was 0.8–0.3 months, 7 patients present.
Association of bacteria with hydrocephalus in Ugandan infants

In January were presumptively infected during the rainy season, and the October cohort was presumptively infected during the dry season.

All CSF samples were collected under strict sterile conditions in the operating room. Samples were collected upon entrance to the brain, almost always with an endoscope, but occasionally with a blunt catheter. Several milliliters of CSF were collected using a syringe and placed in a sterile bowl on a sterilely draped Mayo stand, and sterile and DNA-free pipette tips were used on a calibrated pump to place 50 ml aliquots of CSF onto DNA collection cards or into tubes. All handling of the DNA specimen was performed using an aseptic technique with gloves to reduce sample exposure to contaminants. Two collection techniques were utilized for DNA sampling: WhirlNet FTA cards and Biomatrix Carditubes. The recovery of DNA sequences was similar for both methods of stabilization, and the results were pooled in this report. Both methods permit the stabilization of nucleic acids for long-distance transport at room temperature.

Separate samples of each specimen were sent to the laboratory in Mibuze for bacterial culture, where chocolate agar and in some cases blood agar, failed to demonstrate any growth. In cohort 2, we used bacterial transport tubes (Becton Dickinson BD CultureSwab Plus Collection and Transport System containing Amoxicillin 500 mg/ml with oxygen-scavenging agent) for the transportation of both aerobic and anaerobic organisms to Penn State to attempt recovery of fastidious organisms. No bacteria were cultured from these specimens, either at Mibuze or at Penn State, affirming the high quality of the sterile technique used and the absence of cultivable bacteria in the samples.

Extraction of DNA from the FTA cards was conducted using the procedure described by Black et al. Briefly, the entire extracted sample was washed, mixed, and diluted with 500-500 ul of water at 95°C for 60 minutes using sterile reagents and instruments. The paper and eluate were transferred to a spin column to remove residual material, the eluate was adjusted with 1.0 M Tris to 30 mM Tris pH 8.0, and nucleic acid recovery was achieved using a Quiac DNA lysate and tissue kit.

The PCR reaction was conducted using primers 16S-88 (5’-ACGGTATCGATCACTCATCG-3’) and 16S-S44 (5’-ATTACCGCGGCTGCTGTCG-3’). Polymerase chain reaction products were sequenced directly or cloned into the pGEM-T easy vector (Promega), and cloned products were sequenced.

Sequences were aligned using the MEGA package, version 7, and MEGA, version 4.0. For accurate reconstruction of the relationships of bacteria based on the 16S rRNA gene, a model of how the sequences evolve must be developed. Over 50 models of sequence evolution were evaluated, and the best model for each dataset was selected using the Akaike Information Criterion (AIC) in the Modeltest, version 3.7. The phylogenetic trees, which display the genetic relationships among the individual sequences of Acinetobacter species, were produced using a maximum likelihood tree method implemented in the program PhyML, version 2.4.4. Using the same program, the strength of support for each node in the tree was estimated with 100 bootstrap replicates (a statistical resampling method) in the same program. To infer the relationships among individual bacterial sequences within each Acinetobacter species, maximum likelihood trees were reconstructed using MEGA, version 5.0. Gaps were treated as missing data, and all the sequences were set to connect at the 95% confidence limit.

Results

To determine if bacteria were present in the CSF samples, we amplified the bacterial 16S rRNA gene by PCR and sequenced the products with or without cloning. The phylogenetic representation of each bacterial phylum, which shows all unique sequences obtained from these patients, demonstrates that the bacterial diversity in the CSF samples was similar and that many could not be classified. Interestingly, in the 21 patients in Cohort 1 for whom the gene for bacterial 16S rRNA was amplified, Gamma-proteobacteria (a class of gram-negative bacteria in the phylum Proteobacteria, which includes Pseudomonas, Escherichia, and Acinetobacter) were identified in 19; Acinetobacter species were represented in 95% of these samples (Fig. 3). We subsequently took samples from another 23 consecutive children presenting with PJI in July (Cohort 2) to attempt to improve our culture recovery of gram-negative bacteria such as Acinetobacter, but we were unsuccessful despite the incorporation of multiple media types (Table 1). For Cohort 3, we again focused on DNA extraction and 16S rRNA gene amplification to determine bacterial presence. Proteobacteria (a phylum containing Beta- and Gammaproteobacteria) were also dominant in this cohort, although Betaproteobacteria (gram-negative bacteria such as Burkholderia) were more common (14 of 21 patients) than Gammaproteobacteria (8 of 21 patients). There were also more sequences that could not be classified. The groupings of all Gammatas- and Betaproteobacteria 16S rRNA gene sequences based on evolutionary relatedness obtained in Cohorts 1 and 3 are shown in Appendix Figs. 5 and 6.

Given the findings of enteric bacterial DNA in these children’s CSF, we speculated that environmental exposure might play a role in PJI. Comparing the living conditions in proximity to domestic farm animals and certain cultural practices among some East African peoples (Masai in Kenya and Tanzania and related Nilotic peoples in northern Uganda) involving bovine dung use on vegetable plots, which has been associated with neonatal tetanus, from such reports emerge estimates of the number of cases per year. The Tetanus Clusters project indicates that these clusters of cases per year are more frequent in regions of East Africa that are close to where we work.

We collected samples for culture from 35 cattle, 34 sheep, 353 animals, and water supplies from the villages of 8 of 17 Cohort 1 patients with evidence of Acinetobacter species in their CSF. Our culture efforts targeted the gram-negative bacteria, and a wide variety of species were recovered. Of 35 surveillance cultures, 34.8% were Acinetobacter and 3.5% were gram-negative bacteria. The 16S rRNA genes were amplified from these 24 positive cultures to identify the bacterial species. We note
that these environmental samples were collected during July 2008 and represent dry season specimens.

We further characterized the relationship between *Achromobacter* species from patients and those from environmental sources and compared them with reference strains. These analyses demonstrate how closely related individual bacterial sequences are from each patient sample (Fig. 4 and Appendix Figs. 10 and 11, for more detailed analysis of individual samples). The majority of sequences from Cohort 1 formed a highly related cluster that is most similar to *A. junii*. Within the *A. junii* cluster, only 1 sample was derived from a patient in Cohort 3 (who was infected in the dry season). A second smaller cluster of Cohort 1 sequences matched more closely with *A. parva*, which is a close relative of *A. junii*. *Achromobacter* was only amplified from 2 other patients in Cohort 3; these sequences and those obtained from the environmental samples from the latrine floor or dung collected during the dry season were most closely related to *A. gilbenbergii*. The other sequences from environmental samples were related to *A. achromofaciens*, and no patient samples were found in this cluster. There are 2 important results from this analysis. First, the findings of multiple lineages of *Achromobacter* from different patients suggest that the bacteria were not from a single source, which would be the case if the samples were contaminated postprocessing. Significantly, it appears that there is seasonality to the species of *Achromobacter* identified in patients with PHL and the prevalence of *A. junii* is particularly high in the rainy season.

**Discussion**

Our findings extend those of Handler and Wright and now support the conclusion that the majority of infant hydrocephalus cases in an East African population are postinfectious. We found evidence of fragments of bacterial DNA in almost all patients, with a predominance of gram-negative enteric bacteria as well as evidence for shifting spectra of microbial species depending on the season of the year. The important clinical implication is that most of the hydrocephalus in this population may be preventable.

While previous studies have suggested that neonatal *Achromobacter* infections are most commonly due to *A. baumannii* and are notorious for being nosocomial, little
Association of bacteria with hydrocephalus in Ugandan infants

In known about the routes of neonatal infection in a developing world setting. In reexamining WHO data from Ethiopia, The Gambia, Papua New Guinea, and the Philippines, we note that the spectra of bacteria from infants younger than 4 years of age is similar to the Gram-negative bacteria observed in our infants with PHT. Further WHO data revealed a predominance of Gram-negative bacteria in community-acquired meningitis among infants younger than 50 days of age, with the most common agent being *Adenoviridae* in infants from stans clustered about Manilla.

In an intriguing study from the Sudan, *N. meningitides* demonstrated strong seasonality of PHT coinciding with yearly meningitis epidemics. Although presumably meningitis-cocul in origin, there was no associated bacteriological identification in these data, and neither is it possible to determine the precise timing of the causative infection from these records (they correlated the time of surgical treatment with meningitis peaks). Our cases in Uganda originated south of the seasonal *N. meningitides* belt and appear to be linked to prior NS, and we found no bacterial DNA consistent with the prior presence of *N. meningitides*.

| TABLE 1: Bacterial culture techniques used by Perinatal personnel to attempt recovery of viable organisms* |
|---|---|---|
| Medium | Aerobic | Anaerobic |
| Blood agar | RT (approx 25°C); 30°C, 37°C | 37°C; 5% CO₂; 37°C; 5% CO₂; 5% H₂; 90% O₂ |
| Choclate agar | RT (approx 25°C); 30°C, 37°C | 37°C; 5% CO₂; 37°C; 5% CO₂; 5% H₂; 90% O₂ |
| Mueller-Hinton agar | RT (approx 25°C); 30°C, 37°C | 37°C; 5% CO₂; 37°C; 5% CO₂; 5% H₂; 90% O₂ |

* * approx = approximately; RT = room temperature.
† Three temperatures at which tests were run.
‡ Conditions under which tests were run.
seria meningitidis in any of the samples. The implication is that there are probably multiple bacterial routes to PSH specific to geography and time in sub-Saharan Africa that require untangling.

Although we isolated staphylococcal DNA from 6 patients (Appendix Fig. 6), we rarely encountered staphylococcal strains (3 patients), as opposed to Acinetobacter isolates (22 patients). Consistent with these data, we have found no evidence of the multistep microorganism meningitis seen in older infants with postmeningococcal anemia. Similarly, we have not observed the predominance of Streptococcus pneumoniae meningitis seen in association with HIV/AIDS, perhaps due to the modest percentage of HIV/AIDS cases (5%–15%) among these 3 graduate children. Among Haemophilus influenzae, the Burkholderia species were most common (Appendix Fig. 6) and yet we are aware of only 1 case report of community-acquired Burkholderia species meningitis in the literature.

Contamination is always a concern when interpreting DNA samples such as ours in the absence of viable organisms. Our efforts to ensure sample integrity included the following: First, samples collected at the time of surgery were stored using 2 methods: filter paper and Carrel tubes. These samples were prepared for sequencing at different times and in different labs at Penn State. The initial set of samples was prepared in a lab conducting diagnostic microbiology, and the subsequent set was prepared in a molecular biology basic research lab. Both labs used sterile procedures. None of the organisms identified in patient samples were those under investigation in either lab. Second, we sequenced both directly from FCP-amplified fragments and from clones of PCR products. The latter is more sensitive to detecting bacterial diversity and is an excellent means of assessing contamination with ubiquitous laboratory organisms. None were detected. Third, our phylogenetic analyses indicated that species identified from different patients were not identical. If sample contamination had occurred during processing, the contaminating bacteria should be overrepresented and identifiable. While our analysis shows that identical sequences related to A. baumannii were recovered from several patients, there is sufficient diversity among the Acinetobacter sequences recovered to suggest that they do not arise from a common origin. Thus, even removing the identical Acinetobacter sequences, our interpretation of the relations among the Acinetobacter sequences and the proportion of different bacterial classes would not change. Fourth, in our efforts to culture viable organisms from Cohort 2, we found no growth in any sample retrieved under sterile conditions at surgery, which is consistent with both the quality of our retrieval technique and the local microbiological findings at the locale hospital over the past 10 years.

Because the treatment for NS involving meningitis-ventriculitis should be significantly more prolonged than for NS that does not involve the nervous system, the delineation of NS routes to PSH becomes clinically and economically important. It is believed that much of the harm to the brain from well-treated meningitis is related to inflammation. Vascular inflammation producing thrombosis of an aneurysm and subsequent infarction is described in the pathogenesis of the type of PSH that we
Association of bacteria with hydrocephalus in Ugandan infants

have observed, are the key pathogens of cerebral tuberculomas and tuberculoid leptomeningitis, and are frequent causes of meningitis, encephalitis, and cerebral abscesses. In this article, we review the epidemiology, clinical presentation, laboratory diagnosis, and treatment of bacterial meningitis in children in Uganda. We also discuss the role of bacterial meningitis in the pathogenesis of hydrocephalus and its associated complications.

References
Hydrocephalus in Uganda: the predominance of infectious origin and primary management with endoscopic third ventriculostomy

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Object: The aim of this prospective study was to investigate the cause of hydrocephalus in Uganda, the efficacy of endoscopic third ventriculostomy (ETV) in this environment, and whether existing parameters should be used to guide patient selection.

Methods: Three hundred consecutive children, 81.3% of whom were younger than 1 year of age, underwent ventriculostomy preceding ETV as an initial treatment for hydrocephalus. In 179 patients (66%), the hydrocephalus was caused by ventriculitis. Of these children, 70% of patients the infection had occurred, in the first month of life. In 220 patients (73.3%), ETV was completed; 24% of patients were lost to follow up after less than 1 month and the surgical mortality rate was 1.8%. The first ETV was successful in 165 patients (59%); the mean follow-up period was 15.2 months. The mean time to repeated operation following a failed attempt of ETV was 1.5 months. Sixty-five patients underwent a second endoscopy; 70 underwent a third (14% of initial). A procedure was considered (mean follow-up period 32.5 months). The overall success rate for ETV was 59%. In patients older than 1 year of age, 72.02% of 27 with postinflammatory hydrocephalus (PIH) and 72.69% of 21 with nonpostinfectious hydrocephalus (NPH) the procedure was successful. The success rate for patients with NPH was higher, while those with PIH was lower. The mean age of those patients younger than 1 year of age was 59 (60 of 101) for patients suffering from PIH and 48 (31 of 53) for those suffering from NPH. Age correlated with success for NPH (p = 0.0007) and PIH (p = 0.0441). The success rate of the surgery (for NPH < infants younger than 1 year of age was 90% (44 of 63) among patients with perinatal obstructive, but 45% (14 of 31) among patients with postinflammatory obstructive (p = 0.0254).

Four ventricular age as demonstrated on cranial ultrasonography or computed tomography, imaging was predicted whether the endoscopy was successful (p < 0.0001).

Conclusions: Infections are the most common cause of hydrocephalus in Uganda. In all children older than 1 year of age and in those younger than 1 year of age with T2HFL and aqueductal obstructions, which were reliably predicted by cranial ultrasonography, ETV was effective.

KEY WORDS: endoscopic third ventriculostomy • hydrocephalus • neonatal meningitis • ventriculitis • myelomeningocele • developing country • pediatric neurosurgery

The incidence of hydrocephalus in East Africa is very high. The use of shunts in a developing country—e.g., even if the difficulties of cost and availability are surmounted—presents unique problems. The complications of shunt malfunction and infection are manageable when competent neurosurgical care is available on an urgent basis, in a situation like that in Uganda, however, ready access to such care is impossible for most patients because of financial and logistical barriers. Long-term shunt dependency is more dangerous under these circumstances than it is in the developed world.

In developing countries, ETV presents an attractive option for patients with hydrocephalus in a permanent way without the use of a shunt and its attendant expenses, risks of infection and malfunction, and need for life-long maintenance. The usefulness of ETV has been clearly demonstrated in cases of aqueductal stenosis in older children and adults.45,51-53 However, questions have been lingering concerning its use in infants and 5–4 in cases of hydrocephalus secondary to infection54,55 and those associated with myelomeningocele.65 The majority of our patients present for treatment when they are younger than 1 year old, and the most common cause of hydrocephalus appears to be infectious such as meningitis and meningitis. From the outset, therefore, the usefulness of ETV in our setting was uncertain. Nonetheless, the difficulties and danger of maintaining shunts in the environment of a developing country provided compelling reasons to study the efficacy of ETV in the initial treatment for hydrocephalus of all origins in children of all ages.
Comparison of endoscopic third ventriculostomy alone and combined with choroid plexus cauterization in infants younger than 1 year of age: a prospective study in 550 African children

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Object. The aim of this prospective study was to determine whether, and in which patients, this outcome for bilateral choroid plexus cauterization (CPC) in conjunction with endoscopic third ventriculostomy (ETV) was superior to ETV alone.

Methods. A total of 710 children underwent ventriculostomy or cauterization for ETV or CPC in Uganda. The infant group was 246 infants and the combined ETV-CPC procedure and 284 underwent the procedure and 284 underwent ETV alone. The mean and median ages were 14.3 months and 14.5 months, respectively, and 40 patients (5.2%) were younger than 1 year of age. The hydrocephalus was postinfectious (PIH) in 32 patients (59%), posthemorrhagic (PHH) in 13 patients (22%), postmeningitic in 11 patients (20%), and associated with myelomeningoceles in 15 (26%). The mean follow-up was 15 months for ETV and 14.5 months for ETV-CPC. Overall, the success rate of ETV-CPC (60%) was superior to that of ETV alone (47%) among infants younger than 1 year of age ($p < 0.0001$). The ETV-CPC combined procedure was superior in patients with a posthemorrhagic (PHH) compared with PIH success, $p = 0.0002$ and those with PHH/CPC only compared with PHH success, $p = 0.0025$. Although the difference was not significant for PIH ($p = 0.04$) compared with PIH success, $p = 0.06$, no benefit was realized in those 2.3 infants. For infants at least 1 year of age, there was no difference between the two procedures (98% success for each, $p = 0.79$). The overall surgical success rate was 1.99%, and the infection rate was less than 1%

Conclusions. The ETV-CPC was more successful than ETV alone in infants younger than 1 year of age. However, the study in which a dependence on shunt is dangerous. ETV-CPC may be the best option for treating hydrocephalus in infants, particularly for those with PHH and myelomeningocele.

Key Words: hydrocephalus • myelomeningocele • endoscopic third ventriculostomy • choroid plexus cauterization • developing country • pediatric neurosurgery

Susceptibility to hydrocephalus in children with hydrocephalus is more difficult in causing countries than in developed countries because of the obstacles that prevent access to competent intervention in the event of shunt malfunction or infection. I have previously demonstrated the efficacy of ETV as the primary treatment for hydrocephalus in this context. An ETV was successful in managing hydrocephalus without resorting to a shunt in more than 30% of children older than 1 year of age, regardless of the cause of the hydrocephalus; however, among younger infants (<1 year old), only those with postinfectious obstruction of the aqueduct had an acceptable outcome (70% success). For all other infants younger than 1 year of age with open aqueducts, congenital aqueductal obstruction, or hydrocephalus associated with a myelomeningocele, the success of the ETV was 50% or less. A better treatment solution needed to be developed for these infants.

Because a deficiency in CSF absorption may have contributed to the failure of ETV in young infants, it was decided that the addition of bilateral CPC at the time of the ETV to simultaneously reduce the rate of CPC production, might improve the outcome. Although CPC alone has been previously reported, the combination of the two procedures has not been investigated. Therefore, a prospective trial was conducted in which a CPC was performed in addition to an ETV. On this paper I compare the outcome of the combined ETV-CPC procedure with that of ETV alone among 550 children in whom either procedure was completed at the CURE Children's Hospital of Uganda between June 2001 and December 2004 and identify the patients subgroups that appear to benefit from the combined procedure.

Clinical Material and Methods

Data Collection and Clinical Evaluation

Data were collected prospectively and entered into a Microsoft Access database (Microsoft Corp., Redmond, WA). Clinical information included history, neurological examination, local circumstance, and A topographic. Laboratory data included CSF analysis at the time of the operation. Radiological information included cranial ultrasonography and, when available, a head CT scan. Data entered in the time of the operation included a description of the intramembranous anatomy and of the ETV procedure (including facings of additional membranes below the floor). Whether the interpeduncular and peripontine cisterns were open or occluded, whether a septostomy was performed, and the ocular of the CPC. The patients were categorized as follows according to the origin of their hypotension: PH, PPH, hypotension due to a myelonecrotic, and PPH. Patients with PH and PPH were further subcategorized up to previously described according to age and the stages of the apoplectic as noted at the time of ventriculostomy: Type A (<1 year old with an open aqueduct), Type B (1 year old with an open aqueduct), Type C (<1 year old with a closed aqueduct), and Type D (1 year old with a closed aqueduct). Table 1). This scheme was not applied to patients with myelonecrotic, however, because of the possibility of underserved obstruction to the patent stoma. Patients with PPH were too few in number for further subdivision.

Patient Selection

Between June 2001 and December 2004, ETVs were performed as the initial treatment in 550 patients presenting with headache, the majority of children were from Uganda, but others were from Kenya, Tanzania, Malawi, Somalia, Rwanda, Congo, and Mauritania. The mean and median ages were 14 months and 1 year, respectively. 750 (66%) of 550 were 6 months of age or younger, and 444 (80%) of 550 were younger than 12 months of age. After evaluating the initial results, it was decided to perform bilateral lateral control CPCs in addition to the ETVs to assess the benefit, if any, of the combined procedure among the different patient subtypes.

In the first 250 consecutively treated patients, an ETV alone was performed (with the exception of three patients, who also underwent CPC). In the subsequent 250 patients, a combined ETV-CPC procedure was performed (with the exception of 34 children underwent ETV alone). For various reasons, including a closed CPC. Results of a preliminary analysis in these initial 450 patients resulted in refinement of the protocol for the final 30 patients: PTG: 1) an ETV alone in patients at least 1 year of age; 2) an ETV-CPC in all infants with PPH or PH Type A (aqueduct open); 3) an ETV-CPC in all infants with myelo- necrosis; 4) randomization of infants with PH or PH Type C (aqueduct closed) as either an ETV or ETV-CPC. Overall, a total of 265 patients underwent a combined ETV-CPC, whereas in 254 ETV alone was performed.

Overview of Surgical Technique

The equipment used for the procedure included a flexible endoscope (model 11734, LNS, teleman, model 81, pal 20212002, Iwanima light source (model 11731520), a Halley electrosurgical wire (air powered) (National Park Co., Turin, Italy), and a monitor (Telacount 750MDSE, Sony Corp., Tokyo, Japan). The details of sterilization of the endoscope and camera, operative setup, and the ventriculoscopic procedure in this setting have already been reported.19

The floor was fenestrated with a Halley wire just behind the dura and lacerus by applying brief pulses of electrosurgery on the superficial layer; followed by blunt dissection through the floor. The wire was used to gradually dilate the opening by gently pushing the tissues. A posterior choroid plexus was resected using many maneuvers to dilate the opening were performed.19 The endoscope was passed through the opening in the floor and, when necessary, additional fenestrations (for example, the subarachnoid space at the places at which the cribriform plate or arachnoid adhesions resulting from prior inflammatory procedures were performed until the endoscope could be passed freely into the interpeduncular and peripontine extracranial spaces. If entry was made anterior to the sphenoid portion of the subarachnoid membrane, obtaining the BA, blunt dissection was accomplished with the tip of the wire to fenestrate the membrane. If the cranial nerves were observed to be spared from prior fenestration, a similar technique of blunt dissection to open them was also undertaken. The goal of this intracranial dissection was the direct visualization of a "mandible" BA, its branches, and the cranial nerves. The endoscope was withdrawn from the ventriculostomy and evidence for flow across the stoma was noted.

As previously described, the pons terminales was used as the ETV site if use of the floor was not feasible (usually in a result of severe intraventricular hematoma, although this is not the preferred site).20 Special mention should be made of performing the ETV in patients with a myelonecrotic. The variations in anatomy seen on ventriculostomy among these patients have already been discussed.20 The typically enlarged transverse in- tentum only rarely precluded access to the floor, which was, to all appearances, thickened and revealed no evidence of the BA position inferior. Intracoelomodamic adhesions were common but were usually preserved because the floor was approached around them on top. The floor was gently and bluntly fenestrated posterior to the interpeduncular to fenestrate the membranes, taking advantage of the midline small segment of the floor that was often fenestrated first. There was commonly a prominent interpeduncular adhesion crossed by the floor in this section. At the floor was fenestrated, the dura and lacerus, pituitary, and fenestrations came into view. The endoscope was then gently threaded over the wire into the interpeduncular and peripontine extracranial spaces (after fenestration of the 1 disco- nnect membrane if needed), which were typically very
Endoscopic third ventriculostomy alone and combined with CPC

![Diagram of endoscopic third ventriculostomy]

crowded from anterior displacement of the brainstem and BA complex. In addition, the tip of the BA was usually displaced caudally, with its bifurcation forming an acutely angled Y. As in other cases, blunt dissection of arachnoid adhesions with the tip of the burrhole was sometimes required to open up the cistern.

After the ITV, attention was turned to the CPC. Beginning at the foramen of Monro and gradually moving posteriorly, the CPC of the lateral ventricle was thoroughly cauterized using the burrhole wire and a low-voltage monopolar coagulating current. In cases of severe ventriculomegaly, a portion of the CPC in the posterior roof of the third ventricle was often available for coagulation as well. Care was taken to avoid injury to the thalamostriate and internal cerebral veins or epedymal surfaces. Special attention was paid to coagulating all vessels within the CP completely, including the superior choroidal vein along its entire length. This, together with the burrhole posterior to the thalamus, its tip was flexed and turned to direct the procedure along the CP of the temporal horn, which was then cauterized to similar fashion beginning from its anterior extreme and advancing the wire posteriorly along its length. Cautery was continued until all visible parts of the CP had been coagulated and shriveled (Fig. 1).

In cases in which the septum pellucidum was intact, a septostomy was performed anterior to the posterior edge of the foramen of Monro to gain access to the contralateral CPC in which the same procedure was performed in the contralateral ventricle. The bilateral CPC typically added 15 to 30 minutes to the entire procedure.

If the CP was partially scarred from prior inflammation, all residual parts of the CP were cauterized. In several patients with PEH, the CP was sufficiently effaced by scar tissue such that no cauterization was possible. The patients with a pseudomeningoecele typically had a redundant, robust CP loosely tethered by a thin vascular sheathlike membrane in addition to a carpet of CP-adherent to the ependymal surface along the curve of the thalamus.

In cases in which the child presented with infected, turbid, or bloody CSF that precluded initial ventriculostomy, a reservoir was placed for serial taps until the fluid was sufficiently clear, as described previously.14

Postoperative Follow Up

Patients were generally discharged from the hospital on the 3rd postoperative day, unless their home was too far away. When possible, they were then followed up at 1, 3, and 6 months postoperatively and every 6 months thereafter. Patients lost to follow up were aggressively sought for home visits, often deep in the village, by our social workers, although this was not possible in regions of insecurity. In follow-up examinations, head circumference, character- istics of the fontanel, symptoms, neurological examination, and developmental progress were assessed. Cranial ultrasonography or head CT scanning was also performed at each visit.

Criteria for Success

Success was defined as the avoidance of shunt insertion according to criteria that included a shift in head circumference growth to a normal or less than normal rate as plotted on a standard growth chart, decompression of the anterior fontanel, relief from symptoms of elevated intracranial pressure (such as irritability and vomiting), resolution of eye findings (for example, retching or sixth cranial nerve palsy), and a decrease in ventriculomegaly as determined on ultrasonography or CT scanning by using the Evans index or monomorphous horn ratio.13

Statistical Analysis

Two-tailed probability values, as calculated using the Fisher exact test, were used to assess the significance of
Results

A combined ETV-CPC procedure was performed in 266 and ETV alone in 264 patients, for a total of 530 patients. Of the 530 patients, 21 (1.8%) were lost to follow up at less than 1 month post-intervention, and these were excluded from any further analysis. Seven patients died within 1 month of the operation (1.3% surgical mortality rate). The mean follow up was 39 months for the ETV group and 9.2 months for the ETV-CPC group.

Origin of Hydrocephalus

The origin of the hydrocephalus in each patient was classified according to previously described parameters. Briefly, the designation of PHH was given if there was no history consistent with hydrocephalus at birth and either a) a history of 6-12 months post-intervention and these were excluded from any further analysis. Seven patients died within 1 month of the operation (1.3% surgical mortality rate). The mean follow up was 39 months for the ETV group and 9.2 months for the ETV-CPC group.

Outcomes of Hydrocephalus

The results according to age and outcome are summarized in Table 2. Of the 530 patients, 263 (49.7%) were classified as having normal hydrocephalus, 214 (40.9%) had mild hydrocephalus, 47 (8.9%) had moderate hydrocephalus, and 16 (3.0%) had severe hydrocephalus. The results for the various patient types (age, origin of hydrocephalus, and whether the aqueduct was patent) are summarized in Table 3. Despite the smaller numbers among these individual groups, a significantly superior outcome for ETV-CPC was apparent among the PHH Type A patients (63% compared to 20%, p = 0.003). The difference appeared to be due to the patients who had undergone ETV alone, who showed a much higher rate of success (63% compared to 20%, p = 0.003). For this group, there was a statistically significant difference (57% compared to 35%, p = 0.003). For all patients, the advantage of the combined ETV-CPC procedure was most pronounced among those with patent aqueducts (that is, the Type A group).


<table>
<thead>
<tr>
<th>Proportion of Type A patients (%)</th>
<th>ETV alone</th>
<th>ETV-CPC</th>
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<tr>
<td>100</td>
<td>200</td>
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Table 2: Differences in outcomes based on procedure and age

Patient Age

<table>
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<th>≥ 1 Yr</th>
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<td>266</td>
<td>532</td>
</tr>
<tr>
<td>ETV (combined)</td>
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<td>266</td>
<td>532</td>
</tr>
<tr>
<td>PHH</td>
<td>266</td>
<td>266</td>
<td>532</td>
</tr>
<tr>
<td>NHPP</td>
<td>266</td>
<td>266</td>
<td>532</td>
</tr>
<tr>
<td>Total PHH</td>
<td>266</td>
<td>266</td>
<td>532</td>
</tr>
</tbody>
</table>

Table 3: Differences in outcomes based on origin of hydrocephalus in patients younger than 1 year of age

<table>
<thead>
<tr>
<th>Procedure &amp; Significance</th>
<th>PHH</th>
<th>NHPP</th>
<th>MDM</th>
<th>BPH</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETV alone</td>
<td>200</td>
<td>200</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td>ETV-CPC</td>
<td>200</td>
<td>200</td>
<td>400</td>
<td>400</td>
</tr>
</tbody>
</table>

Table 4: Differences in outcomes based on presence of aqueducts in patients younger than 1 year of age

<table>
<thead>
<tr>
<th>Procedure &amp; Significance</th>
<th>PHH</th>
<th>NHPP</th>
<th>MDM</th>
<th>BPH</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETV alone</td>
<td>200</td>
<td>200</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td>ETV-CPC</td>
<td>200</td>
<td>200</td>
<td>400</td>
<td>400</td>
</tr>
</tbody>
</table>

Table 5: Differences in outcomes based on presence of aqueducts in patients older than 1 year of age

<table>
<thead>
<tr>
<th>Procedure &amp; Significance</th>
<th>PHH</th>
<th>NHPP</th>
<th>MDM</th>
<th>BPH</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETV alone</td>
<td>200</td>
<td>200</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td>ETV-CPC</td>
<td>200</td>
<td>200</td>
<td>400</td>
<td>400</td>
</tr>
</tbody>
</table>

Table 6: Differences in outcomes based on presence of aqueducts in patients older than 1 year of age

The mean and median times to failure of the initial procedure among all patients were 6.8 and 4.4 months, respectively. Among patients who experienced failures, 98% presented within 6 months of the procedure and 55% within 2 months. Five children (2.9%) failed, all with PHH, presented before 1.2 months postoperatively. In all patients with failure of the initial ETV or ETV-CPC procedure, reopening of an occluded ETV or reopening of drainage of fluid below the floor (with or without CPC) was performed, leading to sustained success in 70% who had undergone follow up of more than 1 month.

The overall surgical mortality rate (from any cause within 30 days of the operation) was 1.2% at 550. One patient died of ventriculitis, one of cardiac arrest, one of aspiration, one of pneumonia, and two of undersized aqueducts at home. There were no intracranial deaths. In patients undergoing ETV alone, the mortality rate was 0.2%.

Endoscopic third ventriculostomy alone and combined with CPC

<table>
<thead>
<tr>
<th>Procedure &amp; Liquidation</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETV alone</td>
<td>(19(59))</td>
<td>(6(17))</td>
<td>(54(46))</td>
<td>(0(6))</td>
</tr>
<tr>
<td>total procedures</td>
<td>(33)</td>
<td>(9)</td>
<td>(89)</td>
<td>(15)</td>
</tr>
<tr>
<td>CPC alone</td>
<td>(25(57))</td>
<td>(8(19))</td>
<td>(45(46))</td>
<td>(0(3))</td>
</tr>
<tr>
<td>total procedures</td>
<td>(44)</td>
<td>(9)</td>
<td>(109)</td>
<td>(22)</td>
</tr>
<tr>
<td>p value</td>
<td>(0.1067)</td>
<td>(0.2763)</td>
<td>(0.6209)</td>
<td>(0.2157)</td>
</tr>
</tbody>
</table>

The rate was 1.8% (65 of) 284 patients and in those undergoing ETV-CPC it was 0.75% (two of) 266 patients. Therefore, mortality rates did not increase with the addition of CPC. There were no cranial neuropathies (except for one patient undergoing CPC who had a transient mild paresis) or other neurological deficits. No patient suffered injury to the ICA, and there were no known endocarditis. The infection rate was less than 1%.

**Discussion**

The history of choroidal plexus and CPC has been reviewed by others. The terms “choroidal plexusomy” and “CP coagulation” have also been used in reference to the application of electrocoagulation to destroy CP set “CPC,” as Boyd and Searles’ described the largest clinical series involving endoscopic CPC in their retrospective study of 106 patients who had been examined over a period of 20 years, with sufficient data for evaluation obtained in 92. The means and median ages at the time of operation were 2 years and 5 months, respectively. Only two of 10 patients with obstructive hydrocephalus were considered to have a successful outcome, whereas 13 (65%) of 20 of those communicating hydrocephalus and 14 (47%) of 30 with obstructive hydrocephalus associated with spine bifida were successful in avoiding the need for a shunt. These patients had undergone CPC in the right and left lateral ventricles (many on separate occasions) via an endoscopic approach by using a rigid endoscope. Other authors have reported the results of CPC for hydrocephalus and chronic infected hydrocephalus in a handful of patients. There have been no prior reports concerning combined (ETV and Bilateral CPC) procedures. In this series, care was taken to ensure the entire CP thoroughly in each lateral ventricle. This can be accomplished with the flexible, resectable endoscope, as described in Critical Material and Methods. In contrast, other authors have described cannulation that is limited to the segment of CP from the foramina of Monro to the temporal horn. The authors have suggested that CP within the temporal horn is endoscopically inaccessible. In the present study, access to the anterior extent of the temporal horn CP was gained in most cases, and the more complete cannulation may have contributed to the success. Furthermore, care was taken to cannulate all vessels within the parenchyma, including the super- ior choroidal vessels. The procedure was not considered complete until all visible parts of the CP and the associated vessels had been thoroughly transected and resected. Although the severity of ventriculomegaly usually encountered in our practice (because of early presentation) clearly facilitated endoscopic access to the CP, the temporal horn could be accessed even in patients with moderate ventriculomegaly.

I have previously described the hazards of long-term shunt dependency in sub-Saharan Africa and the advantages as well as the efficacy of hydrocephalus treatment by ETV. In that study, ETV alone was successful in more than 80% of children at least 1 year of age regardless of the cause of the hydrocephalus. In addition, in children younger than 1 year of age who had PPH Type C an ETV was successful in 70%. For the remainder of children younger than 1 year of age, however, an ETV was successful in only 31 to 48% of the various patient subtypes (PPH Type A, PPH Type A, PPH Type C, and hydrocephalus associated with myelomeningocele). This result was consistent with the less successful outcomes in infants reported by other investigators. However, Cassidy and colleagues’ reported outcomes for ETIVs in children younger than 6 months of age with aqueductal obstruction that were the same as those in children older than 6 months, and Helfer and colleagues’ have recently provided an excellent review of the literature. I postulated that the patients with open aqueducts who were successfully treated by ETV alone may have had an obstruction to CSF outflow (due to the aqeductal stenosis) that was effectively bypassed by the ETV (as previously suggested by Kellar and Glinium). That those who had failures may have experienced them because of inadequate CSF absorption, whether by or not by an uncommonly active obstructive component existed. Similarly, ETVs may have failed in infants with congenital aqueductal obstruction (PPH Type C), because sufficient extracellular CSF pathways and absorptive capacity failed to develop. Conversely, infants with postinfections (as opposed to congenital aqueductal obstruction (PPH Type C) may have done well after the ETV because their capacity for CSF absorption could develop prior to the onset of ventriculitis and its resulting obstructive hydrocephalus.

It is followed that for those in whom ETV failed because of an imbalance between CSF production and absorption, reducing the rate of CSF production might remedy the problem in some cases. Milliken and coworkers’ demonstrated in a thrius monkey model that bilateral lateral ventricular plexusomy reduced the rate of CSF production by approximately 30%. Furthermore, although CPC alone has not gained acceptance as a primary treatment for hydrocephalus, it has proven modestly successful among patients with communicating hydrocephalus. It was the premise of this study that an infant in whom the development of CSF absorption had been inhibited due to congenital obstruction (PPH Type C), even a temporary reduction in CSF production after bypass of that obstruction (the ETV) might allow the procedure to be immediately successful and allow for the further development of CSF absorption. This scenario could be the case even if alternative sources for CSF production or any potential regen-
whatever the explanation, patients younger than 1 year of age benefited from the combined ETV-CPC procedure. This benefit held true in all infants with congenital hydrocephalus (those with NFPH and myelomeningocele) and was statistically significant in those with PHH as well. Most of the patients with myelomeningocele were observed to have an open but narrowed aqueduct on endoscopic inspection; however, the cause of hydrocephalus in patients with myelomeningocele is reported to be multifactorial, stemming from obstruction at some point along the aqueduct, the fourth ventricle outlet, the craniovertebral junction, or the anatral canalization. The latter concept makes the ETV-CPC approach especially logical in these patients. Therefore, for the purposes of this study, the distinction between open and closed aqueduct was not made in the patients with myelomeningocele. For patients younger than 1 year of age with NFPH and PHH, the superiority of ETV-CPC over ETV alone was most evident among those with open aqueducts (Type A). Those patients with myelomeningocele and Type A were precisely those for whom it was noted that the addition of CPC would be beneficial. The NFPH Type C group (infants with congenital aqueductal stenosis) also appeared to have, as hoped, an improved outcome with the combined procedure. Although the superior outcome for ETV-CPC is somewhat surprising for either the NFPH Type C or the PHH Type A group, the small numbers of patients in these subgroups failed to provide sufficient statistical power to exclude this from being the case. As anticipated, there appeared to be no added benefit from undergoing CPC for those with PHH Type C.

It must be pointed out that in our East and Central African patient population, PPH in surviving premature infants is rare, and the data presented here shed little light on the efficacy of CPC in this special group of patients. For patients older than 1 year of age (with the exception of NFPH Type D), the results for ETV-CPC appeared slightly better than for ETV alone, but differences for these small numbers of patients were not statistically significant. It is conceivable that for some an advantage might have been demonstrated with a larger study group.

Having conducted this trial in a randomized fashion would have added weight to the conclusions; however, when initial observations strongly suggested a benefit for ETV-CPC over ETV alone, it was my conviction that beginning a randomized trial would not be appropriate (because of insufficient equipoise), especially in our unique circumstances. Only late in the series was randomization begun among groups in whom the benefit of the combined procedure was not yet clear.

It would be noted in the present case better results with ETV-CPC might be due to a learning curve effect (that is, improved technique with the ETV alone), because CPC was added to ETV in the latter half of the patient series. Although this is a consideration that would have been eliminated by a randomized controlled trial, it is an unlikely explanation of the result. An analysis of the success rate in the initial 50 children treated consecutively (with >1 month follow-up) under ETV alone (28 of 50 compared with that in the final 50 children treated prior to the use of CPC was added to the treatment protocol of 45 of 50 demonstrated no difference (p = 0.8441), despite the experience gained over the intervening period of 1 year during which time ETV was performed in more than 100 additional children. Furthermore, an overall improvement in the ETV technique with time should not account for the remarkably different results between age groups on adding CPC (< 1 year, p < 0.0001; ≥ 1 year, p = 0.0003).

From this cumulative experience, then, with 550 patients having undergone either ETV or ETV-CPC, it is apparent that shunt placement can be successfully avoided in most of the patients, regardless of age or the origin of hydrocephalus. An ETV was successful in 90% of children under 1 year of age. The ETV-CPC combination was successful in 75% of infants younger than 1 year of age with congenital forms of hydrocephalus and in 62% of those with hydrocephalus resulting from infection (Table 3). Perhaps the most surprising and encouraging result was the finding that shunt dependency could be avoided from the very beginning in more than 75% of infants with hydrocephalus and myelomeningocele.

These results suggest that ETV-CPC is an effective primary treatment for hydrocephalus in infants, especially in developing countries. Not only might the long-term risk of shunt dependency be avoided in the majority, but other advantages may accrue as well. At our hospital, both the infection and surgical mortality rates for shunt placement procedures are higher than those reported here for ETV-CPC. In emerging countries in which poverty, poor infrastructure, and political insecurity render shunt dependency more dangerous, the ETV-CPC procedure may prove to be a good alternative. The stark difference between the respective practice environments should raise caution, however, in interpreting the relevance of these data to developing countries. Although a strong argument can be made for avoiding shunt dependency in developing countries, any long-term advantage of the neuroradiologic treatment of hydrocephalus in infants and children compared with shunt insertion has yet to be proven, especially with regard to neurecognitve outcome and the incidence of late failure. The importance of longer follow-up is understood, and this goal will continue to be pursued.

Conclusions

The primary conclusion that can be drawn from this study are as follows: 1) The ETV-CPC procedure is superior to ETV alone in infants younger than 1 year of age, particularly among those with NFPH and myelomeningocele. 2) Hydrocephalus can be treated successfully in the majority of African infants and children without the use of a shunt, but longer follow up with neuroradiologic assessment will be necessary to determine whether this approach is ultimately preferable.
Endoscopic third ventriculostomy alone and combined with CPC

Discussion

The author has no financial interest in the materials or processes used in this study.

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