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The female sex hormone saving injured men

Grant Williams, who is recovering from brain injures after a cycling accident, and Shane Desmond

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A trial to help patients with brain injuries has produced startling recovery results using the hormone progesterone

No one knows how Grant Williams came off his bike as he cycled home from work on March 23. Though the accident that shattered the 27-year-old scientist's skull was captured on CCTV, the pictures just show him falling. Perhaps he passed out. Perhaps he just lost control.

What was certain was that his life and health were in grave danger. On admission to Grady Memorial Hospital in Atlanta — part of Emory University, where he was studying for a PhD in microbiology — Williams was found to have a fractured skull, a severe brain haemorrhage and sharply rising intracranial pressure.

When his partner, Shane Desmond, was allowed into the emergency room to see him, Williams was convulsing. "I was told that he'd suffered a traumatic brain injury and that they were doing everything they could to help him," Desmond says. "Then they rushed me out of the room."

Eight months on, Williams has made a spectacular recovery. Not only is he well enough physically to go to the gym, despite an injury that could have caused permanent mental disability, he has returned full-time to his PhD.

He owes his life and his wits to the skills of the surgeons who removed a piece of his skull to relieve brain swelling, but he may also have to thank a hormone that isn't usually associated with men. For as Williams lay unconscious, he was enrolled in a remarkable trial of an unlikely treatment for injured brains. It is investigating the protective powers of progesterone.

Progesterone is one of the more familiar chemicals produced by the human body, but it is usually thought of as a female hormone. It regulates women's menstrual cycles and the hormone and synthetic analogues are used in contraceptive pills. It also plays a key role in pregnancy, when levels in a woman's body multiply a hundredfold.

According to Donald Stein, however, this perception is wrong. "We think of progesterone that way because its functions in the female body were discovered first," says the Professor of Emergency Medicine at Emory. "But it's not just a female sex hormone." It is found in the male body and is made by the brains of both sexes. Stein's research has also established that it may have a strong neuroprotective effect.

In the mid-1980s, Stein became intrigued by a discrepancy in the outcomes of traumatic brain-injury patients. "There were lots of case reports indicating that women tended to recover better than men," he says. "I began to think about what might account for that, and thought about what distinguishes male from female. Maybe it was hormonal differences."

To test his hypothesis, Stein, who was working in Boston, turned for help to the nearby Worcester Foundation for Experimental Biology — the institute at which Gregory Pincus developed the Pill. The experiment they devised involved tricking female rats into thinking they were pregnant by tickling the cervix with a blunted hypodermic. The researchers then inflicted brain injuries at different stages of the false pregnancies. "It was remarkable: at times when progesterone was highest, the brain injury outcome was much better," Stein says. "The injuries were smaller and there was much less swelling. It seemed that progesterone might be having a protective effect."

The discovery set him thinking. In developed countries, traumatic brain injury (TBI) is the leading cause of death below the age of 45, and a major cause of disability. Its direct effects

cost the NHS £1.2 billion a year and its wider impact on the UK economy is estimated at about £8 billion annually. Yet while surgery and intensive care have improved survival rates, no pharmacological treatment has been shown to promote recovery.

Progesterone is very cheap: it has been extracted from plants from the yam family since the 1920s. It is known to be perfectly safe: despite its role as a sex hormone, it has none of the feminising effects of oestrogen. If the rat results could be replicated in human beings, it might fill a huge unmet clinical need.

Patient trials of treatments for TBI, though, have historically faced considerable difficulty. Aside from the complexity of the brain, there is the ethical challenge of conducting them. Treatment must take place quickly after injury for it to have a chance of effect, yet this makes it difficult to obtain consent from patients or their families. The strength of Stein's animal work persuaded Emory University to grant ethical approval for a small trial that could be conducted without patient consent, led by his colleague and collaborator Dr David Wright.

After a safety study found no adverse effects, 100 brain-trauma patients were enrolled in a trial in which they were given either progesterone or a placebo within 11 hours of injury. Four patients were given progesterone for every one given the placebo, and neither doctors nor patients knew which were which.

"We got surprising and incredible results," Wright says. While 30 per cent of patients given a placebo died within 30 days of injury, the death rate in the progesterone group was just 13 per cent. Patients with a moderate TBI also had less disability. There was no difference among those with a severe injury.

Though by no means conclusive, the outcome encouraged the US National Institutes of Health to approve a larger trial, called ProTect. It started last year and will eventually recruit 1,140 patients for a progesterone or placebo test on a one-to-one basis. Williams is among the 362 patients already treated, and an interim analysis will take place once another 18 have been enrolled. Spectacular results could see it stopped early, though Wright says that this is very unlikely.

A similar and complementary international trial is also about to start, including five centres in the UK: the Royal London Hospital and hospitals in Leeds, Preston, Southampton and Coventry. Tony Belli, who leads the Southampton University Hospital arm, hopes to add another centre when he moves to the Queen Elizabeth Hospital in Birmingham next year. The first patients are likely to be enrolled before the end of the year.

Though the doctors are cautious, they believe there are reasons why they may succeed where others have failed. "A lot of other treatments failed because they went for a magic bullet approach, based on a single pathway," Stein says.

"Progesterone is what is known as a pleiotropic hormone: it affects multiple pathways. We think it reduces cerebral oedema [fluid retention] and swelling, it stimulates nerve regeneration and repair, it blocks cell death, it down regulates many inflammatory cytokines. I'm optimistic because of this systemic approach."

He believes that progestrone's primary function may not be as a sex hormone as such. "I think it evolved to protect the developing foetus, that's why levels shoot up in pregnancy."

The hormone could then have been co-opted by the female body to regulate the menstrual cycle.

The potential of progestrone has not escaped another constituency with a direct interest in brain injury. Up to 20 per cent of US soldiers have suffered mild head injuries, often from improvised explosive devices and the Pentagon has recognised TBI as one of the "signature injuries" of the wars in Iraq and Afghanistan. It is now investigating how progesterone might be applied in a battlefield context, should the trials succeed. Wright and Stein are applying for funding to develop a delivery system suitable for military use, possibly as a nasal spray.

Wright believes progesterone's image as a female hormone may have delayed military interest. "I think this has been a hang-up for some in the military. But it's boneheaded: a severely injured soldier isn't going to grow breasts."

The progesterone trial and its military applications will be featured in a BBC Two documentary series presented by Dr Michael Mosley that begins on Sunday. "It was a big surprise to me to learn that progesterone is active in the brains of men and women," says Mosley. "I've often wondered why women tend to recover from head injuries so much better than men. It suddenly seems to make sense."

It also makes sense to Williams and Desmond. Though they will not learn whether Williams received a placebo or progesterone until the trial is complete in two years, they are convinced he was given the hormone. "We are thankful that he was a part of the study and, based on his recovery, we'd be shocked to learn that he got a placebo instead of the good stuff," Desmond says.

Williams still feels some effects of his accident. He'll struggle to find the right word, he isn't good at responding to verbal instructions and at times needs help remembering appointments. But he is back working eight-hour days in the lab and is itching to "get back on track with my research".

He is well aware of how differently things might have turned out, and is particularly grateful to have been enrolled in the trial when he was in no position to consent. He regards this suspension of normal consent procedures, indeed, as the most ethical approach.