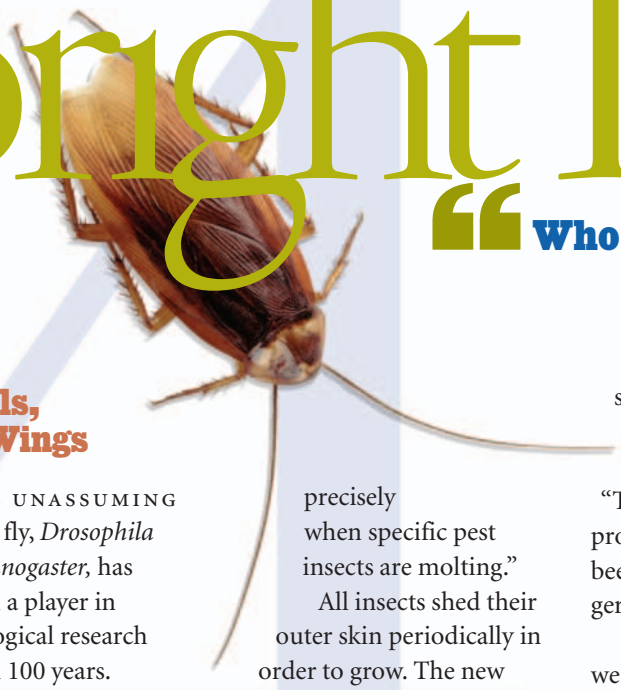
Bright Ideas



"Who would of 'thunk' that you could go to

Soft Shells, Clipped Wings

1. The unassuming fruit fly, *Drosophila melanogaster,* has been a player in biological research for more than 100 years. The same characteristics that make it maddening in your kitchen—small size, prolific reproduction and rapid growth—make it perfect for studying genetics and development.

Yet, the genetic structure of a key hormone in fruit-fly development, bursicon, remained unknown. Now biologists have discovered the structure and genetic sequence of the hormone that allows insects to develop hard outer shells and spread their wings. The research was published July 13 in the journal *Current Biology* by Vanderbilt biologists Hans-Willi Honegger and Elisabeth Dewey and researchers at Cornell University and the University of Washington in Seattle.

Honegger, professor of biological sciences, expects this research and ongoing studies to open new doors for pest control. "Bursicon is absolutely necessary for insect survival. When you know the receptor and you know the hormone, you can produce an inhibitor," he explains. "You could time it precisely when specific pest insects are molting."

All insects shed their outer skin periodically in order to grow. The new outer shell then hardens and darkens. Both processes involve activation of a series of five hormones. The structure, genetic sequence and biochemical properties of four of these hormones have been known since 1990; that of the fifth, bursicon, was not.

Using cockroaches, Honegger's students collected and purified a sample of the hormone and sent it to a Harvard University laboratory that chemically sequenced it. Dewey, a post-doctoral researcher in Honegger's laboratory, compared the sequence to known genomes for other insects and found matches, leading the team to determine that bursicon has the same genetic sequence across species.

Researchers used the sequencing information to determine the structure of the bursicon molecule. They found that bursicon's structure makes it a member of a group of molecules known as the cystine knot proteins. Cystine knot proteins are so called because of their molecular structure, repeated across mammalian species, of three loops of amino acids linked in a unique configuration.

"This is the first cystine knot protein with a function that has been found in insects," Honegger says.

"Based on previous research, we knew certain nerve cells produce bursicon and that these same cells produce another protein, crustacean cardioactive peptide (CCAP)," he adds. Further research determined that the same cell was producing both.

Honegger's colleague at Cornell, John Ewer, then made transgenic fruit flies by using a "death gene" that targeted

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Hans–Willi Honegger

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a gym and expose yourself to a health hazard? —DR. WILLIAM SCHAFFNER

CCAP cells. The cells disappeared, prohibiting production of bursicon and confirming that the genetic sequence researchers had for the hormone was correct.

In the final test, Susan McNabb from the University of Washington looked at mutant fruit flies whose outer shells showed defects or did not harden completely. She found that all had mutations in the gene identified for bursicon.

Researchers injected samples of central nervous systems from fruit-fly mutants into blow flies that had been treated to prevent bursicon release. The blow-fly shells did not harden nor darken as they would have if injected with samples from normal flies. These results were consistent with the theory that a lack of bursicon in the fruit-fly mutants' central nervous systems was responsible for their defects.

The mutants also revealed a surprise: Not only were their shells not properly formed, but they could not expand their wings.

"This means that bursicon has a second function—not just for hardening of the exoskeleton, but also for wing expansion," Honegger says.

2. Dopamine Levels Tied to Uncertainty of Rewards

Dopamine levels in our brains vary most when we are unsure if we are going to be rewarded, such as when we are gambling or playing the lottery. That's the conclusion of research published online April 28 in the *Journal of Neuroscience*.

The chemical neurotransmitter dopamine has long been known to play an important role in how we experience rewards from a variety of natural sources, including food and sex, as well as from drugs such as cocaine and heroin, but pinning down the precise conditions that cause its release has been difficult.

"Using a combination of techniques, we were able to measure release of the dopamine neurotransmitter under natural conditions using monetary reward," says David Zald, assistant professor of psychology at Vanderbilt and an investigator in the Vanderbilt Kennedy Center for Research on Human Development.

Zald believes the primary significance of the study is the possibilities it raises for future research on measuring what causes us to experience reward from a variety of sources and what happens in our brains when we are disappointed in our quest for those rewards. The research lays a foundation for better understanding of what happens in the brain during unpredictable reward situations such as gambling and offers promise for exploring the chemical foundation of problems such as gambling addiction.

"We're moving to a point where we can measure what's happening to people's neurotransmitter systems in a way we haven't been able to do before," Zald says.

Zald and colleagues used positron emission topography (PET scanners) to view brain activity in human research subjects who had been injected with a chemical that binds to dopamine receptors in the brain, but is less able to bind when the brain is releasing dopamine. A decrease in binding to the receptors is associated with an increase in dopamine release, while an increase in binding indicates reduced release of dopamine. This technique allows researchers to study the strength and location of dopamine release more precisely than has been possible previously.

The team studied the subjects under three different scenarios. Under the first, the subject selected one of four cards and knew a monetary reward of $1 was possible, but did not know when it would occur. During the second scenario, subjects knew they would receive a reward with every fourth card they selected. Under the third scenario, subjects chose cards but did not

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David Zald

receive or expect any rewards.

Dopamine transmission increased more in one part of the brain in the unpredictable first scenario, while showing decreases in neighboring regions. In contrast, the receipt of a reward under the predictable second scenario did not result in either significant increases or decreases in dopamine transmission.

"It's probably not just the receipt of money, but the conditions under which it occurs that makes a difference," Zald explains.

The increase and suppression were localized to specific, separate regions of the brain, illustrating that variable reward scenarios, like gambling, have a complex effect on the brain. "The most interesting thing we found is that areas [of the brain] showed increased dopamine release during the unpredictable condition, while other areas showed decreased dopamine release," Zald says. "So other than just dopamine as reward, there is a more complicated action occurring."

The data was collected in Montreal and analyzed in collaboration with Gabriel Dichter at Vanderbilt; Isabelle Boileau and Alain Dagher at McGill University, Montreal; Wael El-Dearedy at Liverpool John Moores University, United Kingdom; Roger Gunn at Glaxo SmithKline, Greenford, United Kingdom; and Francis McGlone, Unilever Research, Wirral, United Kingdom.

The research was supported by grants from Unilever Research and the National Science Foundation.

Shedding New Light on Indoor Sunburn

3 Ever think you could get a nasty sunburn—severe enough to peel—by attending an indoor event? Not only can your skin be affected, but your eyes could also be injured if you spend an extended period of time in a gymnasium that has one or more damaged metal halide lamps.

If the protective glass that covers the bulb in that type of lighting is broken, UV light can filter out. Even one damaged bulb could cause injuries similar to welders' arc burns or snow blindness and can also lead to a peeling sunburn on the face and/or eyelids.

Three outbreaks of injuries from damaged metal halide lamps in Middle Tennessee were reported to the Tennessee Department of Health in the past year. One outbreak at a fund-raising event in a youth-center gym caused eight people to report photokeratitis (severe eye symptoms); another occurred at a three-day wrestling tournament in a gym; and the third was among volleyball players at a municipal gym.

Through a collaborative effort among Vanderbilt University Medical Center, the Tennessee Department of Health, and the Centers for Disease Control and Prevention, the outbreaks were studied and reported in the April issue of the journal *Archives of Pediatrics and Adolescent Medicine.*

"Who would have 'thunk' it … that you could go to a gym and, aside from a twisted ankle, just by turning a switch expose yourself to a severe health hazard," says co-author Dr. William Schaffner, professor of preventive medicine at Vanderbilt and chair of the department.

The lights can be damaged, Schaffner hypothesizes, when an object like an errant basketball hits them, cracking the protective outer shield.

The collaborators contacted 119 of the approximately 600 people who attended the three-hour fund-raiser. Every person contacted responded to the questionnaire; 18 met the researchers' case definition of photokeratitis. Among those, 13 also had UVR burns on their faces, mostly on their foreheads or eyelids. And two people who wore UVR-protective eyeglasses had no eye symptoms but had UVR burns on their faces.

The shortest amount of time a patient with symptoms spent in one of the gyms was one hour; the average was three hours.

Patients experienced a variety of symptoms including conjunctival infection, burning or itching, photophobia, foreign-body sensation, tearing, blurry vision, periorbital edema and skin erythema

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William Schaffner

(lesions). Some visited the emergency room, while others sought treatment from their doctors. Symptoms ceased 24 to 48 hours after treatment.

But how big a problem is this? "Across the United States it probably happens in sporadic fashion," says Schaffner. "Unless a large group came for treatment at the same medical center, it would probably go unnoticed."

It's widely known that one should avoid getting a sunburn, but there is debate whether the eye injuries also could be associated with subsequent cataract development.

To prevent injuries from occurring, Schaffner says, cages should be put over the bulb, or bulbs that automatically switch off once the glass is cracked should be used. But both solutions are costly, and the latter is not as readily available as the standard lights. Once a light is damaged, it may go unnoticed, since the bulbs are typically inspected or replaced only once or twice a year.

The authors hope that by publishing the article, they will bring instances of outbreak to physicians' attention, so that when treating a patient with these symptoms and under similar conditions, doctors will notify their local health department.

The lead author of the report was Dr. David L. Kirschke, a former CDC trainee at the Tennessee Department of Health. Other study authors were Dr. Timothy F. Jones, assistant clinical professor of preventive medicine and deputy state epidemiologist at the Tennessee Department of Health, and Nicole M. Smith of the CDC.

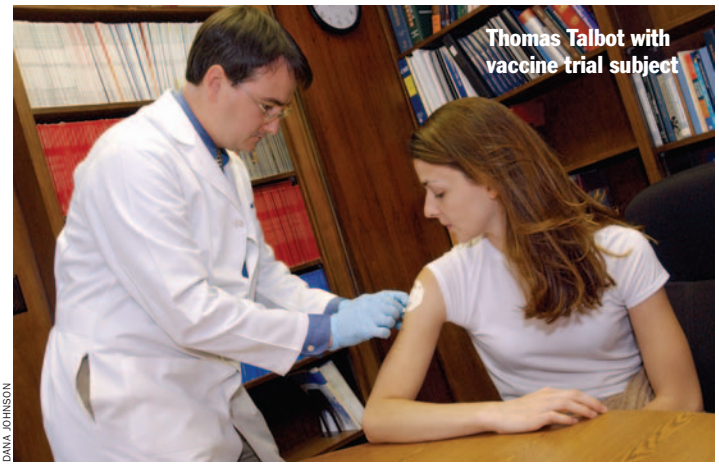
Fifty-Year-Old Smallpox Vaccine Effective Even When Diluted

In 2002, vaccine company Aventis Pasteur discovered a forgotten batch of smallpox vaccine, frozen since the 1950s. Given post-9/11 concerns about bioterrorism, interest in the vaccine was enormous. Would a vaccine nearly 50 years old still protect against smallpox and if so, how much could it be diluted and still remain effective?

Smallpox is caused by the variola virus that emerged in human populations thousands of years ago. It kills about 30 percent of its victims and scars the remainder for life. Thanks to a worldwide vaccination program, smallpox is now considered eradicated and the variola virus has been eliminated except for laboratory stockpiles. The last case in the United States was in 1949. Worldwide, the last naturally occurring case was in Somalia in 1977, and vaccination against smallpox among the general public was stopped.

In 2002 the U.S. resumed limited vaccination, and in 2003 the military inoculated more than 500,000 people. A form of the vaccine introduced in the 1970s could be diluted without significantly weakening its effects—but not enough to meet the Department of Health and Human Services' goal of having one dose for every U.S. citizen.

The National Institutes of Health left it to Vanderbilt's Kathryn Edwards, professor of pediatrics and vice chair for clinical research in the Department of Pediatrics, to determine if the Aventis Pasteur vaccine was still good. Edwards is principal investigator of two National Institutes of Health-sponsored smallpox vaccine clinical trials.


Thomas Talbot with vaccine trial subject

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Since then, studies have been taking place at Vanderbilt and other medical centers. In the most recent findings, Thomas R. Talbot, a fellow in infectious diseases at Vanderbilt, Edwards, and colleagues reported in the Sept. 8, 2004, issue of the *Journal of the American Medical Association* that even diluted doses of the Aventis Pasteur smallpox virus (ASPV) provide a nearly 100- percent effective smallpox vaccine, allowing for expansion of the available stockpile.

Researchers injected 340 healthy young adults at Vanderbilt, the University of Iowa, and Cincinnati Children's Hospital with the ASPV in a double-blind, randomized controlled trial conducted between October 2002 and February 2003. Test subjects were given one of three strengths of the vaccine: undiluted, a one-to-five dilution, or a one-to-10 dilution.

Overall, 99 percent of subjects had a successful vaccination and the rate did not differ significantly between the three groups. Nearly all study volunteers reported at least one post-vaccination symptom in the two weeks following vaccination, including vaccination-site itching, pain, fatigue, muscle pain, headache and fever. One-fourth missed some activities because of reactions to the shot. Dilution of the vaccine did not appear to reduce the occurrence of adverse reactions.

"[T]he existing supply of approximately 85 million doses of APSV can be expanded, leaving an ample stockpile of smallpox vaccine to protect the entire U.S. population in the event widespread vaccination is imminently needed," the authors conclude.

The study was supported by the National Institute of Allergy and Infectious Diseases' Division of Microbiology and Infectious Diseases Vaccine Trial and Evaluation Unit, and grants from the General Clinical Research Center of Vanderbilt University School of Medicine and University of Iowa. Co-authors Edwards and James Crowe received research funding from Aventis Pasteur and MedImmune, and Edwards also received funding from VaxGen.