

# The Promise of Progesterone

For 40 years, neuroscientists have sought to develop an effective treatment for traumatic brain injury. Emory researchers may have found a successful treatment that's safe, inexpensive, and occurs naturally in the brain.

Marc Baskett has made remarkable progress following a car accident that injured his brain. His parents, Jeff and Johanna Baskett, enrolled Marc in a clinical trial to test the effectiveness of progesterone in treating traumatic brain injury.

BY ROBIN TRICOLES

**T**wenty-two-year-old Marc Baskett doesn't remember the catastrophic car accident that nearly claimed his life three years ago. Nor does the strapping former high school athlete remember being flown by helicopter to Grady Memorial Hospital. Baskett arrived at the hospital's trauma unit in critical condition. He had extensive injuries to his femur and ankle and blunt force trauma to his brain. Baskett's parents rushed to Grady shortly after learning of the accident, if only to say good-bye.

Fortunately for Baskett, a group of Emory physicians and researchers was in the midst of conducting ProTECT, a clinical trial to assess the promise of treating traumatic brain injury (TBI) with natural progesterone. With his parents' consent, Baskett was enrolled in the study. Thus began his extraordinary road to recovery, rooted in neuroscience research that began in Donald Stein's laboratory some 20 years ago.

Stein, Candler professor of emergency medicine and a neurobiologist, has dedicated his career to brain injury and recovery. He moved his research lab to Emory more than 10 years ago. Just recently, Stein's work was featured in a front-page story in *The Wall Street Journal* (September 26, 2007).

"This work started when I first began to see anecdotal, single case reports that after stroke or TBI, women tended to recover better than men," says Stein. "But when I began to look at this question more systematically, it was during the women's equality movement. A lot of people didn't want to hear that there might be brain differences between the sexes. It wasn't politically correct."

Stein tried to replicate others' clinical observations using brain-injured rats in his laboratory. "I first looked to see whether female rats with brain damage recovered better on learning and memory tasks than male rats with the same brain injury," he says. "The female rats did, but it depended on where they were in their estrus cycle at the time of the injury."

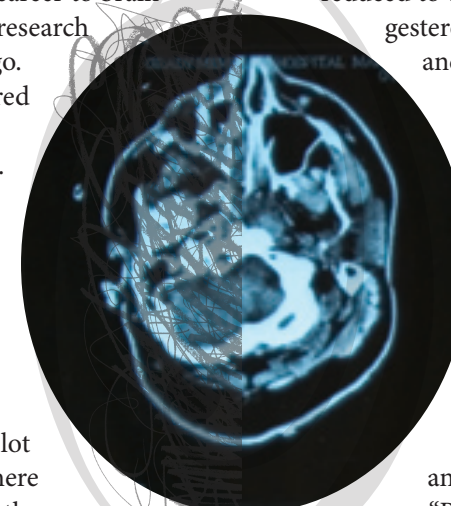
Like the menstrual cycle in women, the estrus cycle

in many female mammals causes fluctuations in hormonal levels, including progesterone. "In the young adult female rat, this cycle is fairly easy to measure," Stein explains, "so we could precisely time the surgery to the phase of the estrus cycle."

"When the females were brain-injured at the time their progesterone level was high, their behavioral outcomes were much better than if the same injury occurred when their estrogen levels were high. Traumatic brain injuries tend to cause cerebral edema. But we noticed a lot less swelling of the brain when progesterone levels were high."

Stein subsequently gave progesterone to male rats to see if there were any benefits. He remembers his colleagues' reaction like yesterday.

"They thought, 'Are you nuts? You're going to give this female hormone to male rats and see what happens?' We did give it to males by injection, and lo and behold what we found was their brain swelling was reduced to the levels seen in the females. The progesterone virtually eliminated cerebral edema, and the animals performed better as well."



## More than a sex hormone

Although widely considered a "sex steroid" because it was first detected in women, progesterone is a true neurosteroid since—unlike estrogen or testosterone—it is synthesized in the brain itself. Laboratory researchers in reproductive physiology have long known that progesterone is critical for normal development of neurons and helps protect brain tissue.

"Progesterone basically does in brain injury what it does during fetal development," says Stein. "It protects the fetus from all those slings and arrows of outrageous fortune that would cause inflammation, swelling, immune rejection, and fetal death if the progesterone wasn't there."

"Many people don't realize that men and women make progesterone in their brains and that men make progesterone in other tissue as well. Men clearly don't make as much of it as women do."

That may be one reason why females tend to recover better under certain conditions of brain injury. “Progesterone,” notes Stein, “is a growth and development hormone, and when you have a brain injury, the process of repair is in many ways similar to the process of growth and development.”

#### Paging Dr. Wright

Armed with years of data on progesterone’s beneficial effects on TBI and recovery, Stein eventually partnered with emergency medicine physician David Wright. Having seen the protective effects of the hormone on brain-damaged animals, Wright wanted to explore progesterone’s effects on TBI in emergency room patients. Like others, Wright thought Stein’s research was fascinating. “I took a sabbatical and starting working in Don’s lab,” he says.

Wright eventually noticed that lab cultures of neurons did not grow or survive unless they contained progesterone. “We knew progesterone had a critical function in the brain,” he says. “We just didn’t know how it worked to provide neuroprotection.”

Only since the mid-1960s have physicians and scientists recognized the validity of neuroplasticity—the brain’s ability to recover structurally and functionally after an injury or from a disease. That may explain why TBI treatments have been so long in coming. Following a TBI, a sequence of events known as a neurotoxic cascade begins. The cascade involves a dramatic increase in the level of excitatory neurotransmitters that can damage and destroy nerve and support cells in the brain.

Normally, these chemicals enter the neurons in a controlled fashion, enabling nerve cells to communicate with one another. But after a brain injury, the nerve cells become hyperexcitable and die or become further injured by inflammatory and oxidizing factors that can cause a lot of swelling—even if those cells are not part of the original injury.

“The lesion may have begun as a small contusion, but it can expand significantly and involve a large portion of the brain,” Wright explains. “If we could stop the neurotoxic cascade and the inflammation that occurs, we could probably preserve more function because the original injury probably accounts for 25% of the dysfunction, and the cascade the majority of the injury.”

In the past, experimental treatments sought to block the excessive release of neurotransmitters and other inflammatory agents. However, this approach has not worked well in humans because the compounds that have been tried cause adverse changes in brain chem-



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istry and morphology. The pharmaceutical industry has long tried to develop new synthetic molecules that can be controlled and patented and have very specific molecular effects. “Unless you happen to be very lucky and hit that one molecule that works,” Stein says, “the treatment fails because a lot of these agents turn out to have very nasty side effects.”

“There have been so many failures,” Wright adds. “The graveyard is full of neuroprotectants—as well as patients. That’s why there’s been so much buzz about the progesterone treatment. This could be the first successful TBI treatment in 40 years.”

That’s great news, given TBI’s harmful effect on

thinking, language, learning, emotions, behavior, sensation, and movement. TBI can also increase the risk of epilepsy, Alzheimer’s disease, Parkinson’s disease, and other brain disorders. In the United States, 5.3 million people live with disabilities resulting from TBI.

The CDC and brain injury associations estimate that TBI costs the nation \$60 billion per year in lost productivity and medical care. In fact, head injuries are the No. 1 cause of death and morbidity in young adult males. Second to falls, motor vehicle accidents are the leading cause of TBI, as in Marc Baskett’s case.

Thus Baskett became one of the 100 patients enrolled in ProTECT (Progesterone for Traumatic brain injury—Experimental Clinical Treatment)—the first clinical trial of its kind in the world. Funded by the National Institute

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of Neurological Disorders and Stroke, the study aimed to assess the promise, practicality, and safety of using progesterone to treat TBI.

To qualify for the double-blind study, patients had to reach the hospital within 11 hours of their injury. Four

out of every five patients enrolled received intravenous progesterone, and one of every five received placebo. Patients had an initial Glasgow Coma Scale score ranging from 4 to 12. A score of 4 to 8 indicates severe TBI or coma, whereas a score of 8 to 12 signals a moderate TBI. Baskett’s score was, alarmingly, a 4.

So far, ProTECT has shown that giving progesterone to trauma patients shortly after brain injury appears to reduce their risk of death and degree of disability. “We found encouraging evidence that progesterone is safe in the setting of TBI, with no evidence of side effects or serious harmful events,” says Wright. “We also found a significant improvement in the functional outcome and level of disability among patients who were enrolled with moderate brain injury.”

What’s more, progesterone is inexpensive, widely available, and has a long track record of safe use in humans in treating other diseases.

#### The road back

Baskett and his parents and doctors eventually learned he was one of the patients who received progesterone. Although Baskett’s doctors credit his athleticism and youth with helping him recover from his injuries, they believe progesterone played a big role. Baskett spent seven weeks in the hospital. Physicians originally thought he would be hospitalized for a year.

Since the accident, Baskett has undergone several surgeries, mostly to his legs and feet. He lives on his own and has returned to work. He rarely notices that he suffered a near-fatal brain injury. Instead, he views the world differently. “I appreciate my parents more. And I see now that this is such a big world, with so many amazing things to offer.”

Baskett hopes to travel to California and New York City and eventually enroll in college. He’s considering a career as a personal trainer. He’d also like to spend time talking with seriously ill children, especially those who must spend time in hospitals.

“I want to tell them never to give up,” he says. “I never stopped fighting. And I’m grateful to be alive.”

*To learn more about the ProTECT study, contact David Wright at [david.wright@emory.edu](mailto:david.wright@emory.edu). For information about Donald Stein’s research, send an email to [donald.stein@emory.edu](mailto:donald.stein@emory.edu).*