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FINDINGS

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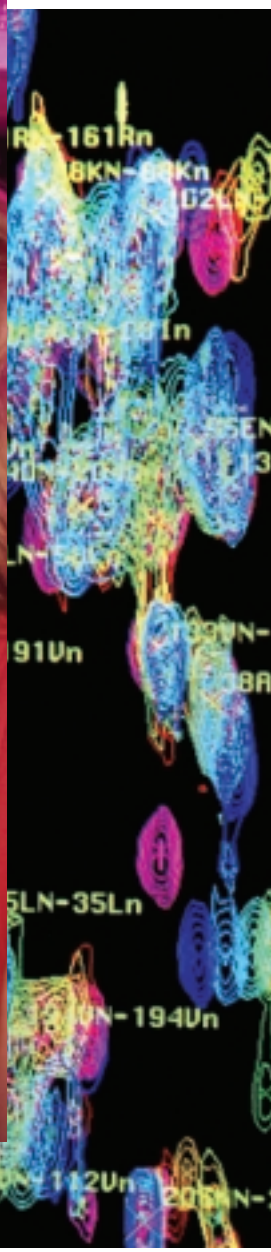

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On the Cover

Photo of Brad Goodner: *David Shoenfelt*

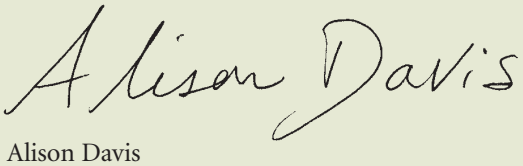
Photo of Dorothee Kern: *Mike Lovett*

Editor's Note

Well beyond childhood, many people still like playing with toys. Wastebasket hoops make tossing trash entertaining, and who doesn't enjoy all those neat kitchen and household gizmos? Scientists also love gadgets, especially those that make experiments more productive—and sometimes more fun to do.

Powerful microscopes can keep a scientist spellbound while gazing at the spectacular imagery of what's going on inside living cells. Huge magnets, like the one biophysicist Dorothee Kern uses to eavesdrop on molecular motion (see story on page 8), cost nearly $1 million apiece, but these scientific gadgets are indispensable for the experiments Kern does every day. Much more than just fancy things to play with, these sophisticated pieces of equipment steer scientists toward precious "Aha!" moments of discovery.

But tools alone cannot make the breakthroughs that lead to new medicines and better knowledge about health and disease. One scientist recently asked me to guess, "What's the most important scientific gadget in the lab?" It's a tool of invention like no other, she continued. And then her answer seemed so obvious. "The human brain," she said.



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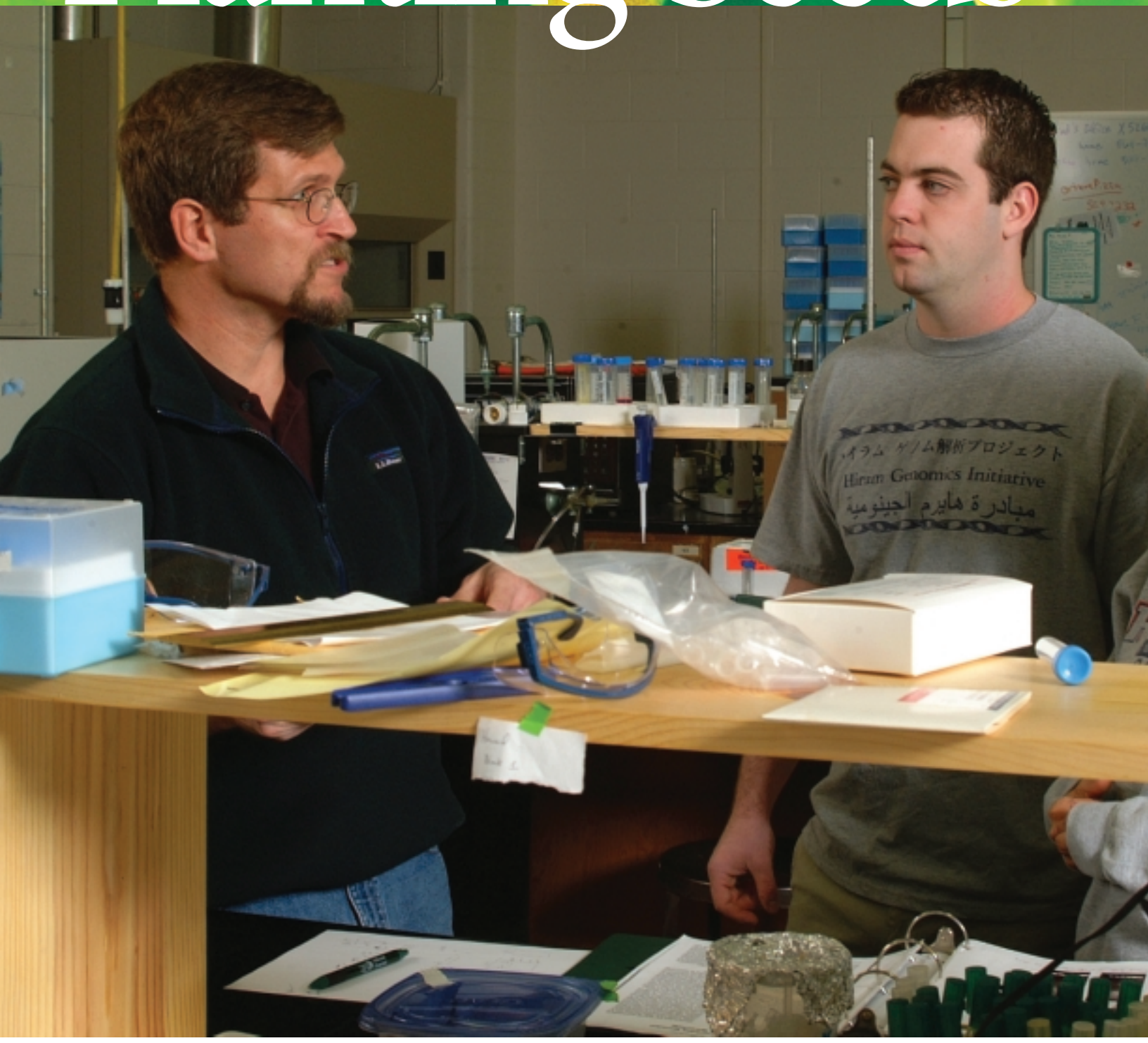
Planting Seeds



David Shoenfelt

Brad Goodner (left) is a biologist at Hiram College in Ohio. Goodner and his students study the genetic secrets of bacteria that can infect both plants and humans.

By Alison Davis

Step inside Brad Goodner's lab at Hiram College and you'll see the usual stuff.

There are computer screens, beakers and test tubes, moldy-looking things growing in culture dishes. And lots of people doing experiments.

The folks growing the slimy stuff in the dishes, working on the computers, and pouring liquids into the test tubes are not graduate students, lab technicians, or even Goodner himself. They are college students—on any given day, biology or chemistry majors, business students, psychology or computer science majors.

Many of them, such as sophomore Adam Ewing, treasure the chance to do research.

"I'm working on a part of something that nobody else has worked on before," says Ewing, a double-major in computer science and biology at this small college near Cleveland, Ohio. He is already planning to move on to graduate school.

Goodner's lab is a hands-on learning wonderland, and that's because the 42-year-old biologist is deeply dedicated to science, particularly to teaching it.

"I love seeing the light bulb go on [in my students]," he says.

But Goodner is also serious about pushing forward his research program, and he believes that college students are an important, even vital, part of that goal. Undergraduates not only help get the experiments done, he says, they also assist in other ways, such as growing the lab's expertise.

Ewing, for example, has acquired valuable knowledge in the area of bioinformatics, a science dedicated to sorting huge amounts of biological data and assigning meaning to it. He is currently applying some of this knowledge to the lab's research goals.

Goodner chooses his projects carefully, to accommodate the schedules and skills of his undergraduates as well as to satisfy his own scientific curiosity.

"I have to be interested in what I am doing, or it isn't worth it," he says.

What kind of science does Goodner find worth studying? The genetic secrets of microbes, particularly so-called plant pathogens. He wants to know how bacteria do their dirty work of causing infections that can lead plants to develop tumors.

Of Plants and People

Do plants really get tumors?

Yes, plants can and do get diseases, some of which cause the growth of external tumors such as those called crown galls on the trunks or branches of trees. One particular bacterium, *Agrobacterium tumefaciens*, injects a piece of its own genetic instructions into a wounded area of a leaf or bark. The inserted material contains a signal that tells the plant's cells to grow rapidly, divide, and form a tumor. Crown gall diseases are responsible for major economic losses in over 600 species of crops.

Goodner is interested in more than the plants or their tumors. He wants to know how some plant pathogens can occasionally infect people. Microorganisms that can pull off this sort of trick are called opportunistic pathogens, and they can be fatal to people with AIDS and other diseases that weaken the immune system.

Brad Goodner (tree), David Shoenfelt (carrots)

Microbes such as *Agrobacterium* can infect a variety of plants, causing tumors.

Over time, evidence has grown to suggest that *Agrobacterium* is among the plant pathogens that can infect animals and humans. Goodner has dug up more than 60 medical reports of opportunistic diseases caused by *Agrobacterium*. His interest lies in understanding the process by which this microbial menace makes its way into people with weakened immune systems.

How could the common soil microbe find access to sick people, you wonder?

"Everyone brings a potted plant to someone in the hospital or tracks in some dirt on their shoes, so *Agrobacterium* is often found on floors and other surfaces," Goodner says.

Most of us do not have to worry about dangers lurking in the soil of our houseplants. Healthy people deal with opportunistic pathogens like *Agrobacterium* with the immune defenses they are born with or by developing immunity during childhood after routine exposure to bacteria. Remember getting a cut while walking barefoot through the grass or consuming a "scrumptious" slice of mud pie?

But to an immune system that isn't working at full steam, otherwise harmless microbes can pose special problems. Goodner wonders if an aging population with more people who have weakened immune systems can bring into the spotlight many pathogens that don't normally cause trouble. Currently, he says, few doctors even know to look for them.

For example, researchers have spotted *Agrobacterium* in blood samples from infected patients only after the usual microbial suspects have been ruled out and a hospital lab technician has gone on to identify a strange microorganism growing in the culture dish, Goodner explains.

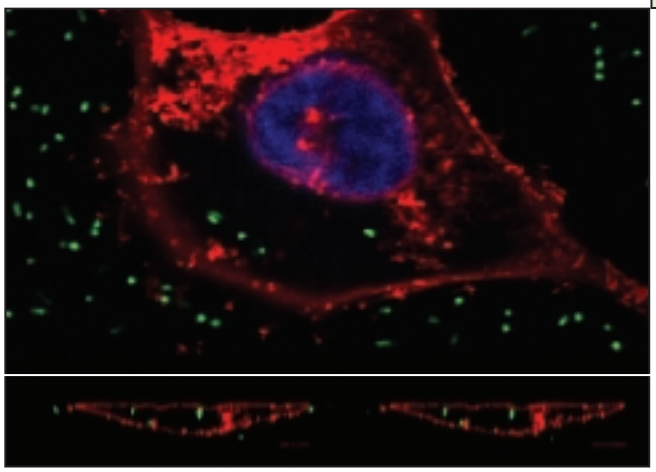
Further complicating the picture is the fact that more than one disease has been associated with an *Agrobacterium* infection. Medical reports have described cases of this bacterium causing an infection of the blood called bacteremia and infections of the muscles, eyes, and abdominal cavity. In each case, the infection site was the place where the bacterium gained access to internal body tissues through a wound, a surgical procedure, or an implanted medical device.

To date, Goodner has tracked down three of the *Agrobacterium* strains isolated from infected patients. He is busy trying to determine how these three versions of the microbe and the plant-infecting *Agrobacterium* strains are alike or different. One thing that stands out immediately is a genetic change: None of the human isolates of *Agrobacterium* contains a tiny circle of DNA called the Tumor-inducing, or Ti, plasmid, which is an essential ingredient of the *Agrobacterium* varieties that cause plant tumors.

And perhaps not surprisingly, none of the human isolates can infect plants.

In careful experiments with cultured animal cells, Goodner and his students have determined that the human-infecting *Agrobacterium* strains may be able to bust their way into cells (see photo, below). Researchers call pathogens that can perform this complicated maneuver invasive.

That's different from the strains of *Agrobacterium* that infect plants. The plant-infecting strains, Goodner explains, are never invasive. Rather, they sit on an open plant wound and "shoot things inside," like a piece of the Ti plasmid DNA that delivers instructions to the plant to make hormones that help the bacteria survive on the plant's exterior.

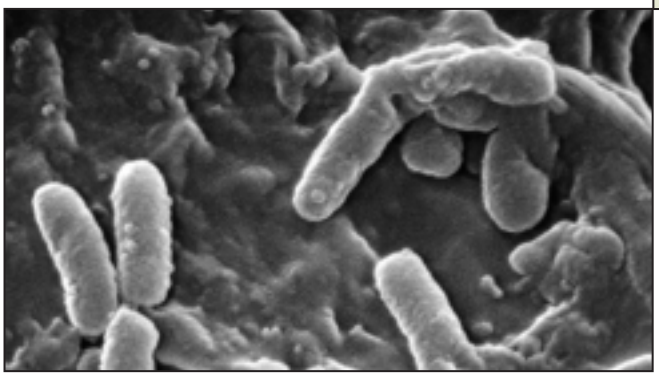


C. Crowe, S. Weeks

Agrobacterium (green dots) isolated from a patient infected with the bacterium can invade mouse cells cultured in the lab. The bottom picture is a microscope's view through the side of the same cell, showing *Agrobacterium* inside.

Jacks of All Trades

Some pathogens—by definition, microorganisms that cause disease—have the uncanny ability to infect a wide range of living things. For example, one notorious opportunistic pathogen, *Pseudomonas aeruginosa*, can infect plants, insects, and humans. In burn patients, *P. aeruginosa* is the most common cause of a life-threatening condition called sepsis, and it is the leading cause of lung infections and death in people with cystic fibrosis.



CDC/Janice Carr

Pseudomonas aeruginosa is a notorious bacterial pathogen that can infect plants, insects, and humans.

Slight changes in the chemical "spellings" of microbial genes can also endow microorganisms with the ability to thrive in different places within the same host. The strains of the *Streptococcus* bacterium that can give us "strep throat," for example, are genetically different from the *Streptococcus* strains that cause scarlet fever or other serious infections like toxic shock syndrome.

Whatever the organism in which a microbe makes its home, a complex relationship exists between the microbe and its host. Some bacteria, like the one that causes ulcers in people, live happily in the intestinal tract for years. *Agrobacterium* can survive in a plant tumor for decades. It's possible, Goodner says, that microorganisms use common tricks to enable them to shift from host to host, and he is hoping his research may unlock some of these secrets. How do strains become different? How do pathogens take advantage of different conditions?

"These are questions we still don't have the answers to," he says.

Goodner thinks that the *Agrobacterium* strains found in sick patients have undergone a number of genetic changes to adapt to a new environment (the human body), since those strains grow better at warmer (body) temperatures, and their DNA is sprinkled with sequences that confer resistance to the weaponry of humans: antibiotic medicines. He is currently pursuing what outcomes those genetic changes may have on the function and behavior of *Agrobacterium*.

To begin to examine these possibilities, Goodner and his students are combing through the microbe's genetic code, looking for genes that direct the production of factors important for communicating with a host cell, or perhaps for stealing some of the host's nutrients.

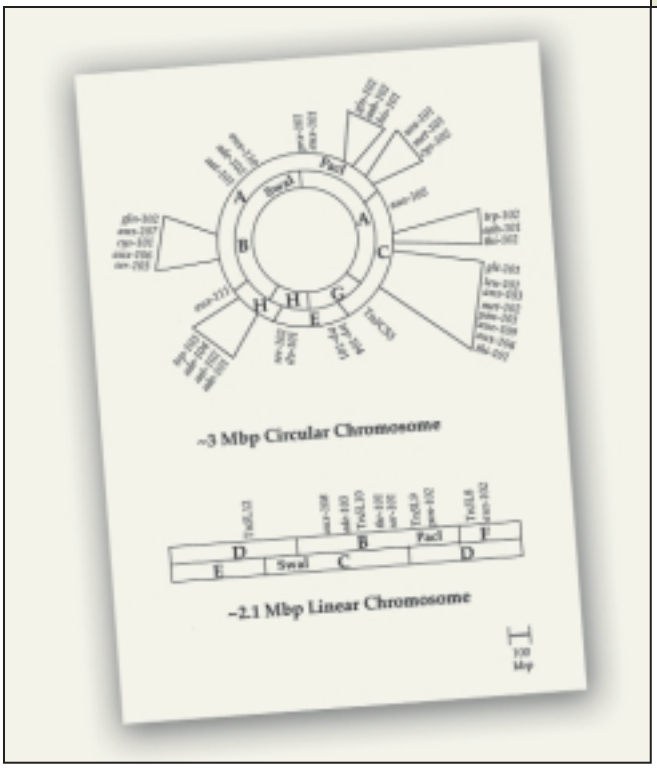
So far, Goodner and his students have unearthed one potentially interesting set of genetic instructions within the *Agrobacterium* genome, those that direct the production of powerful chemicals called polyketides and nonribosomal peptides. These bacterially produced poisons are known to serve as signals between interacting species, and they can be lethal to a microbe's enemies:

Planting Seeds

other bacteria, fungi, or plants. Several medicines, such as the antibiotic erythromycin and the cancer drug doxorubicin, are polyketides. Getting a handle on the roles polyketides might play in making *Agrobacterium* a versatile and effective infectious agent may reveal important details about the pathogen and point to ideas for new therapies.

In the Beginning

Having worked on *Agrobacterium* as a graduate student, Goodner left it behind to concentrate on plant development, first as a postdoctoral researcher and then as a new faculty member at the University of Richmond in Virginia. However, he returned to *Agrobacterium* and has never regretted the decision because it led to a significant research achievement. He and his students led one of two large research teams that published the *Agrobacterium* genetic code in one of the biomedical research world's major journals, *Science*.



Goodner and his students published a genetic and physical "map" (left) that revealed the existence of *Agrobacterium*'s extra chromosome.

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It all started in 1996 when Goodner, while preparing to teach a new course, saw a research article about *Agrobacterium* hinting that the microbe had two chromosomes, not one, as scientists had believed for years. Goodner decided to "do a few experiments" within the course to begin to address this perplexing observation. Those few experiments led him to change his research focus and to a subsequent 2 years of work done by students both within courses and in independent research projects.

The result was a landmark research paper defining clearly that, yes, *Agrobacterium* did have an extra chromosome. The team published a genetic and physical "map" describing the newly discovered genetic characteristics of *Agrobacterium*.

"The second chromosome looked really different, as if it came from somewhere else. We wanted to know more about it, so it became our own little 'mini' genome project," he says of the team effort he embarked upon with his students.

Scientists at Cereon Genomics, a division of Monsanto Company, took notice. At the time, the company had begun an effort to decode the complete genome of *Agrobacterium*. Their interest in the microbe lay in its use as a powerful resource for producing transgenic plants. Some researchers are producing novel medicines, such as edible vaccines, by inserting certain genes into plants with the help of *Agrobacterium*.

"It was clear that Brad's [*Agrobacterium* genetic] map was going to be an extremely useful tool for us," says Steven Slater of Monsanto Protein Technologies. Slater approached Goodner at a scientific conference and asked him if he was interested in pursuing a collaboration that included the students' effort.

According to Slater, Goodner's students were instrumental in carrying out several steps of the project, including creating methods to decode the genome and filling in gaps in the partially completed sequence of genetic code. Slater and his fellow company scientists co-published the *Agrobacterium* genome sequence with Goodner and his student team.

Slater is quick to note that, for him, a major draw of the collaboration was its educational value, so much so that he is doing it again. Slater and Goodner are already working together to decode another microbial genome, *Sphingomonas elodea*, and Slater thinks the setup could be emulated by others.

Another key step in the *Agrobacterium* genome project to which Goodner's students made an important contribution was the process of "annotation," a sort of checks-and-balances process in which gene sequences are verified and matched to potential cellular functions.

These efforts spun off many additional projects that are currently being followed up either by Goodner's students or by Slater's team.

One such effort was launched by student Adam Ewing. He single-handedly created a "proteomics" database that he and Goodner hope will serve as a clearinghouse for the entire *Agrobacterium* research community. Proteomics is the large-scale analysis of all of the proteins encoded by an organism's genome. Ewing's database is a novel tool that will enable researchers to search for proteins encoded by *Agrobacterium* genes based on the proteins' predicted chemical properties, not just on their gene sequences.

Can-Do Attitude

Goodner strongly opposes the notion that "undergrads can't do research." In his lab, they do all the work, with guidance and support from him. Students co-author scientific publications along with Goodner, and they present their projects at national scientific conferences, where they are sometimes the only undergraduate attendees.

Above all, Goodner says, "They learn how to solve problems."

"You don't want to leave college saying, I wonder if…" Goodner says of the advice he gives to students considering doing research projects. "If it's interesting, do it now, while you're an undergraduate."

In the 9 years Goodner has had his own lab, he has supervised about 50 students. They have gone on to obtain graduate degrees; attend medical, veterinary, or law school; or pursue many other careers, such as journalism or business. By and large, his students have been successful in getting interviews and jobs.

"Everybody wants to hire a problem solver," he says. ■

Junior Explorers

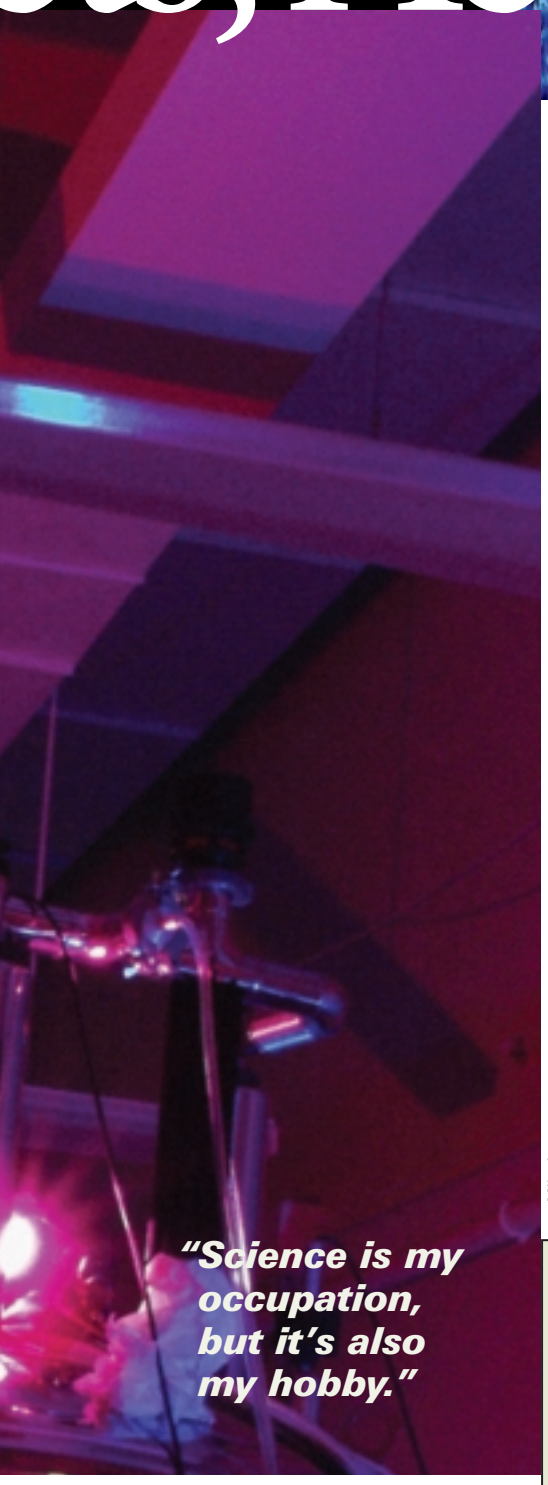
Brad Goodner's experience in getting undergraduates into the research act set the stage for extending teaching beyond his own lab and classroom. Last year, he and a few biology department colleagues launched the Hiram Genomics Initiative (HGI), an outreach program involving Cleveland-area high school students. The goal of the effort, supported by seed money from Hiram College, is to invite high schoolers to design and conduct experiments in collaboration with the college students at Hiram. Linking pieces of the HGI project together is an internal journal, *Genome Explorer*, in which students communicate their research results and hone their critical thinking and writing skills. Working together, the students learn how to generate a genetic and physical map of a genome or how to interpret a genomic sequence, which Goodner describes as looking like "someone aimlessly banged away at a typewriter with only four keys (A, C, G, and T)."

"It was nothing like any other method of study I had experienced in high school," says college freshman Tim Lukianowicz, who participated during his senior year at Benedictine High School in Cleveland. "In no other class was I able to integrate what I learned with real-life studies." —*A.D.*

Enzymes, Magne

ets, Action!

Mike Lovett



Mike Lovett

"Science is my occupation, but it's also my hobby."

Dorothee Kern is a biophysicist at Brandeis University in Waltham, Massachusetts. Kern studies the action of enzymes using a technique called NMR spectroscopy.

By Alisa Zapp Machalek

The point guard breaks free with the ball, dribbles past the defenders, jumps, shoots and—*swish*—two points!

Like star basketball players, worker molecules called enzymes grab, move, and stretch to carry out chemical reactions inside our bodies.

So says Dorothee Kern, a biophysicist at Brandeis University in Waltham, Massachusetts. And she should know. Previously a professional basketball player in the former East Germany, Kern, 37, now examines in fine detail the actions of enzymes. She has found that during chemical reactions, these talented molecules get entirely into the action, much like basketball players who use not only their arms to shoot the ball, but also their eyes to see the basket and their legs to jump up to it.

As a basketball player turned researcher, Kern is "the most energetic scientist I've ever known," says biophysicist Christopher Miller, whose lab is next door to Kern's. "She has a kind of hyperactivity, but a focused hyperactivity. … It's a rare combination and very fun to watch."

Behind the Iron Curtain

Kern says she forged her life path in direct response to the political situation in her homeland. A well-rounded athlete who enjoyed swimming, track and field, and other team sports, she chose to focus on basketball because it wasn't an Olympic sport. In Communist East Germany, she says, coaches of Olympic sports required their athletes "to practice all the time and take a lot of steroids." Because Kern always put school-work before sports, she says basketball was perfect for her.

"It was very competitive, but I could still go to school and get my degree in the normal time period."

Basketball was also more than just a physical game for Kern—it was an intellectual one. For 10 years, she played point guard, first for the East German team and then for the United German National team.

According to Kern, as point guard she was "the thinker on the court." It was her job to plan the plays. She traveled all over the world playing in international tournaments, including some in which she was pitted against the United States.

In addition to influencing Kern to focus on basketball, her objections to Communist ideology also solidified her decision

to pursue a career in science. "I grew up behind the Iron Curtain," she says, where the political and economic system was, in her words, "bizarre." To her, science seemed less vulnerable to politics.

"In science, facts are facts. They can't be twisted easily," she says.

Having a scientific family didn't hurt either. Both of Kern's parents are chemists, her older brother is a physician, and her younger brother is a physicist.

"We used to have arguments over dinner about how to explain what's going on in nature," she chuckles. "My whole family is interested in scientific questions."

An Atomic Radar Gun

The question that intrigues Kern now is how enzymes jiggle around when they carry out, or "catalyze," chemical reactions. An enzyme is a molecule (usually a protein) that works by latching onto another molecule, known as a substrate, and causing a chemical change in it.

Often, the backdrop for Kern's experiments is a three-dimensional structure of the enzyme protein she is studying. These structures are "molecular pictures" that are usually determined with a technique from physics called X-ray crystallography. Kern likens such a structure to a snapshot of a basketball player in action. The photo may show the shape and size of a player, but it doesn't demonstrate her speed, agility, skill, or strategy. In the same way, an X-ray crystallographic structure is just a starting point for Kern.

Dorothee Kern

Before becoming a scientist, Kern (with ball) was a professional basketball player in what was then East Germany.

"We need to go beyond static structures to understand how proteins are working," she emphasizes.

True to her own active nature, Kern is interested in a protein's action or "dynamics."

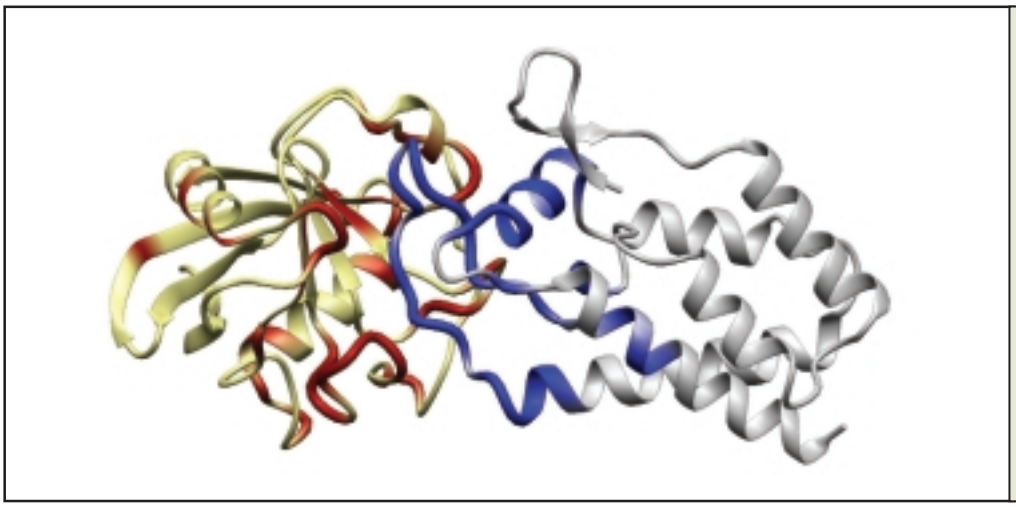
"A little bit of this interest comes because I love sports," she laughs. "Usually, I start my talks with a movie of a basketball game and say, 'that's protein dynamics' demonstrated [on a large scale]."

To study protein dynamics at the molecular level, Kern uses a technique well suited for such work—nuclear magnetic resonance (NMR) spectroscopy. This technology is based on the same physical principles as the magnetic resonance imaging (MRI) machines that doctors use to visualize organs such as the brain, heart, and kidneys. NMR is capable of detecting even the most fleeting movements within molecules. And it can simultaneously measure the motion of many different atoms in a molecule.

Kern has made some remarkable discoveries about the action of a medically important molecule called human cyclophilin A. This protein was originally identified as the molecular target of cyclosporine, a drug that is used by doctors to prevent immune rejection of transplanted organs. A better understanding of how cyclophilin A works may enable researchers to improve life-saving cyclosporine medications.

Since its initial discovery years ago, researchers have learned that human cyclophilin A can do other things. For example, the molecule can be commandeered by HIV, the virus that causes AIDS. Without cyclophilin A, HIV cannot replicate normally within cells. If scientists could find a way to cripple the interaction between HIV and cyclophilin A, they might be able to slow the spread of the virus in people infected with it.

In addition to having clinical relevance, cyclophilin A and related enzymes pique the interest of basic researchers like Kern. These molecules are found in many tissues in the human body and in "simpler" creatures all the way down to bacteria. Scientists suspect that these enzymes play essential roles in getting newly minted proteins to fold properly and in facilitating communication within cells.



Dorothee Kern

One of HIV's proteins (HIV capsid, silver) attaches to the cyclophilin A protein (gold), helping the AIDS virus spread throughout an infected person's body. Kern discovered which portions of the proteins move (blue, red) during this reaction.

Like every protein, cyclophilin A is made of a chain of amino acids. As proteins go, cyclophilin A is quite small, consisting of only 160 amino acids. It catalyzes a reaction called isomerization, in which cyclophilin A flips a part of its substrate 180 degrees, rather like flipping a light switch from an "up" position to a "down" one. And it does this with lightning speed—about 5,000 times per second.

Kern's research team uses NMR to examine the cyclophilin enzyme while it is in its resting, inactive state, as well as when the protein is in action. The researchers do this by supplying the enzyme with varying amounts of substrate. Using NMR, Kern was expecting to get a broad-brush impression of which areas of an enzyme stretch and bend the most. But even better than discovering such "dynamic hot spots," she and her coworkers found that they could use NMR like a radar gun to measure exactly how fast specific atoms in a protein move during a chemical reaction, clocking their speed in microseconds, or thousandths of a second.

Mike Lovett

Kern's research team includes two undergraduates, five graduate students, and two postdoctoral researchers.

Kern was the first scientist to simultaneously measure the movement of many atoms within an enzyme as it catalyzed a chemical reaction. She says that if you consider the protein to be a basketball player, this is like being able to see the movement of each finger and toe.

Initially, Kern identified a handful of amino acids that appear to be involved in grabbing the substrate and one that is necessary to actually flip the substrate switch. Now, as she refines her experiments, she continues to detect movement in new areas of the cyclophilin A molecule. At last count, about 30 amino acids wiggle around when cyclophilin A grabs its substrate, and at least 10 flutter while the enzyme performs its chemical reaction.

Kern's ultimate goal is to understand every quiver and flutter of cyclophilin A so well that she can make a "movie" of the molecule as it carries out its reaction. Watching such a movie would not only teach scientists—in atom-by-atom detail—about the actions and interactions of human cyclophilin A, but it would also shed light on the behavior and properties of many other enzymes.

To that end, Kern is also using NMR techniques to examine the movement of other proteins, including a cancer-associated protein called Pin1 and a molecule called tau, which has been linked to Alzheimer's disease.

Dorothee Kern

Kern and her husband, a biochemist, enjoy hiking, skiing, and many other outdoor activities with their two daughters, ages 5 and 9.

Work Hard, Play Hard

If Kern has a motto, it may well be "work hard, play hard."

When asked what advice she'd give to young people considering careers in science, she responds: "Don't give up your hobbies." Kern believes having interests outside science energizes people and spurs their creativity, both of which she says are key to doing science well.

Kern certainly takes her own advice. She plays regular pick-up basketball games with Brandeis colleagues and students. She also coaches soccer, track and field, and basketball.

"She's a fanatic outdoors woman," says Miller. "She and her husband and two young kids go sea kayaking around Cape Cod, mountain climbing…[and] all sorts of daredevil things."

In order to make time for family, hobbies, and other activities, Kern stresses the importance of working productively. "Efficiency is more important than how many hours you spend in the lab."

Her own efficiency, learned early through juggling school and sports, was further honed during her graduate studies, when she was shuttling between two different countries, playing basketball games every weekend, and attending training camps and international tournaments that could last for weeks.

Kern earned an undergraduate degree, a master's degree, and a Ph.D. in biochemistry all at Martin Luther University in Halle, Germany. In 1989, one month after she began her Ph.D. program, the Berlin Wall fell.

This caused a "big, big change in the lives of everyone in East Germany," Kern remembers.

For her, it opened up a whole new world of scientific opportunity. At the time, Kern's university didn't have NMR machines that could answer the scientific questions that interested her. A professor in Sweden learned of her research and invited her to continue her studies using his NMR facility.

So began 4 years of international commuting. Kern would collect NMR data in Sweden on Tuesdays through Fridays, bring the data back to Germany to analyze it, sleep on the night ferry back and forth, play basketball games on the weekends, and attend basketball practices on Mondays.

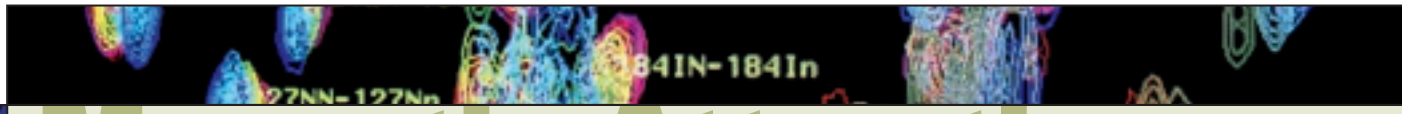
These days, Kern's schedule is still full, but less frenetic. She teaches a graduate course in enzymology and leads a research lab of 10 people. She calls this combination of teaching and research a "dream come true."

"What I'm doing is really a privilege," Kern says.

"Science is my occupation, but it's also my hobby. Compared to a lot of other people who have to work to make money, scientists work because they love it." ■

Bruce Tanner

Kern remembers clearly when the Berlin Wall was torn down, allowing her to travel freely and to interact with scientists in non-Communist countries.



Magnetic Attraction

Mike Lovett

Like many other biomedical researchers, scientists who use NMR spectroscopy rely on harmless lab bacteria to produce "labeled" proteins for their experiments. Here's how it works. First, NMR scientists need to put their bacteria on a special diet because only certain forms, or isotopes, of each chemical element contain the correct magnetic properties to be useful for NMR studies. If a researcher wants to study a protein that contains ^{13}C or ^{15}N, the two most commonly used isotopes in biological NMR research, the bacteria are fed food containing these isotopes.

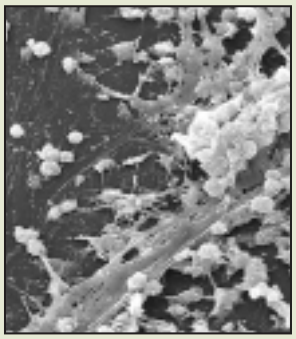
Next, the scientists isolate and purify the protein they want to study and mix it in a chemical solution. They place a few drops of the protein sample into a slender glass tube. To start an experiment, they insert the tube into a powerful, specially designed magnet the size of an industrial refrigerator.

These enormous, superconducting magnets are the heart of NMR research. Cooled with liquid helium to near absolute zero (minus 460 degrees Fahrenheit), their magnetic field is hundreds of times stronger than that on Earth's surface. If you ever visit a lab containing such a magnet, you'll be told to remove your watch and wallet, because NMR magnets are notorious for stopping analog watches and erasing the magnetic data on credit card strips.

Now the special isotopes in the protein sample come into play. Tiny magnetic fields in the centers of the isotopes line up with the NMR magnet just as iron filings align on a toy magnet. The researchers blast the sample with a series of split-second, computer-controlled radio wave pulses that scramble this magnetic arrangement. By measuring the change in magnetization, researchers can analyze the movements of individual atoms within a protein. The entire process can require as little as a second for a single, simple experiment, or weeks to months for a complex molecule.—*A.Z.M.*

Ironing Out Illness

To help fend off microbial enemies, the human body secretes natural antibiotic substances in body fluids such as tears, nasal mucus, and breast milk. These substances act like molecular armor, killing on contact bacteria that can make us sick. If these defenses fail in preventing an acute (quick onset, short-lived) infection, antibiotic medicines can usually quash the infection. On the other hand, chronic infections, which persist for a long time and resist antibiotics, can be ferociously difficult to treat. One of the hallmarks of many chronic infections is the presence of a bacterial biofilm, a specially constructed "neighborhood" of bacteria encased in a protective matrix that contains a network of channels for the flow of nutrients. Biofilms are associated with lung and ear infections as well as with tooth decay. NIGMS grantee **E. Peter Greenberg** of the University of Iowa in Iowa City discovered a biofilm killer, called lactoferrin, hiding in body secretions. Greenberg and his coworkers found that very low levels of this substance could prevent one type of bacteria—the kind that can cause lung infections in people with cystic fibrosis—from forming biofilms. Lactoferrin grips tightly onto iron, an important ingredient for the livelihood of many bacteria. The researchers determined that lactoferrin stimulated the bacteria to "twitch," or wander around in search of iron and other nutrients. While the small amount of lactoferrin the researchers applied to the bacteria was not enough to kill them, it nevertheless kept the bacteria from settling down into a durable biofilm structure. The findings offer possible strategies to interfere with the formation of biofilms and treat or prevent biofilm-related illnesses.



CDC/Rodney M. Donlan, Janice Carr

Finding a Cancer Drug's Mistakes

Years of basic research probing how cells communicate recently led scientists to develop a new kind of cancer drug. Doctors now use this medicine, called Gleevec™, to treat the rare blood cancer chronic myelogenous leukemia (CML). The drug works by blocking a cell-communication stream that is always "on" in this type of cancer. Gleevec's molecular target is a protein called a kinase, which acts like a molecular relay baton to convey messages inside cells. Although Gleevec's discovery was an exciting step forward in the treatment of cancer, in the short time this drug has been in clinical use, cancer cells have scored a gain in the battle against CML. Some patients' cancer returns because the tumor cells have become resistant to Gleevec. NIGMS student trainee **Mercedes Gorre** and researchers at the University of California, Los Angeles, combed through the human genetic code for Gleevec's target, a kinase protein named bcr-abl. Working together with UCLA scientist Neil Shah, Gorre obtained blood samples from 32 patients whose disease had returned after Gleevec therapy. Extracting DNA from these samples, the researchers carefully analyzed the "spelling" of the gene that directs the manufacture of the bcr-abl kinase. Of those samples, 29 of 32 had spelling errors that caused the resulting bcr-abl kinase protein to be misshapen, preventing binding to molecules of Gleevec. This work is expected to play a significant role in developing the next generation of drugs to treat CML.

Vitamin C Improves Skin Grafts

Everyone knows the importance of vitamin C as part of a healthy diet. Now, researchers may have found a new medical use for the classic citrus fruit vitamin. According to NIGMS grantee **Steven Boyce** of the Cincinnati Shriner's Burns Hospital and the University of Cincinnati, vitamin C may improve the treatment of burn patients' wounds. In a recent study, Boyce and his coworkers found that adding the vitamin to lab-grown cultures of human skin cells improved the grafting properties of cultured skin substitutes, which Boyce created by growing skin cells on top of a polymer sheet. The more closely a cultured skin substitute resembles natural skin, the more effective it is likely to be, and Boyce already knew that cultured skin substitutes tend to grow better when bathed in a special mix of nutrients. In the new study, he and his coworkers discovered that the skin substitutes grown with vitamin C provided a better barrier for covering burn wounds. The team also found that after grafting, wounds covered with the vitamin C-treated cultured skin substitutes closed faster than wounds covered with cultured skin substitutes grown without the vitamin added. Another important benefit of vitamin C, Boyce learned, was that cultured skin substitutes grown with

vitamin C remained viable longer in the lab. In the future, this could mean greater availability of cultured skin substitutes for treating patients with severe burns.

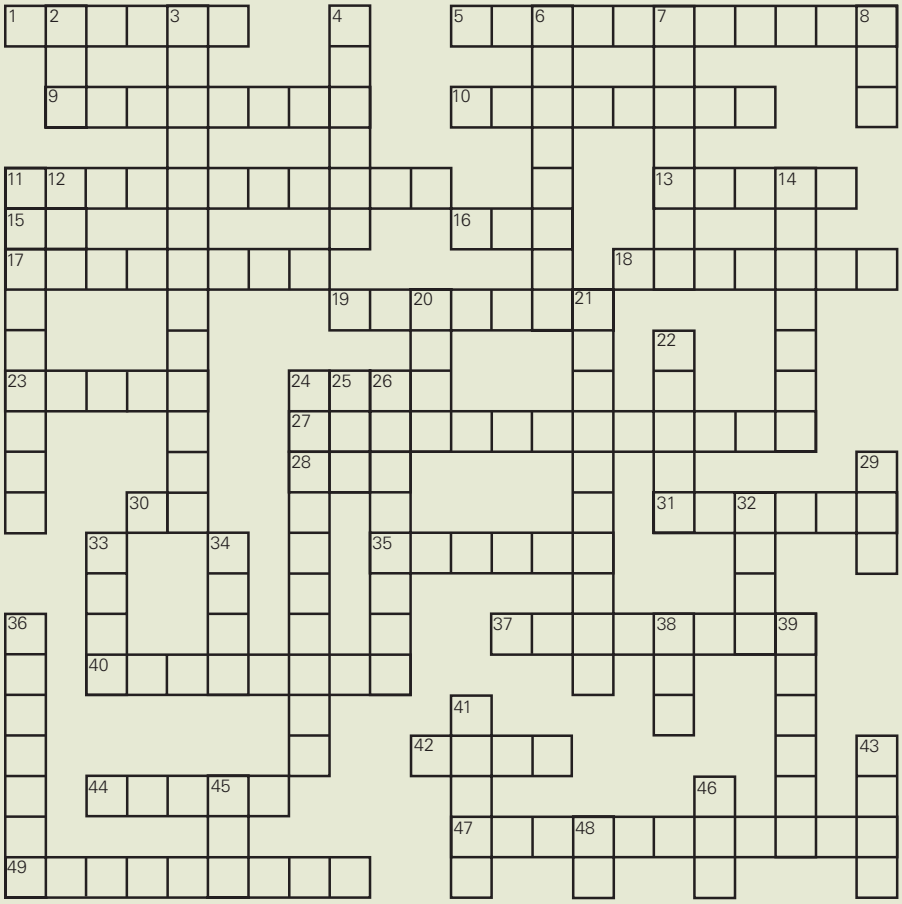
Living Cleansers

As early as preschool, children learn the basics of the food chain—big things eat little things and little things eat littler things. Despite being small and at the bottom of the chain, organisms like microbes and many plants nevertheless play vital roles in maintaining a balanced environment and keeping it healthy for living things of all sizes. Two NIGMS-supported teams of scientists have recently unveiled some of the secrets of how small living cleansers can "eat" toxic chemicals. One case involves chemicals called polychlorinated biphenyls, or PCBs. These chemicals are no longer manufactured in the United States, but they still linger in the environment. Researchers are seeking environmentally sound ways to rid the planet of such poisons through a process called bioremediation, but they haven't yet found many organisms that are naturally good at doing this. NIGMS grantee **Jeffrey T. Bolin** of Purdue University in West Lafayette, Indiana, along with coworkers at the University of British Columbia in Vancouver, pinpointed a critical chemical reaction in PCB breakdown that most microorganisms simply cannot perform. The researchers have plans to engineer microbes in the lab that are able to perform this reaction, potentially providing a tool for gobbling up harmful PCBs. On another front, scientists have recently discovered how to coax plants into soaking up the chemical pollutant arsenic, a significant threat to worldwide health. By cloning arsenic-tolerance genes from the bacterium *Escherichia coli*, NIGMS grantee **Barry P. Rosen** of Wayne State University School of Medicine in Detroit helped his coworkers at the University of Georgia in Athens create genetically engineered plants that could thrive in arsenic. What's more, the two teams designed the plants so that they could accumulate arsenic in their leaves, which can be harvested and disposed of safely. This so-called phytoremediation technique holds promise for improving human health, especially in developing countries where arsenic-contaminated drinking water sickens hundreds of millions of people.

Cocaine Busted

Abusers of cocaine absorb this highly addictive drug into their bodies by chewing, sniffing, injecting, or inhaling it. Any of these methods can lead to the rapid accumulation of poisonous levels of cocaine throughout the body. There is no effective treatment for cocaine overdose, which can result in sudden death. Scientists have reasoned that one way to prevent cocaine's harmful effects on the brain might be to use a natural decoy like a specially made antibody to block cocaine from reaching its molecular targets. Unfortunately, this approach would probably have limited success during an overdose, when overwhelming amounts of cocaine are flowing through the bloodstream. In such a case, rapid breakdown of the drug would be the fastest way to clear this dangerous substance from the body. NIGMS grantee **Ian Wilson** of The Scripps Research Institute in La Jolla, California is making headway in trying to develop this approach. Wilson and his coworkers recently discovered an enzyme that breaks down cocaine into an inactive substance faster than any other such enzyme scientists have examined before. Wilson and his team determined the three-dimensional structure of this enzyme, called a cocaine esterase, which hails from a bacterium that grows in soil adjacent to cocaine-producing plants. The study may point the way to using this protein, or proteins like it, as therapies to rescue people from cocaine overdose.

The Last Word



ACROSS

1. catalyzing molecule
5. iron grabber
9. a chemical change
10. disease-causing organism
11. HIV molecular accomplice
13. Cuban dance
15. male pronoun
16. it's in the ointment
17. cocaine chopper
18. chemical element form
19. scientist Brad
23. Barcelona home
24. pig movie star
27. plant pathogen
28. ocean
30. morn. time
31. movement
35. main meal
37. protein's molecules in action
40. 1,2,3
42. bacteria love it
44. forest components
47. cause of fatal infections
49. learning place

Puzzle answers can be found at
http://www.nigms.nih.gov/findings/

DOWN

2. MRI, for example
3. tiny living organism
4. not rough
6. speed up a reaction
7. diagrams
8. nothing
11. science of molecules
12. affirmative
14. bacterial neighborhood
20. margarine
21. place for eating
22. Goodner's lab location
24. Kern's sport
25. how old you are
26. Kern's lab location
29. beginning opposite
32. powder type
33. scientist Dorothee
34. equal
36. water pollutant
38. got together
39. Nobel country
41. small, round fruit
43. swimmer
45. hearing organ
46. Gleevec treats it
48. Amer.

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