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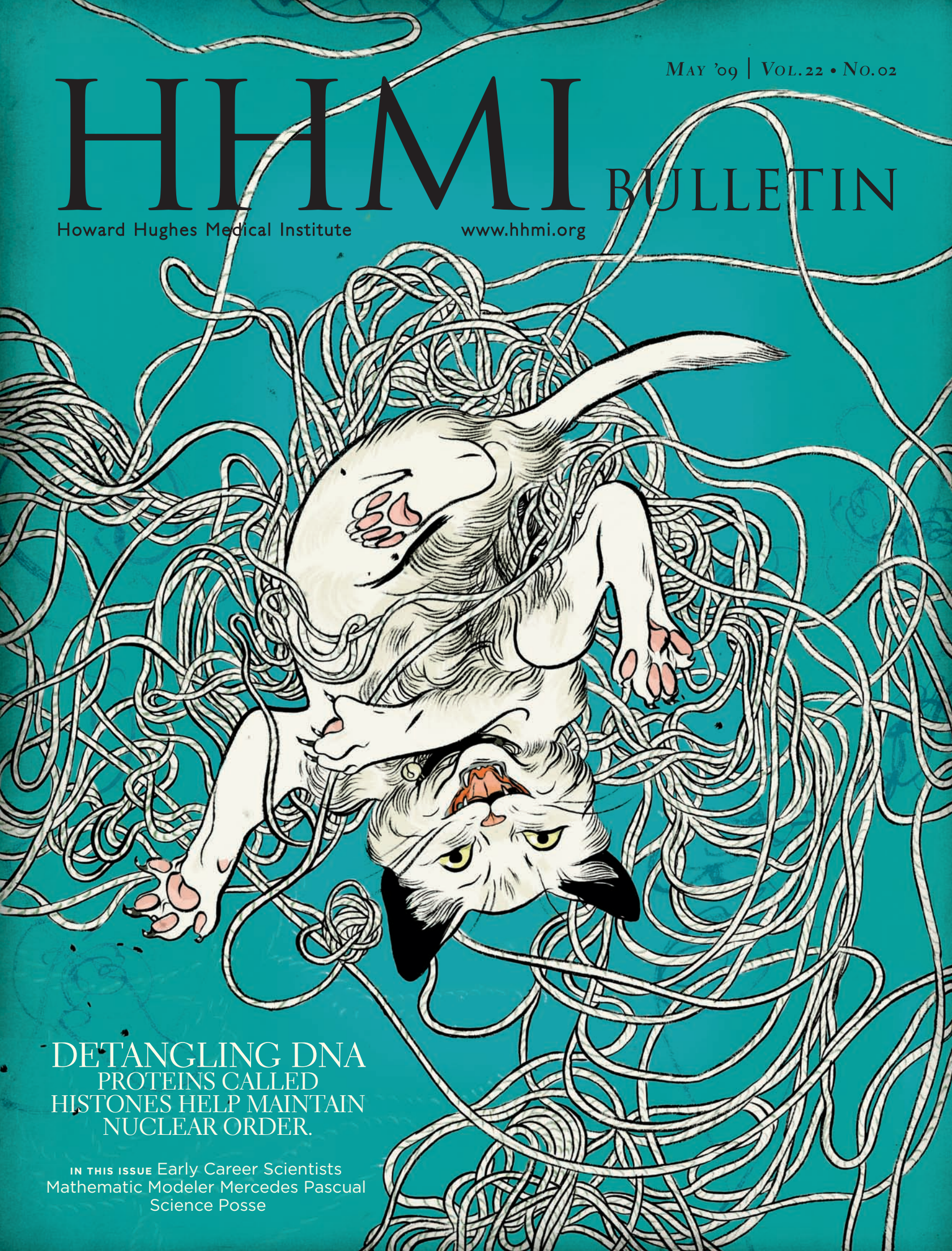
HHMI BULLETIN

Howard Hughes Medical Institute www.hhmi.org



DETANGLING DNA

PROTEINS CALLED HISTONES HELP MAINTAIN NUCLEAR ORDER.

49

This array of shells shows obvious variety in shape, color, and size. But another quality can be used to categorize the shells: whether they are dextral (right-coiling), or sinsitral (left-coiling). Their left-right asymmetries can be traced to the same genes that affect which side of the human body different organs are found on, researchers have found.

Nipam Patel

VOL. 22 MAY '09 NO. 02

DEPARTMENTS

FEATURES

In February, I made my first trip to South Africa. I wasn't sure what to expect. My husband, Paul, and I attended a friend's wedding near Cape Town, and the area was just as picturesque and enchanting as we had heard it would be. Nothing, however, prepared us for the second half of our visit, which took us to the opposite coast, on the Indian Ocean, to the province of KwaZulu-Natal. There we saw a different side of Africa—one not nearly as splendid but much more memorable.

We went there on an assignment for HHMI to prepare for the Institute's announcement of a research initiative in partnership with the University of KwaZulu-Natal, in Durban (see page 46). The focus of the initiative is the dual epidemic of TB and HIV in South Africa, which is progressing at an alarming pace. Paul is a photographer, and our mission was to show, through voices and pictures, why South Africa is the right place to launch this effort and why now is the right time to do it.

During a four-day tour of hospitals, clinics, and research labs, we saw a country reeling from a brutal one-two punch and struggling to stay on its feet. Tuberculosis is not new to South Africa, but the disease has taken a dramatic change of course over the last few years, devastating a population weakened by HIV infection. Once predominantly an ailment of older men, TB is now a disease of the young, most of them women.

One young woman we met was Zanele. She found out she was HIV positive just as her daughter died from extrapulmonary TB, a grueling illness caused when untreated TB moves from the lungs to other organs in the body. The girl had been abducted by Zanele's estranged husband, who had not sought proper medical attention when the child fell ill. With help, Zanele regained custody of her daughter, but it was too late to save her life. Facing overwhelming grief, Zanele learned that her daughter was HIV positive—and that she is infected as well. She is still coming to terms with the news.

I am only the third person that Zanele has told about her HIV status. Even her sister, with whom she lives, does not know. Though the telling was obviously difficult for her, she understood why we were there. She wanted to help.

Against the backdrop of the pervasive stigma surrounding HIV, which makes prevention and early treatment so difficult, South Africa now faces an even larger threat—the combined epidemics of TB and HIV. One-third of the world's cases of TB/HIV infection are found there. South Africans cannot, and should not, face this challenge alone. It is a global problem that requires a global solution, and I intend to hold myself accountable. My first visit to Africa will not be my last.

FOR MORE INFORMATION: To learn more about the KwaZulu-Natal Research Institute for TB and HIV, and to see photos of South Africa with audio, visit www.hhmi.org/research/k-rith.

Mary Beth Gardiner

Paul Fetters

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Fully Engaged

ACTION POTENTIAL DESCRIBES A BURST OF ELECTRICAL activity that gives rise to other events: passage of an impulse between nerve cells, transmission of electrochemical signals across a network to enable thought and movement. As I complete my first month as president of the Howard Hughes Medical Institute, action potential provides a metaphor for what may be my most important leadership responsibility: making it possible for compelling and creative ideas to propagate through our institutional nervous system—the broad and interconnected network of HHMI laboratories and programs in the United States and beyond. It's hard to imagine a more exciting job description or a better job in U.S. science.

For two decades, I have been part of the HHMI community as an investigator at the University of California, Berkeley. I managed, over that period, to avoid formal administrative responsibilities. So it's fair to say that I will have a lot to learn in this new role. I fully expect to make mistakes—and to hear about them when I do—but I also expect that everyone at HHMI will be fully engaged in supporting the work of this remarkable organization, known around the world for the quality of its research and educational programs. To appropriate terminology from my research field—biochemistry—I expect to see high specific activity across the Institute. That expectation squares well with our mission: to catalyze the pioneering discoveries that will ultimately yield new medical treatments by supporting the best scientists possible and the best science that can be done.

These are challenging times for HHMI, given the state of the U.S. economy and the impact of the uncertain financial markets on our endowment. Although our endowment is substantial, prudence dictates that we prune spending across the full spectrum of HHMI activities so that we can prosper in the future and continue targeted investments in new programs. Spending for our core research programs—specifically, HHMI investigators and the scientists at Janelia Farm Research Campus—represents the bulk of the Institute's expenditures and will be subject to modest reductions. We have trimmed generous allocations for new equipment this year and will reduce budgets in the upcoming fiscal year but will cushion the impact on our scientists by granting them greater flexibility in how they manage funds from year to year. Even in this climate, a modest reallocation of current funds may enable us to undertake two important activities that will serve HHMI investigators and others: expansion of our support for postdoctoral fellows and reintroduction of a fellowship program for doctoral students.

In short, we're not standing still and that's a good thing. Thanks to the visionary leadership of my predecessor, Thomas R. Cech, we'll soon be welcoming 50 early career scientists to the HHMI community. These impressive scientists, chosen from among 2,100 applicants, have already begun to make their mark in U.S. science, and we expect much from them over the next six years. You can read about four of them in this issue of the *HHMI Bulletin* and see the entire class on our website, www.hhmi.org.

We're also proceeding with a bold collaboration—with the KwaZulu-Natal Research Institute for Tuberculosis and HIV (K-RITH)—that will bring together HHMI investigators and scientists from South Africa in a program of research in the heart of the entwined epidemics of tuberculosis and HIV. You can read more about K-RITH and our partners in this issue of the *HHMI Bulletin*. This initiative is incredibly interesting and somewhat risky—but if we succeed, it will be a home run. Indeed, HHMI's strength depends on its ability to remain nimble, to rethink current programs, to experiment. Our commitment to international science is a good example: we support many excellent scientists around the world, but can we do it better? For example, should our international efforts track the "people not projects" philosophy that guides our U.S.-based program? Our domestic and international science programs will come under the same administrative leadership as we consider these important questions over the coming months.

Like Tom, who kept a laboratory at the University of Colorado at Boulder throughout his presidency, I plan to remain an active scientist. Weekends will find me at the Janelia Farm Research Campus, where three colleagues and I are working on new imaging technologies that will capture the activity of single molecules. Although I have scaled back the scope of my laboratory at the University of California, Berkeley, it's where you'll find me during many vacations and holidays. I may be something of a workaholic, but this isn't work for me. It's fun—equal to the joys of fishing.

Barbara Ries

> "Action potential provides a metaphor for what may be my most important leadership responsibility: making it possible for compelling and creative ideas to propagate through our institutional nervous system."
>
> ROBERT TJIAN




Waste Not, Want Not

> "I just want a chicken that can run around and be happy."
>
> VANN BENNETT

Vann Bennett aims to raise pigs on his 30-acre property near Hillsborough, North Carolina. But first he's got to convince a county commissioner to go along with the idea—not because zoning is an issue but because the commissioner happens to be his wife, and Bernadette Pelissier isn't convinced that pigs are a good idea.

"She doesn't want to be a pig-sitter when I'm off giving seminars," says the part-time farmer and full-time scientist, who is an HHMI investigator at Duke University Medical Center.

If Bennett can find an alternate caretaker, the pigs will live in a post-and-beam pig pen—near the chicken coop—and dine on organic leftovers, including vegetables from Bennett's four-acre garden.

"I try to live sustainably," he says, "to grow as much of my own food as I can."

Bennett, who studies membrane proteins called ankyrins, takes issue with the country's current model of food production and does everything he can to raise his own food. "Profit is the overall guiding principle, and that means the way we treat animals is appalling," he says. "If you knew how the hens were treated, you'd never buy eggs in a grocery store."

He gets his eggs from his own hens—a dozen chickens from three heritage breeds: Jersey Giant, Araucana, and Dark Cornish. These older varieties have more genetic diversity than newer, more highly selected breeds of chickens used by commercial producers to supply most grocery chains. These so-called "monoculture" chickens can lay more than 300 eggs a year. Bennett's hens lay fewer eggs, but with much more variety—from the standard brown egg to the lovely blue-green eggs of the Araucanas.

Monoculture chickens raised for meat are highly selected for certain traits, such as thighs so muscular the birds can barely walk, Bennett says. "I just want a chicken that can run around and be happy."

Bennett traces his love of nature and preference for sustainability to his childhood in Hawaii, where his father, a surgeon, raised chickens.

"We ate a few of our chickens when I was a kid, but my father would always get depressed afterwards," he remembers. "Still, if you had to kill your own chicken, you'd savor it and use it all; you

Jeffrey McCullough

Peter Arkle

wouldn't waste so much." Bennett can't bring himself to kill any of his chickens; he trades some eggs to a neighbor for locally raised chicken meat.

Reducing waste is another reason for Bennett's food choices. He feeds his chickens vegetable tops and other cast-offs from his garden or from local grocery stores. Then he uses the chicken manure as fertilizer for his extensive vegetable garden, which he's been tending for 15 years. What his family doesn't grow, they buy locally, if possible.

As he thinks about adding pigs to his resources, Bennett plans to offer fenced plots for neighbors who don't have a good gardening area on their own property. He'd also like to get others involved in harvesting the garden. Many of his plans and philosophies are about building community.

"No one depends on anyone anymore, so we're disconnected." *—Nancy Volkers*

WEB EXTRA: Visit the *Bulletin* online for more photos of Bennett and his farm.
FOR MORE INFORMATION: To learn about Bennett's latest research, see "Tag-Team Proteins" on page 50.

Who's Who?

When asked about their careers, many scientists talk about mentors, but few bring up mistaken identity. Not so the Sean Carrolls: a cosmologist at California Institute of Technology, who explores conditions in the universe before the Big Bang, and an HHMI investigator at the University of Wisconsin–Madison, who studies how animals develop and evolve.

Caltech's Sean M. Carroll has had several brushes with fame, courtesy of the muddled monikers. "When I was a postdoc in 1994, there was an issue of *Time* magazine with a cover story about 50 leaders in America under age 40. As a joke, I said, 'I must be in there,' and I was. Sort of." Inside was his name—tied to the biologist's work. "Clearly they had made a mistake," he jokes. "They picked the wrong Sean Carroll."

Years later he was invited to a conference at a villa in the Tuscan hills. "Only after I accepted did the organizer come back, very embarrassed, to tell me I was not the right Sean Carroll."

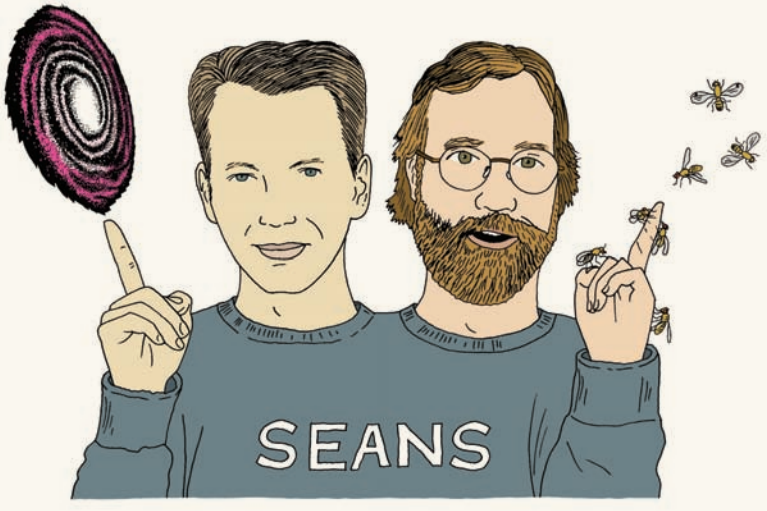
Both cosmologists and evolutionary biologists can get dragged into arguments with those who try to explain natural phenomena with supernatural explanations, says HHMI's Carroll. "In the blog or Web world, because we both deal at times with anti-science forces, people have contacted us to get clarification about something the other has said."

The two subject areas have another parallel, since both address issues of origins, says the Caltech Carroll. "The two most interesting things are life and the universe, and we are both trying to figure out how they came to be what they are."

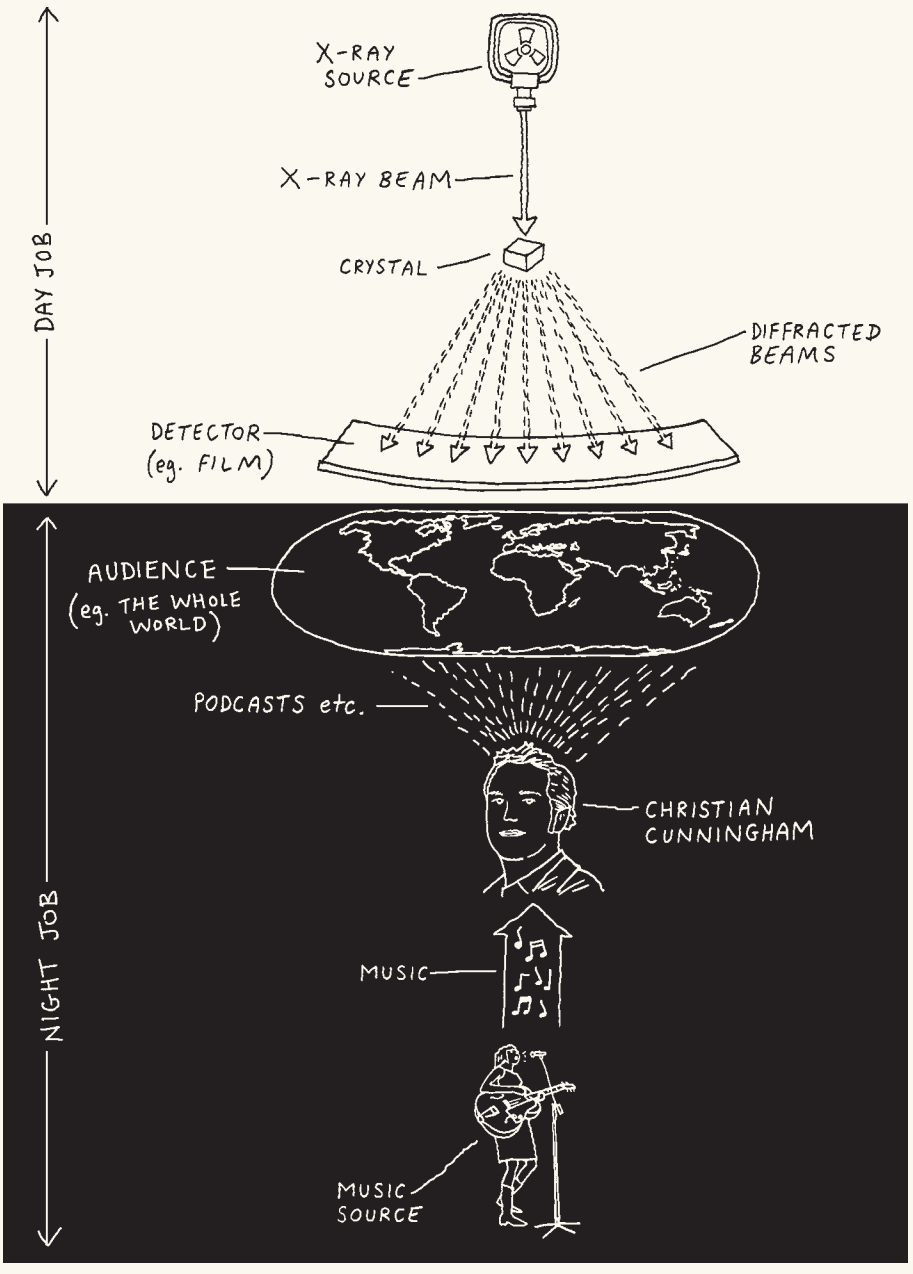
Both Carrolls are prolific writers; the Caltech Carroll is a frequent blogger on astronomy and physics and has even blogged, with humor, about his experience as "the other" Sean Carroll.

But the two have crossed paths only in cyberspace. "I would love to meet him," says the cosmologist of the biologist. "I am furiously typing away at my first popular book, and he has written a couple of books that I've enjoyed." They may just meet up one day on the book tour circuit, he says.

HHMI's Carroll is game: "I'd love to meet Sean. My hunch is that we have similar senses of humor." *—David J. Tenenbaum*



Bay Area Sound



One of San Francisco's hardest working local music promoters spends his days doing x-ray crystallography. Christian Cunningham, a graduate student at the University of California, San Francisco, spends his nights managing The Bay Bridged, a website and podcasting empire focused on the San Francisco Bay Area independent music scene.

"We're trying to spread the word about what Bay Area musicians are doing," says Cunningham, a graduate student in HHMI investigator David Agard's lab. "Great music comes from many places, but it can also come from your home. Our aesthetic has always been to try and promote music from within." He and business partner Ben Van Houten, an attorney, met as undergraduates at the University of California, Berkeley, where they both worked at the school's radio station.

From a rented studio space in San Francisco's Mission District, The Bay Bridged produces three podcasts: a weekly interview with a local band that showcases four of the band's songs, a monthly DJ-style mix featuring eight bands, and "Live this Month," which promotes local and out-of-town bands that are performing in the Bay Area. Public radio station KQED began syndicating their podcasts online last year.

The duo also produces live music shows and festivals, including one at the annual South by Southwest music and media conference in Austin, Texas. At last year's conference, The Bay Bridged booked 15 Bay Area bands on two stages, lined up company sponsors, and advertised to potential party-goers. The show, which they called The Bay Area Takeover, was "a massive success," Cunningham says. "It sold out, it was a ton of fun, and it was written up in all sorts of publications."

The Bay Bridged has grown so much since it launched three years ago that Cunningham and Van Houten now have a 19-person staff, all volunteers who are as passionate about music as they are.

With so much on his plate, one wonders how Cunningham has time to do any science. "It used to be a hobby and now it's a jobby," Cunningham jokes. He says good time management skills help him juggle lab work and his music promoting, which he considers his creative outlet.

Video podcasting is the latest endeavor. They take bands to weird places in San Francisco and record and videotape them in live, acoustic performances. The first event was both "amazing and a debacle," Cunningham says. They invited two bands to perform on Cunningham's roof. "I live in the Mission, in a four-story apartment building, with a 360-degree view of San Francisco," he says. "The idea was to showcase the beauty and grandeur of San Francisco while focusing on the local music." To their surprise, 100 people showed up; after the first band started playing, the police arrived downstairs with bullhorns, ordering them off the roof. "The second band performed indoors," Cunningham deadpans.

What Cunningham finds most satisfying is seeing musicians featured on The Bay Bridged become nationally known. "Ben and I get the biggest kick out of showcasing brand new music from very young bands that wouldn't get press any other way," he says. "The success stories are what make this worth it." —*Corinna Wu*

Peter Arkle

upfront

Research received a much-needed shot in the arm this year, as the White House began restoring America's commitment to scientific discovery in several ways. Hopes are high that the exciting, fundamental questions being asked by researchers across the country will one day lead to fewer infectious diseases, and less death and disability. A few of the more scintillating questions: How does learning and memory happen? What scent draws mosquitoes to humans, and is there a way to block it? Why do some of the eye's photoreceptors die off, resulting in blindness? Can gene therapy help?

In the Groove

Scientists are learning more about how signal strength at the junctions between brain cells affects learning and memory.

WHEN PEOPLE FEEL AS IF A FAVORITE SONG HAS WORN GROOVES into their brain, they're not far off. Repeated stimulation of the synapse, the site of communication between two neurons, induces chemical and structural changes that strengthen connections between those cells. ¶ As a result, nerve signals flow more easily across the synapses, connecting neurons involved in learning and memory, so that hearing the first notes of "A Hard Day's Night" instantly recalls the entire Beatles song.

Alteration of synaptic signal strength underlies "neural plasticity," the brain's ability to be changed by a person's experience—in other words, learning and memory—without manufacturing new brain cells.

Recent discoveries led by HHMI investigators Michael Ehlers at Duke University Medical Center and Pietro De Camilli at Yale School of Medicine have clarified some of the mechanisms that dial signal strength up and down. Their findings may also expand understanding of Alzheimer's disease and suggest new avenues for prevention or treatment.

The discoveries, reported separately in the fall of 2008, involve the "postsynaptic" side of the junction, where signals that have jumped the gap stimulate antenna-like receptors in the dendrites—the branching projections of the receiving nerve terminal. Much more is known about the transmitting, or "presynaptic," mechanisms: "We're at very early days in the postsynapse," says Ehlers. Both teams' experiments were designed to explore trafficking of neurotransmitters and receptors to and from neuronal membranes on either side of the synapse.

Most neurons involved in learning and memory secrete glutamate neurotransmitters into the synaptic gap, where they stimulate specific receptors (termed AMPA and NMDA receptors) anchored in the postsynaptic membrane. The number of these receptors determines the neuron's sensitivity—and as a result, the power of the signal. The receptors are located in nub-like "spines" that protrude from dendrites—neuronal branches that carry the signal from the synapse to the main nerve cell body.

Tiny sac-like vesicles deliver neurotransmitters and their receptors to the synaptic space by fusing with the surface membranes of the pre- and postsynaptic cells, respectively, through a process called exocytosis. After offloading their cargo, the empty vesicles merge with the cell surface membrane and new carrier vesicles form by recycling and pinching off part of this surface membrane, a process called endocytosis.

"We're at very early days in the postsynapse."

MICHAEL EHLERS

Duke Photography

De Camilli has spent nearly three decades investigating vesicle recycling. In 1996, he discovered an enzyme, synaptojanin1, or SJ1, that degrades a lipid compound called PIP2 in cell membranes, including vesicle membranes. In the absence of SJ1, PIP2 prevents vesicles from shedding their cage-like coating, which they need to do to recycle the membrane for another shipment. The result: a logjam of accumulated vesicles and a shortage of membrane to create new ones.

Until recently, "we thought that SJ1 affected endocytosis just on the presynaptic side," De Camilli says. "But then we began to realize that there is a little synaptojanin everywhere in the neuron, and that it could be involved in postsynaptic vesicle recycling as well."

To measure the effect of knocking out SJ1 on synaptic signaling, De Camilli focused on the hippocampal region of the brain, a major memory center that is rich in glutamate synapses. In the November 11, 2008, *Proceedings of the National Academy of Sciences*, he reported that cultured postsynaptic hippocampal nerve cells lacking SJ1 responded more strongly to stimulation than unmodified neurons. The absence of SJ1 on the postsynaptic side hampered the endocytosis and recycling of receptor-carrying vesicles, so receptors accumulated in the membrane, increasing its sensitivity to nerve signaling. In other words, SJ1's normal task in postsynaptic structures is to dampen signal strength.

"A major point is that while pre- and postsynaptic compartments play different and complementary functions, they adapt for those functions some of the same funda-

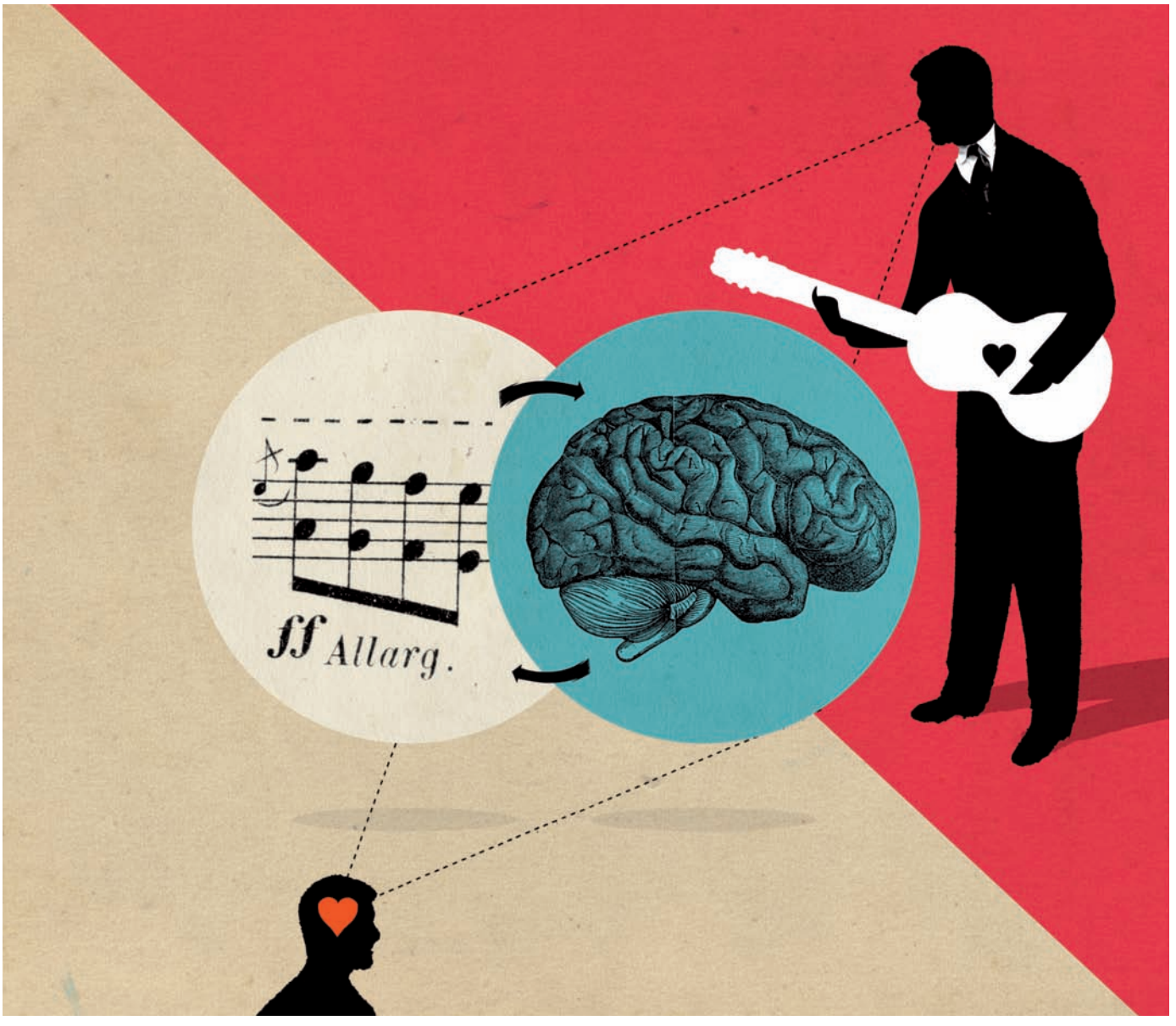


Illustration: Emmanuel Polanco, colagene.com De Camilli: Paul Fetters

mental molecular mechanisms," says De Camilli. "SJ1, a protein thought to be only presynaptic is also postsynaptic."

De Camilli is also investigating a possible link between SJ1 and Alzheimer's disease. The same PIP2 lipid degraded by SJ1 has recently been found by his former postdoctoral fellow, Gilbert DiPaolo, now an independent scientist at Columbia University, to protect brain cells from the toxicity of amyloid-beta, a peptide implicated in Alzheimer's disease. Thus, lowering SJ1 levels could increase the amount of PIP2 in brain neurons, potentially slowing amyloid-beta poisoning.

Ehlers' discovery also involved the exocytosis and endocytosis of receptors in the postsynaptic neuron—specifically, within dendritic spines.

To move receptors from the interior of the dendritic spine to the synaptic membrane, the cell deploys endosomes, containers akin to vesicles but larger. Exactly how endosomes move was a puzzle until Ehlers identified a "molecular motor" that tows them toward the membrane when the synapse is active. The motor is a specific form of myosin—a contractile protein found in muscle—called myosin Vb. He reported the finding October 31, 2008, in *Cell*.

Because this transport mechanism can be triggered in a single dendritic spine of a brain neuron, Ehlers says, it helps explain the fine-tuning that enables a nerve signal to stimulate a single synapse without exciting nearby synapses—a prerequisite for neuronal plasticity.

As much as scientists are discovering about synaptic transmission and plasticity, Ehlers says, the "fundamental mystery" remains to be solved—how the changes that occur in the synaptic membrane within "tens of seconds" are maintained in the much longer term, and why we can call up those Beatles classics years after the songs became hits. ■ –RICHARD SALTUS

"Pre- and postsynaptic compartments adapt some of the same molecular mechanisms."

PIETRO DE CAMILLI

A Better Bug Spray

Understanding mosquitoes' lust for blood may be the key to curbing some infectious diseases.

The smell receptor that mosquitoes use to zero in on victims is likely present in other insects, according to Leslie Vosshall.

Peter Ross

TO LESLIE B. VOSSHALL, THE TWO MINUTES A MOSQUITO SPENDS FEEDING on human blood are full of suspense: a mini-drama in which the insect, in need of extra protein or iron for egg-laying, risks her own life for the sake of her children. Each turning point in the story—the decision to seek blood, the identification of a victim, the escape from the inevitable swat—ignites Vosshall's deep curiosity about animal behavior.

Vosshall, who became an HHMI investigator in 2008, recently added mosquitoes to her Rockefeller University lab (which has focused primarily on fruit flies) because she wants to help block their ability to transmit infectious disease. Schemes to eradicate the pest do not interest her. Instead, she says, "We want to figure out the blood lust."

"Most of what interests a mosquito about you is how you smell," Vosshall says. "If we can understand that and find a way to interrupt it, then we should be able to solve some problems in infectious disease transmission."

Her team is still equipping the lab for mosquito research—constructing a screened-in zone outside a research room to capture escapees, for example—but Vosshall is well prepared scientifically to find out how and why mosquitoes seek their targets. Her career has focused on elucidating the molecular biology of insect olfaction.

As a postdoctoral fellow in 1993, Vosshall joined HHMI investigator Richard Axel's lab at Columbia University, when little was known about how insects receive and decode olfactory information. Working with fruit flies, she found the first major clue: a large family of genes that encode receptor proteins embedded in the membranes of olfactory neurons. Later, from her own lab at Rockefeller, she mapped how the neurons that express these proteins project into the brain, creating an invaluable tool for correlating odorant receptors to the odor molecules that activate them.

Many of Vosshall's more recent discoveries on insect olfaction have surprised others in her field. "The way insects smell odors is very strange," she says. "Their odorant receptors don't look like any other protein on earth." She showed in 2008 that, unlike mammalian olfactory receptors, which activate signaling pathways inside the cell, insect odorant receptors function as channels that open to let ions flow into the cell when an odor molecule binds. Also unusual, she found, is the existence of an olfactory co-receptor that is present in nearly all insect olfactory neurons and that works in tandem with odorant receptors for specific smells.

That co-receptor, OR83b, is a potential target for what Vosshall describes as an "olfactory confusant," noting that "a protein like OR83b exists in every insect on earth. If we find a chemical that jams this receptor and prevents it from working, we should be able to block the sense of smell in every insect." A fast-acting molecule that blocks OR83b could be sprayed indoors or worn on the body to keep bugs away.

> "The way insects smell odors is very strange. Their odorant receptors don't look like any other protein on earth."
>
> LESLIE VOSSHALL

In fact, her lab showed last year that the common insect repellent DEET works in part by inhibiting OR83b. "It works pretty well, but it's not acting as a universal inhibitor," she says. Her lab is screening chemicals for a more effective alternative.

In the January 9, 2009, issue of the journal *Cell*, Vosshall reported further evidence that insects have their own way of smelling. In search of signaling proteins that help relay olfactory messages to the brain, she and postdoctoral fellow Richard Benton mined the genomes of various organisms in search of genes present in fruit flies and mosquitoes but absent in noninsects. They found a new kind of odor-detecting molecule: receptors that are structurally and functionally distinct from odorant receptors.

It was well known that odorant receptors are found on only about 70 percent of a fruit fly's olfactory neurons. The remaining neurons also send signals to the brain in response to specific odors, but how they did it was "a big, dark secret," Vosshall says.

She and Benton discovered a family of genes that were turned on in olfactory neurons that lacked odorant receptors. The genes' protein products, which they call ionotropic receptors, gave cells the ability to detect specific odors. The researchers had stumbled on a new way that insects detect odors.

Those experiments were done in fruit flies, but the pathway is likely to be common among insects, Vosshall says. It's too soon to say whether targeting that pathway could help them devise a better insect repellent—but it fills in a major gap in knowledge about olfaction and brings Vosshall closer to the complete understanding she is striving for.

Her next step is to find out how identical odors trigger different responses under different conditions. Why, for example, do the cues that signal a human source of blood attract a female mosquito only when she is preparing to lay her eggs? And why does she stop seeking blood once she's had enough?

It's easy to see the practical implications of figuring out how a mosquito's attraction to humans can be switched on and off. In trying to understand the basic biology of olfaction, Vosshall hopes to satisfy her own curiosity about genes and behavior and help conquer some major public health challenges. ■ –JENNIFER MICHALOWSKI

A Solution in Sight

Keeping the retina's cone photoreceptors from self-destructing may rely on the neighboring rod photoreceptors. Gene therapy may offer the ultimate remedy.

CONSTANCE CEPKO REMEMBERS THE DAY SHE READ THAT A BRIARD sheep dog had been cured of blindness by gene therapy. The dog, called Lancelot, stopped cowering in corners and acquired the elegant, floating gait of his breed. ¶ It was 2001 and, soon after, Cepko was approached by a family whose son had been born blind. They wanted to fund her research on the retina. "They said, 'You do basic science; is there anything that someone like you could do to help?'" she recalls.

"It becomes more personal when somebody asks you, 'What can you do to help children like our son?'"

Cepko, an HHMI investigator, had a head start. The boy's disorder lay in a spectrum of diseases marked by progressive loss of vision, and some of these diseases were caused by mutations in genes Cepko had been studying in her Harvard Medical School lab. She decided to focus on retinitis pigmentosa, a progressive disease caused by many mutations affecting at least 36 genes. Her group has now discovered that delivering a single gene called *HDAC4* into the retina can save the vision of mice with the disease.

The central portion of the human retina is packed tightly with cells—called cone photoreceptors—which are used for color and high-acuity vision. The periphery of the retina has mostly rod photoreceptors, which are used primarily to sense dim light at night. In retinitis pigmentosa, the rods die due to genetic defects, causing a loss of night and peripheral vision. Early in the disease, people can still read and recognize faces, but many lose even those abilities as they age because their cones eventually die. In hopes of solving the problem with gene therapy, Cepko wanted to know what was killing the cones.

So Cepko and Claudio Punzo, a postdoctoral fellow in her lab, compared four mouse models of retinitis pigmentosa in which vision loss occurs at different ages, from three weeks to about 18 months. For each mouse strain, Punzo determined when cones began to die, monitored changes in gene expression, and looked for similarities.

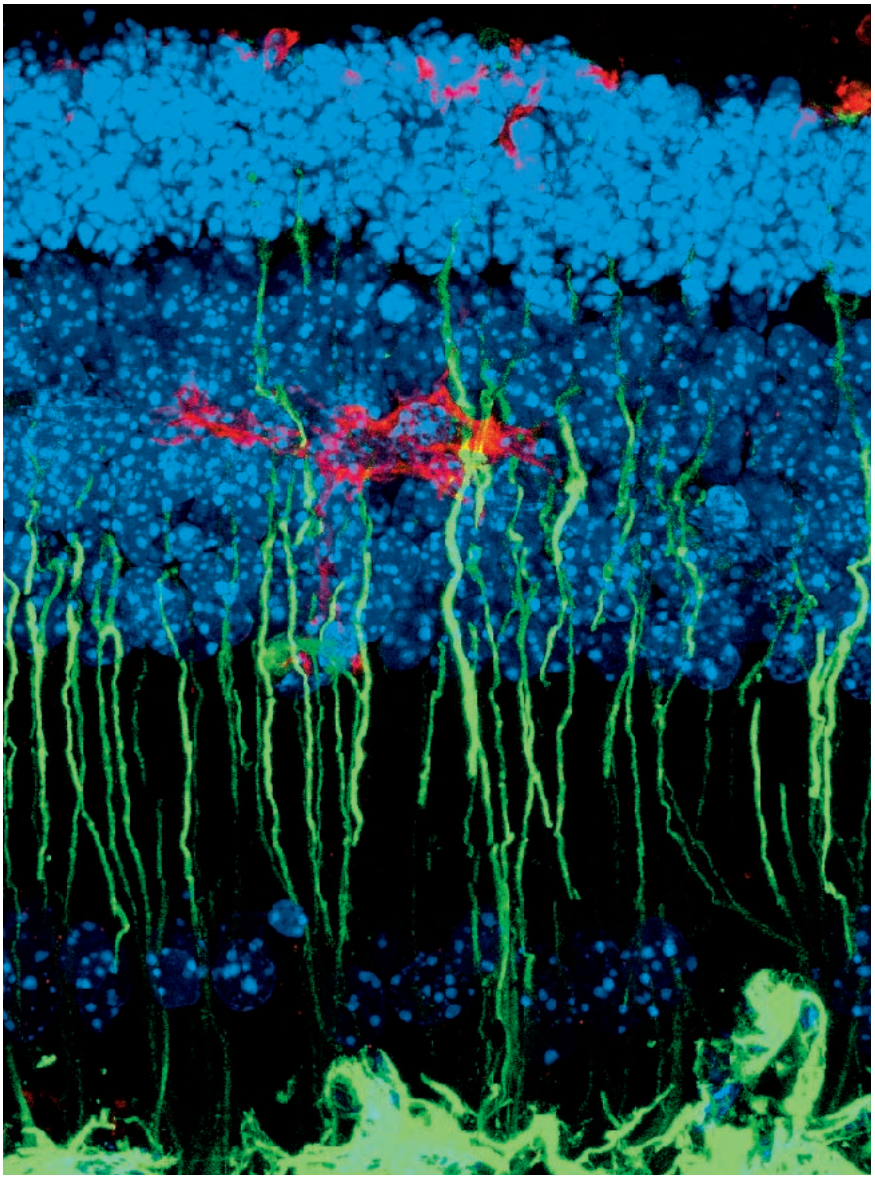
In all four models, as the cones began to die Punzo noted changes in a regulatory switch that senses the availability of nutrients. If nutrient levels drop very low, the switch tells the cell to start digesting itself—a little like burning banisters to heat a house.

The layers of rods and cones normally stay in intimate contact with each other. When the rods die, the cones may lose the connections through which they get food, Punzo and Cepko hypothesize. Or the cones may feel extra pressure from neighboring layers of cells and expend energy to maintain their structures. "Imagine 29

"It becomes more personal when somebody asks you, 'What can you do to help children like our son?'"

CONSTANCE CEPKO

Jason Crow



Constance Cepko is searching for a way to keep retinal cells alive in patients with a genetic disease that kills off cells important to vision. This cross-section of diseased retina tissue shows supportive cells (green), called Müller glia, and macrophages (red) migrating into the retina (all cells in blue) to remove dying rods.

friends standing around you, holding up a circus tent, and next thing you know they're all gone and you're holding up the tent by yourself," Cepko says. The scientists published their findings in the January 2009 issue of *Nature Neuroscience*.

As Punzo digs deeper into why the cones die, other lab members have been looking for ways to keep the rods alive as well—even nonfunctioning rods might help prevent the death of the cones.

Bo Chen, another postdoctoral fellow, found a potential way to save the rods. Chen found that rods require *HDAC4* to survive during development, so he and Cepko decided to try delivering extra *HDAC4* to the retinas of mice with retinitis pigmentosa. The strain they studied typically loses all rods about three weeks after birth and their cones over the next few months. Using a method previously developed in the lab, Chen deposited *HDAC4* DNA behind the retinas of unconscious mice using a needle a little wider than a hair. He then applied an electric current to enable the DNA to enter the retina. More than two months later, the mice still retained many of their rods and cones. The results appear in the January 9, 2009, issue of *Science*.

The method Chen used probably would not work on humans—the electric charge might damage parts of the eye. So, he and Cepko are employing the approach used to restore Lancelot's vision: using a harmless virus to deliver the gene to the retina. Eight years after his surgery, the dog can still see. "By just good luck, the virus is still there," Cepko says.

The team packages the *HDAC4* DNA with the virus and delivers it behind the retinas of mice with retinitis pigmentosa; the virus enters the cells on its own.

Cepko is heartened by the work of researchers at the University of Pennsylvania School of Medicine. A year ago, they gave patients with the same genetic defect as Lancelot's—a mutation that causes Leber congenital amaurosis—the therapy that helped the dog. For some of these patients, vision has improved. ■ –OLGA KUCHMENT

Claudio Punzo / Cepko lab

CELLULAR NEATNIKS

THE ARCHITECTURE THAT CAREFULLY ARRANGES OUR UNRULY STRANDS OF DNA HAS MORE CONTROL OVER GENE EXPRESSION THAN IMAGINED.

BY AMANDA LEIGH MASCARELLI
ILLUSTRATION BY JILLIAN TAMAKI

HISTONES, THE PACKAGING AND ORGANIZATIONAL STRUCTURES FOR DNA, WERE ONCE VIEWED AS IMMOVABLE OBSTACLES, A HINDRANCE TO THE PROTEINS THAT MUST READ DNA'S INSTRUCTIONS.

"People did not think histones were an interesting aspect of a cell's life," says Karolin Luger, an HHMI investigator at Colorado State University in Fort Collins. "They were regarded as very static entities that sat in the way of interesting activities."

That view has changed. Today, these architectural proteins are recognized as essential to nearly every fundamental cellular process.

Their highly dynamic and confounding behavior, however, makes histones difficult to understand. Scientists are still trying to figure out how the bonds between DNA and histones affect gene expression and how a staggering array of chemical modifications to histones activates or silences specific genes. It appears that these modifications help determine cell fate and likely play important roles in health and disease.

TANGLE-FREE GENOME

Histones arrange the two meters of DNA found in every living human cell into a compact library that fits within the nucleus, just two micrometers in diameter. The histones somehow render the long, unwieldy threads of DNA into an organized message.

DNA and histones have opposite chemical charges, so they cling to each other. A length of DNA—about 150 base pairs—neatly wraps around a group of eight histone proteins (two copies each of H2A, H2B, H3, and H4, called an octamer) to form a nucleosome. Nucleosomes line up like beads on the string of DNA. Each histone possesses a floppy tail that hangs from the body of the nucleosome. Between each nucleosome, 50 base pairs of "linker" DNA serve as the string between the beads, spacing the nucleosomes evenly. Thirty million nucleosomes are needed to package all the DNA in a human cell into the cell's chromatin, the structural material of chromosomes.

"If you don't have histones, your DNA will be much like a ball of yarn that your cat got into," says Luger, a self-described "old timer" in histone research. "Histones make the packaging ordered so that the information isn't lost, and they prevent the tangles." This is fundamentally important, says Luger. "If the cell gets knots in its DNA, it can't divide and it can't replicate itself."

Since organisms first began storing their genetic material inside a true nucleus, histones have had a fundamental role in DNA packaging. The H4 histone protein is so highly conserved throughout evolution that only 2 of its 102 amino acids vary among organisms from pea plants to cows. At some point in evolutionary history, DNA simply became too long and unwieldy for the cell, says David Allis, a biochemist and chromatin expert at the Rockefeller University. "Seemingly, histones were the solution," he says. "That packaging strategy must have just been so good it was well worth keeping."

REMOVING ROADBLOCKS

The packaging of DNA by histones is, in fact, so good that mobile, or motor, proteins that need access to DNA to do their jobs have a hard time getting space. For example, RNA polymerase, which constructs RNA by "reading" DNA strands, pauses or stalls entirely when it encounters a nucleosome in its path. HHMI investigator Michelle Wang of Cornell University in Ithaca, New York, is working to understand the mechanics of this process. "If DNA is really tightly packed in the nucleosome, then how do motor proteins, which carry out all the important functions, access the DNA that's buried in the nucleosome?" she asks.

For genes to be transcribed and expressed, DNA carrying the genetic message must temporarily unwind from the histone spools. Something must happen to the bonds between histones and the DNA to allow proteins like RNA polymerase to invade the nucleosome.

In 1997, nearly 25 years after the discovery of nucleosomes, Luger and her colleague Timothy Richmond, of the Swiss Federal Institute of Technology, in Zurich, solved the x-ray crystal structure of the nucleosome in atomic detail. From this discovery, they were able to make suppositions about the strengths of the bonds between histones and DNA, and where they occur. Luger suspected that locations where histones had fewer contact points with DNA required less energy to separate.

To evaluate those bonds, Wang and her colleagues started with Luger's x-ray crystal structure of a nucleosome. A molecule's crystal structure allows researchers to visualize contact points between DNA and histones but doesn't describe the strength of those bonds. In a February 2009 paper in *Nature Structural & Molecular Biology*, Wang and her colleagues describe experiments in which they mechanically "unzipped" double-stranded molecules of DNA one base pair at a time and created a quantitative map that details the locations and strengths of the DNA–histone interactions. They also measured the force required to release DNA from each histone carrier.

Says Luger, "X-ray crystallography can 'see' the interactions, whereas single-molecule studies can 'feel' them."

Wang's measurements confirm Luger's predictions: fewer contacts between DNA and histones result in weaker interactions, but with one surprise. The crystal structure of the nucleosome led scientists to believe that an RNA polymerase pauses or stalls at three obstacles—strong DNA–histone interactions—along the nucleosome before DNA buried in the nucleosome becomes accessible for transcription (the process in which a DNA strand is transcribed into RNA). Wang's study implies that RNA polymerase may need to overcome only two of these barriers before the histones are ejected from the DNA, giving the polymerase "a free ride, as if it moves on naked DNA." Wang's group and several others are investigating whether this roadmap of barriers dictates which genes will be transcribed.

A growing body of research is revealing several processes that make DNA available for gene expression. In some cases, all eight histone proteins in a nucleosome are evicted from the DNA strand. In others, a pair of histones is removed, leaving six histone proteins in place. The histone pairs can be removed ahead of a polymerase and then repositioned behind it by molecules known as chaperones, creating a space for the polymerase to march past the histones.

In 1998, Danny Reinberg, an HHMI investigator at New York University, discovered a chaperone called FACT, for "facilitates chromatin transcription," and in 2003 reported its function. FACT removes one specific histone pair, allowing an RNA polymerase to read the spooled DNA. "What you create is a way for the polymerase to invade the nucleosome and go through," Reinberg explains.

Specific regions of DNA that control gene activity can also become nucleosome-free "in the blink of an eye," says HHMI investigator Steven Henikoff at the Fred Hutchinson Cancer Research Center in Seattle. Highly specific DNA-binding proteins recruit enzymes that strong-arm the nucleosomes from their positions. In a January 2008 review in *Nature Reviews Genetics*, Henikoff described a combination of effects, including the work of histone chaperones, "remodeling" complexes, and other chemical modifications that determine how easily nucleosomes are destabilized. He is also investigating the unique conformation of nucleosomes at the constricted center of the chromosome, the centromere, and their implications for chromatin inheritance and centromere evolution.

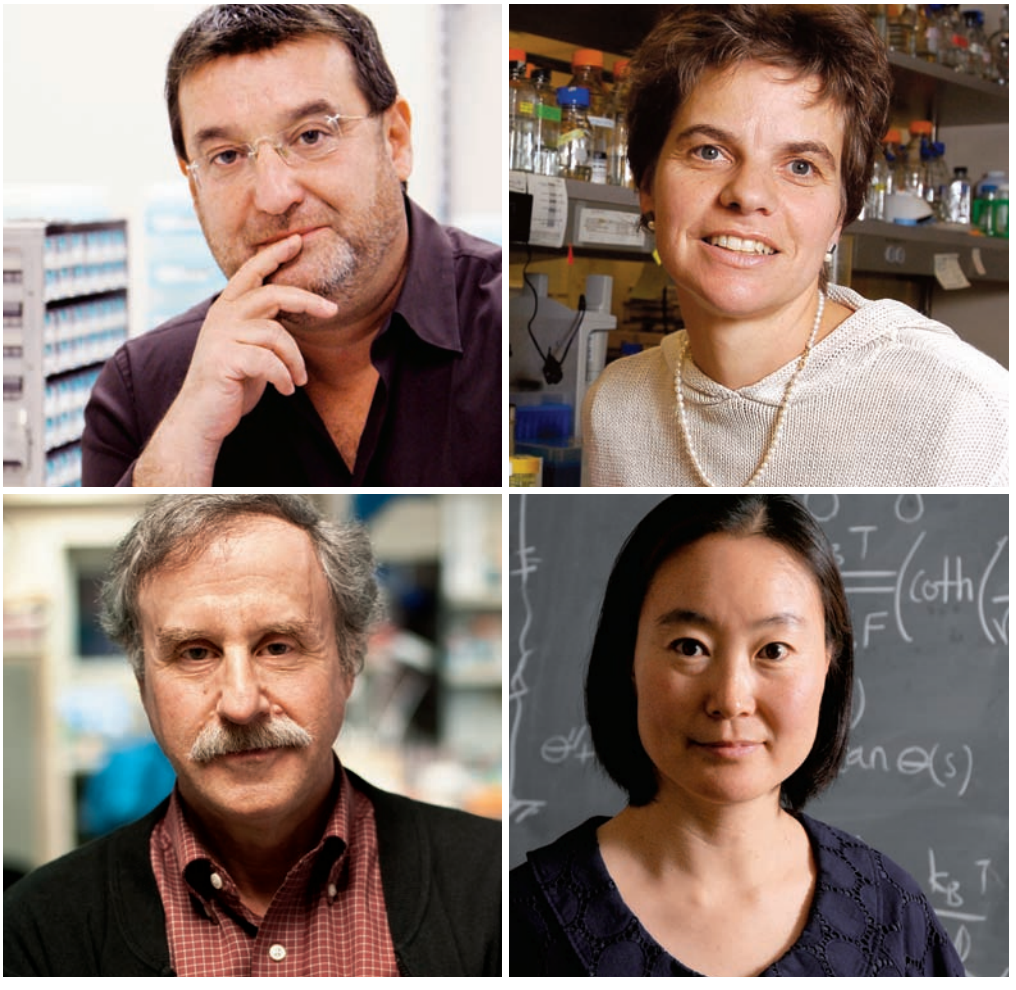
GENES IN A HAYSTACK

There's still much to learn about the processes by which dislodging histones and nucleosomes or loosening DNA from its spool can direct which genes are turned on or off. Reinberg is specifically interested in how gene activation or silencing determines how a cell acquires its identity. For instance, in stem cells, which still have the potential to become a variety of cell types, "you find that the chromatin is more relaxed, more flexible, more uncommitted" than in cells with specific destinies such as liver cells, pancreatic cells, or neurons, Reinberg explains.

Likewise, "housekeeping genes," which are always on because they are required for essential functions by nearly all cells, have very relaxed, open chromatin. However, unneeded genes—for example, genes in a pancreatic cell that are specific to liver function—are tightly packed and inaccessible to transcription machinery. Reinberg has reported that histones play a key role in directing chromatin to remain open and relaxed or to pack down tightly by means of chemical "tags" that attach to the histones.

These chemical tags, or modifications, are believed to orchestrate this gene-activation decision by telling an octamer when to jump off a DNA strand or by directing DNA to loosen from its histone spools. Such modifications include additions or subtractions of methyl, acetyl, and phosphate groups that bring additional instructions to the genetic code, telling the cell which genes should be active and which should be silent. "These histone modifications tell a cell, 'hey, read me, I'm really important at this time,'" Luger says.

Rockefeller's Allis describes these chemical modifications with an analogy he borrows from former colleague Art Beaudet, of Baylor College of Medicine: If you were scanning a book's pages, underlines, italics, or bold type would help you find your words and sentences faster. So while letters in the alphabet often don't change (like bases in DNA), the words take on new meaning, more emphasis. In 1996, his lab isolated the first transcription-associated histone acetyltransferase, an enzyme that adds an acetyl



CLOCKWISE: DANNY REINBERG, KAROLIN LUGER, MICHELLE WANG, STEVEN HENIKOFF

group to certain amino acids. A month later, a research team led by HHMI investigator Stuart Schreiber at Harvard University reported the first deacetylase, which removes acetyl groups from histone proteins. Allis likens the process to writing and erasing. "Now almost all these marks are known to have a pairwise system of 'on' and 'off' enzymes." Acetyl groups play a central role in gene expression by negating positive charge and opening up chromatin; their removal is thought by some to reverse this process. Researchers suspect that acetylation is somehow preparing the chromatin for transcription by altering contacts between histone tails and DNA in chromatin higher-order structures.

Histone tails are richly studded with modifications, but recent studies have also revealed that important chemical markers occur on histone bodies. Chemical markers on both the tails and histone bodies are believed to serve a host of functions, from attracting other cellular proteins to directing chromatin structure and determining which genes are active or silent. But the significance of their locations is not yet clear. "The functions of modifications in the tails versus in the body are still murky," Luger says.

Many fundamental questions remain. "You have this incredibly long thread containing information in an incredibly confined space within a cell. Somehow the cell knows in this mess which genes to find at appropriate times," Luger says. She compares it to the proverbial needle in a haystack, but instead of just finding the needle, you have to find many different-colored needles, "first red, then yellow, then green—and you have to find them within two seconds," she explains. "How on earth does the cell do that? Not only does the cellular machinery know that it has to find these genes, but it also knows how. The mechanisms for this are truly awe-inspiring."

HISTONES AND HEALTH

Understanding these chemical signals in intimate detail is of pressing importance because a growing body of evidence suggests that histone modifications have close connections to disease, obesity, and other health effects. HHMI investigator Li-Huei Tsai at the Massachusetts Institute of Technology studies the cellular mechanisms underlying Alzheimer's disease. In the advanced stages of Alzheimer's, degeneration of neurons is accompanied by severe impairment of learning and memory. She and her colleagues created a mouse model that allowed them to test whether novel chemicals could restore learning in mice, even after a significant number of neurons have died.

After experimenting with a panel of chemical markers, Tsai and her colleagues published a study in *Nature*, in 2007, demonstrating that a group of small molecules called histone deacetylases (HDACs), which compact chromatin and render genes inaccessible

Reinberg: Bizuayehu Tesfaye / AP, ©HHMI Luger: John Eisele / Colorado State University Photography Wang: Kevin Rivoli / AP, ©HHMI Henikoff: Charles Peterson

for transcription, have the effect of restoring learning and long-term memories in their mouse model. "We found that if we give our mice these small molecules, this wonderful thing happens," says Tsai. "We are able to completely restore their learning ability." Now, Tsai and her colleagues have identified a particular HDAC that normally suppresses learning and memory. Thus, chemical inhibitors that selectively target this particular HDAC will likely have more potent and safer effects in clinical applications, they conclude in a study to be published in *Nature*. While much more work remains to be done to pin down the specificity of the molecules, Tsai believes that they may offer therapeutic promise for Alzheimer's.

HHMI investigator Yi Zhang, at the University of North Carolina at Chapel Hill, is also probing the impact of histone packing and modifications on fundamental biological processes and disease. "We are inquiring about what happens to the chromatin when a sperm enters an egg," Zhang says. He wants to understand how germ cell fate is switched to somatic cell fate and how histone deposition and modification contribute to this process.

The Zhang lab is also exploring the role of histone modifications in obesity and leukemia. On February 4, 2009, Zhang and his colleagues published in *Nature* online a study on a knockout mouse that lacked a gene encoding a known histone demethylase, Jhdm2a. The mice were obese. Without the enzyme, they had lower metabolism and were less efficient at burning energy, yet their appetites were unaffected. This finding offers a new anti-obesity target that does not alter brain function, which most appetite-suppressing drugs do.

For her part, Luger is interested in Rett syndrome. When she learned that mutations in the *MECP2* gene lead to this neurodevelopmental disorder (a discovery by HHMI investigator Huda Y. Zoghbi at Baylor College of Medicine) and that the MeCP2 protein is a methyl-binding protein that alters the structure of chromatin, she decided to investigate how interactions between MeCP2 and nucleosomes might offer clues about what causes the diseased state leading to Rett syndrome.

Given the complexity and dynamic nature of histones within the cell, Luger doesn't expect to unravel all their mysteries any time soon. One of the first priorities is to understand how histones orchestrate the multiple layers of DNA packaging, from the linear "beads on a string" to highly compacted chromatin. "We know at the first level how they organize, but we don't really know much else," she says.

But today's structural methods are unlikely to crack the code, Luger says, because chromatin is constantly shape-shifting. Crystallography captures a snapshot of a billion static molecules, while nucleosome–nucleosome interactions are likely to be varied and "fluid" and therefore difficult to image. Luger says it will require a cadre of researchers, using a combination of techniques to elucidate the packaging of nucleosomes into chromatin. "I think a lot of people using very complicated approaches will have to put their heads together to pull this one off," she says. "Which is really the fun part of science." ■

"IF YOU DON'T HAVE HISTONES, YOUR DNA WILL BE MUCH LIKE A BALL OF YARN THAT YOUR CAT GOT INTO. HISTONES MAKE THE PACKAGING ORDERED SO THAT THE INFORMATION ISN'T LOST, AND THEY PREVENT THE TANGLES."

—KAROLIN LUGER

THREE'S A CROWD, TEN'S A POSSE

ONE GROUP OF YOUNG SCIENTISTS AT BRANDEIS UNIVERSITY HAS AN UNBEATABLE SUPPORT NETWORK IN ALL AREAS OF COLLEGE LIFE.

BY SARAH C.P. WILLIAMS
PHOTOGRAPHS BY JÖRG MEYER

IT'S A MUGGY JULY MORNING, WEEKS BEFORE MOST BRANDEIS UNIVERSITY STUDENTS WILL HAUL THEIR BELONGINGS INTO DORMS.

Lecture halls echo with emptiness, and the buzz of construction permeates the hallways. But in one small classroom, 10 incoming freshmen listen intently to feedback on the lab reports they wrote the day before.

"Your conclusion can't be like the third Lord of the Rings movie where you have 11 endings," Marina Dang, a graduate student, tells the group. "But, don't worry, you guys all did a good job on yours."

When Dang finishes talking, the young men and women clump together and talk—about their dorm assignments and class schedules for the fall and how they spent the previous night. They laugh and gossip like old friends.

In fact, the group of high-achieving students from New York City has been deliberately matched up—with each other and with Brandeis—by the Posse Foundation, and they're spending two weeks of their summer at Brandeis for a "boot camp" designed to prepare them for the rigors of college science. They first met 7 months earlier.

The Posse Foundation has been establishing such groups for two decades—but this year's posse at Brandeis is the first to focus on science.

Shortly after his acceptance into the science posse, Usman Hameedi, who graduated from Benjamin Banneker Academy, a public school in Brooklyn, voiced high hopes for the program.

"I think it's going to be really beneficial to have good friends going into college," he said. "We're probably going to be the 10 nerds sitting in the library studying together all the time, but at least we won't be 10 nerds studying alone."

Deborah Bial, founder and president of the Posse Foundation (a Brandeis alum and 2007 MacArthur Fellow) launched the first posse in 1989 after counseling a student unable to finish college. "He said something that struck me," says Bial. "He said he never would have dropped out of college if he'd had his posse with him."

The Posse Foundation has helped more than 2,600 talented urban high school students through college by sending them to schools in groups of 10 to navigate the highs and lows of college life together. In 2008, the Foundation sent students from 6 cities to 33 top-tier schools across the country.

"It started with the idea of a support group, but it has become much more than that," Bial says. "It's also a leadership program, a diversity program, and a program that has transformative powers—both on college campuses and in the workforce." And though each posse is drawn from public high schools in select cities, applicants are not limited by race or gender. They're judged by motivation, academic achievement, and leadership. "Posse is not a minority program," she says, "it's a diversity program. You can see every kind of kid in posse, every race, every religion."

Unlike posses of the past, the 10 students gathered at the Brandeis summer boot camp share one additional quality: a love of science.

TOO FEW STAY IN SCIENCE

HHMI professor Irving Epstein received a $1 million grant from HHMI in 2006 for his plan to mesh the posse model with science education, but he was already an involved participant in the Brandeis posses. Epstein was Provost of Brandeis when Bial first approached him in 1996 about Brandeis joining the posse network, and he lobbied hard for the program. The Posse Foundation has since sent 11 traditional posses to Brandeis, but Epstein was concerned that the program produced very few science graduates.

"In a typical year, there are one, two, three, maybe even as many as four incoming students in the posse who express some interest in science," he says. By graduation, that number is typically down to zero. "Once every other year someone might graduate with a degree in the natural sciences," he says. Epstein saw room for improvement. In fact, he thought posses would be the perfect way to help students through the challenges of science.

"One of the big problems in the sciences is that students hit a wall," he says. "Typically you've done fine in high school, but the experience wasn't nearly as demanding as college-level work. And suddenly you've got to work really hard to keep up. And you begin to think 'I'm not sure I can do this,' and if you're alone it's very easy to convince yourself that you can't do it. Whereas if you have other people to talk to who say 'Yeah, we're going through this,' or 'Yeah we went through this and we came out the other side,' then you're more likely to be able to stick it out."

In 2005, Epstein called Bial at the Posse Foundation and told her he'd like to add a second posse to Brandeis each year—one devoted to science. After what Epstein describes as "a long pause on the other end of the phone," Bial enthusiastically voiced her support.

Two years later, Epstein's idea is playing out in the classroom, with support

SCIENCE POSSE, FROM LEFT TO RIGHT: NANA OWUSU-SARPONG, ANGEL GARCIA, GLORIYA NEDLER, REBEKAH LAFONTANT, VIRGINIA RAMOS, USMAN HAMEEDI, YVONNE PEREZ, ANDY SANCHEZ, EMMANUEL OBASUYI, JANAKI PATEL.

from HHMI. In that July boot camp, the first Brandeis science posse had already pulled all-nighters putting together scientific posters and learning the lessons it takes some college freshmen months to figure out.

"It really exposed me to science at Brandeis," says posse member Emmanuel Obasuyi, who attended the Marble Hill School for International Studies, a small college preparatory high school in the Bronx. "[Boot camp] is very intense and very quick paced, so you have to keep up with the work. And we immediately learned that you have to be able to approach the professor if you're not understanding a topic."

Melissa Kosinski-Collins, a Brandeis biology professor, designed the boot camp with Epstein, drawing on her background as faculty advisor to the United States Biology Olympiad Team.

Along with learning content, she wants the students to get used to a very different type of day. "In college you have to be as on top of your game for a 6 p.m. lab as an 8 a.m. class," says Kosinski-Collins.

Students attended workshops on everything from laboratory methods and terminology to time management and note-taking and book reports. They took a trip to collect water samples from the nearby Charles River and wrote in-depth reports on genetic diseases.

"The two weeks is designed to bridge the gap between expectations and the reality that tends to drive students away from science," Epstein says.

FRONT ROW STUDENTS

Well into their second semester of college, on a blustery January morning when other area schools have canceled classes and roads are slick with ice, the students of the science posse filter into Epstein's 10 a.m. chemistry class, a prerequisite for any natural sciences major. It's a 200-person lecture, and Epstein has loud jazz blasting as students fill the aisles—it's part of his effort to make chemistry more fun.

The posse students nab seats in the front two rows (it's not hard, most of the class sits as far back as possible). And when Epstein, halfway through a lecture on acids and bases, dons a wizard hat and begins pouring different chemicals into glass vials on the lab bench at the front of the room, the 10 posse students have the best view. Epstein, gray-bearded and bushy-eyebrowed, looks the part of a wizard, and the posse students pay close attention to the liquids that turn shades of purple and green, showing how strong the acids and bases are.

Later that afternoon, these students have plenty of good things to say about their year so far. They even reflect on their summer boot camp with good memories.

"Boot camp opens up your eyes," says Nana Owusu-Sarpong, a pre-med biology major in the posse. "I think without boot camp, college would have just hit me on the head."

SUSANNAH GORDON-MESSNER, A FOURTH-YEAR BIOPHYSICS GRADUATE STUDENT, AND MENTOR OF THE SCIENCE POSSE, KNOWS THE NITTY-GRITTY OF THE STUDENTS' LIVES. HHMI PROFESSOR IRV EPSTEIN PROPOSED THE IDEA OF SCIENCE POSSES AFTER NOTICING THE LACK OF SCIENCE STUDENTS THAT CAME OUT OF PREVIOUS POSSES.

Yvonne Perez, another member of the posse, agrees. "When we had to write our first lab report in boot camp, I was clueless, I was like 'Oh my God, what am I doing here?' And now I feel like that's my greatest strength—lab reports."

And if grades and rave reports from faculty members are anything to go by, the posse had a successful first semester.

"They're outstanding students," says Kim Godsoe, dean of academic services at Brandeis. The students all know how to use support resources, she notes, and they all know when to come to her for advice and help.

But the students have a different, at times less positive, take on that first semester—college is an adjustment for any freshman and they are no exception. There's no doubt though, in their minds, that their posse helped them through.

Obasuyi, who hopes to major in neuroscience and minor in philosophy, found his first semester at college especially challenging. "Stuff like managing free time and socializing took their toll," he says. But having his posse there added some security. "Most of the time I was really frustrated, but they were always there. When I see them working, their success is my inspiration, so I keep working. I know that they're having the same experience I'm having. It makes me feel not alone."

Hameedi, now a pre-med student interested in health policy and hospital administration who dreams of becoming U.S. Surgeon General, says the posse provided support to students outside the group, too. "One of my friends would always come to us for help," he says. "She automatically saw us as a resource, even though she didn't even know our grades, she just saw our motivation and would come to us."

A SECOND FAMILY

One night a week, the posse gathers for two hours with their group mentor, Susannah Gordon-Messer, a fourth-year biophysics graduate student. They have academic workshops, talk about their classes, or discuss problems they're all having. Sometimes, says Gordon-Messer, "they just sit there and vent, or discuss whatever social drama has gone on in the past week."

Gordon-Messer is their confidante, the one who knows the nitty-gritty of what is going on in their lives both in and out of the classroom. "I play every role from mom to therapist to academic mentor," she says.

Gordon-Messer also sees the pressure the group is under in the role as the first pilot science posse. "Everyone wants to meet them, and take them out to lunch, and hear about their lives," she says. "They feel so much on display, it makes them think they have to be perfect. But they're human, and they are 18 year olds who are off on their own and they deserve to be college freshmen."

In the first semester, some students began doubting their choice of major, pondering careers other than medicine

and research. Perez, a graduate of the Bard High School Early College—a selective public school in Manhattan—began college with dreams of medical school. She's not so sure now.

"I still love the sciences," Perez says. "However, I've noticed that medical school is precisely not for me, and the natural sciences might not be for me. Chemistry was my least favorite class and my grades show it. Same goes for lab, and I was just thinking about this and I'm not sure I want to spend my next three years doing labs."

Perez is leaning toward public health and sociology now, hoping to combine science with her love of interacting with people. She credits her posse with helping her keep science in the picture at all. "There have been many times I've wanted to drop chemistry, that would make my life easier, but in the long run I know I would regret that, because I know I want to do something related to science. I feel like my posse is what's keeping me in."

The mentors—Epstein, Godsoe, Kosinski-Collins, and Gordon-Messer—agree that it's the student's decision whether to stick with the natural sciences. "We won't talk any of them into anything, or out of anything," says Gordon-Messer. "We'll give them the information they need to make their own choices."

To give them a taste of science, Epstein places most of the students in active scientists' labs for hands-on lab work their first semester. "There is this illusion out there that science is an isolating vocation," he says. "That if you go into the sciences you'll never see people. And in fact, a research group in the sciences is a real community. So part of the plan was to get the posse scholars into labs as early as possible and let them get a sense of that."

Perez, for one, says working in a psychology lab is what spawned her new interest in the social sciences. "This lab is showing me that I want to be out in the world interacting with people rather than just be in a lab where pipettes are my best friends," she says. "And that there's research where I can be in the sciences and figure out how things work, but still get that interaction with people."

ROUND TWO

The 10 members of Brandeis's first science posse were chosen from among roughly 3,000 New York City high school students nominated for Posse scholarships in the fall of 2007—the beginning of their senior year. The first-round interviews were conducted in groups of 100 students. "Instead of it being a pencil and paper test, it's like speed dating," says Bial. "Kids are going through all these crazy activities—building robots out of Legos, having discussions on genetic testing—and all the time we're looking for leadership and problem-solving skills, for the ability to work well on a team. We're looking for the stand-out kids."

When the field was narrowed down, a select group of students was asked whether they'd be interested in the science-only posse instead of one of the more traditional liberal arts groups. Eventually, the Posse Foundation submitted the applications of 20 finalists to Brandeis, which selected the final posse of 10.

Already, this process has repeated itself, and the second class of Brandeis science posse scholars has been chosen. Epstein's original plans called for a two-year pilot program, and the success of this year's class gives him high hopes that the program will continue much longer.

"After one semester it has more than fulfilled my hopes and expectations," he says, "both in terms of how they're doing academically and the contributions they make to the university."

Bial says she considers the science posse a success so far and has had interest from other schools in starting their own subject-specific posses. "We're actually talking to a few schools about an arts posse," she says. "And we have enormous interest from other colleges and universities in science posses. Our big challenge is to make sure that we spend the time we need developing the program before we expand it like crazy."

Meanwhile, the Brandeis posse instructors appreciate the students' large and small accomplishments.

Throughout the students' first semester, says Gordon-Messer, they all learned that working with their peers often led to better grades and a better understanding of material. "When I asked them what was helping them get through their difficult classes," says Gordon-Messer, "they all said the same thing—it was the posse that pulled them through." ■

WEB EXTRA: Visit the *Bulletin* online to hear the Brandeis science posse students and mentors talk about their experiences.

AN ACADEMIC FRATERNITY

Epstein's inspiration to build a science posse was shaped by his own observations of students, by programs at other universities, and by a landmark education study on college calculus. ¶ **In the late 1970s,** Uri Treisman, a mathematics graduate student at the University of California, Berkeley, wanted to know why some students performed so much better than others in calculus. ¶ **His initial survey of the students** eliminated all the leading theories of the time: low income, lack of motivation, poor high school preparation, and lack of family support did not always translate to poor math scores. So he followed 40 students around, videotaping their lives and study habits. His efforts revealed an explanation, epitomized by one group of Asian friends all at the top of the calculus class. "In the evenings, they would get together," Treisman recalled. "They might make a meal together and then sit and eat or go over the homework assignments. They would check each others' answers and each others' English.... A cousin or an older brother would come in and test them. They would regularly work problems from old exams.... They knew exactly where they stood in the class. They had constructed something like a truly academic fraternity, not the more typical fraternity: Sigma Phi Nothing." —*S.W.*


FIFTY
KONRAD HOCHEDLINGER
MOLLY PRZEWORSKI
SINISA URBAN
MING
LEI
KARL DEISSEROTH
AMY WAGERS
KEVIN EGGAN
TAMIR GONEN
JOAQUIN ESPINOSA
BRENT
STOCKWELL
ERIC
GREENE
TIRIN MOORE
NEIL HUNTER
JAMES BEAR
CHRISTOPHER SASSETTI
JENNIFER
ZALLEN
RUSSELL DEBOSE-BOYD
BRADLEY
BERNSTEIN
ANITA SIL
HOWARD CHANG
HUI SUN
HARMIT
MALIK
REUBEN SHAW
MARTIN BURKE
AVIV
REGEV

STORIES

LUIS AMARAL

RACHEL WILSON

MARIA SPIES

PETER BAUMANN

ROB KNIGHT

KENNETH POSS

MARC FREEMAN

JOSEPH THORNTON

IANNIS AIFANTIS

JOSHUA MENDELL

JEREMY DASEN

MARK FRYE

DANIEL BOLNICK

KRISTIN SCOTT

XINZHONG DONG

MARTIN COHN

TOP EARLY CAREER

RYOHEI YASUDA

JOHN WALLINGFORD

MICHAEL LAUB

ACADEMIC SCIENTISTS GET SIX YEARS OF SUPPORT FROM HHMI TO PURSUE THEIR BEST IDEAS.

PETER REDDIEN

MICHAEL DYER

SEAN BRADY

SUSAN KAECH

TOSHIYASU TANIGUCHI

JEFFREY KIEFT

BY JOHN FLEISCHMAN

"SO"

is perhaps the most ubiquitous term in science. "So," says the researcher about to explain why a virus overtakes its host or how proteins fold. And so begins the story that every scientist carries in his or her head, the up-to-the-minute mental narrative of what is really happening—in genes or proteins or phylogenetic trees.

Maria Spies tells "single molecule stories" in DNA biochemistry. She describes what happens when DNA helicases, molecular motors that drive DNA repair, find breaks and "hot spots" in DNA or encounter other proteins bound to the DNA molecule. Spies studies DNA helicases that are linked to breast and ovarian cancer and to rare genetic disorders involving premature aging, stunted growth, and a dangerous sensitivity to sunlight. DNA repair is vital to all cells. By one estimate, every cell in the body must undertake 190,000 DNA repair events every day to keep up with the damage inflicted by ultraviolet light, toxic chemicals, and the dangerous by-products of normal metabolism.

Spies' most gripping single molecule story so far involves the bacterial helicase RecBCD running on a sort of home-built DNA drag strip, a long stretch of nucleic acids laid out so Spies could insert recombination hot spots. Using laser optical trapping and single-molecule fluorescent markers, Spies recorded RecBCD barreling down the DNA track, pausing at a hot spot and then changing speed. The helicase did this by switching the lead positions of its two driving molecule subunits, which run at different speeds. Spies described it as a "molecular throttle." A colleague described this story as stunning.

But Spies has another story, her own, that is equally gripping. She entered Russian science in the mid-1990s, a time when research in the former Soviet Union was in freefall. Her first publication in a Russian journal was a mark of achievement, according to an outside observer familiar with post-Soviet Russian science who noted that any publication at this chaotic time was "an indication of a strong desire and determination to do science."

That determination led Spies into scientific research in three languages: in her native Russian as a student at St. Petersburg State Polytechnic University, in Japanese for her doctorate at Osaka University, and in English, first as a postdoctoral fellow at the University of California, Davis, and since 2005 in her own laboratory at the University of Illinois, Urbana–Champaign. With this long prelude, Spies' independent career is taking off at last.

TIME FOR DARING

There is a third story here. It goes beyond the science or any one scientist. It is the story of what happens to newly launched researchers like Spies in their early careers. It's a story that worries the scientific advisors of HHMI who see many promising investigators heading for a career-deadening crunch. Just as their independent research and their scientific imaginations are supposed to be taking off, they run into professional prudence.

Researchers serve a long apprenticeship, laboring for years in other people's labs, first as graduate students and then as postdoctoral fellows, before the opportunity to strike out on their own as principal investigators, or PIs. Hired for their first tenure track

faculty positions, new PIs are usually greeted with generous institutional start-up funds, protected research time, and "free" lab space. But within a few years, the grim reality of funding sets in. To keep it all going—labs, students, equipment, materials, overhead, and their own salaries—researchers must bring home the bacon, generally in the form of big, multiyear federal grants. With so much on the line, the tendency is to play it safe to win those grants. Mentors advise young colleagues to leave their grand, outside-the-mainstream projects for another day and to write up measured, incremental proposals that approach worthy scientific goals in precise steps.

That's the story HHMI wants to rewrite. In 2008, HHMI issued a call for applications from early-stage, tenure-track researchers in biological and related fields (for example, bioinformatics) for six-year, nonrenewable, all-expenses-covered appointments as HHMI Early Career Scientists (ECS). Beyond salaries and staff, HHMI would underwrite the purchase of critical equipment and the leaseback of their lab space from their home institutions. In all, HHMI would earmark $200 million over six years to support the ECS investigators. More than 2,000 applications flooded in. This March, HHMI unveiled the first 50 ECS investigators: 9 women and 41 men from 33 institutions. Maria Spies is 1 of the 50.

"These scientists are at the early stage of their careers, when they are full of energy and not afraid to try something new," says Jack Dixon, HHMI vice president and chief scientific officer. "They have already demonstrated that they are not apt to play it safe—and we hope they will continue to do something really original."

Given HHMI's long-time preference for choosing "people over projects," it's not hard to see why certain ECS candidates jumped out of the pack. But even being among the best and the brightest was not enough. The selection committee was looking for something beyond sterling credentials, impressive publications, and glowing recommendations. Call it style, originality, grit, or fearlessness. Or call it a compelling story.

CLEARING TECHNICAL HURDLES

Karl Deisseroth tells a dazzling story about controlling neural activity, neuron by neuron, in freely moving mice with a pulse of light. Deisseroth, a physician-scientist at Stanford University, calls his technique "optogenetics." He gave it a grand demonstration of principle in 2007 by waking up mice, not by shaking or startling them but by switching on light-sensitive proteins deep within their brains. Deisseroth's experiment was also an in vivo test of recent genetic findings linking human narcolepsy, a chronic sleeping disorder, to a defective set of cells in the lateral hypothalamus that produce proteins called hypocretins.

To rouse the sleeping mice, Deisseroth borrowed a light-sensitive switch from a microbe (in this case, a single-celled alga) and used a virus to deliver it into the cell membrane of neurons deep in the hypothalamus on the underside of the mouse brain. Then he and colleagues fired laser bursts down an optical fiber, bathing the switch in blue light and opening the microbial ion channel. Sodium ions flooded into the neurons, exciting them and causing them to release hypocretins.

"THESE SCIENTISTS ARE AT THE EARLY STAGE OF THEIR CAREERS, WHEN THEY ARE FULL OF ENERGY AND NOT AFRAID TO TRY SOMETHING NEW."

JACK DIXON, HHMI VICE PRESIDENT AND CHIEF SCIENTIFIC OFFICER

Deisseroth's mice were a wake-up call to a new day in neuroscience when targeted neurons in living animals can be flipped on or off by light.

This is just the tip of the iceberg, says Deisseroth, who has distributed optogenetic technology, free of charge, to more than 350 labs around the world. He is pressing ahead to refine new bio-optical switches that can inhibit as well as excite neurons and to apply the technology to better understand neural circuits in health and disease. Meanwhile, Deisseroth is board-certified by the American Board of Psychiatry and Neurology and continues to care for patients.

Russell DeBose-Boyd's story is about finding a way around the statin stalemate. Twenty million Americans take a statin every day to reduce their levels of "bad" cholesterol—low density lipoproteins, or LDLs. Statins dramatically cut LDL levels in some patients, says DeBose-Boyd, who is at the University of Texas (UT) Southwestern Medical Center, in Dallas. But the body responds to the plummeting cholesterol levels with a feedback system that tells the cells to compensate by making more cholesterol.

To understand the statin impasse, DeBose-Boyd studies HMG-CoA reductase, an enzyme that sets the rate of cholesterol synthesis. Statins block the enzyme but, paradoxically, also seem to drive up reductase levels, he says, by slowing their natural degradation. Blocked by statins, the accumulating enzyme convinces the cell's sensing system that cholesterol levels are crashing, and the cells respond by attempting to rev up synthesis. DeBose-Boyd hopes to make statins work better, or find entirely new drugs that control reductases better and make statins obsolete.

DeBose-Boyd's other story is how he found his way into science. He comes from a tiny farming community in rural Oklahoma and began his studies at Southeastern Oklahoma State University, in Durant, an institution not noted for producing protein biochemists. He followed his interests in biology to the University of Oklahoma Health Sciences Center, in Oklahoma City, where his Ph.D. mentor, glycoprotein biochemist Richard Cummings, recognized his talent. Cummings enthusiastically promoted DeBose-Boyd as a postdoctoral fellow candidate to the UT Southwestern Medical Center research duo of Michael Brown and Joseph Goldstein, who won the 1985 Nobel Prize in Physiology or Medicine for their discovery of the regulation of cholesterol levels by statins. That discovery set off the statin revolution but the exact mechanism and the paradoxical self-limit of statin efficacy stymied their lab for a decade.

Then DeBose-Boyd arrived and turned his attention to the interplay between statins and reductase. He worked his way around a major technical hurdle by discovering a regulated binding partner of reductase that allowed overexpression of the enzyme in sufficient quantities while preserving its natural degradation. This discovery permitted him to map out interactions between reductase and its binding partner and focus on reactions that lead to the enzyme's degradation. It soon became clear to Brown and Goldstein that DeBose-Boyd was someone

CLOCKWISE: MARIA SPIES, KARL DEISSEROTH, HARMIT MALIK, RUSSELL DEBOSE-BOYD

to keep around UT Southwestern and they engineered his move to independent faculty status.

OF CONFLICT, VULNERABILITY, AND DOMINANCE

Harmit Malik's story sounds like a viral fairy tale. In it, Malik and his collaborator Michael Emerman awaken a 4-million-year-old retrovirus to discover how our hominid ancestors evolved a stout genetic defense against it while our chimp cousins did not. What Malik and his colleagues were after was not a microscopic version of Retroviral Park but an evolutionary insight into HIV, another retrovirus that made the long evolutionary trip to modern times where it found human antiviral defenses unprepared for it.

Malik's scientific story is much wider than retroviral measures and countermeasures. He is interested in genetic conflict both within our own cells and between our DNA and that of outsiders like HIV. He has used the conflict paradigm to gain insights into long-standing problems such as the ability of viruses to mimic our proteins and also the evolution of centromeres, structural DNA elements that are critical for proper cell division.

The Harmit Malik story begins with a degree in chemical engineering from the Indian Institute of Technology in Mumbai and takes a turn toward evolutionary biology in a doctoral program at the University of Rochester. His engineering background made him comfortable with the flood of genomic data pouring out of mass sequencing and the ease with which living things could be sorted into evolutionary families, or phylogenetic trees, by new bioinformatics programs.

As a grad student, Malik helped usher the biology department into the bioinformatics age. It earned him a tribute from Barry Hall, the noted Rochester geneticist and author of *Phylogenetic Trees Made Easy*, who wrote in the foreword, "I am grateful to Dr. Harmit Malik, who patiently overcame my antipathy to phylogenetic analysis by teaching me how to use phylogenetic software. Much of the book comes directly from his help." Hall continued, "This book began as an effort to record and organize his advice when we realized we could not keep him on hand forever."

Malik left Rochester for Seattle and a postdoc with HHMI investigator Steven Henikoff at the Fred Hutchinson Cancer Research Center. It was in Henikoff's lab that Malik branched out into genetic conflict at centromeres, which occurs when chromosomes compete for survival during female meiosis. Henikoff soon realized the advantage of keeping Malik on hand for the Basic Sciences Division. In 2003, Malik became the first "in-house hire" of a postdoc for a faculty position at the center in nearly 20 years.

So, careers and stories follow an arc. The aim of HHMI's ECS program is to advance the career trajectory of these 50 talented researchers, and with them the prospects for research bioscience, far into the 21st century. This makes the 50 Early Career Scientists sound like human cannonballs, and they do share a certain scientific derring-do. Their instructions from HHMI are simple: Land somewhere unexpected. Discover something transformative. ■

FOR MORE INFORMATION: To learn about the 50 new HHMI Early Career Scientists, visit www.hhmi.org/news/20090326ecs-ad.html.

Spies: L. Brian Stauffer Deisseroth: Linda A. Cicero / Stanford News Service
Malik: Suzie Fitzhugh DuBose-Boyd: Courtesy of UT Southwestern

Will mathematical models that consider climate change, disease agents, and human immunity—as a start—offer a reliable way to anticipate the next outbreak of cholera or malaria?

by Charles Schmidt | photography by Brian Ulrich | illustration by Darren Booth

The notion that a changing climate can trigger outbreaks of infectious disease has been around since the dawn of medicine. Ancient Romans knew this. Every summer, the wealthy escaped to hill resorts to avoid malaria—"mal'aria," or bad air in Italian.

But while the climate–disease link has been long appreciated, the nature of that link has been shrouded in mystery. Just as the weather is complicated, so too are the innumerable factors that dictate who gets sick from an infectious agent as well as when and why. Combining climate and disease variables into a predictive model—one that might offer early warning of a pending, weather-driven epidemic—is no easy task.

Enter HHMI investigator Mercedes Pascual at the University of Michigan. A marine and theoretical ecologist by training, with a gift for computational analysis, Pascual bridges the worlds of climate and infectious disease research. Her quantitative models—developed with collaborators in meteorology, epidemiology, and other fields—have generated convincing evidence that complex climate patterns influence infectious disease epidemics and their distribution.

Pascual's research has shown that cholera epidemics in Bangladesh vary in accordance with sea-surface temperatures 10,000 miles away in the Eastern Pacific Ocean. More recently, her models have revealed heightened risks for malaria in African highlands, accelerated by long-term warming trends that favor reproduction of the disease-carrying mosquitoes that were once less abundant in this region.

With global warming threatening major changes in how humans interact with infectious agents, Pascual's studies have taken on new urgency.

Looking for Patterns in Nature

Born in Uruguay, Pascual had a nomadic childhood, living in four Latin American countries while her father, a chemical engineer, moved from job to job. From an early age, she developed a love of the ocean that influenced her academic choices and career. An avid sailor, she was a crew member on yachts that traveled long-distance passages up and down the South American coast. And as an undergraduate at the University of Buenos Aires, she spent a summer studying dolphin ecology in Tierra del Fuego, just 600 miles from Antarctica.

Pascual's early interests revolved around marine ecology, but, as her academic career evolved, she found mathematics increasingly appealing. She says she was captivated by how complex dynamics in nature could be described in mathematical terms. "I liked how you could reduce observable patterns in population dynamics to numbers and equations," she explains. "And I liked that even messy data sets had patterns that might give you clues to their behavior in the real world, even though they might not be obvious at first."

When her studies took her to the United States in 1985, a meeting with Simon Levin, a pioneer in theoretical ecology at Cornell University (now at Princeton), helped Pascual realize she could combine her interests in math and ecology. After completing a master's degree in mathematics from New Mexico State University in 1989, she migrated east for a Ph.D. at the Woods Hole Oceanographic Institute to study with theoretical ecologist Hal Caswell.

These were heady times in the field, Pascual says. Scientists in theoretical ecology, including Caswell, were pioneering mathematical studies of "nonlinear" dynamics, which describe how ecological systems change and respond to their environments over time. Because of internal feedback between their components, natural systems almost never exhibit linear or proportionate responses to environmental influences. Plankton populations, for instance—the subject of Pascual's doctoral research—don't grow twice as large if their food supplies double. Many factors play into

"I liked that even messy data sets had patterns that might give you clues to their behavior in the real world, even though they might not be obvious at first."

Mercedes Pascual

those growth rates, including competition among individuals. Given that, plankton populations exhibit complex, nonlinear responses to food increases that can be challenging to quantify.

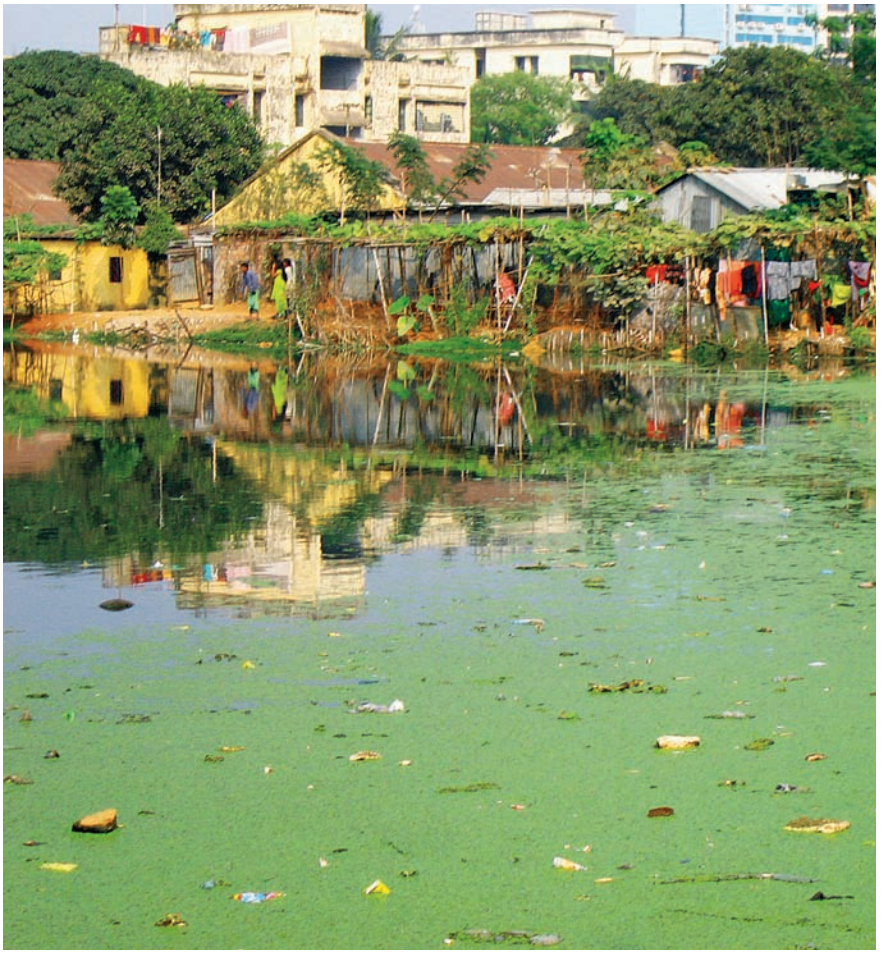
Nonlinear dynamics have been central to Pascual's work ever since. But her emphasis has gradually shifted from their role in marine ecology to their expression in patterns of infectious disease. The transformation toward human illness began when Pascual moved to Baltimore in 1997 to work at the Center of Marine Biotechnology at the University of Maryland.

The Climate–Cholera Mystery

The Center for Marine Biology was headed by Rita Colwell (who later was director of the National Science Foundation from 1998 to 2004). Colwell had spent years studying cholera and was the first to propose that this water-borne illness—the result of *Vibrio cholerae* bacterial infections—could be linked to climatic factors. Her research had shown that the bacteria can survive in aquatic environments in association with plankton. When a massive cholera outbreak struck Peru in 1991, killing 10,000 people and sickening 1 million, Colwell proposed that a recent and remarkably strong El Niño was the underlying cause. In her view, unusually warm Pacific waters and heavy rains induced by the El Niño Southern Oscillation (ENSO) triggered a proliferation of cholera bacteria that fueled the epidemic.

In thinking about the epidemic, Pascual wondered if cholera's response to climate variability was nonlinear and governed not just by ENSO and its effects on the pathogen but also by an important limiting factor—i.e., the fraction of susceptible people in the at-risk population.

Infectious diseases need fuel to spread, Pascual explains, and that fuel comes in the form of susceptible individuals. Those who survive cholera develop temporary immunity to future exposure. When immunity predominates in a population, cholera outbreaks don't spread no matter how strong the environmental pressures. But when the pool of susceptible people rises—perhaps because of new births or human migration patterns—vulnerability to environmental pressures increases, making outbreaks more likely and intense.



A large fraction of the population of Dhaka, Bangladesh, has no access to clean water sources and can be exposed to the cholera pathogen through water bodies such as this pond, photographed during the city's dry season.

Pascual wanted to study the interaction between ENSO and cholera outbreaks, but to do that she had to look beyond the Peruvian epidemic. El Niños occur every three to seven years, but before the 1991 event Peru hadn't experienced a cholera outbreak of any significance for more than a century. To model disease dynamics over multiyear timescales, Pascual needed to look at more than a single outbreak. She needed data from a country that faced cholera threats on a regular basis.

She turned to Bangladesh, where cholera is a fact of life. Bordered by India and the Bay of Bengal, Bangladesh is home to 150 million people, many of them forced by population pressure to the low-lying coast. Inundated by rivers that flow south from the Himalayas and perched on a landscape just a few feet above sea level, Bangladeshis face routine flooding with water contaminated by fecal matter.

Cholera bacteria thrive in this setting; once ingested by a human, the microbes proliferate in the gut, doubling their numbers every eight minutes. Within hours, the disease produces an explosive, clear diarrhea, speckled with rice-like shreds of intestinal lining. Untreated, it can kill in a day.

Cholera cases in Bangladesh spike twice yearly, according to infectious disease specialist Gary Schoolnik at Stanford University School of Medicine. The first spike occurs just after the monsoon rains that pour torrentially from June to September, overwhelm sanitation systems, and liberate *V. cholerae* into water used for drinking and bathing. The second occurs during the hot, dry spring, when shrinking pools of standing water concentrate the bacteria, unleashing another round of infections. Yet, the intensity of these

Mercedes Pascual

seasonal outbreaks also varies on interannual timescales that, Pascual noticed, seemed to correspond to ENSO-generated escalations in ocean temperature.

Pascual had found valuable collaborators at the International Center for Diarrheal Disease Research (ICDDR) in the capital city, Dhaka, who had been monitoring cholera in different locations in Bangladesh since 1966. Their "time-series" data for Dhaka describing cases since 1980 was a crucial resource for Pascual's investigation. By considering those data against ENSO sea-surface temperature changes in a nonlinear model, she found what she was looking for: quantitative evidence tying ENSO to cholera dynamics. "In the end, we discovered a lag of 9 to 11 months between ENSO and an increase in cases," Pascual says.

The finding—reported by Pascual, Colwell, and colleagues in *Science* in 2000—made international headlines. By linking cholera to global climate cycles, Pascual had fueled hopes for an ENSO-driven warning system that might avert outbreaks in Bangladesh and elsewhere altogether. By that time, Pascual had received 10 years of research funding (in 1999) from the James S. McDonnell Foundation; in 2001, she moved to the University of Michigan to become an assistant professor of ecology and evolutionary biology.

The ability to forecast epidemics in advance would be an important breakthrough for public health, Colwell says. Cholera—a symptom of poverty that's been virtually extinguished from the developed world—is an imminently treatable disease. Most patients recover with antibiotics and an oral rehydration solution containing salts, sugar, and clean water. "Better outbreak prediction would make it possible to gather the needed treatments and resources more efficiently," Colwell says. "If you've got a few months to prepare, you can be more effective in dealing with the problem."

Mercedes Pascual's computational models have generated evidence that complex climate patterns influence the incidence of infectious disease epidemics.

Brian Ulrich

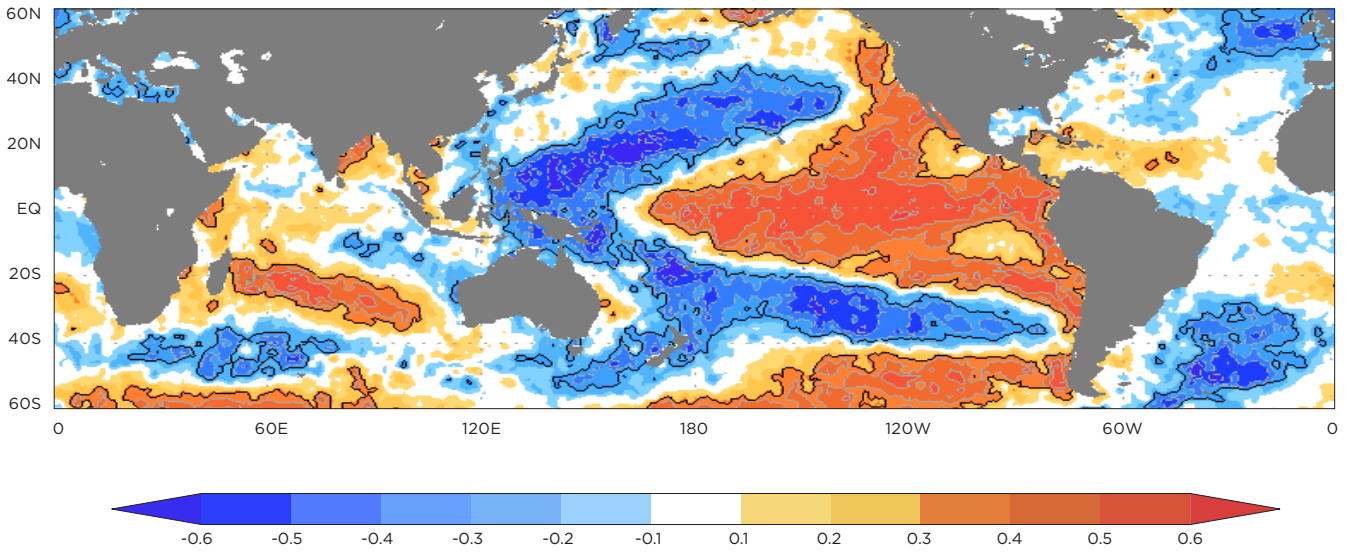
Better Predictions

From Michigan, Pascual continued her cholera studies, following up in 2005 with a paper in *Nature* that teased ENSO's role apart from the contributions of population immunity, which also cycles over multi-year time frames. "I wanted to approach the role of climate with a better understanding of what was happening with respect to the disease itself," Pascual says.

Doing that wouldn't be straightforward. To control for host immunity, Pascual had to know the fraction of susceptible people in the Bangladeshi population over time. Those data weren't available, so she used population data supplied by her collaborators at ICDDR. From 1966 to 2002, ICDDR staff had followed cases among roughly 200,000 people living in Matlab, a rural area just south of Dhaka. This defined population gave Pascual a denominator with which—by applying statistical wizardry—she could estimate the percentage of immune individuals living in the area from one year to the next. With that knowledge, Pascual was able to remove the influence of host immunity from her investigation of ENSO's effects on cholera transmission. She found that ENSO's effects still held up, meaning that the spike in cases couldn't be attributed solely to declines in immunity.

What those results didn't explain, however, was *how* ENSO held sway over cholera dynamics in Bangladesh. To answer that question, Pascual collaborated with scientists at the Climate Research Laboratory in Barcelona, Spain, and the Center for Ocean-Land-Atmosphere Studies (COLA) in Calverton, Maryland. Supported by the National Oceanic and Atmospheric Administration, the National Science Foundation, and the National Aeronautics and Space Administration, COLA scientists believe that the global climate—while chaotic—has predictable elements that allow for accurate forecasting on both short- and long-term timescales.

Crucial to their analyses is a 3,000-mile-long rectangular swath of Eastern and Central Pacific Ocean dubbed "Index 34."



The world's ocean temperatures influence global climate variability and are important to infectious disease dynamics, according to Mercedes Pascual. This global ocean grid shows the correlation between sea surface temperature anomalies in January and cholera cases in September in Matlab, Bangladesh. The large orange area in the Pacific Ocean indicates a significant positive correlation between these variables (the color bar at bottom gives the values of the correlations). Interestingly, this is the same area in the Pacific that warms during El Niño events.

COLA research scientist Benjamin Cash says that during ENSO periods, sea-surface temperatures throughout Index 34 can rise by up to 2.5°C, producing a general warming of the tropical atmosphere. "And if that warming persists long enough to influence monsoon circulation patterns, you see increased rainfall over Bangladesh," he explains. "And Bangladesh is a low-lying country where floods lead to a breakdown in sanitation."

Pascual agrees that heightened rainfall may be the culprit behind the ENSO–cholera connection in Bangladesh. But, she adds, much about that connection remains unresolved. "ENSO produces high amounts of rainfall in some areas in Asia and lower amounts in others," Pascual explains. "Through our work with Ben Cash and Xavier Rodó (Barcelona) we're starting to get a better handle on what mediates the effect of ENSO on cholera in Bangladesh, but we're not in a position to make firm conclusions about the role of rainfall yet. We still need to know more about local climate drivers and how they mediate ENSO's influence. Whether we're better off predicting outbreaks on the basis of local or remote climate variables remains an open question that we're working on now."

Yet another factor to consider, Pascual says, is the role of "inapparent" or asymptomatic cholera infections among the population and how they influence disease transmission. In a paper published in *Nature* in August 2008, University of Michigan's Aaron King, Pascual, and colleagues showed that the fraction of asymptomatic individuals can be greater than anticipated. These more mildly affected individuals have rapidly waning immunity, the scientists found, which could be crucial to interpreting patterns of disease outbreaks.

Climate Change Now

Ancient Romans experienced the impact of seasonal variation in temperatures on malaria transmission. But Pascual's research is supplying quantitative evidence that climate change—a trend of increasing temperatures—is having an important effect on malaria.

In 2006, she published a paper in *Proceedings of the National Academy of Sciences* suggesting that even small temperature increases in the East African highlands could amplify mosquito populations and boost human exposure to the malaria parasite.

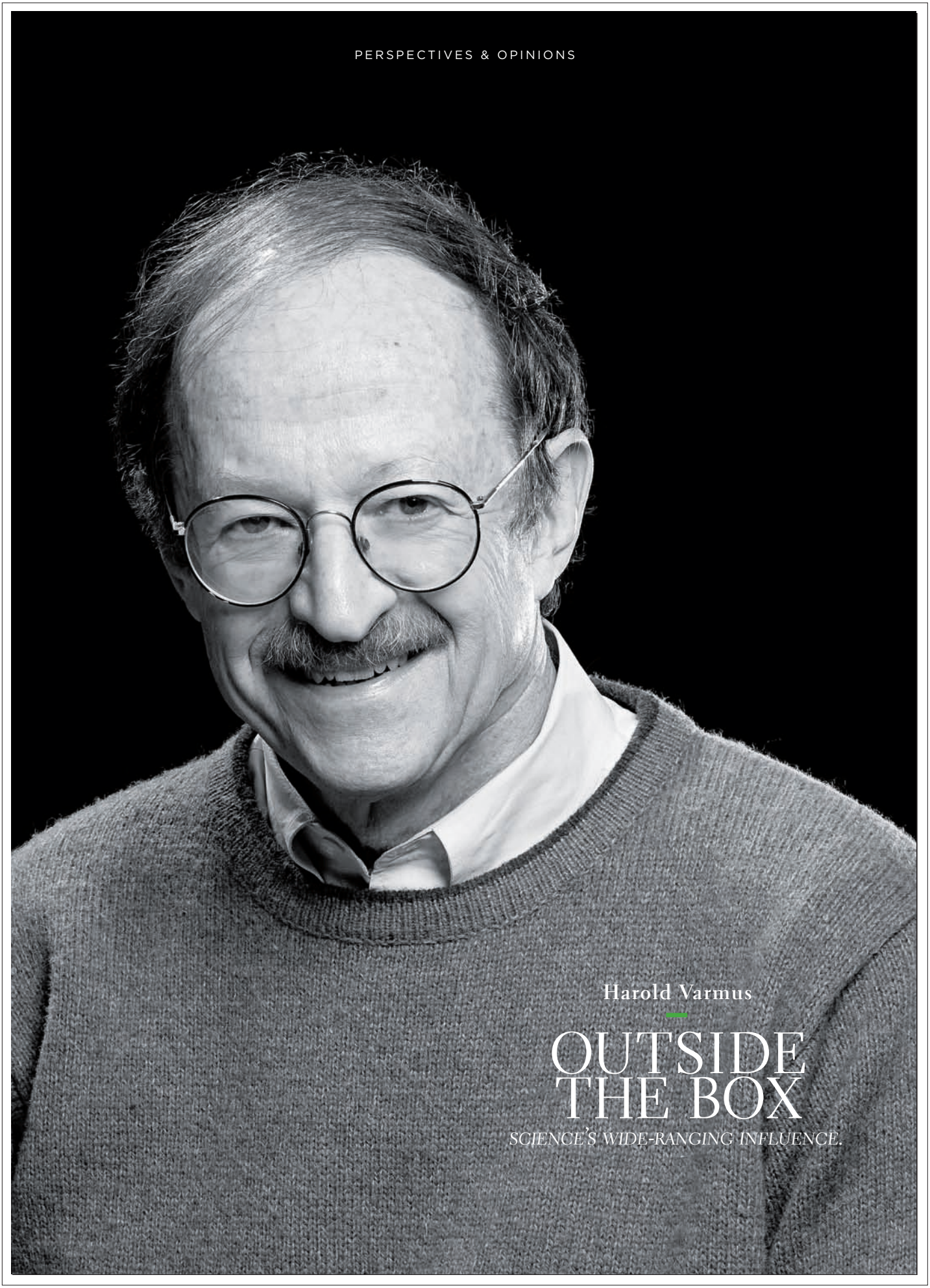
Encompassing mountainous regions of Kenya, Tanzania, Rwanda, and Ethiopia, the East African highlands have traditionally avoided malaria. Mosquitoes don't mind cool, high-altitude climates, but cooler temperatures slow the development of the malaria parasites, limiting disease transmission. Malaria incidence in several East African highland regions, however, has been rising since the late 1970s. What's more, time-series data generated by the Climatic Research Unit at the University of East Anglia in the United Kingdom show that ambient temperatures in the region climbed approximately 0.5°C from 1950 to 2002.

Experts argue about what's driving the rise in cases; some point to growing drug resistance among malaria parasites and changing demographics as probable causes. Pascual doesn't discount those possibilities. But she adds that her modeling results—which suggest that mosquito populations under current warming trends could have doubled in some regions—indicate that local climate change can't be ruled out as a contributing factor.

Andrew Dobson in the Department of Ecology and Evolutionary Biology at Princeton University concurs. He adds that it's difficult to validate Pascual's modeled findings, given the paucity of mosquito population data from the East African highlands and other areas in the developing world. "Scientists are only now

(continued on page 56)

Climate Research, *Vol 36: 131-140m 2008, "Predicting endemic cholera: the role of climate variability and disease dynamics."*



Harold Varmus

OUTSIDE THE BOX

SCIENCE'S WIDE-RANGING INFLUENCE.

Jesse Winter

Harold Varmus was a latecomer to science. After a year of graduate school in English literature he made his way to medical school, research training at the National Institutes of Health (NIH), and a faculty position at the University of California, San Francisco. He served more than six years as NIH director, is president of Memorial Sloan-Kettering Cancer Center, and is a co-chair of President Barack Obama's Council of Advisors on Science and Technology. In his new book, *The Art and Politics of Science*, Varmus describes his unusual route to science, his Nobel Prize–winning research, and his global goals for science policy.

What did you want to achieve in writing this book?

It was designed to show people who are still trying to figure out their career paths that it is possible to have a dalliance with other things and end up on your feet. I'm a big believer in people's ability to get a diverse education before they become bound to a laboratory. Having an appreciation of the arts is one of the things that makes us human, so it would be a shame if we reverted, as I sometimes worry we may be doing, to a more British-type system in which people commit to a single career path at a very young age. I also spell out why I'm passionate about issues like global health and open-access publishing.

You've called for a doubling of global health spending as a "pillar of U.S. foreign policy." Why?

We are spending more money on global health than we have before. But there needs to be more attention to health systems, to building ways for countries to become more self-sustaining with respect to diseases that get less attention, like the garden-variety pneumonia and diarrhea that are actually the big killers of kids in parts of Africa, Asia, and South America.

[Former ambassador] Thomas Pickering and I co-chaired a recent Institute of Medicine report on global health (The U.S. Commitment to Global Health: Recommendations for the New Administration). We would like to see the White House, the State Department, and the Department of Health and Human Services recognize global health—and I would argue global science—as a significant part of our foreign policy effort and coordinate that effort more effectively. We should have more scientists serving in our embassies and also bring visitors to other countries to talk about science. The world of science is a great place to internationalize, because everyone is dealing with shared problems, usually in a shared language.

What other policy changes would you like to see in the Obama administration?

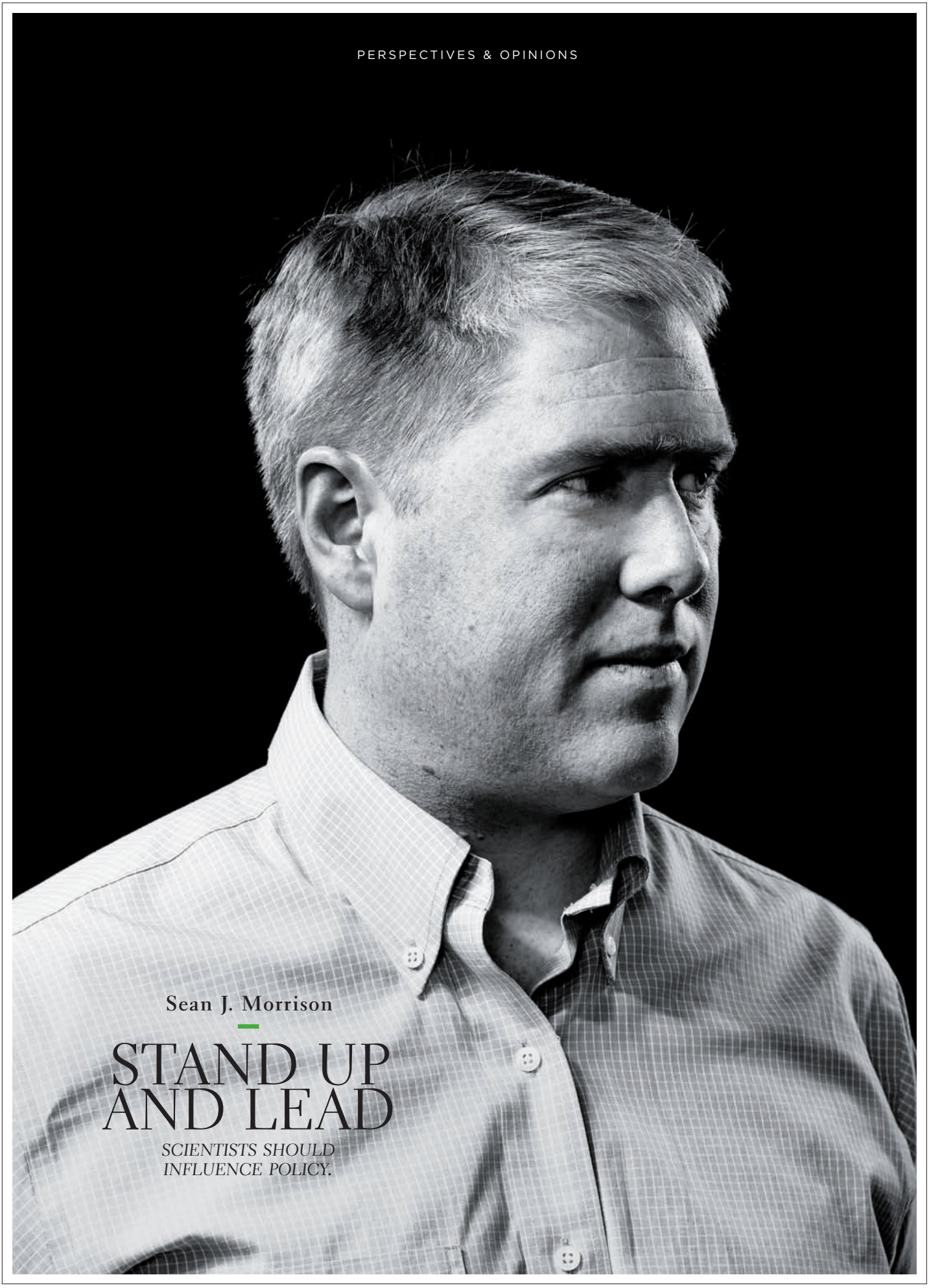
President Obama's interest in science is clear. Before the inauguration he interviewed several scientists to get our take on science and government. The biggest long-term issue will be the funding of research. The President has excellent intentions to try to create an environment in which scientists can expect that there will be continued, moderate increases in funding, with budgets doubling over 10 years, as they have tended to do historically at NIH, but without the peaks and abysses that have characterized funding over the past 20 or 30 years. Feasts and famines create all kinds of havoc. Nevertheless, the President is working in a fiscal environment where the ability of the government to support domestic programs is going to be very limited, and also where Congress makes most of the calls. The intellectual opportunities are extraordinary at the moment, and our field is very optimistic about what science can do. But it can't be done without money.

You're concerned about prospects for young scientists, as well?

There's widespread concern about the increasing age at which young people become independent. Some of our best students spend a very long time in training, not getting faculty status until they are in their 40s. I look at my own career. I was 28 years old before I did any serious science. I learned to work in a laboratory during two years at NIH, was briefly a postdoc, and at the age of 32 was a full-fledged faculty member. We need to face the fact that you don't need to be a trainee for so long. On the other hand, we need to be sure that when people are launched as faculty members they're not so over-burdened that they can't work hard in the lab and educate themselves about things they need to learn. Maybe we should be thinking creatively about how we structure the whole process of becoming a faculty member.

INTERVIEW BY STEVE OLSON. *Harold Varmus is co-chair of the President's Council of Advisors on Science and Technology with Broad Institute founding director Eric Lander.*

WEB EXTRA: *For more of Harold Varmus's thoughts on global health and open-access publishing, go to www.hhmi.org/bulletin/may2009.*



Sean J. Morrison

STAND UP AND LEAD

SCIENTISTS SHOULD INFLUENCE POLICY.

Roy Ritchie

HHMI investigator Sean J. Morrison was a leader in the charge to loosen restrictions on stem cell research in Michigan—going up against a well-funded opposition in the November 2008 election—and won. It was an eye-opening experience.

I'm an immigrant from Canada. People come to the United States from all over the world, partly because history shows that individuals with good intentions can instigate profound change in this country. The meritocracy of ideas is a force that shapes American society and an inspiration for the world. But with opportunity comes responsibility.

In Michigan, we had a law that made it illegal to destroy human embryos for the purpose of research, even though these embryos were routinely discarded by fertility clinics. This law did not save a single embryo from destruction; it only delayed medical research. Proposal 2 overturned this law and protected stem cell research in the state constitution. Few thought we could prevail. Right to Life groups have more control over legislation in Michigan than in any other state. But we went straight to the voters and we won.

In science, we aspire to uncover the truth. We constantly test perceptions against reality. In politics and public policy, perception is reality. And rather than testing policies against reality, people in politics often spend their time trying to shape the perception of reality—for good and for ill.

When you want people to vote against an issue, as did our opponents, you frighten and confuse them. That's politics 101. Every word in the campaign against Prop 2 was a lie. Opponents tested their messages and found that none of their truthful arguments resonated with voters.

So they made stuff up. Their three messages against Prop 2 were: taxes would go up (though it had nothing to do with taxes), scientists wanted to clone people by mixing human DNA with animal eggs (though human cloning remained illegal under Prop 2), and, finally, they compared stem cell research to the Tuskegee syphilis experiments. They argued that Prop 2 would allow completely unregulated medical research that would exploit minority communities. This was the turning point in the campaign.

The backlash was big. All the major media ran editorials about how dishonest the opposition campaign was. Support for Prop 2 among African Americans increased dramatically.

We put a lot of effort into public education and were particularly surprised by the poor understanding of reproduction in the general public. Special interest groups exploit the public's poor understanding to shape inaccurate perceptions.

Within the campaign, we faced a tension when it came to our messaging. Scientists wanted to communicate ideas accurately and in a nuanced manner. Our campaign people emphasized that the word "cure" has more impact than any other word (based on polling) and that we needed to repeat that word as often as possible. But the scientists didn't want to overpromise and risk a loss of confidence later.

The compromise was to say that it might be 20 years before we can cure anything, that diseases are tough problems. But we owe it to those who can't be cured otherwise to do all we can to find a cure. We won't know what is possible until we can do the research. I learned that hope and truth prevail over fear and misinformation, when communicated clearly.

If our opponents had won, you would see the Tuskegee syphilis ad all over the country. Their playbook would be to undermine public confidence in medical research. Now they are still looking for a playbook.

The process was unpleasant—repeatedly debating opponents who lied unapologetically, and being the subject of hate mail. But we must stand up when people try to mislead the public into policies that undermine efforts to improve public health. Policies that are based on ideology rather than fact have little chance of achieving positive outcomes. Those who understand the issues must explain them to the public and to policy makers or we will get bad laws for bad reasons.

Our society will succeed or fail based on its adherence to rational approaches to decision making. Science not only leads to new knowledge and new solutions to problems, it also teaches people to test their perceptions against reality. In these trying times, it is more important than ever that scientists deliver these messages clearly. Many want us to fail in our efforts to challenge the voices that counsel ignorance. We can't afford to.

INTERVIEW BY CORI VANCHIERI. *Sean Morrison is director of the Center for Stem Cell Biology at the University of Michigan.*

Q&A

What has a student taught you about science?

The Latin proverb, "By learning you will teach, and by teaching you will learn," holds as true in science as in any other field. The biggest lessons often come from mentoring and teaching.

— EDITED BY SARAH C.P. WILLIAMS

Richard N. Zare

HHMI INVESTIGATOR
STANFORD UNIVERSITY

"I have learned from my students the importance of passion. Without a burning desire to see some project to its completion, nothing worth very much ever gets accomplished. This observation applies both to the lab and to the classroom. The power of love should never be underestimated. This human emotion has more to do with advancing knowledge than might first be suspected. It is not fear of failing but love of trying to find something new and sharing the delights of discovery with others that drives so much of what we do."

M. Celeste Simon

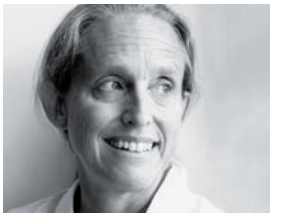
HHMI INVESTIGATOR
UNIVERSITY OF PENNSYLVANIA SCHOOL OF MEDICINE

"Just when I am overwhelmed with and frustrated by grants, paper revisions, editorial boards, and regulatory compliance, an undergraduate or graduate student shows me some exciting data or articulates an interesting new hypothesis. They remind me what a privilege it is to work in biomedical sciences and renew my enthusiasm for what we are doing. I am consistently astonished by the exceptional abilities of the first-year M.D./Ph.D. students I work with during independent study tutorials. These will be the scientific leaders in the future."

Graham Hatfull

HHMI PROFESSOR
UNIVERSITY OF PITTSBURGH

"Well, many things but here are some key ones. First, authentic research is a powerful stimulant for awakening a life-long curiosity in our natural world—perhaps the single most important characteristic of the scientific researcher. Second, standardized tests have no predictive value for research capability. Because it's not obvious which students have aptitude for research, we ought to give as many students as possible the opportunity to try it! Lastly, students thrive when given responsibilities for mentoring other students; to teach what they have learned. If we are going to develop a flourishing culture of scientist-educators, let's start 'em young!"



Darcy Kelley

HHMI PROFESSOR
COLUMBIA UNIVERSITY

"This fall, I advised entering students on 'Frontiers of Science,' a required course in Columbia's Core Curriculum. Most opened the conversation with: 'I am not a science type….' In the U.S., the majority of students categorize themselves as 'non-science' as early as kindergarten. They are shut out of an entire way of thinking about their world before having a chance to find out how powerful scientific approaches are and how beautiful their universe is. What I've learned about science from these students is that this must be fixed."

Zare: George Nikitin / AP, ©HHMI Simon: William Vasquez Hatfull: Annie O'Neill Kelley: Jennifer Altman

chronicle

The fruit flies devouring banana bits on this plastic tray are in for a surprise: they're dragonfly food. The tray is part of an artificial, indoor habitat that allows researchers to study dragonflies' precise hunting skills (see page 52).

Erik Johnson

Tapping into Cool Science

HHMI GRANTEES HAVE DEVELOPED TERRIFIC EDUCATION TOOLS. NOW THEY'RE AVAILABLE AT ONE WEBSITE.

WHO SENT A LOVE NOTE, SIGNED WITH A KISS, TO THE CAPTAIN of the basketball team? A girls' club in Atlanta used chemistry and biology to solve this fictional mystery, and they made the front page of the *Atlanta Journal-Constitution* on February 9th.

It was an early Valentine's Day gift for Patricia Marsteller, HHMI's program director at Emory University, whose student had designed the love-note lesson. Marsteller was thrilled to see it being used as intended. The "Signed with a Kiss" investigative case is one of the varied tools developed over 20 years by hundreds of HHMI grantees.

"Our grantees' work has utility and worth that goes beyond the individual projects that they were funded to do," says Peter Bruns, HHMI's vice president for grants and special programs. HHMI is selecting the most useful resources and making them freely available in one place: its new *Cool Science* Web portal.

Cool Science, which went live in the fall of 2008, pulls together many of HHMI's existing online resources, including the virtual labs and other materials created for the popular Holiday Lectures series. The Web portal gives teachers access to a vast array of resources, gives students the opportunity to pose vexing questions to scientists who post the answers online, and allows anyone to learn how to breed sleepy fruit flies or make bacteria glow green under ultraviolet light.

"*Cool Science* is a way of sharing the best practices. It's a How To: this is how we do it at this particular place," says David Asai, director of HHMI's precollege and undergraduate science education program. "I might know what I want to do but not know how to do it. I'll see what others have done and borrow from them."

The section labeled *For Educators* contains resources like Swarthmore College's guide to designing scientific posters. Swarthmore professor Colin Purrington originally designed the website to help his students get more enjoyment from poster sessions. "Posters demonstrate the fun, cooperative aspect of scientific life," Purrington says. His website has poster templates and wide-ranging, often funny, advice such as "resist the inevitable directives from your mentor to use the white space to cram in more background information."

Each resource on *For Educators* comes with an abstract describing how it has been used, the program director's background and contact information, and links to similar resources. Visitors can search for resources by keyword, grade level, topic, and type. They are encouraged to leave comments and to rate the resources on a scale of one to five flasks. The poster-making website, for instance, has a five-flask rating and the comment "Awesome!"

HHMI staff will be paying attention to those evaluations. "We'll be counting flasks," Bruns says. "We want to know if some resources are used and rated while others just seem to sit there."

Bruns is also very interested in seeing *Cool Science* spark new conversations. "A person who finds one resource interesting will get a sense of the whole program that created it and then might contact its developers," he says. "Connecting people and the resulting networking can be so important." ■ –OLGA KUCHMENT

FOR MORE INFORMATION: Visit *Cool Science* at www.hhmi.org/coolscience.

Oliver Munday

SEA's Second Wave

TWELVE MORE SCHOOLS JOIN HHMI'S SCIENCE EDUCATION ALLIANCE.

LIKE MANY COLLEGES AND UNIVERSITIES, CALVIN COLLEGE is constantly searching for ways to provide more students with the exciting experience of real scientific discovery. "We have younger and younger students inquiring about research experiences," says Randall DeJong, a biology professor at the small Christian school in Grand Rapids, Michigan.

That's why DeJong was thrilled when Calvin was one of 12 colleges and universities chosen to participate in the National Genomics Research Initiative, a year-long course that involves students in scientific discovery on a national scale. The course, now entering its second year, is a program of HHMI's Science Education Alliance (SEA).

The course allows students to make real discoveries in a classroom setting by doing research on bacterial viruses, called phages. In their first term, the students identify and grow colonies of phages from local soil samples. Phages are so diverse that each student's discovery is likely a new life form, which the students get to name. They spend the rest of the semester characterizing the phage and purifying its DNA, which is then sent off for sequencing. In the second term, students use bioinformatics tools to analyze their phage's DNA and identify the genes encoded there.

After just one semester, faculty from the first 12 participating schools say they could never go back to teaching science the way they used to. "The students don't know what the outcome will be, they don't know whether the experiments will work—and indeed, the first time most did not. The students really have to work things out. And that was fantastic," says Kit Pogliano, a biology professor at the University of California, San Diego.

The class itself has been a quick success, with higher student retention in the SEA classes and, in some cases, higher grades for SEA students in their introductory biology courses. But that's not the best part for the participating faculty. "It is pretty exciting to be part of a group of institutions that is trying to improve science education," DeJong says. "We want to be part of that discussion." ■ –ANDREA WIDENER

FOR MORE INFORMATION: Visit www.hhmi.org/news/20090108sea.html for a list of the 12 new institutions.

Gilliam Fellows Program Expands

STEVEN TUYISHIME SOUGHT OUT SCIENCE as a refuge during his difficult transition from Africa to America. Angelica Riestra discovered in high school that research could help her largely Latino community in San Diego. Now these two and seven other inspiring students are pursuing biomedical science Ph.D.s with the help of the Gilliam Fellowships for Advanced Study. This year, the applicants were so impressive that HHMI expanded the number of awards from five to nine. "These students are just outstanding," says Peter Bruns, vice president for grants and special programs. "We expect them to become real leaders in their fields." Now in its fifth year, the Gilliam fellows program aims to diversify science research and academia. Each fellow receives $44,000 in support annually for up to five years.

FOR MORE INFORMATION: To learn more about the 2009 Gilliam fellows, visit www.hhmi.org/news/gilliam20090212.html.

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UNIVERSITY OF CALIFORNIA, LOS ANGELES

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KRYSTAL R. ST. JULIEN
STANFORD UNIVERSITY

STEVEN TUYISHIME
UNIVERSITY OF MARYLAND, BALTIMORE COUNTY

Cardenas: Mark Harmel Chilton: Kathleen Dooher Daye: David Graham Dosumu-Johnson: Mark Harmel Fernandez: Daron Dean Prashad: Mark Harmel Riestra: Mark Harmel St. Julien: Barbara Ries Tuyishime: Paul Fetters

Research Institute Launched in South Africa

HHMI PARTNERS WITH LEADERS AND SCIENTISTS IN SOUTH AFRICA TO FIGHT THE DUAL EPIDEMICS OF TB AND HIV.

WITH SIMULTANEOUS EVENTS IN THE UNITED STATES AND SOUTH Africa, HHMI and the University of KwaZulu-Natal (UKZN) announced the creation of an international research center focused on making major scientific contributions to the worldwide effort to control the devastating co-epidemic of tuberculosis (TB) and HIV. The center also aims to train a new generation of scientists in Africa.

"This initiative adds a new dimension to HHMI's commitment to international research," said Thomas R. Cech, then president of HHMI, at the March 19 press conference in downtown Washington, D.C. "This cross-Atlantic partnership reflects a shared view that direct and substantial investment in basic, clinical, and translational research in the heart of the pandemics of HIV and TB will yield significant discoveries that will alleviate the human suffering caused by these diseases."

Construction of the KwaZulu-Natal Research Institute for TB and HIV (K-RITH) on the campus of the Nelson R. Mandela School of Medicine in Durban is expected to begin this fall. HHMI will provide $20 million toward construction of a six-story facility that will include two floors of high-level biosafety (BSL-3) laboratories equipped for TB research. Additional support will come from UKZN and LIFE Lab, a biotechnology center of the government of South Africa. HHMI has also committed to providing generous research support to K-RITH for the next 10 years.

LEFT (left to right): *Malegapuru William Makgoba, University of KwaZulu-Natal; William R. Jacobs, Jr., Albert Einstein College of Medicine; Adriaan Willem Sturm, Nelson R. Mandela School of Medicine; Salim S. Abdool Karim, University of KwaZulu-Natal; Bruce D. Walker, Massachusetts General Hospital.* RIGHT (left to right): *Malegapuru William Makgoba; Welile Nhlapo, South African Ambassador to the United States; Thomas R. Cech.*

"This initiative signifies an important milestone in the strengthening of global partnerships in the fight against communicable diseases," said His Excellency Welile Nhlapo, the South African Ambassador to the United States. "The world needs robust, practical, affordable, and sustainable solutions to the problems of HIV-AIDS and tuberculosis. South Africa is well positioned to help develop them."

South Africa has more residents infected with HIV than any other nation in the world. By 2007, the nation accounted for 17 percent of the global HIV disease burden—an estimated 5.4 million people are infected—and it has one of the highest per capita rates of TB in the world. TB, a major problem in pre-AIDS South Africa, emerged as a public health crisis in its own right, particularly with the appearance of both multidrug-resistant and extensively drug-resistant (XDR) strains of TB in persons already infected with HIV.

KwaZulu-Natal province, home to more than 10 million people, bears an even greater burden of disease than the nation as a whole—as much as 40 percent of the population may be positive for HIV. When an outbreak of XDR-TB was reported in the rural area of Tugela Ferry in 2006, the region became a focus of international concern even as additional cases of XDR-TB surfaced elsewhere in the world.

"We are embarking on a scientific journey together," said Professor Malegapuru William Makgoba, UKZN's vice chancellor.

Paul Fetters

"There is no better place on the planet to undertake TB and HIV research, in part because there are more people in South Africa with HIV than any other country in the world. By focusing on the twin epidemics of HIV and TB, we are taking on the most challenging global health challenge."

The scientific journey is already under way. HHMI awarded seed grants totaling more than $1.1 million in 2008 to scientists in the United States and South Africa. This year, the Institute will provide an estimated $3 million in grant funding and support for construction of temporary laboratory facilities for the TB research program. The initial effort will focus on the diagnosis, pathogenesis, treatment, and prevention of TB in the context of HIV.

The commitments by HHMI and UKZN go beyond the financial. Two leading HHMI investigators with long-standing expertise in TB and HIV research will participate actively in the program: William R. Jacobs, Jr., of the Albert Einstein College of Medicine, and Bruce D. Walker, of the Massachusetts General Hospital, who directs the HIV Pathogenesis Program in Durban, a joint initiative of Harvard University and UKZN. Walker also directs the newly formed Ragon Institute, which will focus on developing a vaccine against HIV. UKZN scientists helping to direct and plan K-RITH are A. Willem Sturm, a noted TB researcher and dean of the Mandela School of Medicine, who serves as K-RITH's interim director, and Salim S. Abdool Karim, UKZN Pro Vice-Chancellor (Research) and director of the Center for the AIDS Program of Research in South Africa.

"K-RITH will leverage HHMI's deep experience in fundamental research and its financial resources with UKZN's own programs in HIV and TB research in the context of ongoing efforts to manage HIV and TB in KwaZulu-Natal," said Cech. "K-RITH scientists will have an unparalleled opportunity to collaborate with their colleagues at clinical sites in and around Durban in research efforts that focus on the diagnosis, pathogenesis, treatment, and prevention of TB and HIV." ■

Rose Elected to HHMI Board of Trustees

Courtesy Clayton S. Rose

CLAYTON S. ROSE, A SENIOR lecturer at the Harvard Business School and 20-year veteran of J.P. Morgan & Co., has been elected a Trustee of HHMI. He becomes one of 10 Trustees of the Institute, a medical research organization dedicated to the discovery and dissemination of new knowledge in the life sciences.

Rose, 50, will become chair of the Trustee Committee on Audit and Compensation in November, succeeding Kurt Schmoke, Dean of the Howard University School of Law. He will also serve as a member of the Finance Committee.

At Harvard, Rose teaches a first-year course on "Leadership and Corporate Accountability" and a second-year course called "The Moral Leader." He is at work on a project examining the challenges facing general managers in the financial services industry in light of the economic and financial crisis, has undertaken case studies of several affected firms, and will offer a new course on the subject in the fall of 2009. He has also taught at the Columbia University Graduate School of Business and the Leonard N. Stern School of Business at New York University.

Rose held a number of senior management roles during his tenure at J.P. Morgan, where he headed the Global Investment Banking and Global Equities divisions and served as a member of its executive committee. After the merger of J.P. Morgan with the Chase Manhattan Bank in 2001, Rose was vice chairman and chief operating officer of the J.P. Morgan Chase investment bank. He also helped found J.P. Morgan's equity business, represented it during the negotiations that followed the collapse of the hedge fund Long Term Capital Management in 1998, and led a firm-wide diversity initiative.

Rose chairs the board of managers of Highbridge Capital Management, a hedge fund in which J.P. Morgan holds a majority stake. He also serves as a trustee of the National Opinion Research Center, a widely respected social science research organization based at the University of Chicago.

Rose earned a bachelor's degree and a master's in business administration from the University of Chicago. In 2007, he received a Ph.D. in sociology (with distinction) from the University of Pennsylvania with a dissertation that focused on how companies manage the racial composition of boards and senior management teams. ■

Platelets as Defenders

ASPIRIN MAY THWART THE DEFENSIVE ROLE OF THESE BLOOD CELLS AGAINST MALARIA.

In the developing world, treating malaria usually involves anti-malarials to kill the parasite and aspirin to control the fever. But according to new research, aspirin may hamper the body's ability to fight malaria. The study found that blood platelets can kill malaria parasites—in the genus *Plasmodium*—but lose that ability if exposed to aspirin.

Plasmodium parasites infect red blood cells and have highly variable surfaces, making each infection a new challenge for the body, says HHMI international research scholar Simon Foote of the Menzies Research Institute at the University of Tasmania. "It takes quite a bit of time to develop a specific immune response to protect you from malaria. During that time, the body somehow has to stop you from dying."

In the February 6, 2009, issue of *Science*, Foote and his colleagues report that blood platelets—involved in blood clotting—might be one of the body's interim defenses. The group discovered that mice genetically engineered to produce fewer platelets than normal were far more likely to die from a rodent version of malaria than other mice.

To determine whether low platelet levels directly caused this effect, the team gave aspirin, known to inhibit platelet function, to a group of mice lacking the mutation. Like the genetic mutants, the aspirin-fed subjects were more susceptible to the disease.

Foote and his team also exposed *Plasmodium*-infected human red blood cells to platelets. As they watched, the platelets bound to the cells and killed the parasites—an ability they lost when aspirin was added.

Platelets are one of the body's interim defenses against malaria.

It's been known that platelets bind preferentially to malaria-infected red blood cells, says Foote. Researchers had hypothesized, however, that these cell-bound platelets posed a danger to the infected body—they can build up in small blood vessels and cause clots in the brain. "They're essentially the glue between infected cells and vessels … and they promote blockage," he says. The new study suggests that platelets may do some good as well.

According to Foote, it's unclear how platelets' *Plasmodium*-killing ability functions, and the laboratory results don't necessarily translate to infected humans. "I think this needs a really good, closely monitored clinical trial," he says. ■ –BENJAMIN LESTER

IN BRIEF

FOUR BIRDS WITH ONE STONE

A new compound wipes out tuberculosis-causing bacteria in the test tube by disrupting four of their most vital processes. HHMI international research scholar Rajesh Gokhale thinks the compound, which mimics a fatty acid, is a step toward a single tuberculosis drug to replace the difficult four-drug regimen tuberculosis patients currently take to cure their disease.

Gokhale and coworkers at the National Institute of Immunology in New Delhi, India, had been studying how *Mycobacterium tuberculosis* infects human cells. The bacteria get much of their potency from complex lipids on their outer surfaces, so Gokhale's team focused on how to shut down an enzyme—in a class of fatty acyl-AMP ligases (FAALs)—that helps build these lipids from fatty acids. They designed a molecule that resembles a fatty acid but that the FAAL cannot process, stopping it from functioning.

The FAAL, they found, resembles other enzymes the bacteria need to survive at different stages of their infection cycles. The enzymes are similar enough that Gokhale's compound stops all four, delivering a powerful blow to the pathogen.

"The 'one disease–one drug–one target' paradigm that has dominated thinking in the pharmaceutical industry is now being increasingly challenged by the discovery of compounds that bind to more than one target," Gokhale says.

Gokhale's team published the results in the March 2009 issue of *Nature Chemical Biology*.

KILLER TRAINING

A type of immune cell previously thought to forget does have some memory, researchers have found.

Two kinds of cells dominate the immune system: innate immune cells respond early to infection; adaptive immune cells take longer. Adaptive cells, however, were thought to be the only immune cells to remember previous events. "Our findings essentially say: wait a minute, there is evidence for a memory in innate immune cells," says HHMI investigator Wayne Yokoyama, who led the study.

Yokoyama's team found that natural killer cells—a type of innate immune cell—that have been exposed to a stimulus respond more robustly when they are exposed again. Although natural killer cells don't have the same molecular tools that adaptive immune cells use to remember all the specifics, they seem to have some kind of memory of past stimulation with cytokines—hormone-like substances typically produced during infections. And they pass that memory to their progeny. Yokoyama and coworkers at Washington University School of Medicine reported their findings in the February 10, 2009, issue of *Proceedings of the National Academy of Sciences*.

Though the natural killer cells employ a previously unknown property to remember, the researchers hypothesize that other kinds of cells elsewhere in the body may also acquire new memories. And the study suggests that boosting innate immunity may boost a person's health, says Yokoyama.

RAIDING GIARDIA'S CLOSET

Giardia lamblia parasites are like microscopic bandits that evade the immune system for months. If recognized, they just change into another of their nearly 200 disguises. But scientists have now discovered how to see through *Giardia*'s many disguises.

Researchers knew that *Giardia* often goes undetected because it periodically changes the proteins on its surface; it has the genes to make about 200 such proteins, called antigens.

A new study, led by Hugo Luján, an HHMI international research scholar at the Catholic University of Córdoba in Argentina,

Scimat / Photo Researchers, Inc.

Spiraling Back in Time

AGING A GENE THAT DISTINGUISHES LEFT FROM RIGHT DURING DEVELOPMENT.

The same gene that places a human's heart on the correct side of the body also controls whether a snail's shell twists left or right, scientists have found. The discovery suggests that this mechanism is far more ancient than researchers had thought.

All vertebrates express a gene called *nodal* on the left side of the embryo during early development. *Nodal* activates another gene, *Pitx*, leading to the body's normal asymmetry—some organs develop on one side, where there are high concentrations of *nodal*'s protein product, while others develop where there are low levels. Though *nodal* is ubiquitous in vertebrates, researchers had been unable to find this gene in fruit flies (*Drosophila*) and the roundworm *Caenorhabditis elegans*, important model organisms.

The left shell from *Amphidromus preversus*, an Indonesian snail, is sinistral (left-coiling) while the right one is dextral (right coiling).

Patel lab

These animals have left/right asymmetries but control them with a different system, says Nipam Patel, an HHMI investigator at the University of California, Berkeley. So, "the thought was that nodal hadn't been there in the common ancestor of flies, *C. elegans*, and people," he says.

To see how other non-vertebrate organisms control asymmetry, Patel and Cristina Grande, a postdoctoral researcher in his lab, searched for *nodal* in a left-spiraling freshwater snail, commonly known as the bloodfluke planorb, and the owl limpet, a marine snail whose organs have the opposite orientation. Not only did they find *nodal* and *Pitx*, they also showed that, in concert with their asymmetries, the limpet expressed both these genes on the right side of the body, and the freshwater snail expressed both on the left.

The researchers went on to inhibit *nodal* signal in snails. "Most died," says Patel, "but a fraction of those that survived had a straight shell." The findings appeared February 19, 2009, in the journal *Nature*.

The study suggests that a common ancestor of snails and vertebrates used the *nodal* pathway to establish left-right asymmetry, explains Patel. The next step, he says, is to determine what activates *nodal*. Researchers partially understand the process in vertebrates, but "in snails classic genetic studies tell us that the mother puts something into the egg that initially establishes asymmetry, but we have no idea what this is." ■ –BENJAMIN LESTER

IN BRIEF

shows that, to display one kind of antigen at a time, *Giardia* parasites don't simply transcribe one gene—they transcribe all 200 antigen genes and then destroy all but one antigen's messenger RNA. To show that was the case, Luján and coworkers silenced the RNA interference machinery of *Giardia*, shutting down a process that helps destroy the unneeded RNA.

To Luján's surprise, the mutant parasites came out wearing a "Technicolor Dreamcoat" of all 200 antigens. Moreover, gerbils infected with this "Dreamcoat" *Giardia* became immune to the normal parasites; their immune systems could recognize all of *Giardia*'s disguises.

Many pathogens, including those that cause malaria, have developed ways to vary their surface antigens. "The idea of blocking antigenic variation opens a lot of new doors to developing vaccines," says Luján. The research appears in the December 11, 2008, issue of *Nature*.

VOLCANOES IN THE GENOME

Ten million years ago, the genome of a common ancestor of humans, gorillas, and chimpanzees underwent drastic changes, HHMI researchers have found. Segments of DNA began to duplicate faster than ever, and the quick pace of duplication in some areas of the genome created unstable hotspots, which can still be found in humans today.

To determine just when these unstable regions first appeared, HHMI investigator Evan Eichler and colleagues at the University of Washington compared the genomes of chimpanzees and humans with those of macaques and orangutans—which branched off from the same lineage earlier in evolution. Macaques and orangutans, the team found, lack most of the gene duplications that humans and chimpanzees have. The findings appear in the February 12, 2009, issue of *Nature*.

In humans, unstable regions of the genome have been associated with disorders including autism and schizophrenia. However, Eichler points out, the fact that these regions have remained in the human genome for 10 million years, and that they carry rapidly evolving genes, implies that some of the rearrangements created a reproductive edge.

"I believe that the negative selection of having these duplications is being outweighed by the selective advantage of having these newly minted genes, but that's still unproven," says Eichler. The ancient gene duplication, he hypothesizes, could be responsible for the genetic flexibility that has resulted in uniquely human characteristics.

HOW ANTIBIOTICS KILL BACTERIA

The rise of antibiotic-resistant infections has spurred research into how the most effective antibiotics work. While it's known that they disrupt bacteria's ability to build proteins, DNA, or cell walls, these effects don't always have deadly consequences. James J. Collins wanted to know how some antibiotics—called bactericidal—are able to kill bacteria with these methods, while other antibiotics use the steps to simply halt the bacteria's growth.

Collins, an HHMI investigator at Boston University, worked with colleagues to trace what happens at the molecular level to *Escherichia coli* bacteria after treatment with gentamicin, a bactericidal antibiotic. Gentamicin interferes with the *E. coli* ribosome and causes it to build defective proteins, which nevertheless travel to their designated places inside the cells. Faulty proteins in the cell membrane trigger something like a bacterial panic attack—an overblown response to stress—eventually producing free radicals that destroy the cell. Gentamicin became even more effective when the researchers weakened *E. coli*'s protein quality control, potentially pointing out new ways to combine drugs and to lower doses.

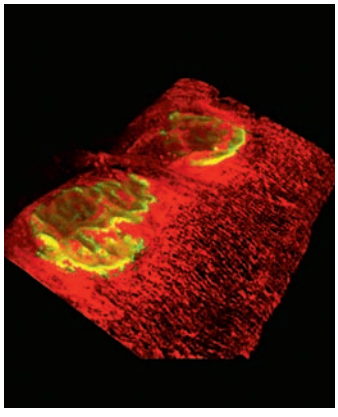
Although other types of bactericidal antibiotics have different cellular targets,

Tag-Team Proteins

A COMPLEX OF PROTEINS PROTECTS MUSCLES FROM COLLAPSING DURING CONTRACTION.

A protein important for maintaining the heart's rhythm also helps muscle cells retain their structure during stress. The discovery has broad implications for other cell types and for human diseases, including muscular dystrophy, says Vann Bennett, an HHMI investigator at Duke University Medical Center.

Bennett's group is studying a family of three proteins called ankyrins, which Bennett discovered in red blood cells in 1979. In many cell types, ankyrins anchor membrane-spanning proteins. The current study—published in the December 26, 2008, issue of *Cell*—focuses on two ankyrins: ankyrin-B, which the Bennett group established as important to heart rhythm, and ankyrin-G.



The surface of a muscle cell, with ankyrin proteins (red) and neuromuscular junctions (yellow).

Mice that lack ankyrin-B die soon after birth. But Gai Ayalon, a postdoctoral fellow in Bennett's lab, found a way to study its effects by suppressing it in the leg muscles of adult mice. In the ankyrin-B-deficient cells, two other proteins known to support cell structure were missing from the cell membrane. One, dystrophin, is key to cellular structure and support (mutations in the human dystrophin gene cause some types of muscular dystrophy). Another, beta-dystroglycan, forms a complex with dystrophin to protect the cell membrane during muscle contraction. Both proteins were still made but were not where they needed to be.

Without the protective proteins, the ankyrin-deficient muscle cells broke apart during exercise, a phenomenon similar to what occurs in muscular dystrophy.

When the group suppressed ankyrin-G in leg muscle cells, dystrophin and beta-dystroglycan were transported to the membrane but were not organized properly.

"These two ankyrins are a tag team," Bennett says. "Ankyrin-B mediates transport of newly synthesized proteins, and ankyrin-G retains them in the right place."

Researchers knew that, without dystrophin, the entire muscle-protecting complex was lost, but nobody knew why. The group found that dystrophin binds directly to ankyrins, and that gave them the beginning of an answer. "We have found the outlines of a pathway through which dystrophin assembles this [protective] complex," Bennett says. The missing piece of the puzzle was the ankyrin proteins. ■ —NANCY VOLKERS

IN BRIEF

somehow they trigger similar stress responses, causing the bacteria to produce free radicals and destroy themselves. The researchers are working to better understand how that occurs. Collins' results appear in the November 14, 2008, issue of *Cell*.

TRAFFIC ON CELLULAR ROADWAYS

To know what a living cell is doing, one needs to know what proteins it makes. Most often, scientists try to elucidate a cell's plans by sequencing its DNA to see what proteins can potentially be made. Then they analyze messenger RNAs (mRNAs)—the intermediate step between DNA and proteins—to see what proteins the cell was preparing to make.

But the method doesn't always tell the full story of what each cell is doing, says Jonathan Weissman, an HHMI investigator at the University of California, San Francisco. According to their needs, cells decide which genes to translate into mRNA, but they also control which mRNA to translate into proteins.

Now, Weissman and colleagues have developed a method to follow the decisions a cell makes at that second step. To translate mRNA to proteins, cells rely on complexes called ribosomes. By identifying which pieces of a cell's mRNA are attached to ribosomes, the scientists can observe which proteins are really being made—not just which mRNA is being made.

Weismann says the new technique, called ribosome profiling, allows researchers to follow what DNA is being turned into protein much more directly. This procedure could lead to a better understanding of how cells work, and how various diseases affect the proteins made by a cell.

"The complement of proteins made by a cell may provide the precise signature of the pathologies and disease states," he says. The findings were published online on February 12, 2009, in *Science Express*.

HEY SUGAR, SUGAR

It's not just the insides of cells that change when a cell needs to do different jobs: on the outer surfaces of cells reside complex sugars, called glycans, that move and change.

A team of researchers led by HHMI investigator Carolyn Bertozzi, of the University of California, Berkeley, has developed a way to monitor these changes. The method can check how glycan numbers, compositions, and positions in living cells and organisms change over time. To capture these changes, Bertozzi's group first chemically modifies sugars to incorporate a small, nontoxic component. Cells eat these sugars and use them to build glycans. Next, the researchers expose the cells to chemical probes that react only with the modified sugars and make the glycans visible with imaging techniques. They have used the method in a variety of ways, including watching the changes in glycans inside developing, transparent zebrafish.

Bertozzi hopes that eventually glycan imaging will be used to detect cancer in humans. Cancer cells exhibit changes in glycan composition and distribution that could not be imaged in living systems before.

Bertozzi and Scott Laughlin, a Berkeley chemist, published an overview of glycan imaging in the January 6, 2009, issue of *Proceedings of the National Academy of Sciences*.

Bennett lab

Q A

If I were stranded in a desert for five days without food or water, what steps would my body take to keep me alive?

Anonymous adult from the U.S.

The human body has a remarkable capacity to withstand various stresses, but there are limits to what it can endure. While humans are fairly well equipped to survive prolonged periods without food, dehydration is another matter.

To keep functioning, the body requires energy. Among the most important functions: lungs need energy to facilitate breathing and the heart requires energy to pump blood. The amount of energy—measured in calories—required for the body's vital organs to function is called the basal metabolic rate. It's the number of calories your body would need to stay alive if you slept in bed all day. Any additional physical activity requires additional energy.

The primary form of fuel the body uses is a simple sugar called glucose. Your body breaks down the food you eat into simple molecules, including glucose, that it can use for energy. Excess carbohydrates, beyond what the body immediately needs, are stored in the liver in the form of a molecule called glycogen, which can be broken down into glucose for energy if it is needed later.

A typical person has about one day's worth of energy stored as glycogen, so the first day you were stranded on the desert, your body would deplete your liver's energy store. After using up this supply, the body turns to muscle and fat for energy. Muscle and fat, depending on how much you have, can allow your body to survive for a few weeks without eating.

The case with water is much different, however. Nearly two-thirds of your body is composed of water, which is necessary for virtually every physiologic process. Every day, the human body loses water—particularly through urine and sweat. Stranded in the desert, you would lose even more water to sweat than usual.

In a state of water deprivation, your body will initially try to hold on to water. Your kidneys will reabsorb it and concentrate your urine. However, if you are unable to find water within a day or so, your body will begin to shut down. Your body temperature will rise as your body is unable to cool itself without sweating. After prolonged dehydration, your blood pressure will drop and your organs will fail due to inadequate blood flow.

All in all, if you were stranded in a desert, my advice would be to first look for some fresh water. If you find it, you will likely have plenty of time to forage or hunt for food.

ANSWER RESEARCHED BY JOSHUA A. ENGLERT, M.D., *a fellow at the Harvard Pulmonary and Critical Care Medicine Training Program.*

FOR MORE INFORMATION
Visit *Discovery Channel Survival Zone*
http://dsc.discovery.com/convergence/survival/guide/guide.html.

Science is all about asking questions, exploring the problems that confound or intrigue us. But answers can't always be found in a classroom or textbook. At HHMI's *Ask a Scientist* website, working scientists tackle your tough questions about human biology, diseases, evolution, animals, and genetics. Visit www.hhmi.org/askascientist to browse an archive of questions and answers, find helpful Web links, or toss your question into the mix. What's been puzzling you lately?

Flight of the Dragonfly Fabricating a playground for this precision hunter may provide the access scientists need to understand its neural circuitry.

FOR MANY ANIMALS, HUNTING CAN SEEM EFFORTLESS. Frogs flick their tongues to catch flies. Whales swim with their mouths open to strain plankton from the sea.

But no matter how straightforward an animal's technique seems, behind each attempt to capture prey whirs an intricate choreography of sensory input, neuronal firing, and muscle response that scientists do not fully understand.

Curious to know more, Anthony Leonardo, a group leader at HHMI's Janelia Farm Research Campus who studies the neural basis of animal behavior, decided to focus on dragonflies, which hunt with incredible precision, rarely missing their prey. Using an advanced video camera, he has been able to capture the insects in action, shooting 1,000 frames per second.

Played back at a speed the human eye can follow, a clip shows a perched dragonfly turning its head as it tracks a fruit fly. With coordinated strokes of its four gossamer wings, the insect lifts off and adjusts its route to intercept its prey. The dragonfly then glides, its hairy legs coming together to create a basket to imprison the fly before devouring it midair.

More important than their aerial grace, dragonflies are large and strong enough to carry a miniature, wireless system that will allow Leonardo to record their neurons firing in real time as they pursue their prey.

But first, he had to design and build an indoor "flight arena" that would encourage dragonflies to behave almost as they would in a natural setting.

"We don't want to reproduce the outside world—there's too much complexity. We want it to be just complex enough so the dragonflies act normally," he says.

One of Leonardo's collaborators, Rob Olberg of Union College in Schenectady, New York, helped with the design. Olberg, who is a visiting scientist at Janelia Farm through this summer, has already identified 16 key neurons that deliver information to the muscles involved in flight and prey capture. These neurons are believed to tell the dragonfly's wings the location of the fruit fly for an accurate capture.

But these findings were based largely on studying dragonflies held in place by miniature restraints. Olberg says his subjects are no doubt more concerned about escaping than about catching a meal. "The nervous system probably works a whole lot differently when the dragonfly is actually flying," he says.

With Leonardo's flight arena, a virtual meadow, understanding that difference might now be possible. Dragonflies are finicky creatures: they require far more space than the typical lab allows, special lighting that mimics the sun's ultraviolet spectrum, and visual cues to orient themselves.

The flight arena fully occupies a basement room about 14 feet wide, 18 feet long, and 15 feet high. In the beginning, it had white walls, a white ceiling, and a white floor. Put a couple of dragonflies in it, and they wouldn't budge; they just sat still on the bare floor. Being visual animals—they have two compound eyes, made of thousands of lenses, plus three simple eyes—they had no frame of reference, nothing to give them clues as to where they were or where they should fly.

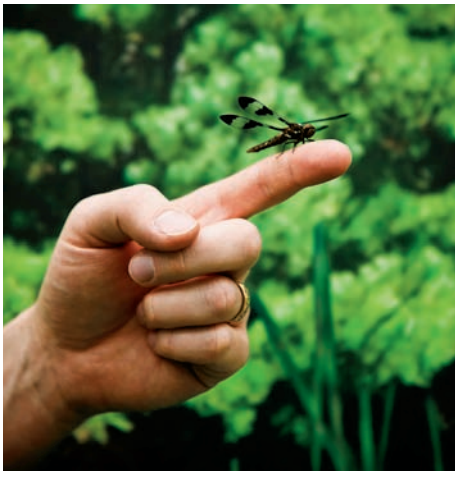
So, Leonardo and his technician, Elliot Imler, started adding high- and low-tech props from floor to ceiling. First they installed a carpet of artificial grass. Dragonflies zipped around the room, but without any other visual references, they flew in circles and into walls. To slow them down, the team put in "speed bumps"—vertical stripes on the walls, which later gave way to wall-to-wall posters of verdant forests and tulip gardens. To make it homier for the water lovers, they added a shallow pond and decorated its edges with plastic flowers and cattails, which serve as perches. Aimed at two of the perches are high-speed video cameras, one per perch.

Mindful of the insects' internal clocks, they re-created dawn and dusk with an array of lights programmed to brighten and dim, from east to west. A humidifier maintains constant moisture and the temperature hovers at 80 degrees; heat lamps directed at flower perches provide the additional warmth that dragonflies prefer.

To prompt the dragonflies to hunt, Leonardo and Imler suspended small plastic trays carrying banana bits crawling with fruit flies. The trays buzz regularly to startle the flies off their feast so the dragonflies can see and pursue them.

What keeps the arena softly humming with a steady stream of four to five dragonflies at a time is the lab's vivarium, where about 10 different species of dragonflies are raised from nymphs netted from Janelia's outdoor pond.

After several months of fine tuning, about half the dragonflies released in the room appeared to behave as if outdoors. Of those, 80 to 90 percent of one particular species, *Libellula lydia*, acted normally—that is, flying and hunting in the room for at least a couple



Anthony Leonardo's indoor flight arena has all the elements that allow dragonflies to thrive: grass, water, food, colorful gardens, daily light cycles, and controlled heat and humidity. To get his research subjects, Leonardo dons boots and a net and catches nymphs from the outdoor pond at HHMI's Janelia Farm Research Campus. So far, he's collected and raised 10 species of dragonfly.

Erik Johnson

of days. This fraction is large enough to satisfy Leonardo that he's figured out an effective, basic formula for producing this complex behavior in an experimentally controlled setting.

Now, he is working with engineer Reid Harrison at the University of Utah on a wireless, electronic "backpack" for his tiny subjects. The pack, which will be glued to the belly of the dragonfly, will carry a mini-telemetry system. It will connect to electrodes inserted into the dragonfly's body. The electrodes will detect signals from the neurons Olberg identified, and a transmitter will send the data to a remote computer while an array of high-speed cameras simultaneously measures the dragonflies' flight path.

Together, the videos and the data from neuronal signals—and eventually muscle contractions—may one day yield a complete picture of how dragonflies' neural circuitry makes them such enviable hunters. ■ –CHRISTINE SUH

WEB EXTRA: Visit the *Bulletin* online to see more photos and hear Leonardo talk about the dragonfly arena.

SPOTLIGHT

Vilcek Prize Awarded to Zoghbi

HUDA ZOGHBI

HHMI investigator **Huda Y. Zoghbi**, of the Baylor College of Medicine, received the 2009 Vilcek Prize in Biomedical Research. Awarded by the Vilcek Foundation, this honor recognizes outstanding achievements by a foreign-born scientist each year. Zoghbi, born in Beirut, Lebanon, was chosen for her body of work studying the genetics and molecular biology of spinocerebellar ataxia, Rett syndrome, and related autism spectrum disorders.

The National Academy of Engineering elected HHMI investigator KRISTI S. ANSETH, of the University of Colorado, Boulder, as one of 65 new members.

CORNELIA I. BARGMANN, an HHMI investigator at Rockefeller University, is the recipient of this year's Richard Lounsbery Award from the National Academy of Sciences. The award recognizes Bargmann's use of genetics to probe the links between nerve cells and behavior in *Caenorhabditis elegans*.

HHMI investigator STEPHEN P. BELL, of the Massachusetts Institute of Technology, was selected to receive the 2009 National Academy of Sciences Award in Molecular Biology. Bell studies the machinery cells use to maintain the integrity of DNA replication.

MICHAEL J. BEVAN, an HHMI investigator at the University of Washington School of Medicine, is the 2009 recipient of the AAI-Invitrogen Meritorious Career Award for outstanding research contributions to the field of immunology.

HHMI senior scientific officer MARIAN B. CARLSON received the 2009 Genetics Society of America Medal, which recognizes outstanding contributions to genetics over the last 15 years. Carlson's Columbia University lab uses yeast to study how signaling pathways activate the genes that cells need to adapt to nutrient deprivation and other forms of environmental stress.

ARUL M. CHINNAIYAN, an HHMI investigator at the University of Michigan Medical School, was elected to the Association of American Physicians. Chinnaiyan, a pathologist, is working to uncover the molecular flaws at the heart of the most common and deadly human cancers.

The 2009 American Society for Microbiology Eli Lilly and Company Research Award was awarded to JOSEPH L. DERISI, an HHMI investigator at the University of California, San Francisco. DeRisi was honored for his work in advancing the basic technology and informatics for DNA microarrays and for using these tools to investigate basic biological regulatory mechanisms.

SARAH ELGIN, an HHMI professor at Washington University in St. Louis, was awarded the 2009 Elizabeth W. Jones Award for Excellence in Education. The award, given by the Genetics Society of America, recognizes individuals or groups who have had a significant impact on genetics education at any level and is named in memory of a former HHMI professor.

HHMI professor JO HANDELSMAN, of the University of Wisconsin–Madison, received the 2009 Carski Foundation Distinguished Undergraduate Teaching Award from the American Society for Microbiology. The award commended her HHMI-supported work on the Wisconsin Program for Scientific Teaching and her leadership of the HHMI–National Academy of Sciences Summer Institute, among other achievements. Handelsman, who studies the communication networks of microbial communities, was also recently named a fellow of the Association for Women in Science.

HHMI investigator S. ANANTH KARUMANCHI, of Harvard University, won the first annual LaRenon-TANKER Foundation Award from the Tamilnad Kidney Research (TANKER) Foundation in India. The award recognized Karumanchi's work in preeclampsia.

DAVID M. KINGSLEY, an HHMI investigator at the Stanford University School of Medicine, won the 2009 Edwin Grant Conklin Medal from the Society for Developmental Biology. The medal is awarded for distinguished and sustained research in developmental biology.

DOUGLAS E. KOSHLAND, an HHMI investigator at the Carnegie Institution of Washington, and VALERIE MIZRAHI, an HHMI international research scholar at the University of the Witwatersrand in South Africa, were named fellows of the American Academy of Microbiology. Koshland studies the structure, integrity, and evolution of chromosomes and Mizrahi's research focuses on *Mycobacterium tuberculosis*, the organism that causes human tuberculosis.

HALLIE KUHN, an HHMI-supported undergraduate at Harvey Mudd College, received a Churchill fellowship to study for a year at the University of Cambridge. At Harvey Mudd, Kuhn worked in the lab of David Asai, now director of precollege and undergraduate science education at HHMI. At Cambridge, she will do research on the human papilloma virus responsible for cervical cancer.

JEREMY NATHANS, an HHMI investigator at the Johns Hopkins University School of Medicine, was awarded the 2009 Edward M. Scolnick Prize in Neuroscience from the McGovern Institute at the Massachusetts Institute of Technology. Nathans studies the physiology and development of the retina

Bob Levey / AP, ©HHMI

and aims to uncover the mechanisms of human retinal diseases.

WILLIAM S. REZNIKOFF, an HHMI pre-college program director at the Marine Biological Laboratory in Woods Hole, Massachusetts, was elected a Fellow of the American Academy of Microbiology.

BERNARDO L. SABATINI, an HHMI investigator at Harvard Medical School, is co-recipient of the 2008 Society for Neuroscience Young Investigator Award, along with Hongjun Song of the Johns Hopkins University School of Medicine. The annual award recognizes outstanding achievements by young neuroscientists. Sabatini uses imaging and electrophysiological technologies to uncover the mechanisms behind synapse regulation in the mammalian brain.

HHMI investigator **RANDY W. SCHEKMAN**, of the University of California, Berkeley, won the 2008 Dickson Prize in Medicine from the University of Pittsburgh. This prize is awarded annually to a leading American investigator who is engaged in innovative biomedical research.

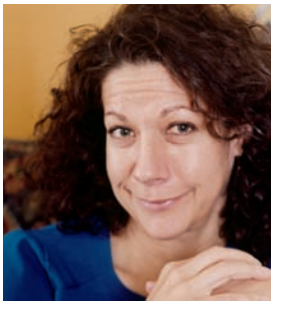
EERO P. SIMONCELLI, an HHMI investigator at New York University, was named a fellow of the Institute of Electrical and Electronics Engineers for his contributions to statistical models of visual images.

HHMI investigator **BERT VOGELSTEIN**, of the Johns Hopkins University School of Medicine, received the 2009 Science of Oncology Award from the American Society of Clinical Oncology as well as the 2008 Robert J. and Claire Pasarow Foundation Award for Extraordinary Accomplishments in Medical Research. Vogelstein is interested in identifying and characterizing genes that cause cancer and has recently detected a number of broken, missing, and overactive genes in pancreatic and brain tumors that were previously unknown.

HHMI professor **RICHARD N. ZARE**, of Stanford University, was named an honorary fellow of the Indian Academy of Sciences. Zare's research focuses on nanoscale chemical analysis. His HHMI project includes an undergraduate laboratory course designed to examine light and photosynthesis in an interdisciplinary way.

SPOTLIGHT

Bassler Recognized with Wiley Prize



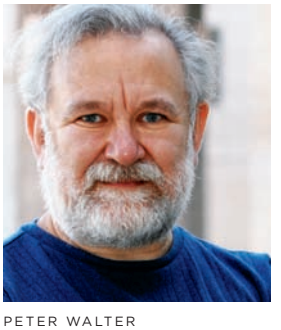
BONNIE BASSLER

Bonnie Bassler, an HHMI investigator at Princeton University, won the Wiley Prize in Biomedical Sciences for 2009. This annual prize, awarded by the Wiley Foundation, recognizes a scientist whose contributions have opened new fields of research or advanced new concepts within biomedicine. ¶ Bassler studies how bacteria communicate with one another using a chemical language. This process, called quorum sensing, allows bacteria to count their numbers, determine when they have reached a critical mass, and then change their behavior in unison to carry out processes that require many cells acting together to be effective.

SPOTLIGHT

Gairdner Awards Go to Losick and Walter

RICHARD LOSICK



PETER WALTER

Richard M. Losick, an HHMI professor at Harvard University, and **Peter Walter**, an HHMI investigator at the University of California, San Francisco, are recipients of the 2009 Gairdner International Awards from the Gairdner Foundation. These prestigious annual awards honor outstanding discoveries and contributions to medical science. Losick studies differentiation, morphogenesis, and multicellularity in the spore-forming bacterium *Bacillus subtilis*. He probes how the morphological features of the developing spore assemble and how they do so at the right time and in the right place. He shares the award with Lucy Shapiro, a developmental biologist at Stanford University. Walter will share his award with Kazutoshi Mori, of Kyoto University, in recognition of "their dissection and elucidation of a key pathway in the unfolded protein response, which regulates protein folding in the cell."

Bassler: Greg Miller Losick: George Nikitin / AP, ©HHMI Walter: George Nikitin / AP, ©HHMI

CONTINUED FROM PAGE 37
(BETTER THAN TEA LEAVES)

beginning to collect the data that allow us to make more predictive models," he says. "But you're starting to see the shadow on the wall—we've got more people with malaria in the highlands and it's my impression that this is the result of more transmission, which is in turn exacerbated by greater numbers of mosquitoes."

That conclusion, Pascual says, has implications for how scientists might consider the influence of global warming on infectious disease. Many current efforts on climate change and malaria focus on scenarios for spatial distribution of the disease in the future. But her ongoing work considers the recent past—the last three decades within her own lifetime—and shows that the effects of warming on disease transmission may already be under way in this highland region, providing an indication of what's to come in the years ahead.

But even as society absorbs information and predictions about the influence of warming on infectious disease, it must accept that modeled estimates are never perfect. Roberto Bertollini, director of the World Health Organization Department of Public Health and Environment, in Geneva, Switzerland, says that climate models need more development and systematic validation before they can be widely used as warning systems for disease outbreaks. "I see them as a very positive development for future applications in public health," he says. "For too long, our approach to public health has been reactionary—we need to become more proactive, more anticipatory when it comes to disease. We're not using these models now, but we encourage their development, we see them as useful tools to managing the effects of climate change."

"If we're going to understand the way global climate change modifies disease exposure conditions, we're going to have to bring a lot more mechanistic rigor into our modeling," says Jonathan Patz, professor of environmental studies and population health sciences at the University of Wisconsin–Madison and a leading expert on climate change and infectious disease. "That's what Mercedes brings to the table—an understanding of how to model climate change's influence on disease ecology and its impact on public health. And that's a component that we really need." ■

Zachary Rossman

DIVINING A DISEASE

In the summer of 1849, the worst cholera outbreak in London's history had roiled the city for a year, claiming more than 14,000 lives. At the time, there were two schools of thought on cholera: the contagionist theory held that the disease passed from person to person like the flu; the "miasma" argument supposed that cholera lingered in the air of damp and unsanitary places. One young doctor, however, disagreed with both. Though John Snow presented his argument in 1849, he was unable to offer evidence for his claims until the next outbreak in 1854, when his elaborate mapping of cholera deaths around the city linked the disease to London's water supply and helped control the epidemic.

Snow also recognized the weakness of the contagionist argument. The same doctor attended both Harnold and Bleckinsopp, spending multiple hours in the room with them during the rice-water phase of the disease. And yet he remained free of the disease. Clearly, the cholera was not communicated through sheer proximity. In fact, the most puzzling element of the disease was that it seemed capable of traveling across city blocks, skipping entire houses in the process. The subsequent cases in Horsleydown erupted a few doors down from Harnold's original lodging house. You could be in the same room with a patient near death and emerge unscathed. But, somehow, you could avoid direct contact altogether with the infected person and yet still be seized with the cholera, simply because you lived in the same neighborhood. Snow grasped that solving the mystery of cholera would lie in reconciling these two seemingly contradictory facts.

We do not know if Snow hit upon the solution to this riddle sometime in the months that followed the initial 1848 outbreak, or perhaps if the solution had long lingered in the back of his mind, a hunch that had first taken shape more than a decade before, as he tended to the dying miners in Killingworth as a young surgeon's apprentice. We do know that in the weeks after the Horsleydown outbreak, as the cholera began its fatal march through the wider city and beyond, Snow embarked on a torrid stretch of inquiry: consulting with chemists who had studied the rice-water stools of cholera victims, mailing requests for information from the water and sewer authorities in Horsleydown, devouring accounts of the great epidemic of 1832. By the middle of 1849, he felt confident enough to go public with his theory. Cholera, Snow argued, was caused by some as-yet-unidentified agent that victims ingested, either through direct contact with the waste matter of other sufferers, or, more likely, through drinking water that had been contaminated with that waste matter. Cholera was contagious, yes, but not in the way smallpox was contagious. Sanitary conditions were crucial to fighting the disease, but foul air had nothing to do with its transmission. Cholera wasn't something you inhaled. It was something you swallowed.

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In the Eye of the Beholder

This isn't a pansy or a poppy blossom. It's a mouse retina, removed and flattened to show the entire surface of the tissue. The concentrated red staining at the top of the image indicates that the cone photoreceptors of the dorsal retina contain high levels of phosphorylated mTOR protein. Phosphorylation of mTOR is a sign that the cells are healthy and receiving good nutrition. This finding suggests a couple of possibilities, according to HHMI investigator Connie Cepko. First, dorsal cones may respond differently to their surrounding environment than ventral cones. Or the nutrient supply, oxygen level, and environmental interactions may differ around the dorsal and ventral cones. Understanding normal cone photoreceptor behavior will help Cepko's team figure out what goes wrong when cone cells die, as in the sight-robbing disease retinitis pigmentosa (see page 12).

Claudio Punzo / Cepko lab