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Why Don't Zebras Get Ulcers?

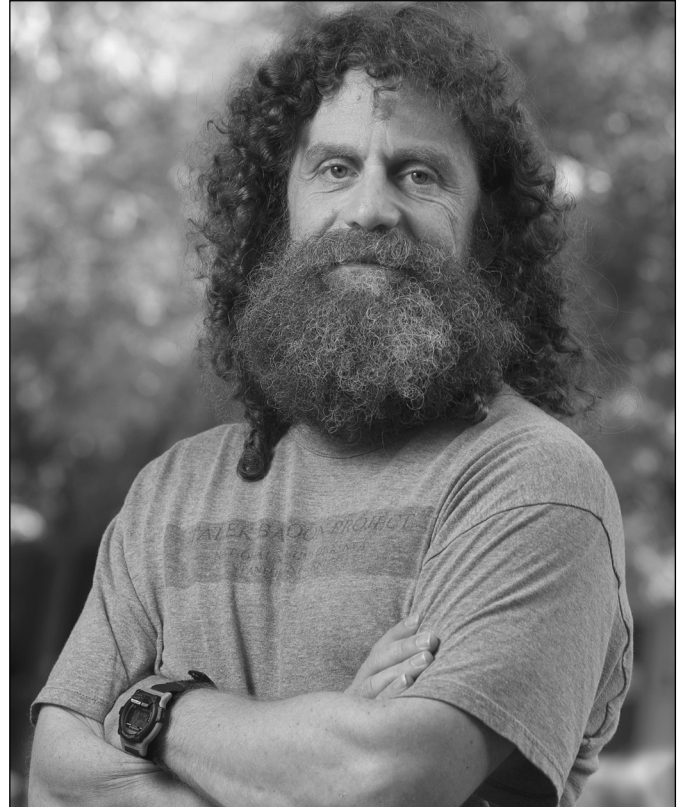
*Annual Helmut Schumann Lecture
Considers the Biology and
Consequences of Chronic Stress*

If you're a zebra and a lion is after you, naturally you feel stressed. Your hormones kick in, you run like hell, and, if you're lucky, live to run another day. In the meantime, don't worry, be happy.

Modern humans, on the other hand, spend less time dealing with immediate physical threats, like swerving to avoid another car, in which case adrenaline comes in handy, and more time worrying about the mundane concerns of our everyday lives. The problem is, worrying about tomorrow's meeting or a credit card bill can trigger the same physiological response as avoiding a head-on collision.

The ability to rise to an immediate threat is useful, but the consequences of prolonged stress on the body is exceedingly unhealthy, says Robert Sapolsky, Ph.D., a Stanford University neurobiologist. "A large body of evidence suggests that stress-related disease emerges, predominantly, out of the fact that we so often activate a physiological system that has evolved for responding to acute physical emergencies, but we turn it on for months on end, worrying about mortgages, relationships, and promotions," he writes in his book, *Why Zebras Don't Get Ulcers*.

Sapolsky will talk about his research into the physical and mental consequences of chronic stress when he delivers the 24th Annual Helmut Schumann lecture, "Why Zebras Don't Get Ulcers: Insights on Stress and Illness," on Septem-



Robert Sapolsky, Ph.D., neurobiologist, presents the 24th Annual Helmut Schumann Lecture on September 26.

ber 26 at 7:30 p.m. in Auditoriums E and F of DHMC. His lecture is free and open to the public.

The Biology of Stress

Sapolsky first began research into the neurobiology of stress in 1978, when he was studying baboons in Kenya as a neuro-endocrinology graduate student at Rockefeller University. He has been described as a cross between "Jane Goodall and a borscht-belt comedian," but the importance of his work was recognized in 1987 with a MacArthur Fellowship, the so-called "genius award." He is now a professor of biology and neurology at Stanford, where his laboratory

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Stress

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studies the biological consequences of stress on brain chemistry, and possible gene therapies for protecting neurons.

Long-term or chronic stress can result in a multitude of bad outcomes, he explains, a few of which are arteriosclerosis, colitis, diabetes, and neurological damage. The “villain,” explains Sapolsky, is glucocorticoids, a class of steroid hormone released during stress. During an immediate, short-term threat, glucocorticoids are essential for life. They get the heart rate going and the muscles moving, they sharpen thinking, and they delay functions that are unnecessary in a crisis, such as digestion.

But if stress continues, and glucocorticoids continue to be released, they can create and exacerbate a multitude of problems, not the least of which is neuron destruction in the brain, which can cause long-term memory loss. “Glucocorticoids are energetically endangering hippocampal neurons,” says Sapolsky. People with Alzheimer’s disease or clinical depression have very high levels of glucocorticoids. “Given how many things glucocorticoid hormones affect, elevated levels can mess up a lot of things,” says Sapolsky.

The good news is that in many cases if the stress stops so does the destruction of neurons. The bad news is that in certain cases of extreme stress—prolonged childhood abuse, clinical depression, combat stress—the damage can be permanent and irreversible. Children are at particular risk. “Everything I just told you about adult stress on the brain...multiply it

ten fold when you think about a ten-year-old’s brain,” Sapolsky told an audience in 2000.

Meet the Sopranos

Sapolsky first recorded the physiological and social dimensions of stress when studying baboons in Africa. For two decades he has traveled from his laboratory in California every summer to the Serengeti to collect behavioral data and measure the glucocorticoid and cholesterol levels of baboons. He wrote a book about his experiences, *A Primate’s Memoir: A Neuroscientist’s Unconventional Life Among the Baboons*.

“Social isolation is a health risk factor.”

— Robert Sapolsky

Baboons, he observed, were much like humans. Given the absence of predators and the plentiful food, they led a privileged life, especially compared, for example, to zebras. Baboon life was full of friendships, family life, play, grooming, rivalries, and competition. Sound familiar?

But it could be said that they had too much time on their hands, most of which they spent in social interactions. The dominant type-A baboons spent most of their day intimidating everyone around them—sometimes just for the heck of it—scheming ways to make everyone else’s life difficult; the rest of the time, not surprisingly, they worried about retaliation. Meanwhile, the baboons who had been bullied into passivity constantly worried about random violence from the dominant baboons. Sapolsky discov-

ered that these stressed-out baboons had elevated blood pressure and cholesterol levels, weakened immune systems, and higher levels of glucocorticoids, the trademark stress hormone.

Different Ways of Coping

Not everyone responds to stress in the same way, even baboons in Africa. Sapolsky discovered that there are specific personality characteristics and social situations that affect the flow of glucocorticoids and the possible development of stress-related diseases.

One characteristic was the ability to tell the difference between a real threat and a minor one. Observing baboons, Sapolsky noted that “some males get agitated even when their rival is taking a nap across the field—the sort of situation that happens five times a day. If a male baboon can’t tell the difference between the two situations, on the average his resting glucocorticoid levels are twice as high as those of the guy who can tell the difference.” In other words, don’t get upset about every little thing.

Also important was the ability to take control of a situation. When facing a real threat, passive types have higher glucocorticoid levels than take-charge personalities. And if you’re the winner of a confrontation, can you tell you’ve won? Or does life feel just as bad afterwards? Baboons who couldn’t tell the difference had much higher glucocorticoid levels.

One of the most important predictors of stress levels was having an available outlet for the inevitable frustrations of life. Sulking alone is not healthy. Being part of a supportive social network is. “Social isolation is a health risk factor,” says Sapolsky. **HFN**

New Guidelines Increase Support for Investigators

Providing a Springboard for Research Careers

“**Y**oung investigators are our lifeblood,” says Ethan Dmitrovsky, M.D. He characterizes in a nutshell why the Hitchcock Foundation has changed the guidelines for two important career development fellowships—the Joshua B. Burnett Clinical Research Fellowship and the Tiffany Blake Fellowship. They have been reconfigured to provide a more substantial launching pad for young investigators pursuing careers in research.

Increased Support

The Burnett and Blake fellowships have become one-year awards given every other year. Supporting the fellowships on alternate years allows the Foundation to increase funding—up to \$170,000—to cover salary, fringe, and operational costs. This significant increase in funding is intended to free up most of an investigator’s time for a year of supervised study and clinical or lab research. “For a successful career, you need the time to do the research,” says Larry Dacey, M.D., chair of the Hitchcock Foundation Board of Trustees. “We want to provide a springboard for people who might otherwise have a hard time getting started.”

Both fellowships are open to investigators up to the assistant professor level. Candidates are expected to devote at least 80% of their time and effort to the fellowship. Operational funding can constitute up to \$20,000

of the award, but the Fellow’s department can provide additional dollars to supplement operational funding for the period of the award.

Bench to Bedside Research

The Burnett fellowship supports clinically trained professionals with a doctoral degree or the equivalent, who are committed to clinical research. Applications will be accepted again in July 2008. While the Burnett is limited to clinical research, the Blake fellowship has a more diverse pool of applicants, since it can be used for clinical, basic, and health services research. Anyone with a doctoral degree can apply. Applications for the next Blake fellowship are due September 13, 2007.

The fellowships are aimed at young investigators who have a strong potential to translate the discoveries made by biomedical researchers into the clinical setting. The specific objectives of each fellowship are tailored to the needs of each candidate, and depend on his or her previous research experience and training. But the overall goal is the same—to gain the skills necessary to carry out high-quality research and compete more effectively for independent support.

“The Hitchcock Foundation wants to give people the tools to start research that has great promise,” explains Dacey. Of the past 39 Blake Fellows, four are currently on staff at

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Fellowships

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Dartmouth: Donald St. Germain, M.D., William Rigby, M.D., Wendy Wells, M.D., and Barbara Jobst, M.D. Heather Wishart, Ph.D., is one of two past Burnett fellows.


Importance of a Mentor

Mentorship is an important component of the fellowships. Applicants must apply in conjunction with a mentor, someone who is an accomplished investigator with a successful track record in training investigators. The candidate and the mentor are responsible for preparing a plan of study and research for the candidate.

Far from being a silent partner, the mentor is actively involved in everything from reviewing methodology to providing a heads-up about expected pitfalls. According to Dmitrovsky, who was a member of the committee that thought long and hard about how the fellowships could be restructured to more effectively support junior faculty and trainees at Dartmouth, "Mentorship is an integral part of the fellowships."

History of Support

The programs and support offered by the Hitchcock Foundation have grown significantly since the organization's founding over 60 years ago. The Burnett and Blake fellowships are just two of many ways the Foundation has supported investigators at the beginning of their careers. Only ten years ago, the Foundation managed around 150 research and education funds. In 2007, it has over 500 active accounts, including sponsored research, student- and faculty-initiated research, clinical trials and special purpose funds, with assets totaling \$24 million.

Dmitrovsky credits the commitment of the Foundation's Trustees, all of whom volunteer their time, and the responsible stewardship of Executive Director Michael Shoob and his staff for making the Foundation's programs a critical asset for students, residents, fellows, and junior faculty at Dartmouth. "We should take pride that the Hitchcock Foundation is here at Dartmouth, and the input it's had and will have in the future," he says. 

Foundation Notes

Grant and Fellowship Deadlines

Application forms for Foundation grants and fellowships can be picked up at The Hitchcock Foundation office in Colburn Hill, requested by email or downloaded from the Foundation website. The next grant application deadline is August 9, 2007. The Tiffany Blake Fellowship deadline is September 13, 2007.

The Foundation Website

The Hitchcock Foundation has a comprehensive website hosted by DHMC. The site allows you to download applications for all Foundation grants and fellowships. The website can be accessed at:

www.dhmc.org/goto/hitchcockfoundation

It can also be found on the DHMC Employee Intranet or through the Dartmouth Medical School website by clicking on "Research" and then "Centers and Institutes."