Searching for Answers

BY JANE HARRIS

AN ENGINEERING FACULTY MEMBER HOPES TO SOLVE A MEDICAL MYSTERY IN THE DEVELOPING WORLD

Pediatric neurosurgeon **Steven Schiff**, the Brush Chair Professor of Engineering and director of the Penn State Center for Neural Engineering, has long focused his research on finding better ways to treat epilepsy, Parkinson's disease, and other nervous system disorders. But a conversation with a fellow neurosurgeon several years ago inspired him to widen his area of interest.

"A dear colleague of mine, Dr. Ben Warf, had decided to live and work in East Africa for six years," Schiff explains. "After about five years, I saw him at a surgical meeting, and over dinner, I listened absolutely entranced as he described what he was doing. As he laid out the problems that he was facing in that highly resource-constrained environment, I thought, 'We can certainly address some of those at Penn State.' Shortly after, I made my first visit to the hospital he helped build and direct in Uganda."

One problem in particular attracted Schiff's attention—the high incidence of post-infectious hydrocephalus among infants in the developing world.

From 1990 to 1998, Schiff was a practicing pediatric neurosurgeon at Children's National Medical Center in Washington, DC. About half the cases he treated there involved hydrocephalus—an abnormal accumulation of fluid in the brain that can cause rapid enlargement of the head in babies and potentially lead to brain damage.

"In the United States and other industrialized countries, hydrocephalus occurs in about one out of every 2,000 live births," he states. Most of these cases, he says, can be attributed to one of two things. Sometimes a baby is born with a congenital anomaly that slows the exit of fluid from the brain. Other cases involve premature infants who develop brain hemorrhages due to immature blood vessels.

Post-infectious hydrocephalus, however, is not widely seen among newborns in the United States and Europe.

"We've always had a bit of trouble—everyone does—with babies that get infections shortly after birth," Schiff notes. "These infections can also lead to hydrocephalus, but we've reduced them significantly with advanced medical systems—mostly by screening mothers for dangerous bacteria that we know have a predilection for getting into babies in the first week of life."

In the developing world, it's very different.

Schiff explains, "It appears that the majority of the hydrocephalus cases in developing countries are the result of infection. This means that a large number of infants around the world have a preventable type of hydrocephalus, but we don't know the agents. We don't know if it's bacterial, viral, or if parasites have a role. We don't know if it changes by geographic region or weather, which means that we don't know how to treat whatever 'it' is to reduce or prevent these infections."

Schiff and his colleagues are hoping to solve this mystery through their work in East Africa. At the CURE Children's Hospital of Uganda in Mbale, they've

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Schiff and his colleagues locate a child who was treated for post-infectious hydrocephalus. The gourd protects the child from sun and rain while his mother works in the field.

The team sampled water supplies in villages where infants with post-infectious hydrocephalus live. Here they examine an unprotected well. Such wells, dug at the lowest point in farm fields, become heavily contaminated with field runoff during rainy periods. Schiff has found evidence of a link between the incidence of neonatal infections and rainfall.

Schiff and Zephania Opio, laboratory director at the CURE Children's Hospital of Uganda, sample cow dung near the hut of an infant with post-infectious hydrocephalus and evidence of a prior bacterial infection. Bacterial DNA found in the dung and on the hut floor was genetically very similar to that recovered from the infant.

collected more than 1,000 well-documented cases of post-infectious hydrocephalus.

"We've extrapolated to try to get a sense of how many cases of hydrocephalus there might be in Sub-Saharan Africa, and with crude estimates, there are probably anywhere from 30,000 to 60,000 cases per year," says Schiff.

In the majority of these cases, the infants had a serious febrile illness in the first month of life, often with epileptic seizures and convulsions. A few weeks later, they were brought to the hospital for treatment with their heads expanding quickly.

Schiff states, "We treat many of these children with surgery, but if what we're doing is saving them for a future which is characterized by often-significant mental retardation, symptoms of cerebral palsy, and probably a substantially shortened life span, then we really need to look for the cause."

The first thing Schiff and his colleagues did was to try to culture the infectious agent from samples of spinal fluid taken from babies at the time of surgery. Could they grow the organisms in the lab? The answer was "no."

Schiff lists possible reasons for this. In some cases, the infection could have run its course before the child was brought in for treatment, or it could have been caused by a virus rather than a bacterium. Additionally, many of the children have been treated with antibiotics before they come for surgical care. "Or it could just be the basic, unpleasant fact that we don't know how to grow most of the bacteria on the planet in the lab," he says.

Next, Schiff's team turned to DNA sequencing. With approval from the ethics review boards in Uganda and at Penn State, they undertook a cross-continent clinical study. At two different times of the year, samples of the brains of hydrocephalic children were taken and tested for a gene that is found only in bacteria. Even though the infections had long since burned out, if they had been caused by bacteria, bacterial fragments would likely be present in the infants' brains.

The team found bacterial fragments in almost every baby's brain. Overwhelmingly, the bacteria they found were coliform—a class of organisms that tend to live in the colons of warm-blooded animals. The bacteria were very dissimilar to the kinds of organisms found in babies in the United States who are infected in the first month of life—but not unlike the types of infections seen in wounded soldiers in military conflicts in places such as Iraq or Vietnam.

Schiff and his colleagues then conducted environmental sampling in the villages where many of the babies lived. "We found some very close genetic matches to certain fragments we had identified," he says. "We also found that at different times of the year, the spectrum of bacteria seems to change, which seems to point to the environment."

There are still a number of unanswered questions, however.

"We don't know if the bacterial fragments were causative of the condition," Schiff states. They also don't know if the AIDS epidemic, now increasing again in Uganda, has anything to do with it or if the introduction of new farm animals in this part of the world is changing the microbial flora that is then transmitted to humans. Also unknown is what piece, if any, is coming from the mother.

For Schiff and his colleagues, the search continues.

Currently, they're collaborating with physicians at a large regional hospital affiliated with the Mbarara University of Science and Technology in Mbarara, Uganda. "They see one case of neonatal sepsis or apparent neonatal sepsis every couple of days," Schiff says. "We've begun a clinical trial there to sample the blood and spinal fluid from those babies. They have very good microbiologists that we've supplied with extra equipment to help culture organisms."

In addition, they're bringing DNA and RNA samples back to Penn State for both bacterial and viral sequencing, and with permission, they're testing the mothers for HIV and taking specimens from their birth canals.

"We're in the process of collecting a cohort of about 75 newborn babies," Schiff says. "If we can grow that to several hundred, we're going to see which fraction of these babies go on to get hydrocephalus. That's the key. And that will tell us if it's just the manifestation of run-of-the-mill bacterial infections in these babies or a special subset of bacteria or viruses that we need to treat differently when we pick it up." ■

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