

SCIENCE SHINES A LIGHT ON THE INJURED BRAIN OF A CHILD | BY CHUCK STARESINIC

INSIDE THE BLACKOUT

About 10 years ago, a 14-year-old boy—we'll call him Cedric—was hit while riding his bicycle through a Pittsburgh-area neighborhood. Even after all this time, it's not known how the accident happened. If there was a witness, that person never came forward. The driver of the vehicle that collided with Cedric apparently fled the scene and has never been identified.

"The bike was all bent up, and he was thrown 30 feet," says neurosurgeon David Adelson, director of pediatric neurotrauma at Children's Hospital of Pittsburgh of UPMC. "It was a horrible injury. We had him in a coma for three or four weeks, and we were doing everything.

"But he was hemorrhaging, and the family was distraught. They were even talking about withdrawing care."

© DAVID WOODS/CORBIS

The devastating thing about brain trauma, says Adelson, is that a child can be perfectly healthy one moment and fighting to stay alive the next. And it happens all the time—on average, a child sustains a traumatic brain injury (TBI) serious enough to cause permanent disability every 11 minutes in this country. Trauma kills more children in the United States than all other causes of death combined. The biggest culprit is TBI, which kills about 7,000 children each year.

Disability from head trauma ranges from memory and cognitive deficits to vegetative states. Despite the enormous toll, there has been almost no pediatric clinical research in TBI. Children are treated as "little adults," though their brains are different. And unlike other diseases, there are few foundations advocating for a breakthrough or funding research.

In part, it's a failure of imagination. It's easy to picture a breakthrough cancer drug or an AIDS vaccine. But isn't head trauma primarily a prevention problem, to be solved by a better helmet or a reduction in traffic accidents?

Prevention may be of paramount importance, but physician-scientists at the University of Pittsburgh believe science can do a great deal to change the outcome for the child with TBI. And they are uniquely located to shepherd discoveries from the lab to the intensive care unit.

The National Institutes of Health made an effort in the 1990s to create several centers of excellence in TBI research. Not all of them have thrived and diversified as Pitt's has, says David Hovda, neurosurgery professor at the University of California, Los Angeles and director of UCLA's Brain Injury Research Center.

"What really puts Pittsburgh on the map, with the Medical College of Virginia and probably UCLA, is there are now very few that have both funded clinical and basic science research programs. And there are only two of the original NIH centers that I'm aware of—Pittsburgh and UCLA—that have funding in pediatric traumatic brain injury."

Robert Clark (Fel '95), Pitt associate professor of critical care medicine and pediatrics and a critical care physician in Children's ICU, says that two or three decades ago, children with lung or heart disease, shock, or overwhelming infections frequently died in the ICU. Back then, he says, "people would have thought that if, by 2006, we could get our ICU mortality around 3 percent, that we were dreaming. But nowadays, it's a reality."

Adelson and Clark are trying to bring TBI mortality in line with these other diseases. Their work in this regard can be traced to the epicenter of TBI work at Pitt—the Safar Center for Resuscitation Research.

The Safar Center is a plain block of laboratory space on Pitt's medical campus. Its vigor lies in the network of physician-scientists who commit a large portion of their professional lives to working in these labs but who also cross the street and care for patients in emergency rooms, trauma bays, and ICUs. For these docs, the name of the game is neuroprotection. And there are two questions to be answered: What are the processes that lead to brain damage in the trauma victim? And how do we mitigate that damage?

Adelson's office at Children's is a small, windowless room lined with floor-to-ceiling bookshelves. On a high shelf behind where he sits is a large teddy bear wearing surgeon's scrubs—the lone indication that this is the office of a pediatric neurosurgeon.

Adelson describes the treatment Cedric received in the ICU a decade ago: "We had pressure monitors in [the skull]. We were draining off cerebrospinal fluid and giving different medications to reduce swelling."

The boy was comatose and on life support for weeks when the parents began to wonder about turning off the respirator. Adelson, now also a Pitt endowed professor of neurological surgery and director of the Walter L. Copeland Laboratory for Neurological Research, remembers how he and other physicians in Children's pediatric ICU told the parents that it wasn't yet time to make that decision. *He is not in any pain,* they said. *We have him medicated so that he remains in a deep coma.* (His injuries were serious enough to put him in a coma. Doctors believed that keeping him there would give him more time to heal.) *Let us try to stabilize him and see if that will control the damage that is occurring in his brain. Then maybe we can begin to wake him up and see where we are.*

This is the blackout period. In serious brain trauma, it can last a few days, or it can stretch much longer. There is no communication with the patient and little objective information that doctors can use to determine the severity of the injury or what the ultimate outcome might be.

The blackout period is one way in which brain injury differs from so many other traumas and diseases being treated in the pediatric ICU.

The blood brims with chemical information—proteins, enzymes, acids, hormones, immune cells—all of which can provide specific details about what is going on inside the body of a patient, even one who is comatose. By analyzing the blood, doctors can tell not only whether the liver, lungs, immune system, heart, or kidneys are malfunctioning, but also the physiological and molecular details of how they might be failing. Depending on the results, there are multiple medications, interventions, and therapies available. Doctors can monitor changes by the hour, or even by the minute, and change treatments accordingly.

Not so with the brain.

After the initial rush to stabilize Cedric and deliver him to the ICU, parents and doctors were met with weeks of radio silence. The doctors tried to control the bleeding and inflammation in his skull to reduce the secondary effects of the brain injury. The initial trauma doesn't cause the greatest damage. The primary insult—say, a bruise in the brain—sets up a biochemical cascade of events contributing to further inflammation and cell death.

Inflammation is the body's reaction to injury. In your joints and limbs, it's usually not a big deal. It even aids the healing process in ways. Inflammation has some healing benefits in the brain, too, but uncontrolled swelling inside the cranium can wreak havoc, causing irreversible damage and even death.

"The skull is a closed box," says Adelson. "Unlike the ankle, where you get a big puffy purple ankle, the brain is a closed system, so if it swells, then blood flow going in is decreased." The brain becomes starved for oxygen, leading to additional injury and cell death.

The tools available to treat TBI are still limited. As they did with Cedric, doctors try to reduce intracranial pressure with medication and by draining cerebrospinal fluid. If this doesn't work, neurosurgeons may perform a decompressive craniectomy, removing a plate of bone from the skull to allow the brain room to swell. When the swelling decreases, the bone is replaced, perhaps several weeks later.

As part of a new clinical trial, children with traumatic brain injuries who arrive at Children's Hospital of Pittsburgh and 11 other hospitals in the country will now have access to an experimental therapy that induces hypothermia. Adelson is the principal investigator on this $14 million, multicenter trial funded by an NIH grant.

A child with TBI who is enrolled in the study is randomly assigned to receive either hypothermia or standard care. In those tagged for

hypothermia, doctors push cold fluids through their veins. They wrap them in cooling blankets to further lower core temperature and keep it low for two or three days.

This is the blackout period on ice.

"The goal is to cool down early and rapidly, within six hours of the injury," says Adelson. "From there, we lower the body temperature down to 32 to 33 degrees centigrade, which is about 89 to 90 [degrees Fahrenheit]. That is a temperature that is cold enough that there is probably a good effect but it doesn't have the complications. Once you get down to 29 to 30 centigrade, then you start having problems—arrhythmias, heart problems, coagulopathy, which leads to increased risk of hemorrhaging and infection. The body tends to shut down."

The treatment is experimental, but Adelson has already led a Phase II study with 75 children that demonstrated it was safe. The Phase III study aims to extend those results with the treatment of an additional 400 patients. By cooling, he and his colleagues believe they will reduce inflammation and thereby reduce the chemical cascade that leads to further cell death and damage.

"The preliminary data [from the Phase II study] showed that we did decrease mortality. In the group that was cooled, mortality was 5 percent, versus 17 percent for those that were not," says Adelson.

If that trend holds up, hypothermia would be a breakthrough.

"This is probably one of our best chances at having something work," says UCLA's Hovda. He cites a long history of evidence leading to this promising trial, beginning with old news reports of children falling through winter ice into lakes and remaining under water for long periods of time—yet recovering completely.

Patrick Kochanek, Pitt professor of critical care medicine and director of the Safar Center,

ABUSE: THE HIDDEN EPIDEMIC

SCIENCE OPENS THE DOOR TO A DARK ROOM

When they come into the ER, shaken babies may show symptoms such as vomiting, irritability, or listlessness, but little else. That can make accurate diagnosis difficult.

If a parent shook the baby, he or she isn't going to admit it. If the babysitter did, the parent probably wouldn't know about it.

Rachel Berger remembers attending a series of morbidity and mortality conferences as a pediatrics resident. Hospital staff had sent home three infants with vague symptoms. Each returned within weeks, in critical condition. Two died; one lapsed into a persistent vegetative state.

They were shaken babies—victims of abuse. Yet despite multiple exams by pediatricians with decades of experience, none was accurately diagnosed in time to avert subsequent injury or death.

"Inflicted brain injury is one of those diseases that nobody thinks about but is actually fairly common," says Berger (Res '99, Fel '01). "The incidence of muscular dystrophy is about one in 4,000; they have a national telethon. It's about one in 3,000 for babies under 12 months with inflicted brain injury—fatal or severe. That doesn't even include any mild or moderate [cases].

"There's very little public attention to what is now rapidly becoming one of the leading killers of babies," she notes, as deaths from sudden infant death syndrome decline.

As a pediatric fellow, Berger, now a Pitt assistant professor of pediatrics, started moonlighting in the ICU at Children's Hospital of Pittsburgh. There, she met Patrick Kochanek, director of the Safar Center, professor of critical care medicine, and attending physician.

Kochanek had learned a thing or two about child abuse in two decades of brain trauma research. In the mid-'90s, a colleague began measuring the levels of excitatory amino acids in samples of cerebrospinal fluid from children. The levels were high in infants with brain injuries, says Kochanek. In shaken babies, they were off the charts.

And unlike the babies with accidental injuries, whose levels started high and tapered off, the shaken babies had levels that rose for days.

Another study from the Safar Center looked for molecules in cerebrospinal fluid known to spike in adults within three or four days of a brain injury. Shaken babies had chronically high levels of the molecules.

Yet when Berger suggested to Kochanek that they look for markers of brain injury in the blood of abused infants, his response was tepid.

"Well, the blood is kind of far from the action," he told her. "The blood-brain barrier keeps things out. You'd have to be lucky. These markers would be in incredibly small amounts."

To persuade him, Berger delivered a large box of European studies that used blood biomarkers of brain injury in adults. Unlike cerebrospinal fluid, blood is routinely drawn, so a reliable test for signs of head injury in the blood could help diagnose a lot of children.

Kochanek conceded it was worth a try.

The result was a paper identifying three biomarkers for head injury in children—proteins released when different components of the central nervous system (neurons, myelin, and glial cells) die or break down. They apparently squeak across the blood-brain barrier in nanograms per milliliter, just enough to detect.

Next, they looked for the biomarkers in infants with symptoms such as unexplained vomiting. For reasons such as cost and sheer numbers, it's just not practical to do head scans on all such babies.

Fourteen out of approximately 100 of the babies were diagnosed with a head injury. (Berger's test was used for research only, not diagnosis. The blood was banked and studied long after the infants left the hospital.) Eleven of the 14 had elevated levels of the biomarkers. If the blood test had been part of the clinical care protocol, says Berger, it would have prompted head scans in those patients.

Another five were not initially diagnosed with a head injury, but were back in the emergency department as victims of abuse within six months. Berger revisited their blood work and found that four had had elevated levels of the biomarkers when they first came in—a clue, perhaps, to brain injury at the time the blood had been drawn.

The criteria seem to work, says Berger. About 6 percent of children in that initial study came back to the hospital identified as abused children: "That's an incredibly high percentage," she says. "We picked the right population to screen."

The next study is already under way, with funding from the Pediatric Clinical and Translational Research Center at Pitt. Berger and colleagues will enroll close to 1,000 babies in Salt Lake City and Pittsburgh who show symptoms that could suggest brain injury, such as vomiting and fever. Each will have a head scan and blood work to measure biomarkers. The study will follow them until they turn 1.

For parents, the specter of a false accusation of abuse is a frightening prospect. But Berger and others in the field say these tests will never reach the level of a definitive diagnosis.

"What she's advocating, which is a wonderful idea, is a way to see which children need to be further screened for head trauma," says Carole Jenny, a professor of pediatrics at Brown University.

You can't put every child with low-grade fever and vomiting into the scanner, says Berger, so better tools for screening are a must. *—CS*

says the first experimental example of hypothermia's benefit in head trauma came from a Safar Center lab pediatric experiment more than 12 years ago. In that study, short bursts of hypothermia led to improved outcomes in young animals with head injury. Years later, Pitt researchers conducted an adult hypothermia trial. That indirectly led to Adelson's clinical trial.

The adult trial was stopped early. It was clear the benefit was not going to reach statistical significance, says Adelson.

"But when they went back to look at the data, what they found was that older patients, those over 40 years of age, didn't do well. In fact, they did worse with the hypothermia. Those under 40 did better. Now that was only a trend, but that gave us an indication that perhaps children would do even better," he says.

Every day that Robert Clark is on the job as an attending physician in Children's ICU, there is at least one child with a traumatic brain injury. It could be a child who was in a car accident that morning. It could be a child who has been in a coma for several days. But always there is someone. Clark is painfully aware of the dearth of clinical trials in pediatric TBI.

"I've been doing this since 1995. There is less variation in treatment now," he says, from hospital to hospital and doctor to doctor. "It's more protocolized. But there have been no breakthroughs."

Clark is quiet and unassuming, with pictures of his two daughters lining the tops of the bookcases in his office at the Safar Center. But he is intense about his work.

"Bob Clark published 11 papers as a fellow, if you can imagine," says Kochanek. "He had multiple R01 [NIH research project] grants—a huge success story."

After his critical care medicine fellowship at Pitt, Clark studied mechanisms of cell death in neurons in the lab. But his cell cultures were a world away from the brain-injured patients across Fifth Avenue in the ICU. To reduce intracranial pressure, ICU staff drained and discarded their patients' cerebrospinal fluid. Clark started to bank this fluid and study it in his lab. It gave him a chance to show that the mechanisms and pathways of cell death and injury he'd observed in the lab were present in humans, too.

"What he did," says Kochanek, "was to link the molecular lab work directly to traumatic brain injury. Everybody quoted it."

Researchers have long noted that boys tend to have worse outcomes in terms of intellectual performance after head injury. Boys and girls also express cytochrome C—a protein prominent in the apoptotic cell-death pathway whose effect is targeted by hypothermia and some drug therapies—differently after brain injury. Right now, in the ICU, boys and girls with TBI get the same treatment. Clark thinks that should change.

He believes that different patients need different treatments. His vision is to tailor drug therapy to individual patients based on gender, age, genetics, and where in the brain the injury occurred—something that doesn't happen much in the ICU today.

TBI can eventually kill brain cells in many different ways, notes Clark. TBI's partners in crime are different proteases, lipases, and other destructive enzymes, some of which appear to be more prominent depending on the gender of the patient. Some are more prominent in an abused infant than a 16-year-old who has been in a car accident. An injury to the hippocampus is different from an injury to the cerebral cortex. Timing makes a difference, too. Mechanisms of injury immediately after the initial insult are different from those seen 12 hours later.

Clark's lab investigates a gene for P-glycoprotein, a receptor on the blood-brain barrier that helps pump molecules out of the brain. He has found that if you have a specific, subtle genetic variant, the efficiency of that pump will vary. Most of the time, "that's not a big a deal," he says. "But when you are under duress—you've got an injury, and you are getting a bunch of medications that you've never seen before—the efficiency of that pump becomes much, much more relevant to how you respond to those medications."

There are many such receptors in the blood-brain barrier. They pump out analgesics, narcotics, and antiseizure medicines, as well as cytokines and toxic byproducts of cell injury. The efficiency of these various pumps helps determine not only the level of medication in the brain but which types of cell damage are most dangerous for a specific patient.

"I'm envisioning in the future being able to get a profile of everyone—age, gender, genotype, and very sophisticated neural imaging that shows where the potential areas of damage are," says Clark. With a complex understanding of each patient, the types of damage occurring, and the process of recovery, doctors could use direct, targeted therapies to treat patients.

"Maybe 10 years from now," he says hopefully.

That's why Adelson's hypothermia trial is so important, Clark says.

"I think we've got to do it now," Clark says.

"Hopefully, 10 years from now, we won't need it. But right now we've got nothing else. And there's nothing else that I'm aware of in the pipeline that's ready to go tomorrow."

Both of these doctors can tell stories of patients and families who never recover what they've lost to a traumatic brain injury. But both are regularly inspired by what Adelson calls the "immeasurable reward" of seeing a child bounce back from what appeared to be a devastating injury. These are the people they think of when they describe the importance of increasing positive outcomes, even by a few percentage points at a time.

He cites a long history of evidence, beginning with old news reports of children falling through winter ice into lakes and remaining under water for long periods of time—yet recovering completely.

Recalling Cedric, Adelson says, "That kid pulled through. He was in rehabilitation for six months. But that kid has graduated college now. When you talk to him, he doesn't have any deficits that you can tell. He has a little bit of memory and cognition issues. He has to work a little bit harder, but he graduated from Penn State."

Clark describes a similar experience with a wry twist. He had a patient who was in an accident on an all-terrain vehicle while not wearing a helmet.

"He had a bad head injury," says Clark. The boy couldn't talk and couldn't walk. The father was by his side every day in the ICU. He told his son that as soon as he could walk, he would buy him a motorcycle.

"The dad came back a year later with a picture of the kid next to his motorcycle," says Clark. "I do think he had a helmet in hand."

Clark acknowledges that the boy is not a poster child for prevention. "But God bless him. He left the ICU, and we had doubts that he would be neurologically intact enough to ride a motorcycle." ■