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BRAIN, INTERRUPTED

It affects thousands per day, yet has no treatment, and receives only a small fraction of the funding allocated to much less common diseases. Now, researchers studying traumatic brain injury are making a last-ditch effort to transform the field.

By Megan Scudellari

On a sunny Friday, postdoc Suzanne McKenna pulled into a left turn lane in Cary, NC, and stopped, waiting for the light to change. It was time to wrap up a few errands and head home after a long week of work at the National Institute of Environmental Health Sciences. Suddenly, the afternoon hum exploded with a deafening noise. McKenna looked up into her rearview mirror. The front of an SUV was in her backseat. And her head hurt.

In July 1998, McKenna was a workaholic who had recently moved to North Carolina after winning a competitive postdoctoral fellowship from the National Institutes of Health. Only 3 weeks earlier, at the annual meeting of the Endocrine Society, the tall, blue-eyed brunette had presented her work on the responses of estrogen receptors to environmental compounds that mimic the hormone.

But on July 10th, a driver hit the back of McKenna's car going 40 miles (65 kilometers) per hour, without braking. McKenna's neck was thrown forward, slamming her brain against her forehead. As her body recoiled from the impact, the soft brain tissue ricocheted backwards, contorting again as it hit the back wall of her skull. When an emergency worker arrived, McKenna declined treatment and drove her still-operable car home. On the way, she stopped at a friend's house. The friend asked if she was okay. McKenna's eyes looked vacant.

After a few days off, McKenna returned to work, but things weren't the same. She began to spell phonetically. She couldn't remember her phone number or address. At a lab meeting, she was shocked to look down at her notebook to see scribbled numbers and symbols instead of words. "I thought I was going crazy," says McKenna. And her head continued to hurt.

On July 10, 1998, McKenna was one of the 4,700 people who sustain a traumatic brain injury (TBI) in the United States every day—that's 3 people per minute. In Europe, brain injuries cause 66,000 deaths and land 1.6 million people in emergency rooms every year. Overall, 1.7 million Americans suffer a TBI annually, more than the number diagnosed with breast, lung, prostate, brain, and colon cancer *combined*. In 2009, those five cancer fields received $2 billion in NIH funding. Traumatic brain injury research received just 4 percent of that—$86 million.[1] ▶

TBI is an epidemic—the number one killer of young adults and children in the US—but it is not a new epidemic. A scant quarter inch of bone and a layer of fibrous membranes protect our brains from sudden trauma caused by a jolt, blow, or penetrating object. TBIs result from falls and car accidents, even an act as simple as a child tumbling off a swing.

Yet for the millions affected by TBI, science and medicine have little to offer. Methods for classifying patients remain rough and antiquated. And there are no effective drugs for TBI: Since the 1970s, not a single Phase III clinical trial has shown a significant benefit.[2] It's not from a lack of trying, though. From 1980 to 2009, there were at least 27 Phase III trials in TBI. Doctors have tested steroids, hyperbaric oxygen therapy, magnesium, calcium-channel blockers, and other receptor-blocking agents. None showed significant treatment effects.

It's time to pause and step back, researchers say. "We are surrounded by years and years of failure," says Geoff Manley, codirector of the Brain and Spinal Injury Center at the University of California, San Francisco. "When you have 28 failed drug trials based on really good preclinical data done by smart investigators, you can either say none have worked or take a fundamental look around and admit something is going horribly wrong."

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The first doctor sent McKenna home with ibuprofen. She visited another doctor, then another, all the while trying to keep up the appearance of normalcy in the lab. Finally, a month after the initial injury, a neuropsychiatrist she picked from the phone book gave McKenna a full battery of neuropsychological tests. Shortly after, he invited her into his office and asked her to sit down. You have a mild brain injury, he said. But there was little they could do about it.

Brain injuries differ dramatically from patient to patient depending on the location, type, intensity, and duration of the injury. An injury can immediately cause rips in the white matter, brain hemorrhage, swelling, and, most commonly, bruising. One insult is superimposed on another as, following the injury, the brain begins to experience reduced blood flow and oxygen deficiency.

Within minutes or hours after an injury, tiny holes rip through neuronal membranes and ion channels get stuck open, leaking proteins and neurotransmitters. Free radicals and calcium spread, causing cell death and tissue damage. Early gene activation of apoptotic enzymes sends more cells into a death spiral. Mitochondria sputter, then fall silent. Astrocytes swell. The damage can be isolated or extensive.

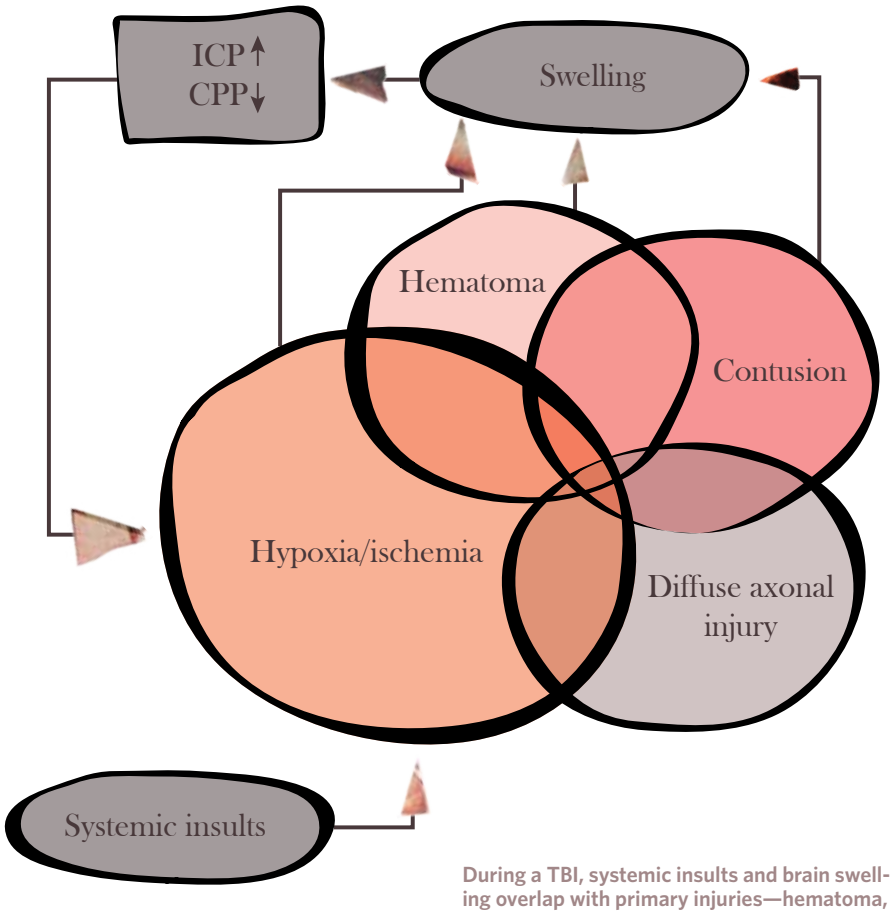
In the early 1800s, diseases were routinely classified by symptoms. Tuberculosis, for example, was called consumption, as it seemed to consume people from within. By the 1900s, doctors began to make more accurate diagnoses based on the true cause of the illness, such as microbes as the cause of pneumonia. Yet the field of neurotrauma didn't get the memo. Today, individuals walking or rolling into an emergency room with a head injury are classified into one of three categories on a 15-point Glasgow Coma Scale, a neurological scoring system rating eye, motor and verbal responsiveness, developed in 1974 at the University of Glasgow. Patients are diagnosed with mild (14–15), moderate (9–13) or severe (3–8) brain injury. A GCS score indicates a patient's level of consciousness, but not much else. It does not define what an injury is—bleeding, bruising, swelling, etc.—or where it is, both important factors for diagnosing a condition recognized for its heterogeneity. According to the GCS, a concussion is a mild TBI. So is McKenna's debilitating injury, for which she needed three neurosurgeries by the time she turned 40.

"We treat based on phenotype," says Alex Valadka, chief of adult neurosciences at the Seton Brain and Spine Institute in Austin, Texas. It's like treating everyone who complains of chest pain with antibiotics, no matter if it's pneumonia or heart attack or a broken rib, he says. "That's where we are with brain injury. Because [all the patients] show up in a coma, we start treating them all the same way."

"The artificial differentiation which we've been making—into severe, moderate, and mild—is crazy. It's ridiculous," says Andrew Maas of the University Hospital Antwerp, one of the most experienced clinical researchers in TBI today. Maas, along with Manley, is one of several researcher-physicians championing an overhaul of the TBI classification system. But to design a new system, researchers need more than just symptom-based evaluations of TBI; they need evidence-based data—imaging, physiological, genetic, and biomarker data. Unfortunately, data collection in the field is just as motley as the disease itself.

In 2003, the NIH-funded International Mission on Prognosis and Clinical Trial Design in TBI, the IMPACT project, began exploring existing TBI data to look for ways to better design and analyze TBI clinical trials. "Ignorant as I was at the time, I had no clue how much work it would be," says Maas, PI of the project and past presi-

Mechanisms of traumatic brain injury



During a TBI, systemic insults and brain swelling overlap with primary injuries—hematoma, contusion, and DAI—which can cause even more swelling, leading to increased intracranial presure (ICP) and decreased cerebral perfusion pressure (CPP).

dent of the International Neurotrauma Society. It took Maas's team 10 person-years of work to simply compile data from 11 studies into a compatible format.

In 2007, Maas and Manley joined forces with the National Institute of Neurological Disorders and Stroke (NINDS) and four other government agencies in an effort to revamp data collection standards for TBI, starting with a conference held in October.[3] Over 50 researchers attended the strategy session. There was some enthusiasm for the project, but 6 months later, nothing had changed.

Ramona Hicks, program director at NINDS in charge of TBI research, decided to do something about it. In March 2008, she and the other agencies involved in the project initiated a series of working groups, each assigned a specific topic: biomarkers, neuroimaging, outcomes measures, etc. After a year of discussions and emails, the experts gathered again in March 2009, now 137 scientists strong from 50 institutions.

This time, it worked. A series of manuscripts outlining suggested Common Data Elements (CDEs), a list of definitions, and recommended measurements and tools to help researchers collect TBI data in a universal language are on the fast-track to publication in the *Archives of Physical Medicine and Rehabilitation* and should be out later this summer or early fall, says journal editor Leighton Chan. The CDEs will also be published on an NIH website and encouraged, if not required, for use in future clinical trials. "Considering how many mistakes have been made [in the past], we've actually been making really rapid progress," says Hicks. Meanwhile, Manley and his colleagues have secured a $4.1 million Grand Opportunity Challenge Grant to beta-test the new recommendations during data collection, to ensure that the new standards predict clinical outcomes.

The new standards should have the greatest effect on clinical trials, researchers hope, since mild, moderate, and severe are not simply classifications for treatment, but are the basis for enrolling patients in clinical trials. "At all kinds of meetings, people stand up and say, 'My patients do better than others,' and their results seem to demonstrate that," says Maas. "But if you go into detail, you find they've been studying a different type of patient, and it's not comparable."

With a new, validated system, researchers will be able to divide TBI patients into subgroups based on the type and location of injuries, not based on their consciousness. Then, therapies that benefit specific injury types can be targeted to those subgroups. It could be the initial step toward a positive clinical trial for TBI—a phenomenon the field has never seen.

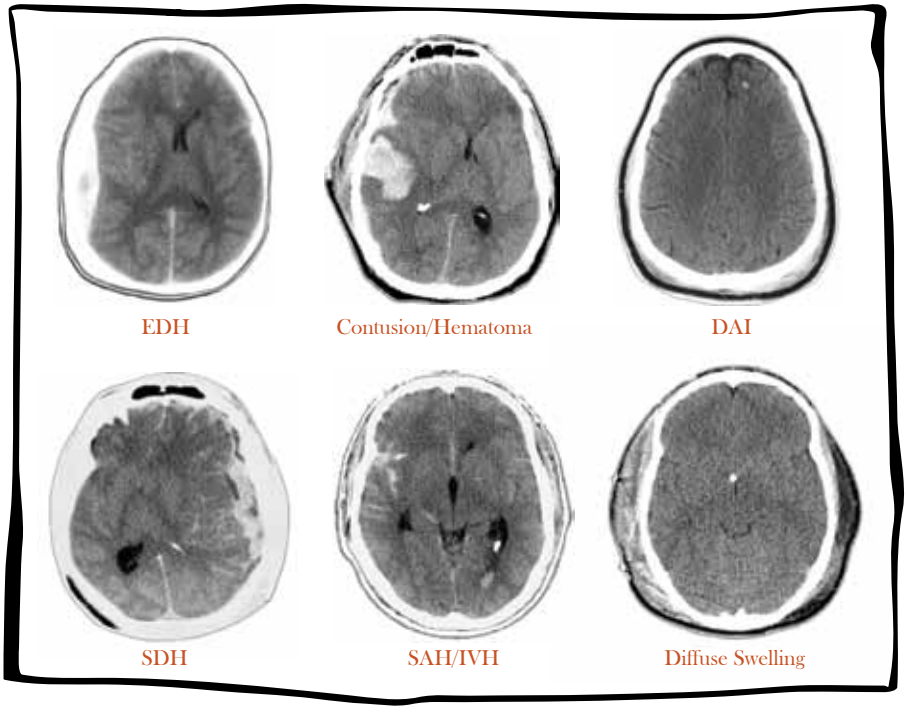
Researcher David Wright sat in a coffee shop at an Embassy Suite in Washington, DC, sweating. He glanced at the closed doors, behind which an NIH data safety monitoring board was meeting. It was November of 2005. Three hours earlier, the panel had invited Art Kellermann, PI of the proTECT Phase II trial for traumatic brain injury, into the room. He was still in there. "We figured we were killing people. Why else would they hold him in the room that long?" recalls Wright, a co-investigator of the trial and professor at Emory University in Atlanta, Ga. Finally, Wright was invited into the room and handed a manila folder. It contained ▶

a single piece of paper divided into two columns, a list of the results from a double-blind trial of progesterone as a treatment for brain injury. Wright sat down and scanned the sheet, Kellermann standing quietly over his shoulder. There were no serious adverse advents on either side—they hadn't killed anyone. But there was something else. Group A had a 50 percent reduction in deaths compared to group B. Wright began to sweat harder. "Please tell me the treatment group is Group A," he pleaded. Kellermann smiled. The men cheered and high-fived. They picked up the phone and called Don Stein.

In the early 1980s, researcher Don Stein had the crazy idea that the female hormone progesterone could be a treatment for TBI. Then a professor at Clark University in Massachusetts, Stein tested his hypothesis, based on anecdotal evidence that women recovered from stroke and brain injury better than men, by systematically testing hormones in rats. He found that female rats, tricked into thinking they were pregnant by stimulation of the cervix so they were naturally flooded with progesterone, fared much better after a brain injury than control females. The same was true for both male and female rats injected with progesterone. But at the time, scientists hadn't realized that the hormone could affect the brain. "When I started this work, people said, 'This is nuts. It can't work that way,'" recalls Stein, now a professor at Emory University.

The resistance to the idea was so intense, Stein would spend the next 27 years working to prove his critics wrong. "If it had been discovered as a neurosteroid first and then a female hormone, things might have been different," says Wright. Today, progesterone is known to be produced in the brain as well as the ovaries and can easily cross the blood brain barrier. Contrary to previous assumptions, both men and women have progesterone receptors in their brains.

Due to Stein's efforts and those trying to disprove him, more than 150 publications in 22 different models of brain injury in four species now demonstrate the wide-ranging neuroprotective effects of progesterone. In the lab, the "sex steroid" has been shown to prevent the expression of inflammatory cytokines in the brain, block apoptosis, stimulate growth-promoting factors, and even have a role in remyelination of neurons. Perhaps due to such mechanisms, studies show that progesterone decreases the accumulation of fluids in the brain after injury, reduces secondary neuronal loss, and improves outcomes in rats. "It's the Swiss army knife of therapies," laughs Douglas Smith, director of the University of Pennsylvania's Center for Brain Injury and Repair. "It can take care of everything." Kellermann and Wright's Phase II trial was an early inkling that the same might be true in humans, leading to a current Phase III trial that could finally be the field's first clinical triumph—or yet another dead end.



CT scans of six different patients with severe TBI, including epidural hematoma (EDH), contusions/parenchymal hematomas, diffuse axonal injury (DAI), subdural hematoma (SDH), subarachnoid hemorrhage with intraventricular hemorrhage (SAH/IVH), and diffuse brain swelling.

If it fails, it will join the nearly 30 candidates that didn't make it past Phase III. So why have TBI trials been so unsuccessful? In addition to poor classification of patients going into trials, like many other diseases it comes down to inadequate animal models. Rats have strikingly different brains than humans, and it may be that some brain injury mechanisms important in rats are not so important in humans or vice versa. Amyloid deposits, a neurotoxin that has been shown to aggregate in the brain of some TBI patients as well as Alzheimer's patients, simply don't form in rat models of TBI.[4] Smith at the University of Pennsylvania now uses the pig model instead, whose brain is primarily folded white matter, like the human brain, rather than smooth like a rodent's brain.

At the University of Cambridge, David Menon no longer studies brain injury in lab animals, but sticks to human data. "The failure of [clinical trials] suggests that we are obviously getting something wrong, so it was quite important to make the change," says Menon.

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After a successful Phase II trial, progesterone is moving to the hot seat. ProTECT III, a $28 million clinical trial funded by the NIH and run through an NIH-supported network of 17 hubs and 31 participating hospitals, began enrolling patients last March. The study plans to include 1,140 patients and will begin progesterone treatment within 4 hours of injury, says Wright, PI of the trial. "I'm all about maximizing the opportunity for success," he says. The trial, stuck at an awkward moment in time where old trial methods are under fire but new standards are yet to be validated, will attempt to integrate some of the newly proposed Common Data Elements but will still be using the Glasgow Outcome Scale (GOS)—the research version of the Glasgow Coma Scale—though in a modified way.

In most previous TBI trials, moderate and severe TBI patients enrolled in trials were designated one of two categories: favorable (none to moderate disability) or unfavorable (vegetative or severe disability). Investigators would judge the success of a treatment based on how many patients made the jump from unfavorable to favorable, an unrealistic expectation for the most severe brain injuries. ProTECT III will use the GOS, but on a sliding scale, assessing injury severity at the beginning of treatment to judge progress by the end of the trial. "We have one shot to show this drug works, and only one shot," says Wright. "We're trying, absolutely trying, not to make the same mistakes."

Outside researchers, many with their own experience in failed trials, are optimistic, but cautious. "I think this is a very exciting study," says Guy Clifton, chair of neurosurgery at the University of Texas Medical School at Austin, who led multiple trials investigating the benefits of hypothermia after TBI, finally concluding it only helps if administered within 2.5 hours after injury to treat hematoma, or blood pooling in the brain. "The data are very strong. Who would have imagined progesterone?"

A current Phase III trial of progesterone could finally be the field's first clinical triumph—or yet another dead end.

"It's a well-founded trial with good preclinical evidence, but by experience, I have become a little skeptical," says Maas. But that doesn't mean they shouldn't do it, just be realistic, he adds. Smith shares the sentiment: "I'm hopeful for the current progesterone trial, but we've been here 30 times before."

But if proTECT III were to fail, how many more chances will the field get? "It keeps me up at night," says Wright. Most pharmaceutical companies have already walked away from the field: When a string of expensive Phase III trials in the 1990s failed, companies lost hundreds of millions of dollars. And it will be a hard sell to bring them back into the fold, either to retest previous therapies—"I think it's too late," says Clifton—or try new ones. "We'll need to find ways of suggesting to them which interventions are more likely to translate or not," says Menon.

Luckily, there has been a recent increase in federal funding, largely from the Department of Defense, in reaction to the dramatic incidence of TBI in returning veterans. Because of the frequency of blast injuries—more than 100,000 troops have been diagnosed with mild TBI since 2003, according to the *Army Times*—TBI is called the signature injury in veterans of the Iraq and Afghanistan wars.

Today, the NIH is funding the few TBI trials still left in the United States, including the ProTECT III trial, a Phase IIb trial assessing erythropoietin, a hormone that induces red blood cell production, and a children's study of hypothermia. "Our clinical trial methodologies are getting better and better," says Clifton. "We'll keep working until we figure it out."

With the help of medication, McKenna returned to science in 2002, working for a few years for a small biotech in Research Triangle Park, NC—investigating, of all things, traumatic brain injury. But the return was short-lived as she began to experience cognitive and then motor seizures, followed by three brain and spinal surgeries. Today, after 3 years on social security disability, McKenna is hoping to go back to the biotech as a part-time grant writer, a small way to keep a foot in the world she used to inhabit.

McKenna never got the chance to publish her data on estrogen receptors. A few years later, another postdoc replicated and published the work. McKenna cried when she saw the paper. ■

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