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## **RESEARCH**

# **Understanding PTSD Takes On Urgency** **Expecting a spike in cases after Sept. 11, researchers** **puzzle out the biology of the disorder**

By Douglas Steinberg

Thousands of cases of post-traumatic stress disorder (PTSD) will likely emerge from the Sept. 11 terrorist attacks. Many cases will last a few months, but severely traumatized witnesses could suffer for the rest of their lives. How can a single horrific experience with nasty aftershocks sear the psyche for decades? Answers to this question appear increasingly urgent in an atmosphere of war, anthrax scares, and continual television replays of the World Trade Center collapse.

Researchers have linked PTSD to changes in the brain and body. But association is not causation, and biologists hotly contest the significance of these changes. Inconsistent findings fuel the debate, and the ethical limitations of psychiatric research, combined with a lack of animal models, might make some issues impossible to resolve. The stakes in these scientific disputes are high: greater consensus could channel resources into better prevention and treatment strategies.

"When a field has a lot of controversies, it means to me that there are a lot of missing pieces of a puzzle," observes Rachel Yehuda, director of the traumatic stress studies division of New York's Mount Sinai School of Medicine. The terrorist attacks might spur discovery of some of those pieces: PTSD researchers are already submitting grant applications related to the disaster. Steven E. Hyman, director of the National Institute of Mental Health (NIMH), where many of these submissions are headed, expects them to focus initially on epidemiology and treatment. But he adds that NIMH eventually plans to put a "major emphasis" on understanding the basic biology underlying PTSD.

### **An Ancient Affliction**

PTSD patients persistently re-experience a trauma, avoid stimuli associated with it, and feel numb. They show signs of hyperarousal, such as irritability, insomnia, and an inability to concentrate. PTSD has delayed-onset, acute, and chronic forms. Some studies suggest that 10 to 25 percent of victims never recover,<sup>1</sup> but that figure could be much higher after exposure to extreme trauma. Depression and drug abuse often accompany the disorder.

First officially recognized by the American Psychiatric Association in 1980, PTSD is similar to afflictions known throughout history. "Soldier's heart," for example, was a Civil War analog, according to J. Douglas Bremner, an associate psychiatry and radiology professor at Emory University School of Medicine in Atlanta and the author of an upcoming book on the disorder.<sup>2</sup> Research into biological processes implicated in PTSD began in the late 1960s, when John W. Mason, now an emeritus psychiatry professor at Yale University School of Medicine, and colleagues analyzed the urine of soldiers serving in Vietnam.

Most PTSD work focuses on combat veterans and victims of physical and sexual abuse. Relatively few studies examine witnesses to notorious catastrophes. Yehuda is tracking PTSD in Holocaust survivors. Arieh Y. Shalev, a psychiatry professor at Hadassah University Hospital in Jerusalem, monitors terrorism victims in Israel. And Carol S. North, a psychiatry professor at Washington University School of Medicine in St. Louis, has investigated a dozen disasters, including the 1994 Northridge, Calif., earthquake and the 1998 embassy bombings in East Africa.

An oft-cited model for epidemiological research on the Sept. 11 aftermath is a study of survivors of the 1995 Oklahoma City bombing.<sup>3</sup> Six months after this event, a team drawn from Washington University, the University of Oklahoma, and the Oklahoma State Department of Health, found that 34 percent of 182 survivors had PTSD. A year later, "most people who had PTSD to begin with still had active PTSD," recalls North, a team member. Patients had recovered far less from PTSD than from major depression.

This project didn't measure treatment efficacy because scientists can't dictate who will and won't be treated. (Studies that *compare* treatments are more ethically acceptable.) "The sicker people go for treatment, so you're going to find that it is associated with worse PTSD," says North. The recent terrorist attacks have delayed a six-year follow-up project that was to include physiological tests, she adds.

## **Findings Stir Controversy**

Stress causes the adrenal glands to release glucocorticoids, including cortisol. Excessive amounts of these hormones damage the hippocampus, a memory center in the brain.<sup>4</sup> In a theoretical leap, some researchers have proposed that certain traumas damage the hippocampus, thereby helping trigger PTSD. The presumptive proof: Four studies published between 1995 and 1997, as well as a recent unpublished study by Bremner, found smaller hippocampi in PTSD patients, compared to the hippocampi of matched controls without the disorder.<sup>5</sup>

This hypothesis, nevertheless, remains highly controversial. Pre- and post-trauma studies of PTSD might confirm or disprove it by having subjects serve as their own controls. But no such studies have been published, though they're conceivable and would not cross an ethical boundary if independent events, and not researchers, inflicted the trauma on human subjects. Robert M. Sapolsky, a Stanford University professor of biological sciences who specializes in the cellular effects of glucocorticoids, muses that researchers could examine soldiers before and after military operations.

Five articles published this year in the journal *Hippocampus* reveal the controversy's flashpoints.<sup>6</sup> Yehuda notes that her work consistently demonstrates *lower* cortisol levels in PTSD patients, a finding not replicated by some investigators. Bremner argues that the issue can't be resolved unless researchers measure cortisol levels at the moment of PTSD-inducing trauma—clearly an unfeasible experiment.

In the *Hippocampus* debate, Roger K. Pitman, an associate psychiatry professor at Harvard Medical School, describes six alternative explanations for smaller hippocampi in PTSD patients. One explanation is that pre-existing smaller hippocampi might increase a traumatized person's vulnerability to developing PTSD. Another explanation is that PTSD might somehow cause hippocampal atrophy, rather than atrophy causing PTSD. "It would be a big mistake to prematurely conclude that stress is damaging brain tissue until we've ruled out these other possibilities," says Pitman in an interview.

A new paper by Pitman and Shalev raises new doubts about the hippocampal atrophy hypothesis. They used magnetic resonance imaging (MRI) to evaluate the hippocampi of 37 survivors of traumatic events, mostly car accidents, one week after the trauma and six months later. (Earlier studies took one-time snapshots of the hippocampus.) Ten survivors developed PTSD, and their hippocampi were no different from the controls' and showed no change over six months.<sup>7</sup> During that time, some hippocampal atrophy might have been expected if it truly caused PTSD.

Pitman and Bremner now are independently testing that causal link by examining pairs of identical twins, one of whom served in Vietnam and the other who didn't. Some veterans, unlike their twins, suffer from PTSD. A finding that PTSD patients' hippocampi match those of their non-afflicted twins would be a powerful argument that hippocampal size doesn't cause the disorder but is likely a predisposing risk factor.

Whatever the hippocampus' exact role in PTSD, some studies correlate smaller size with memory deficits. To the extent that these contribute to PTSD, an unpublished study by Bremner should provide some encouragement. He treated 26 PTSD patients with Paxil, a selective serotonin reuptake inhibitor now prescribed as an antidepressant. (Based on its own clinical data, manufacturer GlaxoSmithKline is now seeking a PTSD indication for Paxil.) Bremner reports that hippocampal volume in treated subjects increased 5 percent and verbal declarative memory function improved 20 percent. Paxil, he notes, has been shown to promote neurogenesis and foster neuronal branching in the hippocampus. For his part, Pitman views the amygdala as more relevant to PTSD than the hippocampus, because the amygdala is involved in acquiring conditioned fear responses. Its size doesn't change during PTSD, but Pitman says his functional MRI studies "suggest that the amygdala is overactive or over-reactive in people with PTSD." He concedes, however, that imaging studies using positron emission tomography often don't confirm amygdala activation.

In a recent pilot study, Pitman found that administering the anti-adrenaline drug propranolol within six hours of a traumatic event reduced PTSD. The idea behind the trial, he explains, "is that stress hormones are involved in strengthening emotional memories. That effect takes place in the amygdala, and it can be blocked by giving a drug that

blocks the effect of noradrenaline or adrenaline."

#### Projects Planned, Money Needed

Pitman says he cannot test propranolol on witnesses to the Sept. 11 attacks because too much time has elapsed. But about a dozen other investigators are working with NIMH to devise attack-related studies. Randall D. Marshall, an associate professor of clinical psychiatry at New York's Columbia University College of Physicians and Surgeons, is already writing two grant applications to NIMH. He expects to learn more about the relationship between PTSD and the level of exposure to the disaster. "There are many levels," he observes. "It's much more complicated than an industrial accident, for example. We're seeing people with symptoms who simply saw [the attack] live on television."

To speed up the funding process, NIMH is encouraging investigators to apply for RAPID grants, which are awarded to pilot projects. (RAPID stands for rapid assessment post-impact of disaster.) The institute is also supplementing existing grants if the studies can be broadened to encompass the recent attacks. NIMH devoted about \$29 million to PTSD in fiscal 2001 and is seeking \$32 million in 2002. Says director Hyman: "We hope that Congress recognizes a need for increased funding." The Department of Defense and Department of Veterans Affairs also support PTSD research.<sup>8</sup>

If the money materializes, researchers hope to develop fresh strategies to deal with the expected wave of PTSD cases. Yehuda sees a "moral obligation" to study PTSD, explaining that "we don't know a lot about what happens in the early aftermath of trauma, and we're going to need to know."

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#### References

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8. The Department of Veterans Affairs Web site about PTSD can be found at [www.ncptsd.org](http://www.ncptsd.org)