Botox Boom

UW researchers continue to probe a poison they helped refine.

Ever since UW-Madison biochemist **Ed Schantz '31, PhD'34** cooked up his first batches in the 1970s, botulinum toxin — better known as Botox — has been on a therapeutic roll.

JEFF MILLER (3)

Botulinum toxin, commonly known by the trade name Botox, is helping to smooth the wrinkles of the aging process for millions of people. But the potent poison can do a lot more than erase frown lines — and its potential has UW scientists smiling.

Used first to treat crossed eyes, the nerve poison made by the bacterium *Clostridium botulinum* has filled a growing biomedical niche. Most famous by far is the cosmetic application of the toxin to smooth frown lines and wrinkles — which has spawned a lucrative industry and the existence of "Botox parties." With 1.6 million people receiving the cosmetic injections in 2001 alone, the market for the drug now exceeds $500 million annually.

But Botox isn't just for wrinkles, says **Eric Johnson,** a professor of bacteriology and food microbiology and toxicology who has become one of the leading authorities on the toxin. In the lab, Johnson is exploring the biomedical applications for the poison, including its potential in treating pain, a quality recognized when cosmetic users of the toxin reported diminished effects of migraine headaches.

That line of inquiry began with Schantz, who joined the UW Food Research Institute in 1972 and is generally acknowledged as the master of botulinum. Now ninety-five, Schantz got his start in the poison business during World War II, as a young Army officer at Fort Detrick, Maryland, then the home of the Army's biological warfare program. His job was to develop toxin countermeasures, as military intelligence worried about the potential of botulinum and other bacteria being used against American troops. Because the toxin loses its potency in the environment, it would never have measured up as a battlefield weapon, Schantz recalled in a 1992 interview. But he thought the toxin's unique characteristics might be valuable in other applications.

Six million times more powerful than rattlesnake venom, botulinum toxin works by attaching itself permanently to nerve endings and blocking chemical signals from reaching a muscle, weakening it and, with enough deadened nerve endings, causing paralysis. Victims of botulism-induced food poisoning usually suffocate after their chest muscles are paralyzed.

But the ability to neutralize motor neurons and paralyze muscles also lends the toxin to mitigating disease. It has been useful in treating a class of human ailments known as dystonias — runaway muscle spasms caused, scientists believe, by involuntary nerve impulses from the brain. Other applications have included treating the cramps that plague professional musicians, calming the muscles of children with cerebral palsy, and relieving the spasms suffered by some victims of stroke.

"It's really helped all kinds of people," says Johnson, who has seen it injected into the legs of a close friend to alleviate the symptoms of mild cerebral palsy. "It helps them live a better life."

Beginning in 1985, Johnson worked hours each day with Schantz to learn the fine points of making the poison — a process that is as much art as science. Purifying the toxin has been likened to making fine wine: even with a recipe, not everyone can do it, and the difference in toxin quality can be the same as that between a fine Bordeaux and cheap vino. "There can be a lot of batch variation," Johnson explains.

When used in therapy, the toxin is injected in minuscule doses, targeting just those muscles underlying a condition. To smooth wrinkles, for instance, a

small dose — usually about one-millionth of a teaspoon — of purified toxin complex is injected into the forehead, the usual target. There, the agent blocks the release by nerve cells of acetylcholine, a chemical that tells muscles to contract. In about a week, the wrinkles disappear.

Despite its widespread use, there are still many unknowns about botulinum's basic biology. Johnson's lab continues to create and study new generations of the toxin, and the lab has licensed its technology to a company called Mentor, which has opened in the University Research Park to develop botulinum-based drugs. Others on campus, such as Medical School physiologist **Edwin Chapman,** are puzzling out the secrets of how the toxin enters cells.

"It acts on different maladies in ways we don't understand," says Johnson. If you don't know the basics, "it's hard to predict just how something will be used medicinally," he adds. "But it has helped so many people that we're almost sure to find new uses. By no means is it finished in its development as a drug."

— Terry Devitt '78, MA'85

On the Biodefensive

Botox, as Eric Johnson notes, is "the most poisonous substance known." And while that makes it an important target for science, it also underscores the need for careful security surrounding it.

As the federal government ramps up research on potential agents of bioterror, those security measures are getting new scrutiny. While the university has always taken precautions to ensure that work with pathogens and toxins is conducted safely, the terrorist attacks of September 11 have forced universities and the government to reassess security measures. Several new procedures, ranging from physical barriers to stepped-up cyber-security and screening of lab personnel, are now in place at UW labs that work with hazardous agents.

But in some cases, new federal regulations are also bringing costs and hassles for researchers. The ability of faculty to place students in labs, exchange materials, and host visiting scholars has undergone fundamental change.

R. Timothy Mulcahy PhD'79, associate vice chancellor for research policy and Graduate School associate dean for the biological sciences, says the university is working to ensure that labs are safe and secure without diminishing productivity or hindering free inquiry. "The basic research we do is critical to a better basic understanding of how these organisms and their toxins work," Mulcahy says. "It's our best path to improved treatment and countermeasures for bioterrorism, and it has significant implications for improved public health."

Recent UW-Madison advances have included discovery of the receptors for both anthrax and botulinum toxin, which may make it possible to develop strategies to neutralize the toxins before they enter cells. UW-Madison researchers are also involved with the new Midwestern Regional Center of Excellence, based at the University of Chicago, one of several new centers the federal government funded to coordinate work on biosecurity threats, including anthrax, botulism, tularemia, hemorrhagic fever viruses, and plague.

"If we didn't do this work, and agents like these were used in a mass attack, as a nation we would be ill prepared to respond," says Mulcahy.

— T.D.

COOL TOOL

Two-Ton Tummy

UW's Big Stomach takes a bite out of the state's supply of infected meat.

Hungry enough to eat a cow? UW-Madison's mobile tissue digester can down three full-sized bovines and still have room for side orders. Affectionately known as the "Big Stomach," the stainless steel tank can hold up to four thousand pounds of meat, which is then reduced using heat and chemicals to a sterile slurry. The Wisconsin Veterinary Diagnostic Laboratory, one of the main sites for testing deer tissue for chronic wasting disease, has used the machine to safely dispose of some fifteen thousand samples from potentially infected deer. "It's the world's only large-scale, mobile tissue digester," says **Robert Shull,** the lab's director. Previously, animals infected with pathogens had to be incinerated, but the Big Stomach offers a safer, more environmentally sound way of deactivating the agents responsible for CWD "and anything else of an infectious nature that might be in there," says Shull.

— M.P.

Going for the Green

Can old tires improve your golf game?

Poised to putt a dimpled ball a few yards to the hole, **Jae "Jim" Park** thinks about what's happening beneath the golf course.

MICHAEL FORSTER ROTHBART

UW-Madison researchers John Stier, Jim Park, and Bob Lisi are proving that shredded tire chips can help make golf greens greener.

For several years, the professor of civil and environmental engineering — not to mention avid golfer with a six handicap — has investigated ways to keep the tons of fertilizers used on golf courses out of the groundwater. Recently, he may have hit upon the perfect blocking device: used tires.

Scrap tires pose their own environmental problem: most states forbid dumping tires in landfills, which has led to millions of discarded tires being stockpiled around the country. These piles tend to collect rainwater, creating a breeding ground for mosquitoes. Some have caught fire, causing severe environmental damage.

Based on his earlier research, which showed that confetti-sized pieces of scrap tires can absorb harmful compounds, Park imagined the chips could soak up pesticides and fertilizers applied to turfgrass. Nearly one thousand pounds of these chemicals are applied annually to most of the country's twenty-three thousand golf courses.

"Because many greens are built near groundwater levels or wetlands," explains Park, "it is vital to consider the mitigation of environmental contamination caused by the pesticides and fertilizers applied to golf courses."

Park — along with **John Stier,** a horticulture professor, and **Bob Lisi '01, MS'02,** a civil and environmental engineering graduate student — took the theory to a research site near the University Ridge golf course. They inserted a layer of the tiny tire chips between the layers of sand, peat root mix, and gravel commonly found beneath golf greens. They then soaked the test greens with water spiked with nitrate, a chemical often used as a fertilizer.

The researchers found that fields with a ten-centimeter layer of tire chips released about 58 percent less nitrate than samples without rubber bits. Plus, the plots appeared healthy, suggesting the rubber layers didn't alter turfgrass quality or growth.

But won't chemicals from the tires just percolate into the environment? Park says the tires give off minimal amounts of chemicals compared to what they can trap. He estimates that a rubber layer underneath just one eighteen-hole course could reuse up to seventy-two thousand scrap tires, helping erode mountains of waste.

— Emily Carlson

The Joy of Worm Sex

Birds do it, bees do it, and worms do it ... even though they don't have to.

The *C. elegans,* a species of worm often studied by biologists, comes in two forms: male or hermaphrodite. The latter has the capacity to self-fertilize, which would seem to make the former pretty much useless. Yet males persist, and hermaphrodites often choose to mate with them rather than ... well ... themselves. Those in the science community short on romance have pointed out that this doesn't make much sense: why would worms go to the trouble of having sex when they can get the same result on their own?

SPENCER WALTS

The answer, says genetics professor **Elizabeth Goodwin,** is that "sex is good." Her studies have shown that the offspring of sex with males have some cool developmental options not available to self-propagated worms. For one thing, they can switch sexes — a handy trick, since males can forage for food over greater distances.

"The advantage of having boys around is you have more flexibility in development and gene expression," Goodwin says. "It's probably not the only reason, but it seems to be one of the reasons *C. elegans* has kept boys around."

— M.P.

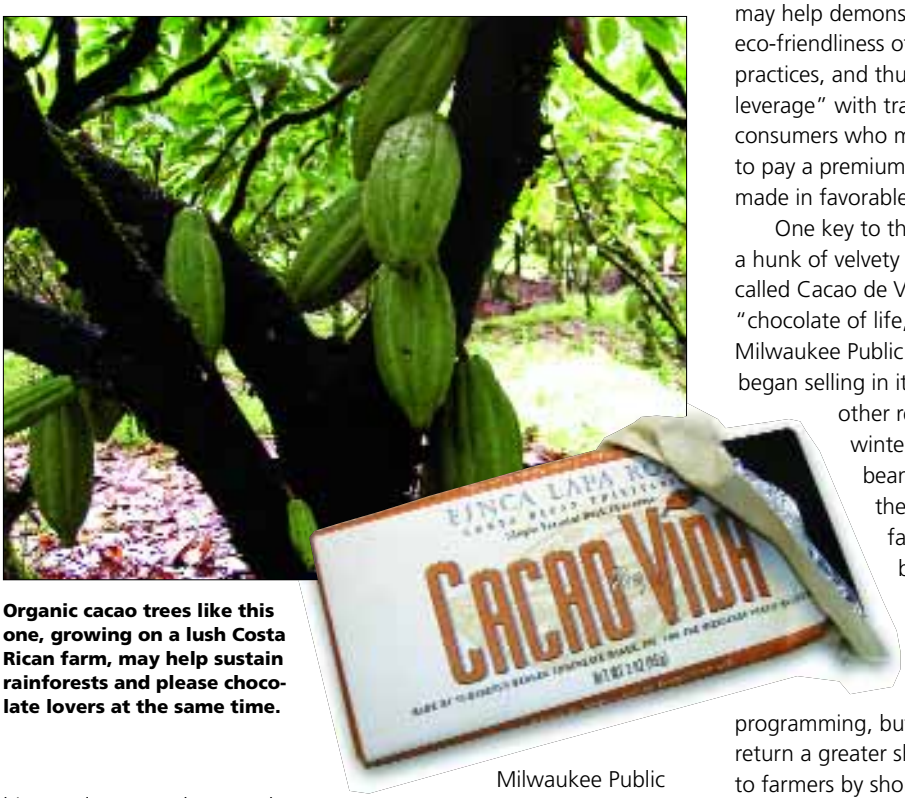
Looking for a Good Bar

UW joins the search for environmentally friendly chocolate.

If you think everyone loves chocolate, meet José Alberto Moore. He's had plenty of bad experiences with the stuff.

It's not a matter of taste. Moore runs a small-scale farm in Costa Rica, and, while his father made a living growing cacao, the bean behind the bars, terrible prices and ailing trees have soured José on the crop. When UW-Madison scientists **Ray Guries** and **Chris Vaughan** met him not long ago, he was about to give up on the beans entirely.

KERRIE CUNNINGHAM



Organic cacao trees like this one, growing on a lush Costa Rican farm, may help sustain rainforests and please chocolate lovers at the same time.

That is news the two researchers don't like to hear. Cacao trees often grow in forested landscapes replete with plants and animals — just the sort of lands ecologists want to protect. But in Costa Rica, which has a higher standard of living than the West African countries that harvest most of the world's cacao beans, a farmer can make more money planting bananas or, worse, selling his land to developers.

"We'd like not to see that happen," says Guries, a professor of forest ecology. "But if you want to stop that, part of [the solution] has to be creating enough value for cacao so that farmers will continue to grow it."

For the past few years, Guries and a group of scientists from UW-Madison and the Milwaukee Public Museum have been trying to keep farmers like Moore from abandoning cacao (which generally refers to the trees, while the Anglicized word *cocoa* refers to the products made from them). The team has set up experiments on a number of cacao farms, evaluating everything from lighting conditions to the animals that live among the trees, in the hopes of finding more sustainable ways of growing the beans. The goal is to describe a set of win-win conditions — where farmers make a decent living while protecting the ecological wealth of their environment.

"These are smart guys, and they understand the connections that can be made," says **Chad Wilsey,** a conservation biology graduate student who this summer will begin observing birds on a dozen cacao farms in the region. He says studies like his may help demonstrate the eco-friendliness of the farmers' practices, and thus "give them leverage" with traders and consumers who may be willing to pay a premium for products made in favorable conditions.

One key to that equation is a hunk of velvety dark chocolate called Cacao de Vida, or "chocolate of life," which the Milwaukee Public Museum began selling in its stores and other retail sites this winter. Made from beans grown on the cooperating farms, the bars benefit the museum's research and educational programming, but they also return a greater share of profits to farmers by shortening the chain between producer and consumer.

"The bars are important, because they provide tangible evidence to the farmers of what we've been doing," says Guries. "If farmers can see economic value to doing what we suggest, there will be a reason for them to remain in farming." And that's a solution that tastes great to everyone.

— Michael Penn

SPENCER WALTS

A group of lab mice strung out on runner's high are yielding evidence that **exercise can be addictive.** When three zoology researchers studied the brain activity of mice with a special affinity for their exercise wheels, they found the animals' love of running may be wired into their brains. In fact, if the mice aren't allowed to run for a day, the same regions of their brains activate as those in addicts when they are prevented from getting their daily fix of cocaine or morphine. The finding could explain why some people demonstrate great desire to exercise, while others have to force themselves to the gym.

Hospitals usually help people get well, but new research suggests that they also harbor many germs that make patients sick. In one study, Dennis Maki'62, MS'64, MD'69 of the UW Medical School found that nine in fifty EKG wires used to monitor patients' hearts were contaminated with **drug-resistant bacteria,** even after they were cleaned. Many hospitals — including the UW Hospital and Clinics — are now re-evaluating their procedures for handling medical equipment.

Wisconsin has more certified **organic farms** than all but two states, but government and universities provide relatively little support for them, according to a new report by the Center for Integrated Agricultural Systems and the Gaylord Nelson Institute for Environmental Studies. The state's organic production grew 92 percent from 1997 to 2001, which the researchers say makes it ripe for public and private investment.