Team dreams of reducing the crib-death rate

The number of deaths from sudden infant death syndrome (SIDS), also known as crib death, has been cut in half over the past 20 years. Even so, SIDS remains the leading cause of death in infants between one month and one year old. Researchers have identified several risk factors—such as soft bedding and putting babies to sleep on their stomach—but so far no one knows exactly what triggers SIDS. Recent work at DMS led by Eugene Nattie, M.D., a professor of physiology, is helping to piece together clues about the underlying causes of the syndrome.

Last year, a team that included Nattie and was headed by a neuropathologist at Harvard found that babies who had died of SIDS had lower levels of serotonin in their brainstem than infants who had died of other causes. Serotonin is a neurotransmitter that helps regulate various functions of the brain, and the brainstem regulates involuntary processes, such as breathing. Based on this research, a group of scientists—including Nattie and others at DMS—has been collaborating on studies in mice to try to better understand the role of serotonin in SIDS.

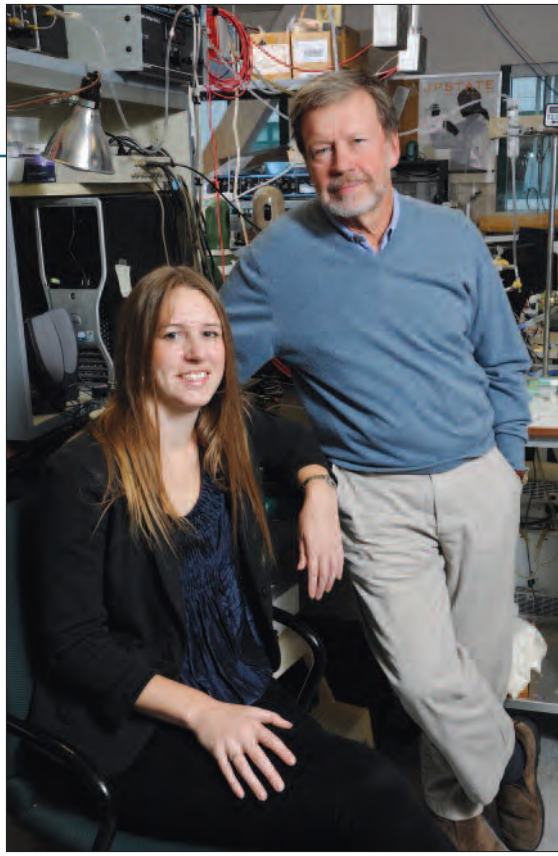
Low: Nattie's team has been using a strain of mice—called Pet-1—that is genetically engineered to have low serotonin levels. In one study published recently in the *Journal of Applied Physiology*, they exposed newborn mice to repeated bouts of low oxygen, returning the air to normal concentrations between each bout. Normal mouse pups stopped breathing when oxygen levels were low, then started to take in large gasps of air when levels were raised again. When oxygen levels returned to normal, the heart rates of the mice likewise returned to normal. "The normal mice can autoresuscitate as long as they have normal air to breathe after the low-oxygen event," Nattie explains.

In contrast, the Pet-1 mice were much less successful at recovering from the bouts of low oxygen. They did not gasp as quickly, and some died as a result. Nattie says that though the mouse model is an imperfect one, the results are still important for understanding SIDS. "This study suggests a possible mechanism by which human infants who are deficient in serotonin could die unexpectedly," he says. Infants who die of SIDS sometimes show evidence of being exposed to low oxygen levels—caused, possibly, by interference from a blanket or bedding or by an upper-respiratory-tract infection.

Stress: In another study, this one published in the *Journal of Physiology*, Nattie and colleagues exposed both Pet-1 and normal newborn mice to very mild cold stress. The mice are usually kept in a warm setting—a thermal "neutral zone" that does not require them to make any physiological adjustments to stay warm. For this study, the mice were put into a room just five degrees Celsius cooler than the neutral zone. Even with that relatively small change, the Pet-1 mice became unable to regulate their body temperature. "This shows us that mice deficient in serotonin have problems with their sympathetic nervous system regulation," says Nattie. The sympathetic nervous system enables mice (or humans) to respond to environmental stresses through changes in heart rate, blood pressure, and other mechanisms. So perhaps the sympathetic nervous system plays a role in SIDS, too.

Nattie has been trying to understand the role of serotonin in SIDS.

A third recent paper—authored by Nattie and a number of researchers at other institutions and published in *Science*—describes a new technique that makes it possible to selectively turn off serotonin neurons for about 45 minutes. Susan Dymecki, M.D., Ph.D., a professor of genetics at Harvard, developed this neuronal silencing tool. She took a newly designed protein, called a DREADD receptor, and inserted it into serotonin neurons in mice. The researchers then injected those mice with a drug that unlocks the DREADD receptor, turning off the serotonin neurons.



JON GILBERT FOX

Nattie, right, and Corcoran are among the DMS researchers who study sudden infant death syndrome.

Andrea Corcoran, Ph.D., a postdoctoral fellow in Nattie's lab, explains what happened when they turned off the serotonin neurons in the adult mice. "The mice were no longer able to maintain body temperature," she says. "They also were unable to adequately respond to increasing levels of carbon dioxide." Normally, as carbon dioxide increases in the air, mice (and humans) increase their breathing rate. "These animals were unable to increase their breathing rate once we turned off their serotonin neurons," says Corcoran.

Tool: The group is using the neuronal silencing tool to repeat this experiment in newborn mice to see if they respond as the adult mice did. "The exciting thing about this new technique," says Nattie, "is that we can now look at very specific populations of neurons and turn them on and off at will. That's a very powerful tool."

He hopes these efforts will eventually lead to further reductions in the SIDS death rate. "We'd like to find . . . a useful potential treatment," he says.

LAUREN WARE