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Researchers at Pitt are shedding light on the shadowy field of traumatic brain injury. Their work is helping athletes, soldiers, accident victims, and others.

THE REPERCUSSIONS OF TRAUMATIC BRAIN INJURY ARE BECOMING CLEARER

BY CHUCK STARESINIC

WHAT HIT HER

Katy Korber knew exactly what hit her. It was a volleyball—a blistering spike from the outside hitter on the opposite side of the net. Katy, 15 years old and starting her first season on varsity, had gone straight to the net for the block, timing her jump with arms extended, palms flat and braced for impact. When the ball blazed past her hands she had only a fraction of a second to react. She turned her head and took it in the right temple, hard.

In another, very real sense, Katy didn't know what hit her, and neither did her parents. She crumpled to the hardwood. The game stopped. Everything stopped. Eventually, she wobbled off the court with teammates and coaches supporting her. Her mother came down from the bleachers to help her home. By the next morning, it was clear that this wasn't just a pain that would go away with aspirin. The headache was intense. She was fatigued. She couldn't think clearly and was unsteady on her feet. Her mother called the doctor.

Traumatic brain injury (TBI) is a broad category describing any blow or jolt to the head that disrupts normal mental function—everything from the sports concussion that leaves a player seeing stars and momentarily dizzy to the high-speed collision on the highway that renders a victim profoundly and permanently disabled.

The Centers for Disease Control and Prevention estimates that 1.7 million people per year in this country suffer a traumatic brain injury. Katy's injury was the most common type—a concussion, which is also described by the rather oxymoronic term "mild traumatic brain injury."

"We're in the golden age of traumatic brain injury [research and awareness]," says Patrick Kochanek, a critical care medicine physician and researcher at the University of Pittsburgh. This statement summarizes a reality full of contradictions. Scientists know more than ever about injuries to the brain, and they are finding ways to help patients regain lost function. At the same time, they are learning that there are significant risks even with mild TBI—especially if a patient resumes activity too soon and suffers what is known as "second concussion syndrome." In people who suffer severe TBI, there is increased risk of later developing neurodegenerative diseases like Alzheimer's. At Pitt and other institutions, researchers are gleaning eye-opening details about exactly what is going on in the injured brain and what dangers might lie ahead. And they are showing us how doctors might one day treat patients so that they can avoid many of the often menacing short- and long-term consequences of these injuries.

Confoundingly, the more that airbags, seatbelts, helmets, and body armor are successfully deployed (and the longer the country remains at war), the more survivors there are struggling with moderate to severe TBI. The math is simple: As the death rate goes down, the number of patients goes up.

Thirty percent of severe TBI patients had Alzheimer's-like plaques, even the young people.

Your brain is suspended inside your skull like an oversized yolk crowding the confines of an egg. This yolk is exceedingly fragile, of course, but it does come with significant protective systems. The most obvious is your shell: the aforementioned skull, which is a quarter-inch thick. Less obvious is the dura mater, a leather like covering surrounding the brain and spinal cord (there are two other thinner coverings as well). Filling the space between the dura mater and the brain is the clear cerebrospinal fluid, which slows and cushions the motion of the brain in the skull as you move about.

Your brain does not sit inside your skull—its weight would impede blood flow just as sitting in a chair for too long does to other parts of your anatomy. Neither does the brain float like a duck, which would create the same problem up top as it pressed against the roof of the skull. The brain has neutral buoyancy, like a densely compact jellyfish suspended in the sea. The result of neutral buoyancy is that the human brain, which might weigh 1,400 grams when the coroner sets it on the scale, effectively has a weight of 25 grams or so when it is properly suspended in its bath of cerebrospinal fluid.

All of this is well and good, right up until the moment you slip on the ice and your head whips backward to meet this unforgiving surface. Same goes for the sudden blast of a volleyball to the side of the head or the unsettling deceleration from 65 mph to 0 mph in a split second, even when the impact is cushioned by an airbag. For soldiers clad in body armor and bullet-proof helmets, the blast wave produced by the detonation of an improvised explosive device turns out to have its own unexpectedly sinister fluid dynamics. The blast is a wave of energy that rolls across the skull, compressing the bone as it travels across the surface—even beneath a helmet. It squeezes the skull with forces completely out of proportion to what one would expect based on the actual movement of the head because of the blast.

Today there is increasing public awareness of and research funding for these injuries, especially in sports medicine and in the care of soldiers returning from Iraq and Afghanistan. And Pitt has emerged as a TBI center with few peers. The reasons for this are multiple and multidisciplinary. Pitt has exploited several points along the broad spectrum of TBI to intervene and investigate—from concussion to blast injury—and individual multidisciplinary teams have grown at each of these points.

"There's been a generation of [TBI] trainees who came in as young faculty and now have their own funding," says C. Edward Dixon, who joined Pitt's Brain Trauma Research Center in 1995 and is now its director.

The result of this decades-long organic process is that the individual domains of multiple investigators, clinicians, and research programs at Pitt now overlap and inform one another, creating a rich research environment. Pitt is home to some of the world's very best people in the arenas of sports concussion, severe TBI, rehabilitation medicine, blast injury, and neurodegeneration. There isn't a single city in the country that has more TBI researchers than there are in this one institution, notes Dixon. That said, these docs have their work cut out for them.

One of the long-standing problems with studying TBI is the difficulty of defining and describing the injury so that you can reach scientific conclusions.

"When we talk about severe brain injury, we are usually talking about injury severity as measured by the Glasgow Coma Scale (GCS)," says Joseph Ricker, a clinical neuropsychologist and associate professor of physical medicine and rehabilitation in the School of Medicine. "A score of 3 to 8 is severe. Moderate is 9 to 12, and mild is 13 to 15. … But even with severe TBI, there is a huge range of presentation and outcome. Initial severity doesn't predict outcome perfectly. I've had patients with severe TBI at initial presentation with surprisingly good results. And I've had patients with injuries classified as mild that had outcomes that were much poorer than you'd expect."

Kochanek, an MD professor of critical care medicine, director of Pitt's Safar Center for Resuscitation Research, and noted researcher in severe TBI and blast injury, points out that the *Journal of Neurotrauma* once published a cover showing six CT scans of humans with brain injuries and a GCS of 4. Each looked completely different, illustrating that TBI may need to be considered as a complex of multiple diseases in the same way that cancer is now understood as multiple diseases. In TBI, one patient may have a contusion, another diffuse injury, another diffuse swelling. Then there are those who are bleeding into various spaces between the three membranes surrounding the brain: One has a subarachnoid hemorrhage, another has a subdural hemorrhage, and another has an epidural hemorrhage. Each flavor of TBI means different symptoms, prognosis, and treatment. To complicate matters further, TBI often occurs in tandem with shock and trauma to the limbs and trunk. Were a particular course of treatment given to all six of the TBI patients featured in the journal, it may help some, harm some, and have no effect on others. How is a researcher to study TBI in animals, or even describe symptoms of TBI, in such a "messy" disease?

"Scientists like total control," says Kochanek, "so, for many years, [articles on] traumatic brain injury couldn't get into higher-tiered journals."

One person who played a major role in opening avenues for laboratory-based TBI research is Dixon, a Pitt professor of neurological surgery, vice chair for research in that department, and codirector of the Safar Center for Resuscitation Research. After earning a PhD in psychology at the Medical College of Virginia in 1986, Dixon began a postdoctoral fellowship at General Motors research laboratories in Warren, Mich.

"They had a crash-injury biomechanics group studying the relationship between TBI and mechanical forces relevant to automobile crashes," says Dixon. "The ultimate goal was to develop computer models of brain injury, and they were doing large-animal research to validate their computer models."

At Pitt, Dixon joined a blossoming TBI program. Founded in 1991 as a sort of minicenter with a modest grant from the National Institutes of Health, the Brain Trauma Research Center was designated a full-fledged NIH center of excellence for TBI less than five years later. Through a combination of laboratory research and clinical trials, it has advanced the science and treatment of TBI in several ways. Pittsburgh was one of the first clinical sites to show clear benefits of using therapeutic hypothermia, which is now the standard of care for control of intracranial pressure. (TBI often leads to brain swelling and a deadly rise in pressure inside the skull.) Dixon and colleagues have published a large portion of the studies looking at neurostimulants such as methylphenidate (Ritalin) and amantadine, which are commonly used in TBI and show some promise (though a large clinical trial hasn't been conducted).



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Confoundingly, the more helmets and other prudent safety measures are used, the more cases of moderate to severe TBI occur. As death rates go down, the number of injured goes up.

Dixon was interested in more than biomechanics. He wanted to understand the behavioral consequences of TBI, so he developed one of the first rodent models which is now the most widely used model of head injury in laboratories worldwide.

"Ed's contributions were enormous in that regard," says Kochanek. "It's simple. It can be done in any credible lab, and it's not terribly expensive." The animals remain stable afterward and can then be studied for important metrics like memory and learning. When Dixon joined the Pitt faculty in the '90s, he brought that expertise in developing laboratory-based functional-outcomes assessments with him.

With better understanding of the mechanisms of TBI and recovery, researchers are increasingly turning to a big frontier in TBI research—the question of long-term consequences.

Two-and-a-half months after she suffered a concussion during a high school volleyball match, Katy Korber was back at the UPMC Sports Medicine Institute. She sat beside her father at a small conference table. On the wall behind her was an autographed poster of Merril Hoge—a former Pittsburgh Steelers running back who retired from football after a series of concussions and persistent postconcussion symptoms. The sign outside the closed door read, "Sports Concussion Room." Katy and her father had become familiar with this room. Between her regular appointments here, she'd missed weeks of school and pared down her activities in an attempt to rest and recover from nagging postconcussion symptoms like headaches and difficulty concentrating. Katy and her dad were hoping for good news.

When she arrived that morning, Katy sat down at a computer screen in another room and took an online test called ImPACT—Immediate Post-Concussion Assessment and Cognitive Testing. It's the same baseline test required for athletes in the National Hockey League, the National Football League, and college football. It's one of several tools used to evaluate a player's injury and recovery before he is cleared to return to play.

A series of words was displayed on the screen, and Katy was instructed to remember them. Using a standard keyboard, she completed interactive tasks measuring reaction time and comprehension. Then she was asked to recall the words shown to her earlier. ImPACT includes a series of activities like this. It takes about 30 minutes, and it immediately provides scores in memory, visual motor speed, reaction time, and impulse control. Katy had taken the test every few weeks since her injury so her scores could be compared over time. If her cognitive function was improving, it would show. Even better, Katy took the test at the start of the season (hers is one of many school districts that tests all athletes), so every subsequent test could be compared to her performance before the concussion.

Outside the concussion room, Pitt's Mickey Collins, a PhD neuropsychologist and associate professor of orthopaedics and neurological surgery, stands with one hand in his white coat pocket and reads from Katy's chart: "Took a spike to the right temple in September. Persistent headache, nausea, fogginess, fatigue, concentration difficulty, sensitivity to light and noise, blurry vision left eye, pain. X-ray of neck, CT of head—all normal. Next day, she had migraine and proceeded to sleep most of the next several days."

He points to Katy's scores in verbal and visual memory, motor speed, impulse control, and reaction time. Here she is at baseline, he says, then postinjury, three weeks postinjury, and six-weeks postinjury. "She's normal, then grossly impaired, grossly impaired, grossly impaired." Measured as a percentile relative to others free of injury, Katy's baseline scores were average to above average. After the concussion, she was lower than the first percentile. "She was grossly impaired. But look here," says Collins, pointing to today's results. "She's getting back to normal. Still a little low in visual motor speed and reaction time, but not bad."

Collins was a collegiate athlete, and he still looks the part. He played baseball for the University of Southern Maine in the 1989 NCAA Division III World Series. Like a lot of clinicians in sports medicine, he's a big fan and a fervent believer in the benefits of competitive sports. Few things make him happier than telling a young person that she can go back to the field. "She's probably going to be a happy girl," he says before going in to talk with Katy and her father. "She's doing much better."

"When I started doing this in the mid to late '90s, 'How many fingers am I holding up?' and smelling salts predicated return to play," says Collins. He was beginning his neuropsychological graduate work at Michigan State when he realized that he missed athletics. He made his first trip to Pittsburgh in 1995, when the city hosted the first major sports concussion conference, and met brain trauma researcher Mark Lovell and Joseph Maroon, a neurosurgeon and Pittsburgh Steelers team physician who was goaded into a neurocognitive epiphany by the team's head coach, Chuck Noll. Maroon describes Noll as "a well-read Renaissance man" and "a Socratic gadfly."

Part of Maroon's job was to make sure that players were medically cleared to play after injury. One day, he asserted to Noll that the quarterback, who had suffered a concussion a week earlier, wouldn't be ready for Sunday's game.

Noll wanted to know why.

He has a concussion, said Maroon. *The guidelines say he should sit another week.*

Who wrote the guidelines?

Well, I was on the committee that wrote the guidelines, said Maroon.

Noll pressed on: *And what data did you use to draw up the guidelines? What objective data do you have that says he should rest two weeks instead of one?*

Maroon grudgingly admitted he did not have data. But it was his feeling that the quarterback needed another week.

The thing that got under Maroon's skin was that Noll was correct. There was no reliable way to test injury severity or recovery. This story marks a critical point in the prehistory of the ImPACT test. Maroon, a Pitt professor of neurosurgery (who's competed in six Iron Man triathlons), huddled over the problem with Lovell, a PhD. Their starting point was the only sort of test available at the time—a doctor sitting across the table from a patient with paper, pencil, and a series of exercises to test memory and cognition. Important metrics like reaction time couldn't be measured very closely and couldn't be compared from one test to another.

They concluded that they needed to develop a repeatable, computer-based test that would work for NFL players and young athletes alike.

When Lovell relocated to Henry Ford Hospital in Detroit, he continued to collaborate with Maroon on neurocognitive testing for athletes. After meeting these two in Pittsburgh, Collins returned to graduate school and applied early versions of the test to the Michigan State football team. After completing his PhD, he started a postdoctoral fellowship in Lovell's lab.

Maroon pitched the early version of ImPACT to Noll and the Steelers organization, which became the first NFL team to adopt baseline neurocognitive testing of players. Today, ImPACT is required by the NFL for all players. It's used in collegiate athletics, recreational sports leagues, and school districts throughout the country.

In 2000, both Collins and his mentor Lovell relocated to Pittsburgh for the establishment of the sports medicine concussion program at UPMC, with Lovell as its founding director. In the ensuing 10 years, with Maroon and other colleagues, they have solidified Pittsburgh's place as the premier center for sports concussion. The center trains hundreds of physicians a year in treating concussion.

"We recently tested 30,000 special ops forces who are being shipped out to Iraq and Afghanistan," says Maroon. "We're also developing ImPACT for use in doctors' offices with patients [without brain injury] who might develop mild cognitive impairment, which is a very common thing in people after age 50. … We're working on a test that can be done in 15 to 20 minutes."

"Concussion, in my opinion, is the next Agent Orange for the army," says Maroon. "I say that in the sense that it was the long-term effect—one year, two years, five years afterward—that members of the military in Vietnam developed a syndrome. If these guys suffering concussions in Iraq and Afghanistan start developing dementia, it could come back on the army as a postconcussive injury."

A man or woman who has survived a TBI may look okay outwardly. Yet returning soldiers and other TBI victims may be dealing with cognitive and emotional issues—including poor memory, decreased concentration, impaired executive functioning, irritability, anger, and depressed mood, "making it difficult for many individuals to live alone or even with others," notes Pitt's Rory Cooper, professor in the School of Health and Rehabilitation Sciences, in a recent paper.

Maroon brings up a question that is still unresolved. A small number of NFL players with a history of concussions or even subconcussive blows to the head have been found to suffer from what looks like chronic traumatic encephalopathy (commonly found in boxers). But the number has been too small to make a definitive connection.

Concussion experts like Collins say there probably are long-term risks that go along with concussion, but large epidemiological studies have to be done before we can understand the nature of the risk, who is at risk, and how to minimize it.

Unlike the potential link between concussion and later neurodegeneration, an epidemiological link between severe TBI and Alzheimer's has long been known—if you suffer a severe traumatic brain injury, you have a greater risk for developing Alzheimer's down the line, even before old age. But the mechanisms behind this risk are not fully understood. But several years ago, Pitt researchers realized a last-resort surgical technique provided a rare opportunity to study brain tissue after TBI.

Because the skull is a tightly closed system, brain swelling after TBI has the potential to cause death or devastating damage to the brain. In some cases, surgeons will remove a section of the skull to give the injured brain room to swell. In other cases, small sections of brain tissue are removed for the same purpose. These bits of tissue present a rare opportunity to examine brain tissue from someone who'd survived severe TBI just hours or days prior.

Milos Ikonomovic, an MD associate pro-

fessor of neurology, explains what he and colleagues in Pitt's Brain Trauma Research Center found: About 30 percent of the severe TBI patients had Alzheimer's-like plaques. This was the case even in young people, which is very unusual. The plaques that neuropathologists evaluate to establish a diagnosis of Alzheimer's disease are called neuritic plaques, says Ikonomovic. "The plaques that we saw in brain trauma patients were of a diffuse type, an early form of amyloid deposits, as opposed to these mature plaques seen in Alzheimer's disease. This supports the idea that the pathology that we detected after severe trauma was a very early form and most likely developed subsequent to brain injury within hours to days of the insult."

Subsequent studies by Ikonomovic and colleagues are beginning to reveal the mechanisms responsible for the development of the amyloid plaques that are linked to Alzheimer's. "We have shown that trauma not only induces upregulation of the amyloid precursor protein but also increases the accumulation of amyloid beta and amyloid beta peptides, which are thought to be neurotoxic."

In mouse models of TBI, Ikonomovic and colleagues are looking into potential therapies that will block neuronal cell death linked to trauma-induced increases of amyloid beta peptide. They have achieved success with caspase inhibitors, which block a protease involved in cell death, and with statins, which reduce amyloid beta concentration and improve neuronal survival and functional recovery.

Basic science research from many areas provides a springboard for clinical advances. Faculty members in Pitt's Department of Physical Medicine and Rehabilitation research and implement new and refined treatments for TBI. They include MDs exploring the effects of neurostimulants on patients in sports medicine and clinical neuropsychologists like Ricker, who takes traditional psychosocial and cognitive approaches to treating brain trauma. Ricker and collaborators are taking advantage of the University's leading-edge imaging capabilities to conduct extensive imaging of brain-injured patients. "What we hope," says Ricker, "is to use this diagnostically in the clinic someday, to do a scan to determine which areas of the brain were injured and how much."

Kochanek is a believer in the future of TBI treatment. From the NIH alone, support for TBI research at Pitt is very strong—Dixon is the principal investigator on a large TBI program project grant that is now in its 18th year, and the Brain Trauma Research Center has been continuously funded since 1991. But NIH money is matched or exceeded by funding from the Department of Defense. The military, says Kochanek, wants answers and wants them now. DOD-funded projects include blast injury research designed to identify new drug therapies. Pitt research projects with potential implications for both the battlefield and the ball field include a project to detect biomarkers of head injury in blood (or other bodily fluids) with a strip of paper. Also with DOD support, Kochanek is leading a five-year project aimed at identifying new drug therapies for TBI. For this multicenter project, researchers have identified 10 promising agents that they will rigorously test in multiple labs in multiple ways. Five are what Kochanek calls "low-hanging fruit." They are FDA-approved for other uses; some are off-the-shelf neutraceuticals like resveratrol. The other five he calls "high risk, high reward"; these are not FDA-approved and only have a few promising studies behind them, but they could dramatically change the status quo if they pan out.

"Concussion, in my opinion, is the next Agent Orange for the army."



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As it passes through a skull, a blast wave turns out to have its own unexpectedly sinister fluid dynamics.

The ranks of those who could benefit from such advances are wide ranging. They include victims of automobile accidents and falls, soldiers shipping out today and in the future, and the future Hall-of-Famers that now inspire such admiration on the field.

And then there are those high school athletes, like Katy Korber, who just want to have a good game, be a part of a team, and be a better person for having given it all. These are the same things Katy's parents—and her physicians—want for her. Despite the obvious concerns about injuries to the head, there's no evidence that a single concussion is a risk factor for any long-term consequences, provided the person fully recovers. One could make the argument that the health risks of not participating in a team sport like volleyball are as great or greater than the risk of participation.

Katy, incidentally, is one young athlete who can expect to have many opportunities to have the game of her life.

Her final visit to the sports concussion room ended with an enthusiastic fist-bump from Collins and an "all-clear-to-play." ■