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# FINDINGS

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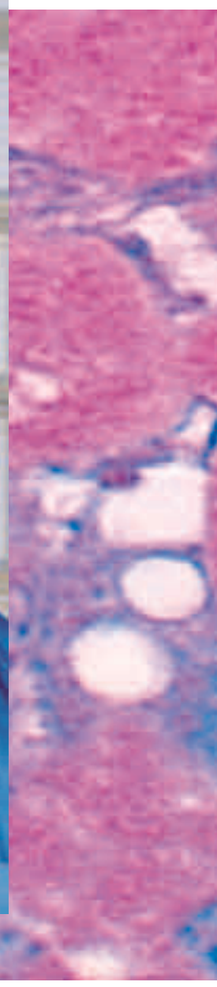

## inside

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**On the Cover**

Photo of Terry Gaasterland: *Arnold Adler*

Photo of Hobart Harris: *Chris T. Anderson*

# Editor's Note

What, exactly, is biology research?

It's a mixed bag. These days, many scientists studying biology do so by performing experiments with lab organisms like rats, fruit flies, or bacteria. Some researchers are also trained as doctors, whose understanding of the enormously complicated human body points them regularly to the most pressing unanswered questions on health. On page 8, read about how surgeon and physician-scientist Hobart Harris is trying to solve the molecular mysteries behind a deadly body-wide infection called sepsis.

Other biology researchers are neither doctors nor even biologists. They are mathematicians, and they use the awesome, unrelenting power of computers to sift data. Thanks to decades of hard work, biology now has at its doorstep a flood of information. The results are just waiting to be analyzed and converted into life-saving medical treatments. On page 2, read about Terry Gaasterland, an expert on artificial intelligence, who is getting computers to learn how to read the language hidden in our DNA.

Both funded by the National Institute of General Medical Sciences of the National Institutes of Health, Harris and Gaasterland are only two of the many faces of biology today. New faces are needed—will one of them be yours?

Alison Davis

Editor

http://www.nigms.nih.gov/findings/

# Taking a Byte Out of Biology


Terry Gaasterland

Arnold Adler

Terry Gaasterland (left) is a bioinformatics scientist at The Rockefeller University in New York City.

Gaasterland sees DNA sequence information (top) as just another language.

***By Alison Davis***

No mice, no worms, no fruit flies.

No petri dishes, refrigerators, or whirring centrifuges.

In Terry Gaasterland's Rockefeller University lab, you do not hear these routine sounds of biology research, but what you do hear is a quiet, constant hum of electronics. Yet a lot is going on here—beneath a clean, smooth surface, her computers are relentlessly reading and analyzing DNA data, searching for genes and figuring out what they do.

Gaasterland has three computers and a video monitor in her uptown Manhattan office-lab. A computer closet down the hall is home to stacks upon stacks of hard drives, 300 in all, adding up to more than a terabyte of computer disk space. If you didn't know, that's nearly a thousand times more than your home PC. A single byte of computer storage holds about one character, such as the letter "a." Oh, and there are two 10-ton air conditioners in that closet, to quench the intense heat produced by the machines.

Gaasterland, 39, is a new and different kind of biologist.

Really, she's not a biologist by formal training—Gaasterland is a computer scientist, with a track record in artificial intelligence, the art of training computers to "think." Her lab deals in bioinformatics, the science of piecing together data from thousands of biology experiments, looking for patterns that themselves are a new and different kind of data.

## Birds, Genes, and Shiny Things

There are no real animals in Gaasterland's lab, but sooner or later you do notice an animal theme: birds. Gaasterland creates software to analyze experimental genetic data, and she has named all the programs after birds. The acronym for the first computer program she developed, MAGPIE, is a lot simpler than its real name, Multipurpose Automated Genome Project Investigation Environment. MAGPIE's job is to comb through reams of DNA sequence information (millions of DNA "letters" called nucleotides), searching for patterns that signify hidden biological information.

The acronym, Gaasterland explains, fits perfectly.

"What do magpies do? They go and collect shiny things and bring them back," she says.

Subsequent computer programs have perpetuated this bird theme: EGRET, HERON, SANDPIPER. The names of each of

# Taking a Byte Out of Biology

these programs spell out different computer-performed tasks, each aiming to discern multidimensional meaning from two-dimensional genomic information, which resembles words on a page.

To bioinformatics scientists like Gaasterland, bits of information and patterns among the data are "shiny things." Her far-reaching goal, and that of other computer scientists who concentrate on biological mysteries, is to get computers to apply logic to biology, which by nature is incredibly complicated. It will take many years, she says, but ultimately future versions of computer programs like MAGPIE will swallow huge amounts of genetic data and spit out predictions about how biology works.

## Same or Different?

One project Gaasterland is currently working on involves analyzing the gene readout data from the lungs of smokers and non-smokers. She is trying to figure out why some people get lung cancer and some don't, so she wrote a computer program to analyze the two sets of data, asking an elementary question: What's the same and what's different?

Gaasterland's experiments require a terabyte of computer disk space—nearly a thousand times more than a home computer.

What Gaasterland found is that some of the differences can be very, very tiny, showing up only when you look at gene activity in individual cells and ask which genes are turning on or off. Genes that are turning on are getting ready to make proteins. These dynamic changes in gene readout, or "expression," can be so subtle that they may not themselves lead to any noticeable change in appearance and/or behavior—something scientists call a "phenotype." Lots of little changes can add up, though, to make a new phenotype.

Here's how it works. The gene readout data that feeds into Gaasterland's computer comes from biologists all over—to date, a few hundred researchers. The data is usually posted on the researchers' Web sites, from where she can download it. In setting up a collaboration, Gaasterland first talks to the scientists, asking them questions about what they are trying to discover. The researchers hand over their experimental results, she says, in return for Gaasterland's promise to work with them to figure out what new information they can pull out of the data. She then uses computer logic to come up with new ways to "query" the data.

But it's not just a matter of "smoothing out" the edges with standard statistical tools, Gaasterland explains. Rather, she applies principles of artificial intelligence to get the data to reveal its hidden secrets, and importantly, to pose new questions to researchers.

Gaasterland's experiments have the potential to make new discoveries by linking information from different fields of study. For example, she explains, she has huge bodies of data from scientists studying heart disease, obesity, and diabetes. In combining and analyzing these different data sets, Gaasterland and her students and postdoctoral researchers essentially "connect the dots." It's exciting, she says, because she has a bird's-eye view that individual researchers—each with their own data alone—do not have.

## An Eye on Science

How does a computer scientist learn biology in the first place? Gaasterland says that half the fun is picking it up along the way. She concedes to having on hand a few "consultants" (computationally minded biologist friends) who she can freely ask to fill in gaps in her knowledge about cells, organisms, and how they function.

Despite gaps in her detailed knowledge of biology, however, Gaasterland has never had a lack of enthusiasm for biomedical science.

"My schooling has been totally and completely computers," she says, "but I've always been fascinated by medicine."

"My father introduced me at an early age to the idea of studying animals to figure out how to treat people," Gaasterland says. Her father, Douglas Gaasterland, is a physician-scientist at Georgetown University in Washington, DC. When Terry was growing up, he had a research lab at the National Institutes of Health in Bethesda, Maryland, where he used lasers to study and treat glaucoma in monkeys.

"At 5 years old, I was used to seeing eyeballs in the lab fridge," she laughs.

She grew up with science, but math has always been front and center in Gaasterland's life. She took algebra in 7th grade and completed calculus by 10th grade. During her junior and senior years in high school, she was done with classwork by lunchtime, leaving afternoons for ballet classes and evenings for differential equations at the local community college. On Saturdays, she traveled an hour north to Baltimore, where she took a neurology course at The Johns Hopkins University.

James C. Leupold, U.S. Fish and Wildlife Service

Gaasterland's gene-analyzing computer programs, such as MAGPIE and EGRET, are all named after birds.

Today, Gaasterland breaks the stereotypic mold of a computer scientist. If you saw her roller-blading with friends in Central Park after dark ("It's safe!" she insists) or hanging out in New York's Soho jazz and blues clubs, her zest for living would be apparent. A perfect Saturday afternoon is spent strolling around New York's museums and art galleries, she says, "where you can find truly cutting-edge art."

Strolling is the operative word, since she doesn't own a car anymore. Gaasterland enjoys watching Manhattan life by walking its vibrant streets or hopping around in cabs. Liking city apartment living so much surprises even her. "I thought living in a crowded apartment would be awful," Gaasterland says, remembering her childhood days in a quiet, tree-lined Washington, DC suburb.

Gaasterland is passionate about Manhattan, but also about the marriage of computers and biology. She is on a mission to train computers to help scientists understand how genes mastermind the precision functioning of organisms ranging from bacteria to people. So much information is hidden in our genes, Gaasterland says, and researchers simply need to learn how to interpret it.

***"DNA is just another language."***

## Shaping Up

DNA is indeed the language of our lives, spelling gene "words." Genes instruct the body how to make worker molecules called proteins, which combine in wondrous ways to allow us to think and to sense the world around us.

But while DNA represents two-dimensional information (akin to words on a page), proteins are three-dimensional things. Each protein has a characteristic shape that suits it to its unique biological task. A protein in the wrong shape can be a problem, sometimes causing illness and disease. In order to understand how misshapen proteins affect our health and to figure out ways to mimic or block protein shapes to fight disease, scientists need to see up close what proteins actually look like. To do this, researchers called structural biologists rely on high-energy physics techniques. Such researchers blast X-rays at protein samples and, based on how the X-rays are scattered, the scientists can piece together the shape of a protein.

Gaasterland is getting computers to help with that problem, too. She is part of an organized effort, called structural genomics, that aims to predict protein shapes from their DNA (genomic) sequence. Gaasterland is a member of the New York Structural Genomics Consortium, which gets research funding from the National Institute of General Medical Sciences.

"Three-dimensional properties of proteins are lurking in two-dimensional sequences," Gaasterland says, describing the prevalence of sequence "signatures" that point to telltale genetic directions for making recurring protein shapes.

# Taking a Byte Out of Biology

By comparing gene properties and examining the DNA information from creatures throughout the vast biological kingdom, Gaasterland can figure out which characteristics have proven indispensable for the proper functioning of organisms spanning millions of years of evolutionary time. For example, she says, certain pairs of amino acids, the building blocks of proteins, always change together across species. Since amino acids fit together much like LEGO® pieces, recognizing recurring pairs of them hints that such molecular duos translate three-dimensionally into signature folds or bends in protein shapes.

According to Gaasterland, her role in the structural genomics effort is in finding so-called protein targets—"families" of proteins whose three-dimensional structures are likely to be similar and can be used as benchmarks in predicting the structures and functions of other proteins. The goal of structural genomics is to find the three-dimensional shapes of all the parts (proteins and other large molecules) in a cell.

Terry Gaasterland

Up close, a protein molecule (right) has all sorts of twists and turns.

## A Full House

To begin to understand the concept of selecting cellular targets, consider a metaphor of a cell as a house full of contents and activity. By taking an inventory of what's inside a cell, or a house, and observing when and where things happen, you can make certain assumptions about where to look for new information. These can serve as new "targets."

In a fictitious house-cell, structural biologists might piece together the molecular parts that make up the furniture and appliances, revealing the identity of the couches, chairs, and refrigerator, for example. In a real cell, the "furniture" might be the cell's protein scaffolding, and the appliances mini-molecular machines that generate energy for the cell. Such an effort generates a "parts list" for the interior of the house, or the inside of a cell.

Context is key—you can often infer the function of an object by observing other nearby objects and checking out the conditions under which they are used. For example, in a house, a room with a flat surface and two chairs could be either a dining room or an office—or both, at different times of day. If the room is used in the late evening or very early in the morning, the surface is more likely to be used as a desk than as a formal dining table. A search for other contextual clues, like a bookshelf, would strengthen the assumption that this room is used as an office.

Central Park is one of Gaasterland's favorite roller-blading spots.

Along with the placement of things, activity can also point to possible function.

"If you see the lights go on in the garage at 7:00 p.m., you can infer that the people are doing something in there," Gaasterland says. "That's a new target for study."

Further looking may uncover details about what exactly is going on in the garage in the early evening, as would analyzing more contents of the dining room/office.

## Proteins, Proteins, Proteins

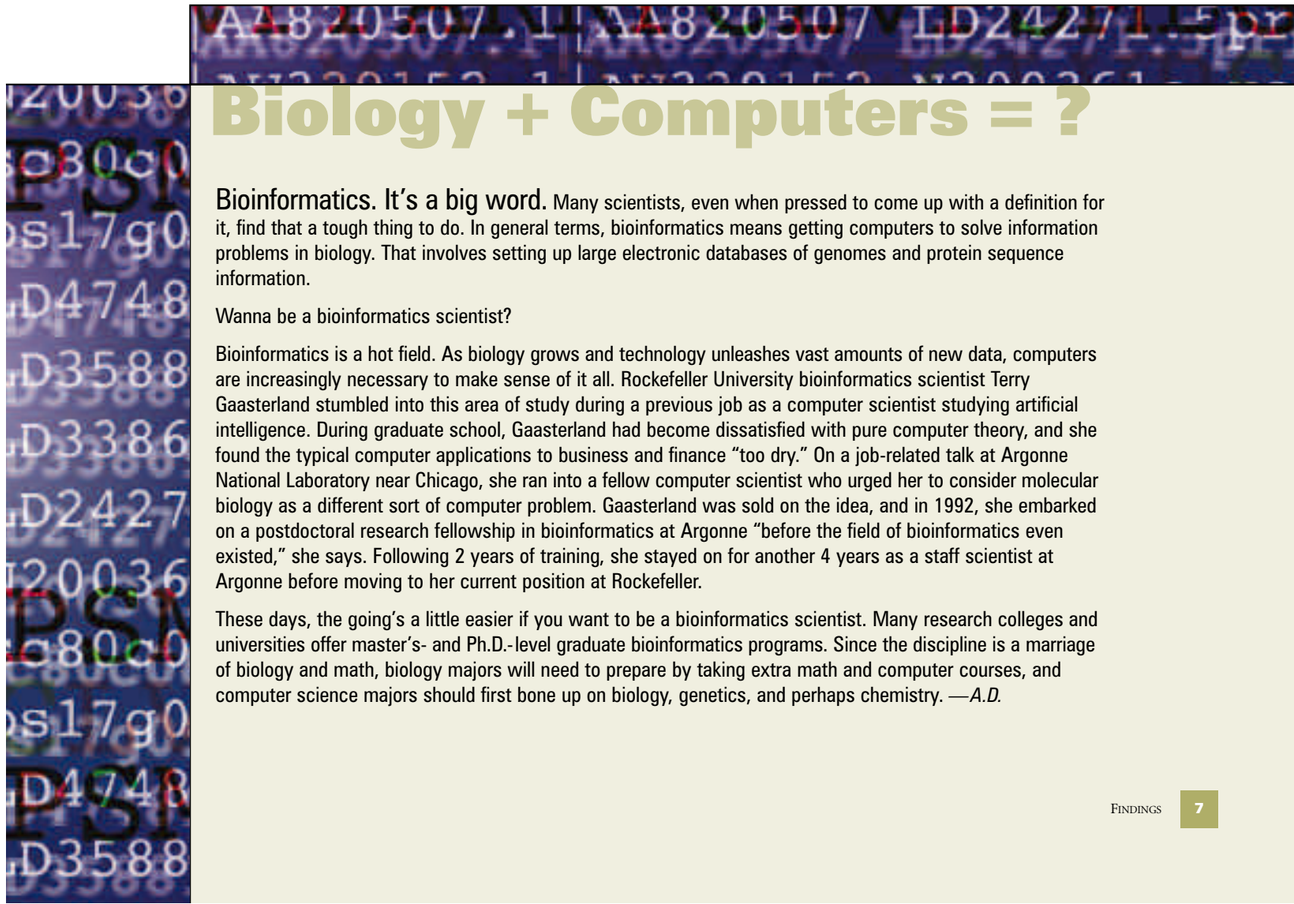
Hidden deep within two-dimensional genomic information are many clues about cell function. Using knowledge in hand to make assumptions and predictions about what is not known can speed the pace of biological discovery, leading to better ways to diagnose and treat disease.

There are lots and lots of proteins we know little about, Gaasterland explains. She estimates that researchers have a hunch about what roughly 50 percent of our protein-making genes do, based upon previous experiments. Another 20 percent can be guessed because they look so much like the genes of other organisms, like fruit flies or mice.

But for the remaining 30 percent, Gaasterland says, "we don't have a clue."

Much like Manhattan, Gaasterland sees a cell as a lively neighborhood, bustling with constant activity. Communications and negotiations between proteins are constantly going on. She is confident that, with their "absolute precision," computers can make sense of the mayhem, using logic to find rules and order hiding in the letters of our genome.

"DNA is just another language," she says. "We are only just beginning to learn how to hear the individual words—let alone listen, understand, and speak." ■



# Biology + Computers = ?

**Bioinformatics. It's a big word.** Many scientists, even when pressed to come up with a definition for it, find that a tough thing to do. In general terms, bioinformatics means getting computers to solve information problems in biology. That involves setting up large electronic databases of genomes and protein sequence information.

Wanna be a bioinformatics scientist?

Bioinformatics is a hot field. As biology grows and technology unleashes vast amounts of new data, computers are increasingly necessary to make sense of it all. Rockefeller University bioinformatics scientist Terry Gaasterland stumbled into this area of study during a previous job as a computer scientist studying artificial intelligence. During graduate school, Gaasterland had become dissatisfied with pure computer theory, and she found the typical computer applications to business and finance "too dry." On a job-related talk at Argonne National Laboratory near Chicago, she ran into a fellow computer scientist who urged her to consider molecular biology as a different sort of computer problem. Gaasterland was sold on the idea, and in 1992, she embarked on a postdoctoral research fellowship in bioinformatics at Argonne "before the field of bioinformatics even existed," she says. Following 2 years of training, she stayed on for another 4 years as a staff scientist at Argonne before moving to her current position at Rockefeller.

These days, the going's a little easier if you want to be a bioinformatics scientist. Many research colleges and universities offer master's- and Ph.D.-level graduate bioinformatics programs. Since the discipline is a marriage of biology and math, biology majors will need to prepare by taking extra math and computer courses, and computer science majors should first bone up on biology, genetics, and perhaps chemistry. —*A.D.*

# A Chance Discovery

Hobart Harris




Chris T. Anderson

Hobart Harris (left) is a physician-scientist at the University of California, San Francisco.

Harris grows liver cells (top) in the lab to study the body-wide infection called sepsis.

***By Dan Hogan***

Growing up, Hobart Harris dreamed that he would one day become a doctor.

Driven by his thirst for knowledge and his determination to become a physician, Harris, now 43, graduated from high school a year early, at age 16.

With little invested in the outcome, he decided to apply to Harvard College. According to Harris, up until that time in the mid-1970s, schools like Harvard seemed alien to many African Americans like himself who had struggled against formidable social and economic odds.

He got in.

"I had no awareness of what an Ivy League college was like," Harris remembers. "What impacted me most was the environment—my fellow students and professors. It was a wonderfully diverse and incredibly challenging environment that opened my eyes to other possibilities."

"I was not born into a family of scientists," says Harris, now a surgeon at the University of California, San Francisco. "My father was born just a few miles outside of Boston, but he might as well have been born on another planet when it came to the idea of attending Harvard."

At Harvard, Harris began to consider the idea of becoming not just a physician, but a physician-scientist. "I was gradually drawn to science," he explains, "because it allows you to ask questions, to be creative, and to contribute to a greater body of knowledge."

During college and medical school (also at Harvard), Harris got involved in many different research projects that piqued his curiosity—everything from how drugs called opiates affect the human brain to how people's diets play a role in heart disease.

After earning his M.D., he did an internship and residency at the University of California, San Francisco Medical Center. There, he began a research project investigating the causes of heart disease. Unexpectedly, the project changed course rather suddenly and led Harris to explore an entirely different area of science, the human immune system.

## Germ Wars

Our immune systems are constantly protecting our bodies from invading germs—bacteria, viruses, fungi, and parasites—that can make us sick and sometimes even kill us. Waging this war on our behalf is an army called the immune system. On the

# A Chance Discovery

front line are cells called white blood cells, which travel throughout the body fighting infection.

Yet sometimes, our natural defenses are not enough. This is especially true in the case of a potentially fatal body-wide infection called sepsis, one of the leading causes of death in hospital intensive care units today. Sepsis can follow traumatic injury or other serious infections.

In the United States alone, sepsis strikes approximately 750,000 people every year, killing some 200,000. Symptoms can progress from fever and chills to severe inflammation, and ultimately, multiple organ failure and death. The most deadly form of sepsis is caused by "Gram-negative" bacteria, a class of bacteria that get their name from a staining technique that microbiologists use to distinguish bacteria based on the structure of their cell walls. The cell walls of Gram-negative bacteria contain molecules of a toxic substance called endotoxin. When these cell walls break down, the endotoxin molecules are released into the bloodstream, spreading the deadly poison throughout the body.

Aero Photo

Harris attended both college and medical school at Harvard (right), where he became interested in pursuing a research career.

## Fat Fights Infection

Researchers have long suspected that fat molecules in our blood play some role in fighting infection. "For many years, scientists thought high levels of fat-containing molecules called lipoproteins were the body's way of mobilizing its stores of fat to provide energy to fight infection," Harris explains, adding that as early as the late 1950s, doctors had noticed that patients suffering from deadly bacterial outbreaks of cholera had unusually large amounts of lipoproteins coursing through their blood.

When you eat fatty foods, the lipid components (fats) in those foods are transported throughout your body via your bloodstream. Just as oil does not mix well with water, lipids do not readily dissolve in blood, which consists mostly of water and blood cells. The body solves this problem by coating small droplets of fat with other molecules that are able to mix with both fat and water. These coated fat droplets are called lipoproteins, and they come in a variety of molecular flavors. The lipid part of lipoproteins can contain different types of fats, such as cholesterol or triglycerides.

*"Many discoveries in science are made by serendipity."*

So-called high-density and low-density lipoproteins (HDLs and LDLs) are rich in cholesterol. Other types of lipoproteins, such as very-low-density lipoproteins (VLDLs), contain triglycerides instead.

By the 1970s, scientists had figured out that cholesterol-rich lipoproteins could react with endotoxins, shielding the endotoxins and making them less toxic. "But no one had ever examined whether lipoproteins containing triglycerides could interact with endotoxins as well," Harris notes.

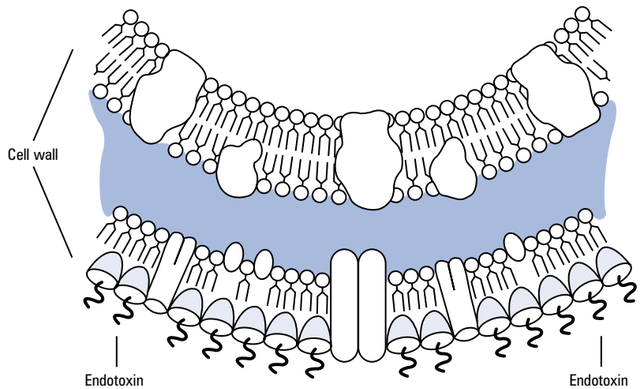
## Troubling Mystery

It was 1988, and Harris was in the middle of conducting a set of experiments designed to shed light on why people develop atherosclerosis—a narrowing of the arteries that is caused by the buildup of cholesterol and fat. Atherosclerosis often leads to heart disease.

Harris and his coworkers had been particularly interested in how the human body naturally clears fat from the bloodstream. The researchers designed experiments to track the movement of lipoproteins in the body by first removing the lipoprotein molecules from the blood of healthy volunteers.

The carefully designed experiment involved drawing blood from a group of people who had agreed to participate in Harris' research study, mixing each person's blood

Long, jagged molecules of a poison called endotoxin jut out from the cell walls of Gram-negative bacteria.






# A Lucky Horseshoe

George Lower/Marine Biological Laboratory

**Strolling along the eastern shores of the United States,** you may find a disk-shaped shell with a spiked tail that resembles the remnants of some prehistoric creature. In all probability, the shell came from a horseshoe crab, whose scientific name is *Limulus polyphemus*.

Horseshoe crab shells cover East Coast beaches, but these marine organisms have also proven to be an important medical tool. Researchers use horseshoe crab blood to screen for the presence of dangerous bacterial poisons called endotoxins.

In 1988, when Hobart Harris was studying atherosclerosis at the Department of Veterans Affairs Medical Center in San Francisco, the blood of one of Harris' research participants was tested for the presence of endotoxin using horseshoe crab blood, a method that is now called the "Limulus amoebocyte lysate (LAL) assay." Ironically, the physician-scientist whose discovery originally led to the development of that test, Jack Levin, was at the time working two floors down from Harris, and it was Levin's laboratory that tested Harris' samples.

Just as Harris' finding that triglyceride-rich lipoproteins could mask endotoxins was made by accident, so was Levin's initial discovery that led to the development of the LAL assay. Working with scientist Fred Bang of the Marine Biological Laboratory in Woods Hole, Massachusetts, Levin discovered in the early 1970s that horseshoe crab blood exposed to the bacterium *E. coli* would quickly clot, forming a mushy lump. Further experiments confirmed that endotoxins from the specialized cells called "amoebocytes" in the bacteria are what cause the gel-like clot to form.

The LAL test, a widely used medical tool and a multi-billion dollar enterprise, arose out of those early experiments. The test is routinely used to rapidly and efficiently detect the presence of potentially deadly endotoxins in medicines, blood products, and medical devices such as pacemakers and catheters. —*D.H.*

# A Chance Discovery

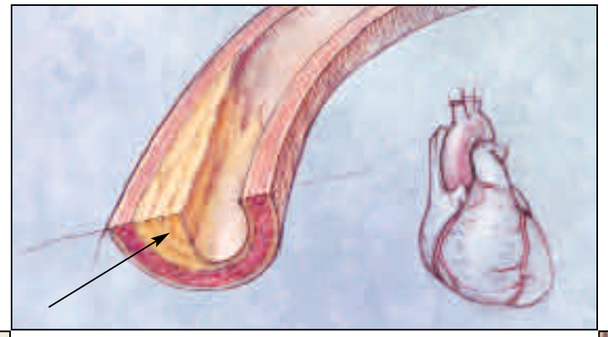
with a natural chemical label, then re-infusing the blood back into that person.

Then, something terrible happened.

Suddenly, one of the study volunteers became sick, as if his blood had been exposed to the endotoxin poison.

Harris rushed to intervene, but fortunately the volunteer's reaction was relatively mild, and he soon recovered.

But for Harris, the reaction remained a troubling mystery. As researchers learned years later, endotoxin is everywhere; small traces can even survive harsh sterilization procedures. Likely, Harris suspected, a small amount of endotoxin got into the study volunteer's blood before it was infused back into him.



Fat-containing molecules called lipoproteins are an important part of the blood vessel blockages (right, arrow) associated with atherosclerosis.

Surprisingly, however, the man's blood had tested negative for bacterial endotoxin in a separate test (see sidebar).

So what had gone wrong? Did something else cause the man to become sick? Or, Harris wondered, perhaps the endotoxin was there but was somehow hidden and undetectable?

"We began to think that maybe lipoproteins could somehow attach themselves to the endotoxin molecules, making the endotoxin undetectable but still active," Harris explains.

The man's reaction, and Harris' possible explanation for why it happened, ended up steering Harris' research career in an entirely new direction—the human immune system.

19th-century chemist Louis Pasteur coined one of Harris' favorite quotes, "Chance favors only the prepared mind."

## Cell Cultures

If fatty lipoproteins really were interacting with endotoxin, Harris and his colleagues reasoned at the time, then perhaps they were acting like molecular "sponges." Such sponges would "soak up" the endotoxin molecules and shield the body from the endotoxin's poisonous effects. If that were true, the result would be a lipoprotein-endotoxin duo that has the poisonous part neatly hidden inside the fat droplet, invisible to the immune system.

Harris' thought was just a hunch, and it needed testing.

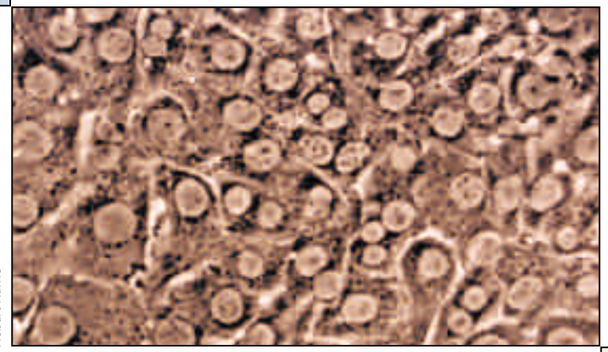
To test his molecular-sponge idea, Harris began a series of experiments using lab mice to model what happens in the human body. His hunch proved correct: The researchers discovered that when endotoxin was tied to a lipoprotein, it was in fact much less toxic to mice than was endotoxin by itself.

In his next set of experiments, Harris wanted to know exactly what happened to endotoxin molecules stuck to lipoproteins. He found that the lipoprotein-endotoxin complexes are processed by specialized liver cells called hepatocytes. Since the liver also contains many other types of cells besides hepatocytes, Harris decided to grow the hepatocytes in plastic lab culture dishes. "We do virtually all our work in cell cultures now," Harris notes, explaining that cell cultures offer a more controlled environment than whole organs, with fewer variables that can interfere with the experiments.

From these cell culture studies, Harris discovered that when endotoxins are bound to triglyceride-rich lipoproteins, the hepatocytes become less responsive to molecules called cytokines. One job of these small hormone-like molecules is to help bring about the process of inflammation, a normal part of the way our bodies deal with infection or injury.

## Better Treatments?

Harris is now trying to gain a better understanding of how this process works, but many pieces of the puzzle still need to be found before better sepsis treatments can be developed.



Hobart Harris

Harris performs many of his experiments with liver cells called hepatocytes, which are grown in laboratory culture dishes.

When the body is exposed to dangerous bacteria, Harris explains, a couple of things can happen. The body assembles certain molecules to cause inflammation, and other molecules to shut off inflammation.

"What we think happens in sepsis is an upsetting of this balance. The body overreacts, and the [inflammation-causing] responses overwhelm the [inflammation-stopping] responses." Harris' research might also explain why previous attempts to treat sepsis have been largely unsuccessful. One early approach was to develop anti-endotoxin therapies, using antibodies and chemical absorbents to soak up the rogue endotoxin molecules. These therapies did not work.

"The problem is that by the time you try to treat the patient, the horse is already out of the barn," Harris notes. "The endotoxin that you're trying to counteract has already had its effects." Similar therapies designed to block the cytokine molecules—produced by the body in response to endotoxins—have also failed, Harris adds.

So, instead of trying to block the molecules that stimulate inflammation, Harris suggests, perhaps sepsis could be better treated by encouraging those processes that help stop inflammation.

"Doctors are always looking for ways to push back the frontier, to redefine what is lethal and to find ways for people to survive events or diseases that they would never have been able to survive before," Harris says. "Organ transplantation and open-heart surgery are examples of this. And perhaps we'll be able to conquer sepsis one day as well."

## Science and Serendipity

Looking back to that fateful day 12 years ago when the participant in Harris' research study suddenly got sick, Harris is thankful, in a sense, that events turned out the way they did.

"That day was both the worst and the best experience of my scientific career," Harris recalls.

"It was the worst, because we had a complication in a human subject who was also a friend of mine. But at the same time, it was the best—because it opened up a whole new area of research that has become very productive."

That day also reminds Harris of a famous quote, engraved in stone in his dormitory at Harvard: "Chance favors only the prepared mind." The phrase was coined by the great 19th-century French chemist Louis Pasteur, whose germ theory of disease laid the foundation for modern microbiology.

"What Pasteur was referring to was the fact that many discoveries in science are made by serendipity," Harris explains. "And, if you're too focused on finding one thing, you may be unprepared for finding something completely different."

Harris often shares the lesson with the many students he now mentors.

"Young people often seem to be overwhelmed by the prospect of becoming a scientist. They say, 'How could I ever get there from here?' In actuality, it's a day-by-day, step-by-step process. … One of the things that I try to encourage people to do is not to limit themselves, but to be daring and to be willing to experience new environments and new challenges," Harris says. ■

## Heart Drug Prevents Muscle Loss After Burns

Life after a severe burn injury can be extremely difficult. Burn patients—many of them young children—are often left with severe scarring and other physical impairments. Significant muscle and bone loss is one of the most frustrating consequences slowing recovery from a severe burn injury. Researchers have long known that a badly burned body breaks down its own muscle and bone, presumably in an effort to heal itself. This breakdown process, called "catabolism," can significantly impact time to recovery. NIGMS-supported burn surgeon **David N. Herndon** of the University of Texas Medical Branch in Galveston has come up with a promising medical treatment to thwart this devastating muscle and bone loss. Herndon and his colleagues performed a small clinical study on 25 badly burned children, who had experienced burns covering more than 40 percent of their bodies. Half of the burn patients received a 2-week course of a standard heart rate-lowering drug called a "beta-blocker." After the study was complete, Herndon discovered that the children who received the beta-blocker (which lowers the body's heart rate and overall metabolism) gained muscle and protein, as measured by levels of hormones and electrolytes in body fluids and X-ray analysis of muscle and bone mass. In contrast, the control subjects (who received no beta-blocker treatment) lost muscle and protein mass.

## Fruit Flies for Health

To many people, fruit flies are the annoying consequence of buying too many on-sale bananas. Yet these tiny red-eyed creatures—known to scientists as the insect species *Drosophila melanogaster*—hold a secret key to curing human diseases. Fruit flies first jumped into the research fray 100 years ago, when a biologist named T.H. Morgan noticed a fly on the wall of his lab that had white eyes instead of the usual red ones. Years later, scientists discovered that this particular strain of fruit fly had white eyes because one of the fly's genes hadn't worked properly. Today, *Drosophila* is one of the most valuable research tools available to scientists who study the relationship between genes and health. For example, one recent study performed by NIGMS-supported scientist **Ethan Bier** of the University of California, San Diego unearthed 548 fly genes that are so similar to genes involved in 714 different human genetic disorders that the likelihood of the similarity occurring by chance alone is 1 in 10 billion. What this means is that scientists can look for causes and treatments for blindness, cancer, Parkinson's disease, diabetes, and other disorders using lab fruit flies that are inexpensive and can be bred very quickly. Bier predicts that a few hundred fly "disease" genes will make proteins that are indistinguishable from their human counterparts. Ultimately, Bier says, fly genes can play an important role in the study of at least 1,000 of the 5,000 known genetic diseases in people. Pretty impressive for an insect!

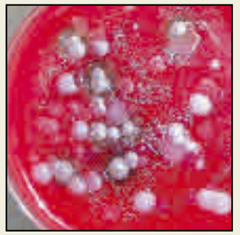
Jay Hirsh

## Sour Orange Juice Gives Medicines An Extra Punch

Swallowing certain medicines with a glass of grapefruit juice can provide an unwanted surprise. For 10 years now, scientists have known that a natural chemical in grapefruit juice can boost the blood levels of a variety of medicines in some people. Researchers figured out that grapefruits do this by knocking back the activity of a drug-chewing intestinal enzyme called cytochrome P4503A4, or CYP3A4. Doctors have observed this "grapefruit juice effect" with more than 20 different medicines, including drugs used to treat allergies, heart disease, and infections. NIGMS-supported researcher **Paul B. Watkins** has now discovered that Seville (sour) orange juice—but not regular orange juice—has the same effect on the body's handling of these medicines. Watkins and his coworkers at the University of North Carolina at Chapel Hill assembled 10 people who volunteered to participate in the juice-medicine study. Each person took a standard dose of felodipine (a drug commonly used to treat high blood pressure) diluted in grapefruit juice, sour orange juice, or plain orange juice. The researchers measured blood levels of the medicine at various times afterward. The team observed that grapefruit juice and sour orange juice led to the same increase in felodipine levels in the blood while regular orange juice had no effect. Since both juices contain a chemical called dihydroxybergamottin, the scientists suspect that this chemical may be the molecular culprit accounting for the grapefruit juice effect, although further lab tests are needed to confirm this suspicion. Who drinks sour orange juice? While not a typical breakfast choice, Seville oranges are often ingredients in food products such as marmalade. However, further studies will need to confirm whether the amount of dihydroxybergamottin in such food products is enough to affect the body's processing of medicines.

## Fingerprinting Anthrax

Biologists play a key role in sleuthing bioterrorism cases. Last fall, when potentially deadly anthrax bacteria showed up in letters addressed to Senate Majority Leader Thomas A. Daschle (D-S.D.) and NBC News anchor Tom Brokaw, biologists went to work to identify the source of the bacteria, which also infected and killed photographer Bob Stevens of American Media, Inc. in southern Florida and four others. Just as a criminal can be identified by a unique fingerprint pattern, a bacterial strain can be pinpointed through analysis of its genetic fingerprint (DNA). Samples of DNA from bacteria that evolved from the same microbial ancestor have DNA with a nearly identical sequence of genetic "letters"—building blocks called nucleotides. NIGMS-supported evolutionary biologist **Paul Keim** of Northern Arizona University developed the molecular technique used by authorities to identify the anthrax strains used in bioterrorist attacks in the fall of 2001. Keim has also used his DNA fingerprinting technique recently to analyze the strain of anthrax bacteria released in 1993 by the Japanese cult Aum Shinrikyo. His analysis showed that the attack failed because the cult members used a veterinary vaccine strain of anthrax that is not dangerous to humans.

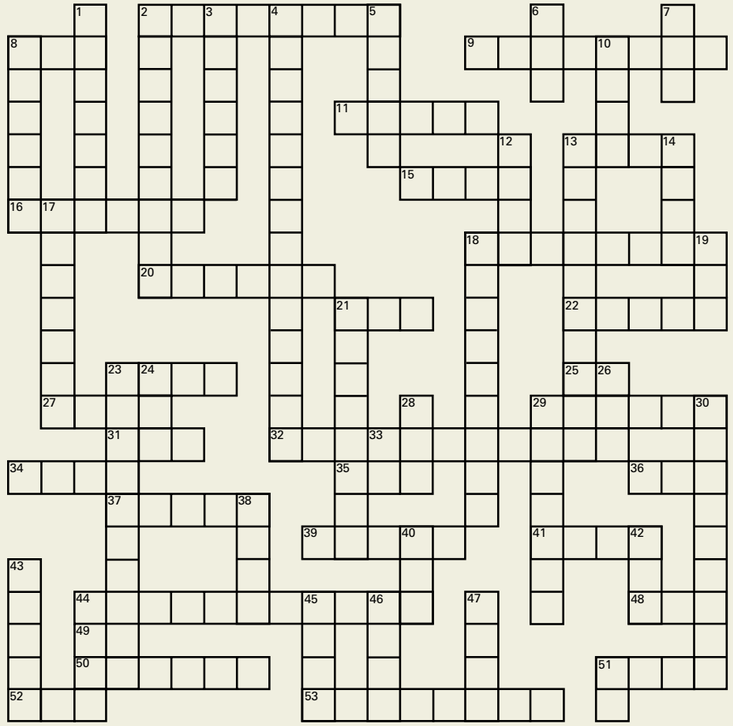


Paul Keim

## How Feverfew Works

The use of herbal therapies is on the rise in the United States. While millions of people take herbs routinely to treat various health problems, many herbal concoctions can be harmful and some have proven to be deadly. Unlike many prescription (or even over-the-counter) medicines, herbs contain many, many different ingredients—sometimes thousands of them—and researchers do not know in the majority of cases how herbs work inside the human body. Because herbs are natural products, they are not regulated by the U.S. Food and Drug Administration. Scientists have not performed careful studies to evaluate the usefulness and safety of most herbs. Certain herbs, however, are showing medical promise. For example, a handful of controlled scientific studies in people have hinted that the herb feverfew is effective in combating migraine headaches. Scientists have suspected that this herb, which is also known by its plant name "bachelor's button," exerts its effects by halting inflammation, a standard immune system response that is one of the body's most basic defense mechanisms. Recently, NIGMS-supported chemist **Craig Crews** of Yale University discovered how an inflammation-fighting ingredient in feverfew may work inside the cells of the body. Crews used chemistry and biology experiments to show that the ingredient, called parthenolide, disables a key cellular process involved in kickstarting inflammation.

# The Last Word



## ACROSS

2. 1,000 billion bytes
8. you breathe it
9. infection fighter
11. lime's cousin
13. protein-making instructions
15. always
16. gatherer bird
18. machine for assembling data
20. library of genes
21. lipid
22. back opposite
23. basic constituent of any living organism
25. you and me
27. radiation-produced photo
29. not big
31. after nine
32. luck
34. results from experiments
35. rotten-fruit lover
36. together with
37. body's watery circulation system
39. like sugar
41. right's mirror-image
44. fat-containing molecule
48. container
49. similarly
50. body's defense system
51. average
52. vehicle
53. large trunked animal

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

## DOWN

1. at the steering wheel
2. exciting
3. on a bike
4. science of getting computers to sift biology data
5. type of white heron
6. consumed
7. cholesterol-rich lipoprotein
8. Star-Spangled Banner, for example
10. skeleton component
12. threesome
13. its juice can affect medicines
14. rim
17. deadly bacteria
18. group of people with common interests
19. mouse-like rodent
21. bachelor's button
23. body's breakdown process
24. seeing organ
26. pig home
28. whichever
29. horseshoe crab
30. bacterial poison
33. alphabetically, before em
38. house entry
40. long, long time
42. small flap
43. storage site for old items
44. wild animal's resting spot
45. it's evergreen or deciduous
46. still, inactive
47. region
51. med. degree



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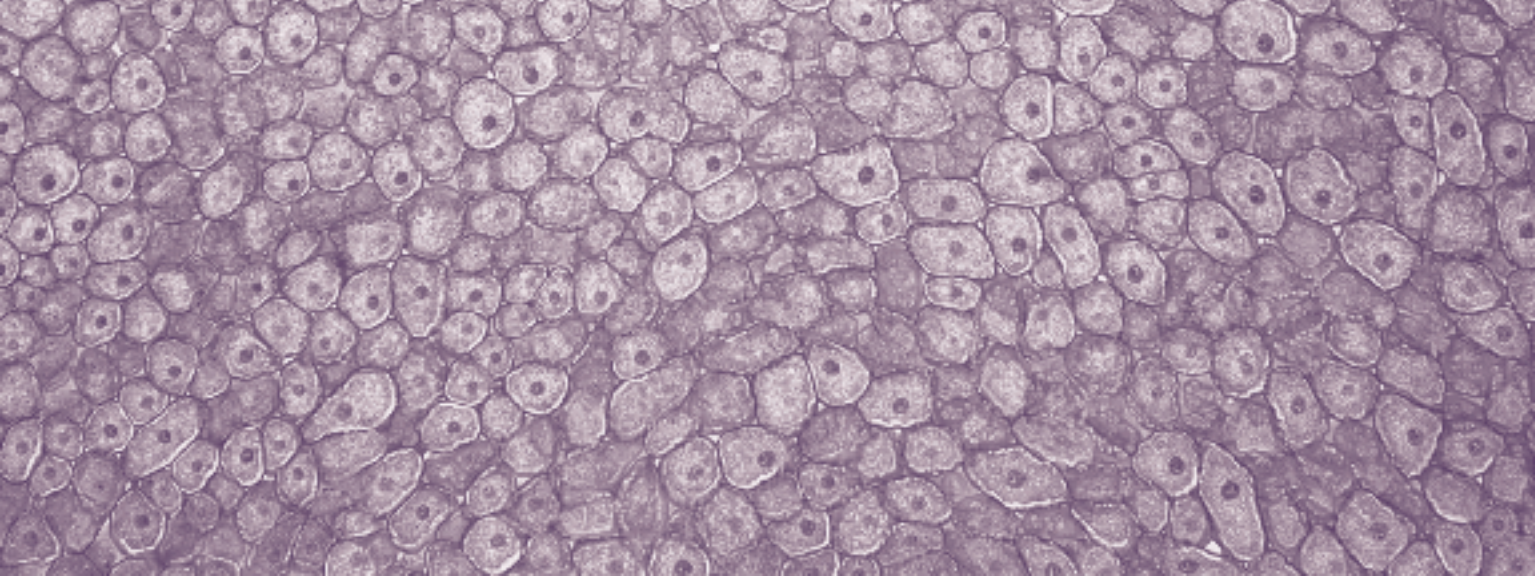

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