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inside

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On the Cover

Photo of Bonnie Bassler: *Denise Applewhite*

Photo of Ram Sasisekharan: *L. Barry Hetherington*

Editor's Note

Many people learn a new language by taking a class. But often the quickest way to make the new words and phrases stick is by *living* the language and absorbing the culture that enriches it.

Scientists, who immerse themselves in their topics of study, learn new languages all the time! Their translation skills pay off for all of us, building a foundation of new knowledge that helps us stay healthy.

Bacterial geneticist Bonnie Bassler's mission is to decipher the chatter of non-humans. Pretty cool, huh? By spying on glow-in-the-dark bacteria, she is helping researchers better understand how microbes can harm people (see story on page 3).

On page 9, read how biological engineer Ram Sasisekharan is cluing into the fascinating language of carbohydrates. These sugary molecules help cells talk to each other and protect us from germs.

Most scientists would agree that we truly understand only a small fraction of the grand language of biology. Listening carefully to its many dialects will speak volumes in helping us to understand ourselves.

Alison Davis

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Bugging the

National Institute of General Medical Sciences

e Bugs

BONNIE BASSLER

DENISE APPLEWHITE

"Science is an incredibly creative endeavor. If you're good at it, it's art."

Bonnie Bassler is a bacterial geneticist at Princeton University. Bassler studies how bacteria, or "bugs," communicate with each other.

By Alisa Zapp Machalek

Bonnie Bassler is a spy.

Like a secret agent, she gathers intelligence by bugging conversations. But Bassler is not after people. She is eavesdropping on much tinier beings: bacteria. Her goal—the cornerstone of espionage—is to decode a secret language, then possibly scramble or redirect the discussions.

Bassler, 42, a microbial geneticist at Princeton University, leads a research team investigating bacterial communications that underlie a long list of ailments, including cholera, tuberculosis, typhoid, pneumonia, and food poisoning. By revealing how to disrupt key bacterial exchanges, Bassler's work might help vanquish these ailments.

Let It Glow

The bacteria Bassler investigates do not cause illness in humans, but float free in the world's oceans, live in sand, and coat fish, coral, and debris. Most remarkably, they glow in the dark.

Such glowing, or "bioluminescent," marine bacteria are extremely common. People dining by candlelight or peering into refrigerators with burned-out bulbs sometimes see their seafood sparkle. For Bassler, this blue-green glow shines a light on bacterial communication.

"Bacteriologists have had it wrong for a couple hundred years," sighs Bassler. "We always thought free-living bacteria lived asocial, reclusive, individual lives, but that's not the case. They could never do all they do without communication systems."

Bassler studies *Vibrio harveyi* (abbreviated *V. harveyi*) bacteria, which can only glow when they are in a sufficiently large group known as a quorum. Using a chemical strategy dubbed quorum sensing, the bacteria manage to assess their own population size and distinguish themselves from all other kinds of bacteria.

Besides its role in bioluminescence, quorum sensing is used by many kinds of bacteria to mastermind behaviors ranging from mating to releasing toxins and triggering disease, an activity known as virulence. Most notably, quorum sensing is used by many harmful bacteria to avoid a full-blown response from our immune systems—until it's too late for us. The bacteria appear relatively innocuous as they quietly grow in number. Then, when their population reaches a certain level, their behavior,

Luminescent bacteria can make seafood glimmer blue-green. Next time you see raw fish, turn out the lights and check out the glow!

appearance, and metabolism instantly change, culminating in an infection that can ambush and overwhelm our immune system defenses. It's akin to thousands of pedestrians in a city intersection simultaneously walking into the street, locking arms, and paralyzing traffic.

We Have a Quorum

Quorum-sensing bacteria leak into their surroundings a chemical that, like body odor, indicates their presence. As the bacterial population increases, so does the concentration of this chemical, called an autoinducer. When the amount of autoinducer reaches a certain level, the whole bacterial neighborhood is transformed. The once-independent, solitary bacterial cells suddenly become part of a large, multicellular organism.

Communication is key to the formation of biofilms, the slimy bacterial communities that can cause infections and are often stubbornly resistant to antibiotics.

An everyday example of such bacterial transfiguration is the tenacious slime that can accumulate on teeth, ships, bathtubs, and kitchen drains. These slippery coatings are actually sophisticated microbial communities called biofilms in which bacteria either become part of protective coatings, walls, or nutrient-filled channels, or they swim around inside these structures as highly mobile, independent cells.

Tapping into the chemical communiqués needed to make biofilms has many applications, according to Bassler. Biofilm-blocking substances could reduce illness caused by infected catheters and other implanted medical devices. They could prevent bacterial buildup in industrial cooling towers and swimming pools. And, if added to toothpaste or mouthwash, they could battle tooth decay.

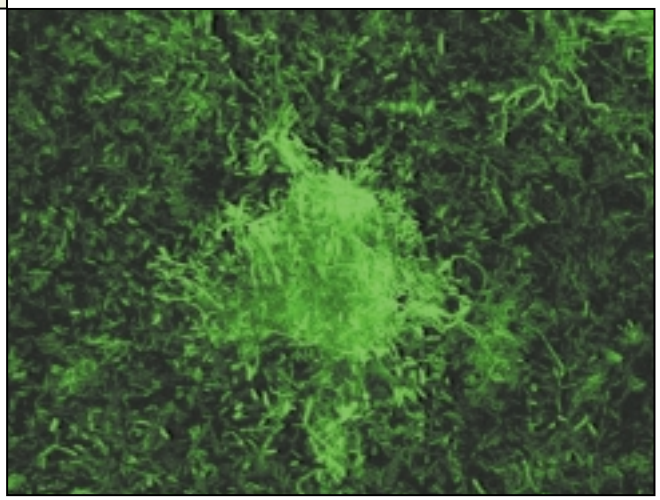
By studying the way bacteria join together into organized groups, scientists also learn how humans and other higher organisms developed, Bassler says. After all, our bodies are essentially collections of genetically identical cells that, based on chemical cues, specialized into different tissues (skin, bones, a heart, brain, and so forth). According to Bassler, these tissues probably interact with each other using chemical crosstalk similar to that in bacteria.

Knock Their Lights Out

The idea that bacteria communicate was considered "fringe science" for decades after the early 1970s, when researchers first showed that some marine bacteria not only gabble, but turn the lights on when the party gets big enough. Bassler says many scientists originally dismissed the work as "quirky results in non-interesting, non-[disease-causing] bacteria."

Bassler's fascination with bacterial communication, quorum sensing, and luminescence began in 1990, while she was a graduate student. She heard a visiting scientist describe his discovery, made years earlier, of the first genes for quorum sensing. Instantly excited about the topic, she charged up afterwards and persuaded the speaker to hire her onto his research team.

That's how Bassler's spy work started. She began her investigation trying to "knock the lights out" of the mysterious, glowing bacteria. In other words, she was trying to use molecular techniques to find the genes needed for bioluminescence by disabling or "knocking out" these genes. If she succeeded, the result would be a "dark" strain of bacteria, incapable of glittering.



P. SINGH AND E. PETER GREENBERG

Despite repeated efforts, Bassler's bacteria kept shining. Then suddenly, a light went on in her own head.

"Maybe these bacteria have two communication systems and knocking out one is not enough!"

She was correct. Bassler determined that *V. harveyi* contains not only the original quorum-sensing system that had been discovered a decade earlier, but another, even more complicated system. In the original system, quorum-sensing behaviors are sparked by a molecule called AI-1, for autoinducer 1. Each species of quorum-sensing bacteria makes and detects its own version of AI-1 and doesn't recognize the molecules made by other bacteria. In effect, each strain of bacteria is speaking its own language.

In contrast, the system Bassler discovered—one she likens to "bacterial Esperanto"—is a universal language that can be recognized and used by many, if not all, quorum-sensing bacterial species.

Bassler concluded that quorum-sensing bacteria are bilingual. They use a special code to talk to members of their own species and a common language to converse with all others.

Having two different communication systems offers clear advantages for bacteria, Bassler explains. They can covertly track their own numbers, spy on their competition, and monitor their environment, while also building alliances with other microbes.

Esperanto Espionage

Upon finding the new communication system, Bassler's next mission was to unmask the main Esperanto message molecule. Using several laboratory techniques, she decoded each step in the biochemical pathway that bacteria use to make the universal signal molecule. But all her genetic tools failed to reveal the molecule's true identity.

Bassler decided to switch tactics. She recruited an X-ray crystallographer, a scientist who blasts high-energy X-rays at microscopic crystals of molecules to illuminate their detailed structures and chemical properties. The idea was to get at the Esperanto molecule by examining its cellular alliances, specifically LuxP, the molecule to which Esperanto attaches in order to initiate cellular communication. In essence, they moved from gathering intelligence on the main suspect to snooping around the phone booths the suspect uses to talk with contacts.

The plan worked—the image the scientists captured of LuxP had 13 too many atoms, meaning they had photographed not only the phone booth, but the suspect inside it! Bassler could finally identify the Esperanto message molecule. She called it AI-2, for autoinducer 2.

Then the plot thickened again. Something didn't look right about AI-2. Most molecules in living creatures contain large amounts of the elements carbon, hydrogen, oxygen, and nitrogen, and a sprinkling of phosphorus and sulfur. AI-2 appeared to contain the element boron.

Boron is used in a range of industrial products, including insulation fiberglass, laundry detergent, and pyrotechnic flares (the green ones). Although boron is found in plants and in some bacteria, until Bassler's investigation, no one could pinpoint a biological role for it.

Boron's mystique also helped Bassler recruit a chemist to make AI-2, and similar molecules, from scratch. She reasoned that such molecules could serve as decoys to subvert, rather than incite, virulence and other quorum-sensing behaviors. If researchers can get this "trick" to work in *V. harveyi*, the same strategy might help topple the bacteria that cause diseases in people.

Boron is found in or used to make a variety of industrial and household products. Bassler was the first to reveal a biological role for it.

"If all bacteria use AI-2, you can fantasize about one anti-AI-2 molecule that could serve as a broad-spectrum antibiotic," muses Bassler.

Most current antibiotic drugs are designed to kill bacteria. The "bugs" that survive this treatment go on to breed generations of microbes that are invulnerable to the antibiotics. According to Bassler, targeting quorum sensing would be a radical new antibiotic approach that might be less likely to foster this sort of drug resistance.

"The hope is that, instead of killing the bacteria, we could try behavior modification drugs. It would be like putting

earmuffs on the bacteria so they couldn't hear the quorum-sensing signals." This would tip the balance in favor of our immune systems, which would then be better able to combat the bacteria, she explains.

Case Closed, Doors Open

Bassler and others have now exposed a network of molecules that *V. harveyi* uses to make, send, or detect quorum-sensing messages. All these signals eventually reach the kingpin—a master regulator protein called LuxR, which turns on the 100 or so genes that launch quorum-sensing behavior.

But until recently, a critical player in this network eluded Bassler and her team. What molecule serves as "command and control," switching LuxR on and off? Her recent studies divulged the answer—or actually, answers. It turns out that there are four molecules responsible for controlling LuxR. And, even more surprising, they are not proteins, as are all the other molecules in the communication chain. Instead, they are small RNA molecules (sRNAs), chemical cousins of DNA in genes.

EDITH WIDDER

Deep-sea angler fish make good use of luminescent bacteria. Female anglers lure prey using a long spine as a fishing rod, the tip of which is lit up by millions of the bacteria.

Bassler named these newly discovered molecules Qrr 1 through Qrr 4, for quorum regulatory RNA 1 through 4. Independently, each can trigger quorum sensing in an instant, but to turn it off, you need all four.

Bassler is now focused on trying to understand how each sRNA works and how the four operate together. Small RNAs were only detected in the past few years and are associated with processes ranging from the development of embryos and the formation of the nervous system to cancer. If the sRNAs that Bassler uncovered prove similar to these medically important sRNAs, they may offer tantalizing possibilities for new ways to study, detect, prevent, or cure illness.

If that happens, Bassler won't be surprised. She's continually aware of the broader implications of her research.

"I think every day that what I do is valuable. We're asking fundamental questions about how nature works—how information is transferred from outside to inside an organism," Bassler says.

"I'm working on a glow-in-the-dark bacterium because that's absolutely the best system to use to understand this question," she continues. "But everyone in my lab knows that we're not just working on *V. harveyi*, we're working on you and me."

Bassler says her research in the past few years has gone in directions she never dreamed. In addition to her collaboration with a crystallographer and a chemist, she's invited a theoretical physicist to join her team. He is using computer modeling to help understand bacterial chatter.

"What's most exciting to me is that this work has really stretched me as a scientist," she remarks.

Taking her work into areas outside her own expertise is not only thrilling, it is also helping Bassler train a new generation of interdisciplinary scientists.

"As a bacterial geneticist, I never imagined I'd be making molecules in my lab or doing crystallography. But now the postdocs and grad students in my lab understand these subjects. They are developing into scientists of the future, limited only by their imaginations."

Secret Life

Hundreds of scientists now study bacterial communication, and practical applications of this work multiply almost as fast as the microbes themselves. Bassler's pioneering work in the field was recognized in 2002, when she was one of 24 scientists, artists, scholars, and activists who won prestigious MacArthur Fellowships.

This honor, commonly called the "genius award," recognizes not only intelligence but also exceptional creativity and promise. Bassler was cited for work that "reveals new insights into the basic biology and ecology of bacteria, findings that may have direct application in the future

treatment of disease." She was awarded $500,000 over 5 years to spend any way she would like.

Bassler's enthusiasm and creativity extend beyond her time in the laboratory. Early in the morning, for 5 days a week over the past 20 or so years, Bassler has taught aerobics classes at the local YMCA. She says it's a way to ensure she gets her own exercise. "If I didn't teach the class, I wouldn't go," she chuckles.

She also takes singing (jazz and opera) and acting lessons. "I am a curious person, so I wonder about these other things," she says. "I'm just trying them for fun. It's my other secret life."

Yet Bassler is quick to point out that science is really what drives her. "I'm glad I was lucky enough to find the career that's right for me," she says. "I think about science much more than I think about singing. I think about it in the shower, while going to sleep, all the time."

Science itself is a means of creative self-expression for Bassler. "We scientists discover things about nature the same way that an artist or choreographer or dancer creates new work," she says.

"I think science is an incredibly creative endeavor. If you're good at it, it's art." ■

Squid Row

JOHN FORSYTHE

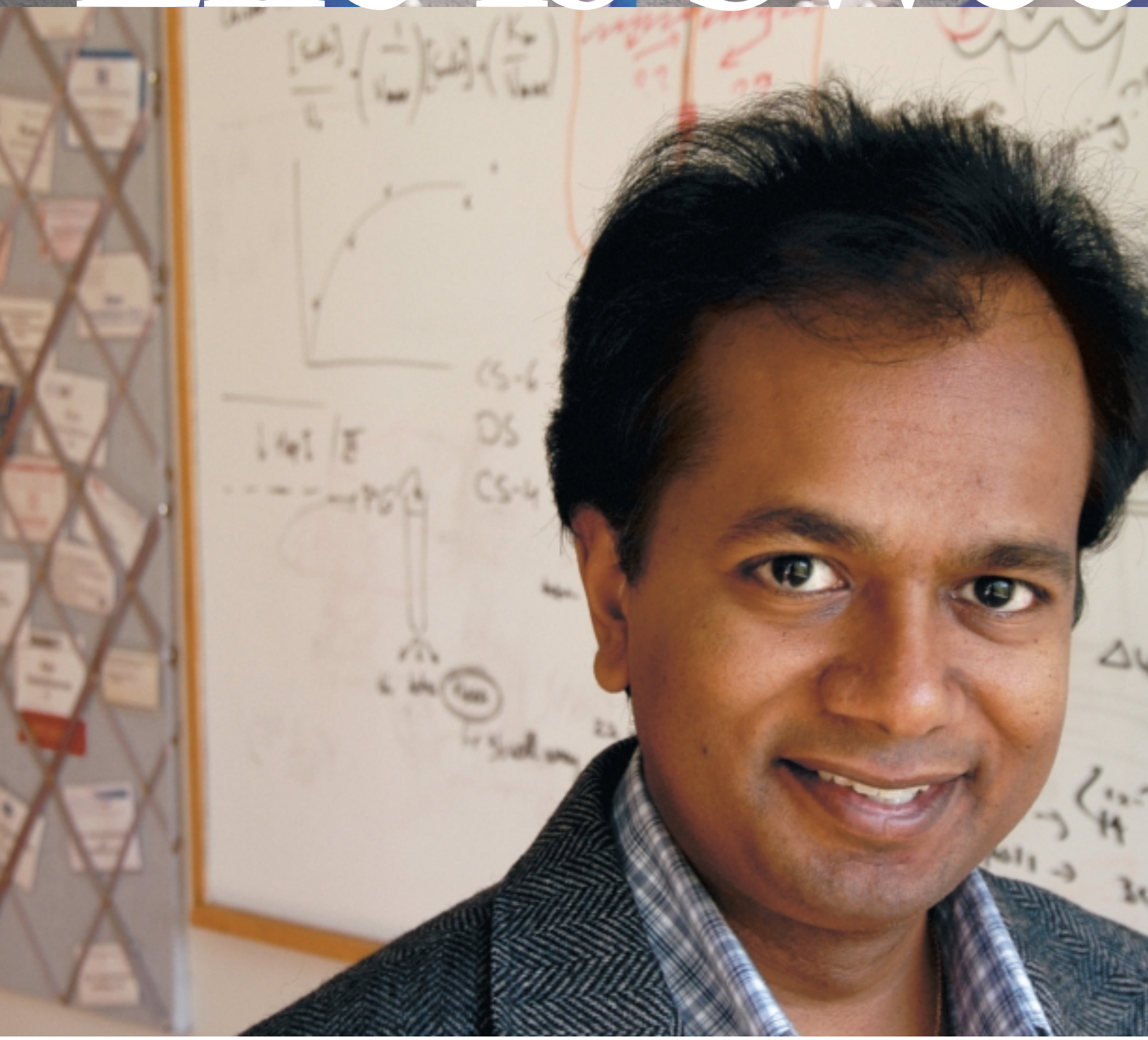
On land, only a handful of creatures shimmer in the dark—fireflies and some earthworms, mushrooms, and algae. But in parts of the world's oceans, up to 90 percent of creatures glow, or luminesce. Light helps these organisms find food, mates, homes, and—if delivered as a blinding flash—repel predators.

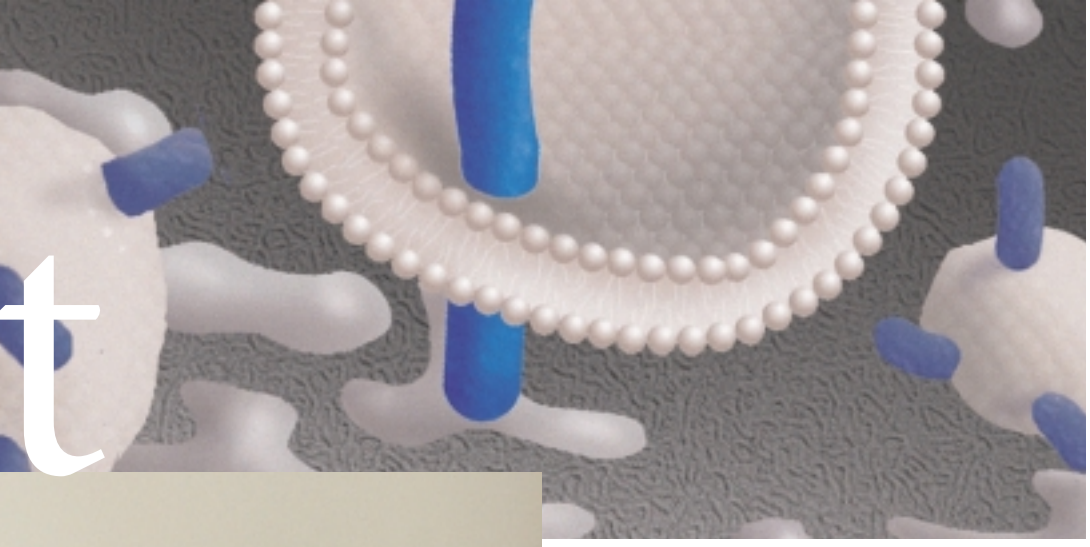
Take bobtail squid, which use light not only to illuminate the night, but also to hide. Living in knee-deep waters around Hawaii, these miniature squid nurture large populations of glittering *Vibrio fischeri* bacteria, close cousins to the *V. harveyi* that Bassler studies (see main story). The *V. fischeri* live happily in the light organ on the squid's underside, where they dine on a rich fare of amino acids and other nutrients. In return, the bacteria provide light that the squid deftly control in order to camouflage themselves from predators.

During the day, the strawberry-sized squid bury themselves in the sand. At night, they wriggle out to hunt for shrimp, worms, and small fish. The squid keep a coat of sand on their backs so that when seen from above, they blend in with the sea floor. But on bright moonlit or starry nights, the squid have a problem since they cast a shadow on the sand, advertising a bite-sized calamari snack for roving eels, barracuda, or seals. With light sensors on their backs, reflective proteins, and a shutter-like opening in their light organ, the squid tune their bacterial glow to precisely match their surroundings. Cloaked in ambient light, they and their shadows essentially disappear.

At sunrise, the squid squirt out about 95 percent of the bacteria in their light organs. Depleted of their shining guests, the squid grow dim and retire to their sandy burrows. As they sleep, the remaining 5 percent of the bacteria multiply. By dusk, the bacterial population reaches a quorum. Flip! The squid begin to glisten, and it's time to hunt. —*A.Z.M.*

Life Is Swee





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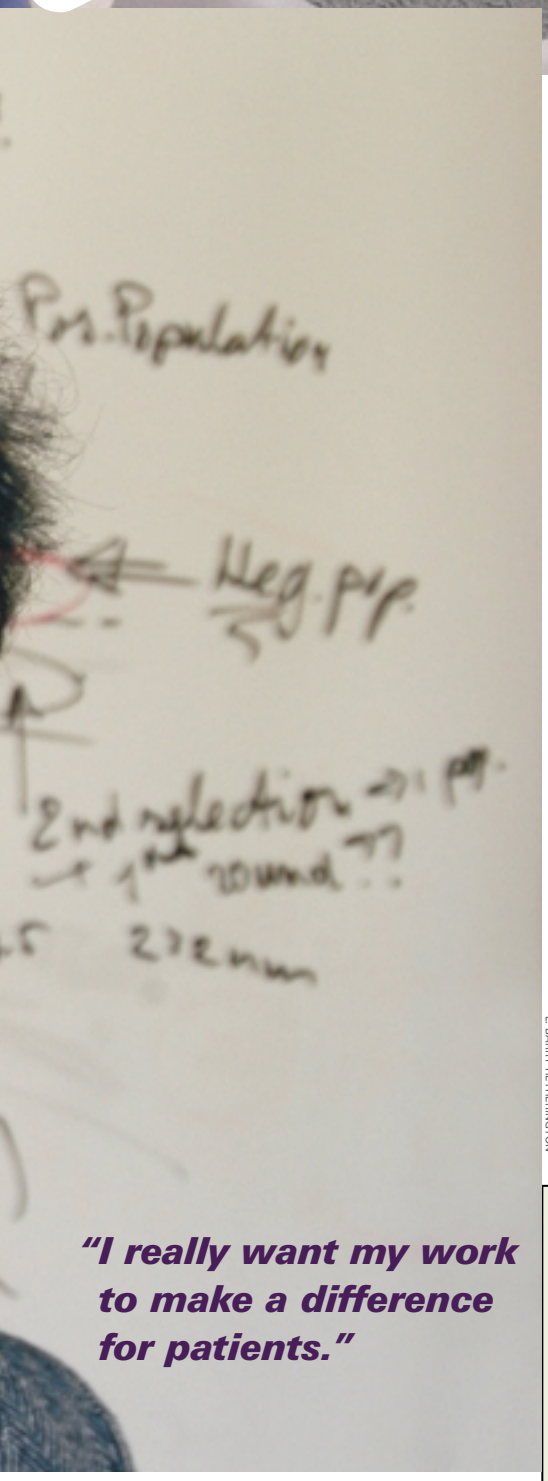


L. BARRY HETHERINGTON

"I really want my work to make a difference for patients."

By Alison Davis

Ram Sasisekharan's first experiments with human biology began early. Like most kids, he suffered the "battle wounds" of an active child's growing-up years. Sasisekharan was continually amazed to see his scabs disappear and new skin grow back, over and over again.

"I was absolutely fascinated by how my body automatically healed when I got hurt," he says. "It just seemed too bizarre to be true."

Now 39, and with fewer cuts and scrapes available for scientific analyses, Sasisekharan is still eager to find out what's going on underneath his skin.

How do the cells stitch themselves together to form skin, tissues, and organs?

A professor of biological engineering at the Massachusetts Institute of Technology in Cambridge, Sasisekharan got his bachelor's degree in biophysics and a Ph.D. in medical sciences. His goal is to learn life's basic rules for design.

Knowing how cells come together to form skin, tissues, and organs, he says, will lead to a deep understanding of the language of life and the tools required for editing mistakes that cause disease or the problems that arise from injury. And though Sasisekharan's childhood curiosity has not waned with time, he says that these days curiosity alone is not enough.

"I'm not satisfied with just doing cool stuff in the lab," he says. "While that's what makes science fun, I want to take my science as far as it can go. I really want my work to make a difference for patients."

Sugar Rush

Sasisekharan studies biological sugar molecules called carbohydrates, which are indispensable for life on Earth.

In most life forms, carbohydrates come in many varieties, ranging from simple to complex (see sidebar, page 13). In their simplest form carbohydrates equal energy, and they are sweet. This is the "sugar rush" we all know well. Simple carbohydrates like sucrose, glucose, and fructose are the molecules that give sweetened breakfast cereal, orange juice, candy bars, and many other foods their sugary taste.

Ram Sasisekharan is a biological engineer at the Massachusetts Institute of Technology in Cambridge. Sasisekharan studies sugar molecules called carbohydrates.

Life Is Sweet

Simple and complex carbohydrates are present in many different foods.

Complex carbohydrates, on the other hand, are made up of simple sugars linked together in various combinations. Complex sugars are not necessarily sweet, and they include substances like the starch in potatoes and pasta and the fiber in apple skins and vegetables.

Complex carbohydrates are part of a healthy diet, and they are also a big part of our bodies.

In fact, complex carbohydrates are among the magical molecules that helped fix Sasisekharan's skinned knees. These gluey substances perform an astounding number of biological roles ranging from holding cells together to communicating messages throughout the body.

Most complex carbohydrates are bundled into packages that also contain proteins and other types of natural chemicals. Scientists refer to these biological mixtures as glycans. Just about every cell in your body has a sugary, glycan coat, and these abundant substances populate the spaces between cells too.

But despite the thousands of important roles carbohydrates play in maintaining our health, they remain poorly understood by scientists.

According to Sasisekharan, researchers know very little about how sugars work in the body because carbohydrates have traditionally been ferociously hard to study. The main reason, he explains, is that complex carbohydrates come in a zillion "flavors."

Unlike a simply organized, linear string of connected units (DNA, for example), complex carbohydrates can be both linear and branched. They look something like trees, with branches big and small extending in every direction.

What's more—unlike our DNA, with its strings of "letters," and our proteins, made of chains of amino acids—carbohydrates are not made from a blueprint. Rather, the body makes complex carbohydrates through a sort of community effort, via the collective work of different enzymes acting in ways that remain stubbornly complicated for researchers to understand or predict.

For many scientists, these characteristics of carbohydrate research spelled "nightmare," not "interesting problem." Despite years of hard work, many researchers had great difficulty determining how sugars get assembled in nature.

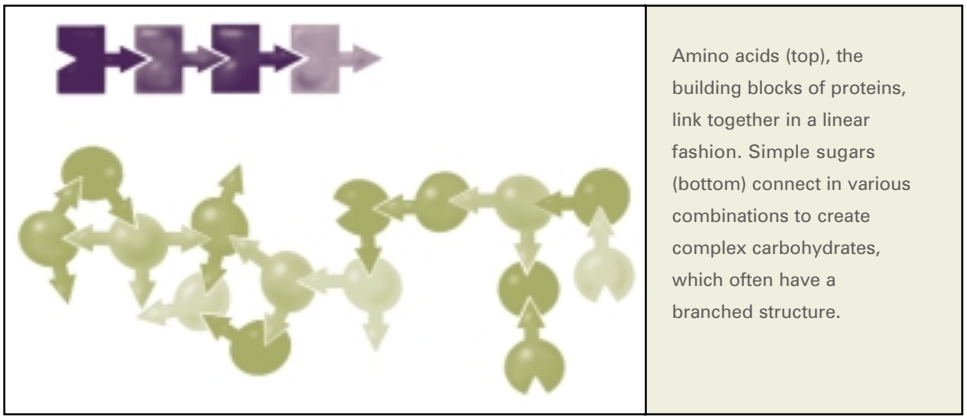
As a graduate student, Sasisekharan saw this as a challenge and decided to try his hand at it.

"It was probably a dumb thing to do then, but I was lured by the excitement of the unknown."

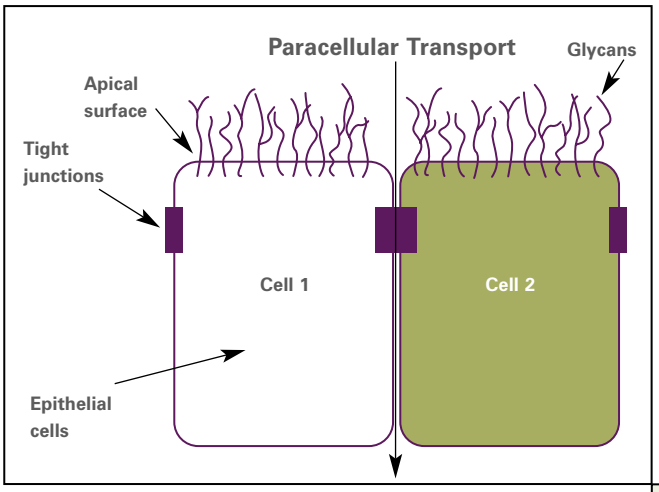
He hit the jackpot. Sasisekharan figured out a way to decipher nature's carbohydrate code: how to "sequence," or put in order, the many different constituent parts of a glycan called heparin. In doing so, he opened the door to studying sugar molecules in intricate detail.

Open, Sesame

Among the many ways sugars affect our health is by policing the gates between so-called epithelial cells. These are the cells all over the body that line organs, such as the stomach, lungs, and brain. The body strictly guards the passage of molecules through epithelial cell gates, a process called paracellular transport.



Amino acids (top), the building blocks of proteins, link together in a linear fashion. Simple sugars (bottom) connect in various combinations to create complex carbohydrates, which often have a branched structure.



Sasisekharan has discovered that paracellular transport, in which molecules pass between epithelial cells, appears to be gated by a "sugar code." The code is specified by glycan molecules that coat the top, or apical, surface of these cells.

If the wrong molecules slip through the gates, "bad things can happen," says Sasisekharan. Asthma, diarrhea, and many other health problems are directly linked to problems in transporting molecules across epithelial cell barriers.

Recently, Sasisekharan's experiments have led him to suspect that the epithelial passages are marked with a sugar code that restricts entry to only the molecules that fit just right. It makes sense that the body would do this, says Sasisekharan, since carbohydrates can be constructed in thousands of subtly different ways. That adds up to many, many different combination locks.

"It's sort of like Ali Baba and the 40 Thieves," says Sasisekharan, explaining that specific sugars only recognize molecules that precisely match the correct code, then respond with the chemical equivalent of "Open, sesame."

"If the code is correct, the cellular trap door can swing open and let certain molecules pass through."

While Sasisekharan needs to do more experiments to fully understand what's going on with sugars and epithelial cells, the practical aspects of the findings jump to his mind almost immediately.

"What if we could learn a way to use the correct sugar as a 'key card' to keep cell doors shut when needed?" he wonders. That type of strategy, he says, would be useful in cases where you know the code is too loose—like in asthma.

And what about the other way around, he ponders. "What if we could use the sugar 'key card' to open the door and get medicines inside?" Precise delivery of medicines to their desired job sites in the body could help alleviate side effects caused by drug molecules acting in the wrong place.

Another Dimension

Sasisekharan has lots of projects going on in his lab to investigate the multitude of roles that carbohydrates play in the game of life.

But it's easy to get wrapped up in the details, he notes. While Sasisekharan is undaunted by hard problems, he thinks one of the biggest keys to his own success has been his ability to step back and look at the many dimensions of a research puzzle.

One way he does this is by drawing pictures.

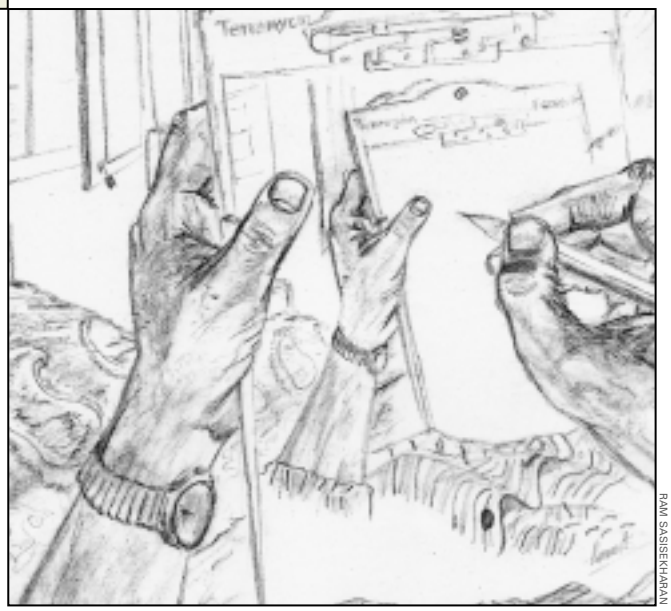
"I love to doodle and sketch," says Sasisekharan, adding that scratching on a pad of paper helps sharpen his thinking and his ability to appropriately gauge the depth of a problem.

Sasisekharan says that for him, drawing serves as a link between the analytical world and the visual world, bringing new ideas into view.

"It's important to zoom in," he says, "but it's also essential to zoom out."

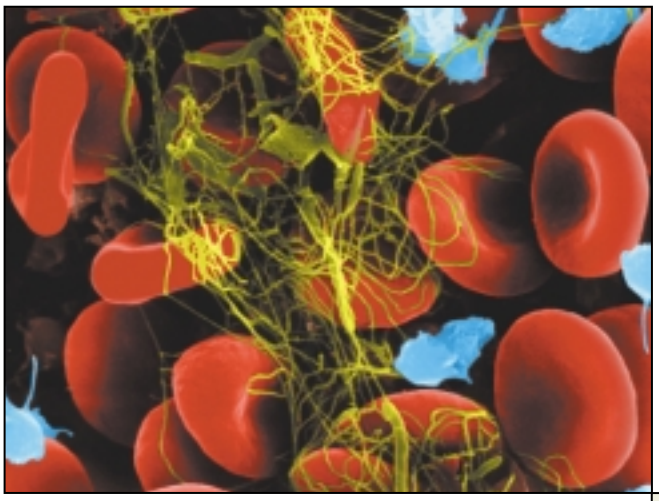
Having the ability to shift focus is absolutely necessary in today's data-rich world of medical research, Sasisekharan believes.

"Biology and science in general are increasingly complex," Sasisekharan says, and making discoveries requires creative approaches to handling large amounts of data.



Sketching helps Sasisekharan visualize research ideas.

RAM SASISEKHARAN



Commercial preparations of heparin vary widely in their ability to prevent blood clots, in which strands of fibrin (yellow) form a meshwork and trap red blood cells in a clump.

Mix and Match

Instead of breaking apart a huge problem into tiny chunks and studying every teensy aspect of a particular chunk, Sasisekharan prefers a different method. He likes to build new models, juxtaposing the individual pieces in many different combinations, and then see what happens.

Sasisekharan did just that when he determined the sequence of heparin, a sugar-based drug and one of the most widely used medicines in the world. Heparin, and a similar, but smaller version called low-molecular weight heparin, are glycans that doctors use during and after surgery to prevent the formation of blood clots that can lead to heart attacks and strokes.

Knowing the overall size and dimensions of a large heparin glycan molecule, Sasisekharan began by asking his computer to generate a master list of all the possible individual sugar pieces that could theoretically connect together to make up the larger carbohydrate. Computers are excellent at crunching through millions of combinations, doing in a few hours what would take a person months.

Many of the potential solutions derived by the computer dropped out immediately when Sasisekharan gave the computer instructions to deal with practical considerations such as the basic rules of chemistry and the natural abundance of specific sugar types.

Through chemical tests and the process of elimination, pretty soon only one possible structure came out at the end of the exercise. Using what he'd learned, Sasisekharan could then custom-make different varieties of heparin with special properties.

Sasisekharan's work is very important medically. While heparin is one of the top-selling drugs in the world, in many patients it can produce potentially worrisome side effects such as excessive bleeding. The trouble is that there hasn't been a quick and easy way to break the glycan apart and determine how much of the active ingredients are actually present in a given bottle of medicine.

Most commercial preparations of heparin come from pig intestinal lining, and these preparations contain widely varying mixtures of different sizes of glycan molecules. Because the drug is not completely "homogenous," or pure throughout, it is hard to know ahead of time how well a particular batch will work in patients.

Sasisekharan's custom-made, "designer" heparins have the potential to be safer than current preparations because the molecules work predictably. What's more, the way the molecules are designed enables scientists to neutralize them easily to prevent bleeding in a person's arteries or veins. This has been a hit-or-miss process with the old varieties of heparin.

Sweet Treatments

Ever eager to speed his lab discoveries to patients, in 2001 Sasisekharan helped to form a biotechnology company called Momenta Pharmaceuticals, which is located in Cambridge, Massachusetts. According to Sasisekharan, the company's goal is to use the tools he has developed to make new forms of heparin and other sugar-based drugs. Progress is under way, and human tests of Sasisekharan's designer heparins are set to start within a year.

Sasisekharan's basic studies have led in another direction important to public health: fighting cancer. Researchers have known for some time that sugar molecules that "decorate" the surface of cancer cells play a role in how fast the cells grow, and some sugars actually appear to slow tumor growth.

A few years ago, Sasisekharan began experimenting with heparinase, a chemical "scissors" that clips sugary glycan molecules from cell surfaces. He reasoned that by altering the sugar coating on cancer cells, he might be able to control tumor growth.

Studies in mice worked. One particular form of heparinase actually stopped cancer growth in these lab mice, and Sasisekharan is hoping the findings will someday translate to treating human cancer as well.

The possibilities seem endless, and Sasisekharan hopes that novel uses of biological sugars will lead the way not only to new medicines, but also to safer versions of existing drugs.

Research Ecosystem

Looking back in time, Sasisekharan recalls another spark that interested him in the world of science.

"I was spellbound by the space around us," he says, remembering as a child being in complete awe of subjects like astronomy and geography.

Sasisekharan recalls thinking to himself, "Wow, how does weather happen? How does it contribute to the ecosystem?"

In a sense, those early wonderings were a hint toward Sasisekharan's future thinking. His approach in the lab is to stay in touch with the ecosystem of science and how it is always changing.

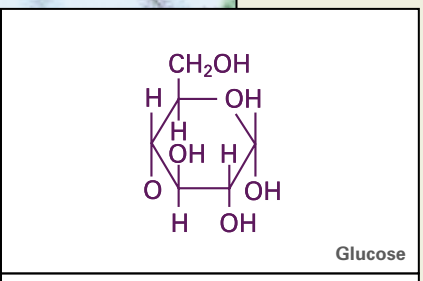
"Science has evolved," says Sasisekharan. "It is very different now than it was 20 or 30 years ago, and it will be even more different in another 20 or 30 years."

Future biology labs will be home to mathematicians, computer scientists, engineers, and physicists, Sasisekharan predicts, adding that it will be very important for scientists of all stripes to work together to improve health.

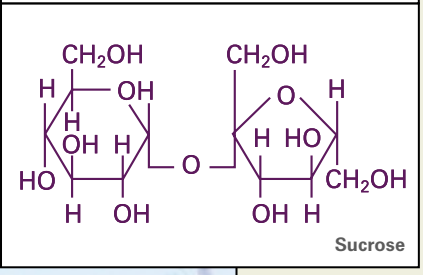
He thinks there's never been a more exciting time to do research and that science can offer long-lasting impacts to society.

"The number of unanswered questions grows every day," Sasisekharan says, "and patients are waiting." ■

Carbs Made Simple



Glucose



Sucrose

Carbohydrates are the main energy source for the human body. You probably know that your body converts the carbohydrates from your diet into energy. Plants do the opposite—through the process of photosynthesis, plants take energy from the sun and turn it into carbohydrates, giving off oxygen as a byproduct.

Also called sugars, carbohydrates are indeed the stuff of life. They exist in several different forms: monosaccharides, disaccharides, and polysaccharides. As the prefix "mono" implies, a monosaccharide contains one simple sugar molecule, and glucose is an example. Disaccharides contain two simple sugars linked together, from the prefix "di" for two. Sucrose, or table sugar, is a disaccharide, consisting of glucose and fructose chemically linked together.

Polysaccharides—literally, "many sugars"—are long, interconnected complexes of monosaccharide or disaccharide units that repeat in a pattern. Often, certain atoms within a polysaccharide contain extra "decorations" that add a negative charge to the overall sugar or change its shape. These chemical modifications help customize sugars for their many different tasks.

Nestled together with proteins, polysaccharides form complicated bundles of molecules called proteoglycans, which are everywhere in our bodies. Because of their structure, proteoglycans can twist and bend. They help to thicken the fluid in joints and are key components in cartilage and connective tissue. Proteoglycans also dot cell surfaces and help cells roam around the body.—*A.D.*

Spice Therapy?

A potential new treatment for cystic fibrosis comes from a surprising source: turmeric, the spice that makes mustard yellow and gives curries their hallmark taste. NIGMS grantee **Michael Caplan** of Yale University in New Haven, Connecticut, found that feeding curcumin (the intense yellow pigment in turmeric) to mice prone to developing cystic fibrosis dramatically cut the experimental animals' death rate. The mouse studies are promising enough that the Cystic Fibrosis Foundation has begun a small clinical trial with curcumin in people with cystic fibrosis.

In cystic fibrosis, thick mucus clogs the lungs and other organs. In most people with the condition, the root cause of the excess mucus is the loss of function of a protein that forms a channel to control the flow of chloride into and out of cells. In diseased cells, policing mechanisms automatically quarantine the channel protein, which hasn't folded properly, to a waste bin where it is later destroyed. With the channel confined, chloride (a component of common table salt) is trapped inside the cells, leading to a thickening of mucus that traps bacteria and causes life-threatening infections.

Based on what Caplan knew about curcumin's chemical properties, he suspected that the spice might be working by interrupting the protein quarantining process. This would let the channel protein—still reasonably effective in ejecting chloride—do its job. Caplan confirmed the hunch with experiments showing that curcumin restored normal chloride flow out of cells. While the findings are encouraging, people should not self-medicate with curcumin, Caplan advises. Scientists do not yet know, for example, if the substance, sold as a dietary supplement, might interact with prescription drugs.—*A.D.*

Hot Flash News Flash

Tamoxifen (Nolvadex®) is an effective therapy for some types of breast cancer. However, roughly 80 percent of women who take the drug experience hot flashes. While not life-threatening, hot flashes can be so uncomfortable that people stop taking the medicine. To make this cancer-controlling drug tolerable, doctors can treat Nolvadex-triggered hot flashes with antidepressants such as paroxetine (Paxil®).

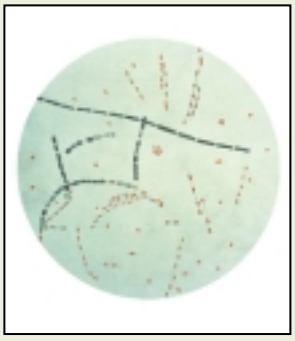
New evidence hints that taking both drugs together may not be such a good idea. NIGMS grantee **David A. Flockhart** of the Indiana University School of Medicine in Indianapolis knew that the body breaks down Nolvadex and Paxil with the same enzyme. He wondered whether taking both drugs together might affect blood levels of either or both of them. To test this, Flockhart and oncologist Vered Stearns of the Johns Hopkins University School of Medicine in Baltimore, Maryland, performed a study with 12 breast cancer survivors who had been taking Nolvadex for at least 1 month and were having severe hot flashes. The researchers gave Paxil to the study volunteers for 4 weeks and then took blood samples.

Women who took both drugs at the same time had substantially lower levels of a key byproduct of Nolvadex, chemical evidence that Paxil does affect how the body processes Nolvadex. But the effects differed among the women depending on their innate capacity to process drugs, which helps explain why Nolvadex's effectiveness can vary among people. Flockhart cautions that until further data become available, the results of his study should not alter treatment recommendations because the health implications are still uncertain at this point.—*A.D.*

From Hepatitis to Anthrax

The 2001 bioterrorism attacks on the U.S. mail system proved that anthrax can be fatal. Nearly half of those infected in the attacks died, and many survivors continue to face difficulties such as fatigue, shortness of breath, and memory problems. Antibiotics work well if given soon enough after exposure, but once an infection begins, the bacteria that cause anthrax release toxins that can kill a person even after the microbes themselves die. Although new drugs against anthrax toxins are being developed, none are yet ready for use in humans.

NIGMS grantee **Wei-Jen Tang** of the University of Chicago has studied an anthrax toxin called edema factor for several years. He previously determined its atom-by-atom structure and showed how the toxin hijacks normal cell function. In a recent stroke of luck, another researcher who was studying a hepatitis B drug called



CENTERS FOR DISEASE CONTROL AND PREVENTION

Hepsera® read about Tang's work and wondered whether the drug, which mimics a natural biological target of the anthrax toxin, might also work against edema factor. Tang confirmed the hunch, discovering that Hepsera grips tightly to edema toxin and prevents it from damaging lab-grown mouse cells.

If anything, Hepsera appears more potent against the anthrax toxin than in its approved use against a hepatitis B viral protein. Since the medicine is already known to be safe in humans, researchers could potentially test its ability to treat anthrax relatively quickly. Although the drug only blocks the action of one of the three major anthrax toxins, the poisons apparently magnify the effects of each other, so blocking one of them would be of great benefit.—*Karin Jegalian*

Blocking Bacteria

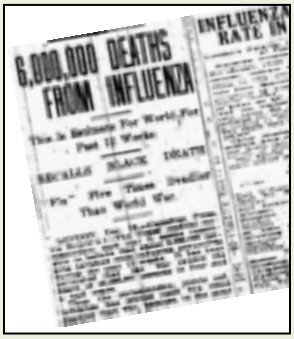
A well-known complication of surgery is infection, which can be caused by bacteria that are harmless in healthy people but sometimes turn deadly in those whose defenses are down. People hospitalized in an intensive care unit and receiving intravenous fluids are at higher risk of infection because their intestines become leaky and vulnerable to bacterial invasion. Bacteria such as *Pseudomonas aeruginosa* sense this stress and re-program their strategy to attack mode. Instead of growing calmly, they take advantage of the easy entry and make their way into the bloodstream, causing widespread, potentially deadly infections.

NIGMS grantee **John Alverdy** of the University of Chicago wondered if a peace-making approach toward the germs might work. In experiments with mice, he tested whether a waxy material called polyethylene glycol, or PEG, might protect the intestines from bacterial invasion. Alverdy suspected that PEG molecules might serve as a kind of artificial mucous barrier that the bacteria would find appealing, keeping them safely in place. He found that all of the mice that had undergone liver surgery and then received PEG could resist *P. aeruginosa* infection. Alverdy backed up the findings in experiments with isolated human intestinal cells, showing that PEG prevented *P. aeruginosa* from latching onto cells.

If studies in humans have similar results, patients undergoing major surgery may someday be given PEG routinely to coat their intestines and prevent *P. aeruginosa* infection. This approach might also be more ecologically friendly than the prolonged use of multiple antibiotics, which encourages the growth of menacing, drug-resistant bacteria.—*K.J.*

Reconstructing a Deadly Flu

The "flu," short for influenza virus, strikes millions of people every year. Some years most cases are mild, whereas other years—most notably during the 1918 "Spanish flu" pandemic—the outbreak is deadly. Why the 1918 flu killed more people than died in World War I is still a mystery. To better understand how deadly flu strains arise, scientists examined the molecular details of hemagglutinin (HA), the virus protein responsible for infection.

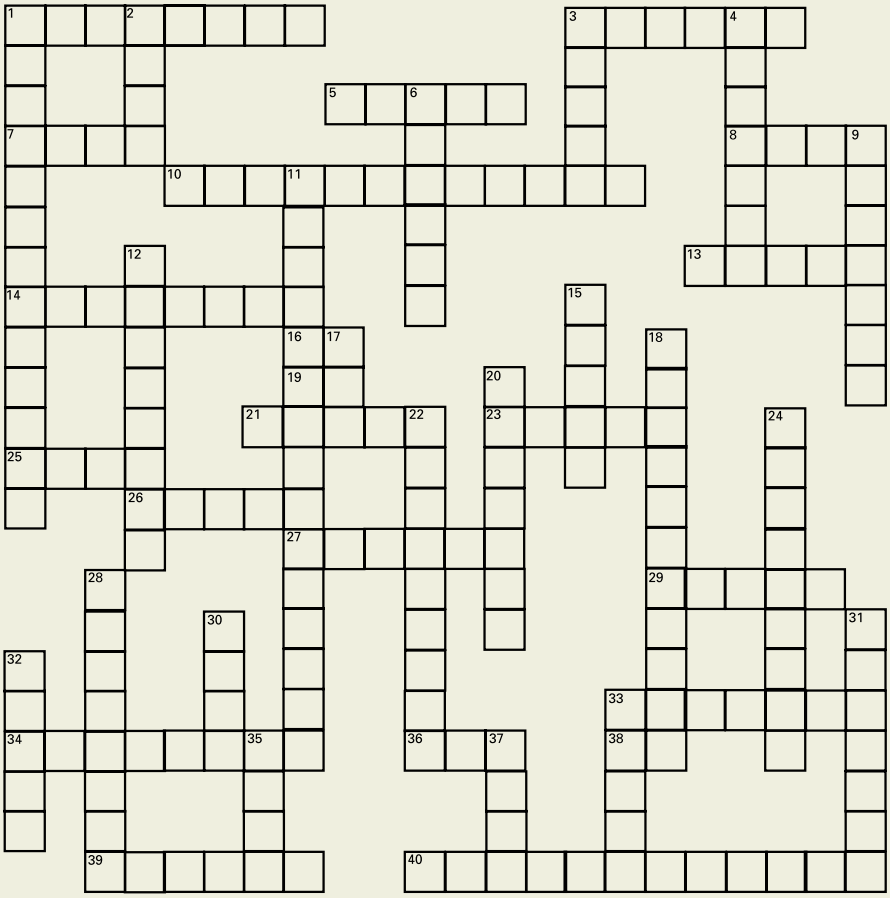


In a team effort with scientists across the country, NIGMS grantee **Ian Wilson** of the Scripps Research Institute in La Jolla, California, figured out the three-dimensional molecular shape of the HA protein from the now-extinct 1918 flu virus. One of Wilson's collaborators, Jeffery Taubenberger of the Armed Forces Institute of Pathology in Washington, DC, collected genetic material from preserved tissue specimens and from the remains of people who died of the flu in Alaska and were buried in the permafrost. He then pieced together the sequence of the gene for the HA protein and made enough of it in the lab to determine its structure.

Knowing the exact shape of the 1918 HA protein, the researchers were able to compare it to HA proteins from humans, birds, and pigs. They found that the 1918 variety most resembles HA from birds, which suggests that the 1918 flu pandemic possibly arose from a bird virus that was unusually good at infecting people. Viruses passed from birds and other species to humans are rare and potentially very dangerous, since human immune systems are unaccustomed to them and have a tough time fighting them off.—*Audrey Huang*

These stories describe NIGMS-funded medical research projects. Although only the lead researchers are named, science is a team sport and it is important to realize that many researchers work together to carry out these studies.

The Last Word



ACROSS

1. turmeric ingredient
3. enough bacteria
5. dark opposite
7. has to
8. too
10. sugar
13. synthetic fiber in stockings
14. merry-go-round
16. not down
19. same as I
21. day's opposite
23. watchful
25. leave out
26. America's bird
27. learning spot
29. Hollanders
33. glycan drug
34. half of table salt
36. U.S. research sponsor
38. where surgery happens
39. strand
40. biological engineer Ram

DOWN

1. means of passing news and information
2. jacket
3. comforter type
4. often
6. complex carbohydrate
9. what you think
11. blue-green glow
12. number-cruncher
15. what monosaccharides are
17. bacterial barrier
18. chemical signal for bacterial action
20. bacterial geneticist Bonnie
22. breast cancer drug
24. framework
28. disease-causing
30. opposite prefix
31. keep within
32. overabundant in cystic fibrosis
33. mare or stallion
35. what experiments give you
37. punches

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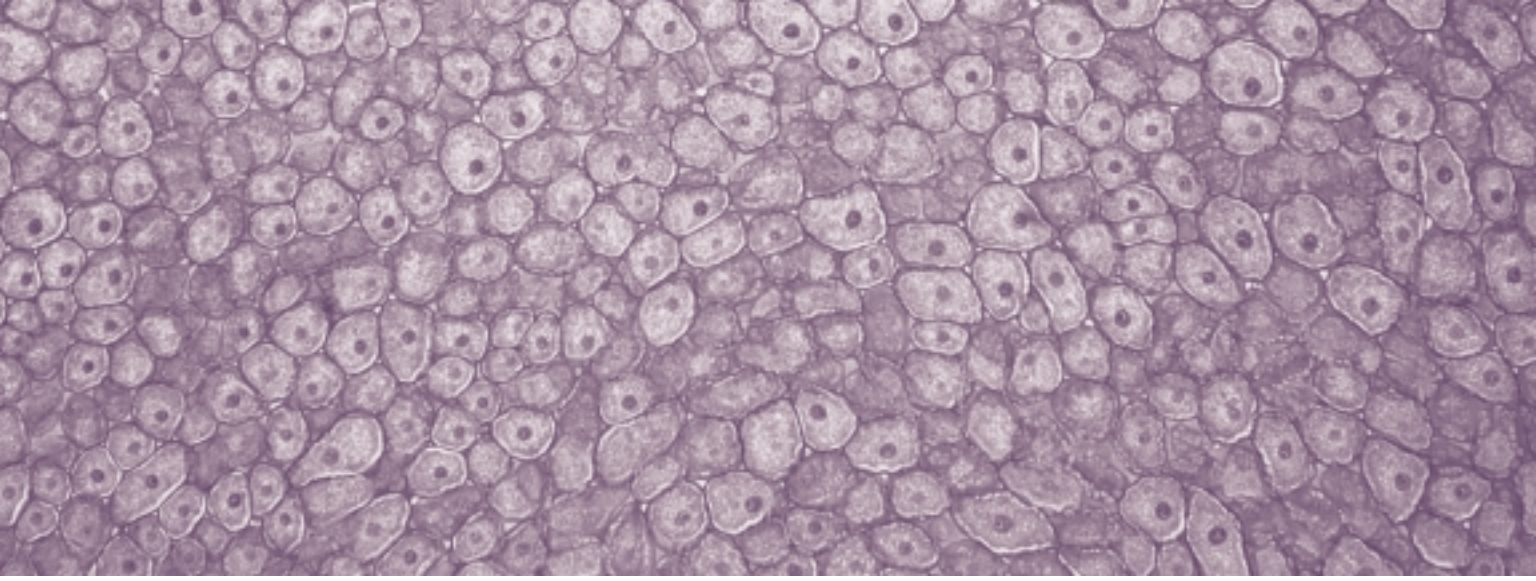

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