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On the Cover: Photographs by Kathleen Dooher.
James P. Allison, HHMI investigator at the University of California, Berkeley, won the 2002 Public Service Award from the American Society of Immunologists and the 2001 Centeone Award for Innovative Breakthroughs in Immunology.

Five HHMI investigators have been named fellows of the American Academy of Arts and Sciences: David J. Anderson, California Institute of Technology; Cornelia I. Bargmann, Ronald D. Vale and Peter Walter, University of California, San Francisco; and A. James Hudspeth, The Rockefeller University.

Three HHMI investigators and two of the Institute’s leaders were named as “Biotech Geniuses to Watch” in the June issue of Discover magazine: David Baker, University of Washington; Elaine Fuchs, who recently moved to The Rockefeller University; Stuart L. Schreiber, Harvard University; Thomas R. Coch, HHMI president; and Gerald M. Rubin, vice president and director of planning for Janelia Farm.

Nine HHMI investigators were elected to the National Academy of Sciences. New members are Philip A. Beachy, The Johns Hopkins University School of Medicine; Patrick O. Brown, Stanford University; Carlos J. Bustamante, University of California, Berkeley; Constance L. Celko, Harvard Medical School; Jennifer A. Doudna, who recently moved to the University of California, Berkeley; Charles T. Esmon, Oklahoma Medical Research Foundation; Richard A. Flavell, Yale University School of Medicine; and Thomas Südhof, University of Texas Southwestern Medical Center at Dallas. Thomas M. Jessell, Columbia University College of Physicians and Surgeons, is a new foreign associate.

Three HHMI investigators, Pamela Bjorkman, University of Wisconsin–Madison, and Stanley J. Korsmeyer, Dana-Farber Cancer Institute, were elected to the American Philosophical Society.

HHMI President Emeritus Purnell W. Choppin received an honorary doctorate of humane letters from The Johns Hopkins University at its 2002 commencement.

The Royal Society, the United Kingdom’s national academy of science, named Roger J. Davis, an HHMI investigator at the University of Massachusetts Medical School, one of its 2002 fellows. Peter H. Raven, director of the Missouri Botanical Garden and program director of an HHMI precollege science education grant there, was elected a foreign member of the society.

Stephen J. Elledge, an HHMI investigator at Baylor College of Medicine, won the 2002 National Academy of Sciences Award in Molecular Biology. The award recognizes a young scientist who has made a recent notable discovery in the field.

David Ginsburg, an HHMI investigator at the University of Michigan Medical School, won the 2002 ISFP Prize from the International Society for Fibrinolysis and Proteolysis.

Philip Green, an HHMI investigator at the University of Washington, was a winner of the 2002 Gairdner Foundation International Award. The award recognizes individuals for their achievement in the field of medical science. He received the award, according to the Foundation, for “his contributions to development of the computational tools essential for sequencing of the human genome. Further, he provided compelling early evidence for a dramatically reduced number of human genes.”

HHMI’s Holiday Lectures on Science, an annual Webcast educational program presented by HHMI investigators for high school students, won two national awards for the 2001 lectures by HHMI investigators David C. Page, Whitehead Institute for Biomedical Research at the Massachusetts Institute of Technology, and Barbara J. Meyer, University of California, Berkeley. The program received the 2002 Bronze Telly Award and the 2002 Videographer of Distinction Award. The awards are given by panels of producers and other communications professionals.

H. Robert Horvitz, an HHMI investigator at the Massachusetts Institute of Technology, received the 2001 Genetics Society of America Medal.

Andrzej Jerzmanowski, an HHMI international research scholar at Warsaw University, has been elected to the Polish Academy of Sciences.

Saulius Klimašauskas and Virginius Šiksnys, HHMI international research scholars in Lithuania, received the 2002 National Science Prize from the government of the Republic of Lithuania.

Louis M. Kunkel, an HHMI investigator at Children’s Hospital, Boston, won the 2002 LIFE International Research Award for scientists whose research has led to clinical applications. The award is presented annually by the Lois Pope LIFE Foundation.

Two HHMI international research scholars, Pedro Labarca of Chile and Raúl A. Padrón of Venezuela, have been elected to the Academia de Ciencias de América Latina, the Latin American Academy of Sciences.

Robert J. Lefkowitz, an HHMI investigator at Duke University Medical Center, received the 2002 Pasarow Award for Cardiovascular Research from the Robert J. and Claire Pasarow Foundation.

Richard P. Locksley, an HHMI investigator at Yale University School of Medicine, won the American Society of Hypertension’s 2002 Richard Bright Award.

Richard M. Locksley, an HHMI investigator at the University of California, San Francisco, is one of five new members named to the National Advisory Allergy and Infectious Diseases Council, the principal advisory board for the National Institute of Allergy and Infectious Diseases of the National Institutes of Health.
Mario R. Capecchi, an HHMI investigator at the University of Utah School of Medicine, received the National Medal of Science from President George W. Bush at a White House ceremony in June. Capecchi accepted this award—the nation’s highest scientific honor—with 14 other scientists and engineers, all of whom have made lasting contributions to scientific research. Capecchi was honored for developing gene-targeting technology, which has been used to generate mouse models of human diseases. Researchers worldwide use the technique to determine the function of individual genes. His previous honors include the 2001 Albert Lasker Award, the Bristol-Myers Squibb Award, the Gairdner Foundation International Award, the General Motors Corporation’s Alfred P. Sloan Jr. Prize and the Kyoto Prize. The award also went to Harold Varmus, a member of the HHMI Medical Advisory Board and president of Memorial Sloan-Kettering Cancer Center in New York City, for his discovery with J. Michael Bishop, University of California, San Francisco, that normal human and animal cells contain genes capable of becoming cancer genes.

John B. Lowe, an HHMI investigator at The Rockefeller University, received the 2001 Perl-UNC Neuroscience Prize for solving the crystal structure of the potassium ion channel.

Joan Massagué, an HHMI investigator at Memorial Sloan-Kettering Cancer Center, won the 2002 Howard Taylor Ricketts Award, the highest honor given by the University of Chicago Division of Biological Sciences and Pritzker School of Medicine.

Two K–12 science education programs supported by grants from HHMI have won state environmental education awards. The Mercer Slough Environmental Education Center received the 2001–2002 Community Catalyst Award from the Environmental Education Association of Washington. The Utah Association for Environmental Education chose the Red Butte Connection for its 2001 Program of the Year Award.

Nancy P. Moreno, HHMI precollege science education program director at Baylor College of Medicine, received the 2002 Fullbright & Jaworski LLP Faculty Excellence Award for achievement in education and development of educational materials.

Sean J. Morrison, an HHMI investigator at the University of Michigan Medical School, was named to Technology Review’s 2002 TR100, the magazine’s annual list of top young innovators in business and technology. A native of Canada, he was also named a top young scientist in Time magazine’s Canada edition.

William T. Newsome, an HHMI investigator at Stanford University School of Medicine, received the 2002 Distinguished Scientific Contribution Award from the American Psychological Association. He was recognized for his neuroscience research.

Peter H. St. George-Hyslop, an HHMI international research scholar at the University of Toronto, Canada, won the Richard- son Lectureship Award from the Canadian Neurological Society for contributions to neurological research.

HHMI investigators Christine E. Seidman, Brigham and Women’s Hospital, Boston, and Jonathan G. Seidman, Harvard Medical School, were joint recipients of the 2002 Bristol-Myers Squibb Award for Distinguished Achievement in Cardiovascular Research.

Jonathan S. Stamler, an HHMI investigator at Duke University Medical Center, won the 2002 Saul J. Horowitz, Jr., Memorial Award from the Mount Sinai School of Medicine for contributions as a medical investigator.

Joan A. Steitz, an HHMI investigator at Yale University, received the 2002 Lewis S. Rosenstiel Award for Distinguished Work in Basic Medical Research from Brandeis University.

Roger Y. Tsien, an HHMI investigator at the University of California, San Diego, won the 2002 Dr. H.P. Heineken Prize for Biochemistry and Biophysics from the Royal Netherlands Academy of Arts and Sciences and the 2002 American Chemical Society Award for Creative Invention.

High school students participating in a University of California, San Diego, science education program supported by an HHMI grant placed first in a 2002 regional competition of the National Organization of Black Chemists and Chemical Engineers (NOBCChE) and second in the senior division at NOBCChE’s 2002 national competition in New Orleans.

Thomas J. Wenzel, a chemistry professor at Bates College, Lewiston, Maine, was one of two educators in the United States to receive a 2002 Council on Undergraduate Research Fellows Award. Wenzel provides research opportunities to students in a program supported by an HHMI undergraduate biological sciences education grant.
LETTERS

Women Scientists in Training
I was pleased to see “Accomplished Women” (June 2002, p. 20). As you pointed out, and my recent discussions with female students suggest (Nature Medicine 2002 May; 8: 439–41), we still have a long way to go before women are proportionately represented in science. Young women worry about balancing a demanding career with raising children. They feel they must accomplish more than their male counterparts to be viewed as equals. They are directed away from physician-scientist careers—being told they can’t do it all—often by well-meaning but misinformed undergraduate advisers. Finally, most young women have little direct exposure to women who have achieved stature in the scientific community. Important steps must be taken:

- We need to change the culture of academia to encourage teamwork and discourage competition at the expense of others. This will make science more appealing to young women who are disheartened by the aggressive behavior they view as “part of the job.”

- We need to sustain an effort to place women in respected positions in our scientific institutions. Female students should have female role models and mentors with the clout to help them develop their careers. And all students should see that women’s contributions can rank with those of men.

- We need to view work/family balance as an issue for young scientists of both sexes. We must escape a system that discourages men from choosing to be equal participants in parenting.

Nancy C. Andrews
HHMI Investigator, Children’s Hospital, Boston and Director, Harvard-MIT M.D., Ph.D. Program

While exploring your Web site today, I came across “Accomplished Women.” As a woman who is considering returning to graduate school for a science degree in the next few years, I found the article helpful, uplifting and insightful.

As a mother with two daughters, I have copied the article for their future. My eldest daughter, age 10, is extremely interested in science. She has taken a science enrichment class through our local school. She enjoyed the classroom experiments but wanted to do more. She convinced us to buy a hamster so that she could build a maze and run the hamster through it. She made observations about the hamster’s babies in a notebook. My husband and I want to continue to foster her interest in science. I plan to share this article with her and instill in her the confidence that if she wants to do science, she can do it.

Carolyn S. Stahl
Norwood, Massachusetts

Gleevec Brings Hope
I read “Gleevec’s Glory Days” (December 2001, p. 10) with great interest because my 23-year-old son, Andy, has chronic myelogenous leukemia (CML). It’s a well-written, informative article that provided me with the names of the people who’ve made such a huge difference in Andy’s life: Owen Witte, whose work led to the development of Gleevec, and Brian Druker, who persevered in getting the drug on Novartis’ radar screen. When Andy was first diagnosed a little over a year ago, Gleevec had not yet been approved by the FDA. He was put on hydroxyurea, a debilitating temporary treatment to reduce his white-cell count, which had spiked to 500,000. He has achieved remission on Gleevec, with only minor side effects, and is thus far able to lead a relatively normal life. Hope and optimism have replaced our fear.

Mirinda Kossoff
Burroughs Wellcome Fund
Research Triangle Park, North Carolina

Send your letters: Via e-mail to bulletin@hhmi.org or to Letters, Office of Communications, Howard Hughes Medical Institute, 4000 Jones Bridge Road, Chevy Chase, MD 20815-6789. Letters will be edited for space and clarity. Please include your name, address (e-mail or postal) and phone number.

HOWARD HUGHES MEDICAL INSTITUTE
Presents the 2002 Holiday Lectures on Science
Scanning Life's Matrix
Genes, Proteins and Small Molecules

THE LECTURERS
Eric S. Lander, Ph.D.
Director, Whitehead Institute/MIT Center for Genome Research
Stuart L. Schreiber, Ph.D.
HHMI Investigator, Harvard University

DECEMBER 5 AND 6, 2002
For more information: www.holidaylectures.org
A Creative Influence

In chemistry, equilibrium describes a set of reactions that are internally dynamic but stable overall. Once a steady state is achieved, no net change will occur without outside influence.

I like to think of the Howard Hughes Medical Institute as providing that outside influence, when the equilibrium of science and of the teaching of science could benefit from net change. Part of our mission, as I see it, is to use our resources to introduce new elements that will alter the steady state in creative directions. Two HHMI initiatives—a competition for investigators who conduct patient-oriented research and grants for topflight scientists committed to undergraduate education—are certainly in that spirit.

Both of these initiatives direct our support to individuals who are well placed in the nation’s research institutions and universities and who have the skills and motivation to shift the equilibrium. Both groups of scientists welcome the opportunity to meet the demands of equally important and often-conflicting endeavors—in one “reaction,” laboratory research and patient care; in the other, scientific exploration and undergraduate teaching. By empowering them with resources and recognition, we hope to make a difference. The goals are to enhance translational research and provide new models for what it means to teach biology.

This issue of the Bulletin features the winners of the new investigator competition (see page 14). We selected 12 outstanding physician-scientists from 138 candidates nominated by medical schools and hospitals throughout the country. These professionals are extraordinarily accomplished, and they will bolster our existing cadre of investigators who derive their inspiration from the patients they treat and then move the problems into their laboratories, where they ferret out a detailed understanding of the disease process. The eventual goal is to return to the bedside with new clinical treatments.

Joseph Goldstein, from the University of Texas Southwestern Medical Center at Dallas, who chairs our Medical Advisory Board (MAB), and David Nathan, at Dana-Farber Cancer Institute, also a member of the MAB, deserve credit for encouraging HHMI to expand the number of investigators who conduct patient-oriented research. As scientists whose own work has helped solve significant clinical problems, Goldstein and Nathan understand the value of research that combines clinical expertise with the powerful tools of molecular biology. As research administrators, they also understand how daunting it can be for physician-scientists to work on the boundary between science and medicine. After all, as the equilibrium exists today, only 11 percent of all medical school graduates plan careers that include a substantial commitment to research.

Altering the steady state in undergraduate education is, in many respects, an even more daunting task. Yet, speaking from the perspective of someone who taught undergraduate chemistry and biochemistry for two decades, the opportunities are substantial. I am delighted with the 20 HHMI professors we have selected—they are highly regarded scientists who will bring creativity and ingenuity to the endeavor (see page 39). It was also a pleasure to work with Alice Huang of the California Institute of Technology, who chaired the selection committee, and her panel of scientist-educators; our meetings were lively and thought provoking.

As a group, the successful candidates more than answered our challenge to create new models for teaching biology and related sciences. The array of ideas they plan to pursue is breathtaking: enriched opportunities for promising students, new courses in chemical biology, lectures for non-science majors that focus on the ethical and social issues raised by current research, development of Internet-based teaching materials and many others. I am struck by the fact that each proposal seeks, in one way or another, to create a community of scholars at the undergraduate level by giving students a window on the way science is practiced today.

Our own community of scholars has been diminished by the recent death of W. Maxwell Cowan, who retired two years ago as the Institute’s vice president and chief scientific officer. Max had already made significant contributions to neuroscience—as both a practicing scientist and a leader in the world of academic research—when Purnell Choppin recruited him to HHMI in 1987. At the Institute, Max worked to establish the high standards for which our science program is known and helped identify promising new areas of research. His willingness to support bold moves had an impact on my own research, when he approved a request for equipment to determine crystal structures of large RNA molecules and in the process showed his enthusiasm for the work. And certainly Max’s encyclopedic knowledge of the research occurring in every HHMI laboratory set him apart. The work of our investigators frequently delighted and sometimes frustrated him, but it always engaged his scientific curiosity and his intellect. We shall miss him.

Thomas R. Cech
President
Howard Hughes Medical Institute
Field biologists have long been trying to discover exactly where migratory animals go on their seasonal journeys. In a world of rapidly vanishing habitats, such insight would help those trying to protect sensitive lands. With more than 20 percent of the world’s forests having disappeared in the past 300 years, habitat loss ranks as one of the biggest threats to wildlife, especially migratory birds, which rely on two locations—a winter and a summer home—for shelter and food.

Dustin R. Rubenstein, currently a Cornell University graduate student in behavioral ecology, concentrates on migratory songbirds. These small, hard-to-observe creatures are especially vulnerable because many of them depend on large, uninterrupted tracts of forest to survive. The challenge for field biologists, says Rubenstein, an HHMI predoctoral fellow, has been overcoming the “needle in the haystack” limitations of traditional capture-and-recover field studies; thousands of birds may be captured and fitted with leg bands, but only a few are ever recovered once they complete their migratory journeys.

As an alternative, Rubenstein, 25, in collaboration with Dartmouth College biologist Richard T. Holmes and Stanford University geochemist C. Page Chamberlain, started monitoring stable isotopes—alternative forms of chemical elements—that exist naturally in the environment. They capitalized on a technique, pioneered by Chamberlain, that uses the “chemical signature” of stable isotopes locked in birds’ feathers to tell where a bird has been spending its time.

The stable isotopes of elements such as carbon, hydrogen, sulfur and strontium form durable patterns in the soil that vary predictably from place to place and can thus serve as tracers. Taken up by plants, isotope signatures are subsequently expressed in the insects that eat the plants and, ultimately, in the birds and other animals that eat the insects. “You are what you eat,” says Rubenstein. In birds, these signatures manifest themselves in the chemical makeup of the feathers and thus can serve as natural markers for where a bird has been. By sampling a single tail feather from a captured bird or even a museum specimen, scientists can identify where a bird lived. The isotopic signature reflects the latitude at which the bird has been living and where it grew new feathers.

As a Dartmouth undergraduate on an HHMI research internship, Rubenstein helped orchestrate one of the first comprehensive studies using stable isotopes to ferret out the closely held secrets of a particular migratory songbird, the black-throated blue warbler—a species that summers and breeds over a deep swath of eastern North America (from Ontario to Georgia) and winters in the Caribbean. In the process, he and colleagues discovered “the astonishing fact that warblers from different breeding regions have distinct migratory patterns”—a discovery that not only revealed a previously unknown migratory behavior of the black-throated blue warbler in particular but, by extension, raised the possibility that many other migratory songbirds might behave in the same way.

Their findings, published in the February 8, 2002, issue of Science, showed that the warblers that summer in northern sections of North America tend to winter in the western Caribbean and those that summer in the southern United States winter in the eastern Caribbean islands. To learn where the migrating birds were coming from as they traveled south for the winter, Rubenstein and his colleagues first determined the isotopic pattern found in
feathers of birds whose breeding locations were known. They then compared those signatures with the isotopic signatures extracted from birds of unknown breeding location caught in their wintering grounds.

“Isotopes have been used [before] to study bird migration, butterfly migration and fish migration,” says Rubenstein. “Our study, however, was the first really comprehensive one that sampled birds from across a species’ entire breeding and wintering range.” It illustrated the technique’s promise not only for field biology but also for conservation—by linking declines in regional summer populations to environmental change occurring where the birds spend their winters. “Variable rates of deforestation and habitat loss on the different Caribbean islands may affect some breeding populations more than others,” says Rubenstein. The severe deforestation occurring in Haiti, for example, is thought to be contributing to the decline of the black-throated blue warbler’s southernmost breeding populations (those birds that spend their summers in Georgia and North Carolina), which usually migrate to the more easterly islands of Hispaniola—where Haiti is located—and Puerto Rico for the winter.

The stable isotope method as used by Rubenstein “is a way to investigate in some detail where some birds are spending the winter,” according to Kevin J. McGowan, a researcher at Cornell University’s Laboratory of Ornithology. “It’s surprising what we don’t know about the wintering ranges. For a lot of birds, we just don’t know where they go. It’s impossible to watch these behaviors unfold across the surface of the globe, and when we get access to tools like this, it really helps us out.”

Rubenstein, Chamberlain and Holmes believe that their recent work sets a standard for other studies that seek to reveal the hidden lives of wild animals. And Rubenstein’s contribution, say his senior colleagues, notably transcended its original purpose as a senior thesis at Dartmouth.

“When Dustin came on board, he was facing a tremendous amount of work, much more than a traditional thesis would require,” says Chamberlain. “The number of analyses on one species—numbering in the thousands—is unprecedented, and without him pushing to do this, the study never would have been done. It’s the kind of work that was Ph.D. quality.”

To publish in Science as an undergraduate was testimony to the quality of the work, note both Holmes and Chamberlain. For Rubenstein, the achievement was a kick, he says, but he adds, “It’s somewhat daunting since this was my first paper. I hope I haven’t peaked this early in my career.”

—TERRY DEVITT
Curriculum Congestion

The explosion in scientific knowledge is overloading undergraduate biology courses. What to take out is a thorny problem.

Imagine a 17th-century Dutch naturalist given the privilege of looking through Leeuwenhoek's microscope at the previously unknown world of microbial life. His first reaction must have been, "How wonderful!" His second reaction was probably, "How am I ever going to make room for this in my studies?"

This imagined example of an overwhelmed naturalist has a real, modern counterpart: Today's biology educators must make tough decisions about what new information to make room for and, also, what to leave behind. "Contemporary biology has seen a geometric progression in knowledge, breadth and impact," says Peter J. Bruns, vice president for grants and special programs at HHMI. Everything from Watson and Crick's DNA structure to the publication of the entire human genome has occurred within the past 50 years, and the undergraduate curriculum is straining under the load. Plus, "modern biology brings in other, associated sciences—chemistry, mathematics, physics, computer science—that it didn't so powerfully in the past," adds Bruns.

Given that at least two major processes are required to keep the curriculum current—courses must be updated as well as made more interdisciplinary—one might assume that the biology curriculum is now in tremendous flux nationwide. Yet "it's probably not in flux enough," says Bruns. "New things are not being added fast enough, and secondary information is not being cut. I think the response requires a big rethinking."

Gabriele Wienhausen, a principal investigator of the HHMI Undergraduate Science Enrichment Program at the University of California, San Diego, acknowledges that this process is difficult, daunting and deadly slow. Faculty "do see the need for these changes, but actually making them can be painful," she says. "Still, it has to happen. You really have to start arguing with people and work out the pros and cons."

The needed changes will likely be driven not by committee but by individuals. "It's rare—but it does happen—that an entire department will get together and decide to redesign their entire curriculum," says Sondra G. Lazarowitz, a professor of plant pathology at Cornell University. "But the more common thing is that new people come into an environment who have strong ideas about the coursework and decide they're going to change it. Historically, universities have relied on new faculty with new perspectives to invigorate courses. It's more evolution than revolution."

For example, shortly after coming to Cornell four years ago, she and Gary Whitaker of the university's veterinary college overhauled a course on virology. "We basically threw out the old curriculum," says Lazarowitz, who also directs the HHMI Cornell Program in Undergraduate Biology and Precollege Outreach. "The traditional approach would be to provide an overview of the features and replication of all groups of animal viruses. We made the course more interdisciplinary, using key viruses to emphasize general principles of molecular virology and to explain the experimental basis for our current understanding of how animal, plant and bacterial viruses interact with their hosts."

One solution to the overcrowded-with-content curricula has been adopted just about everywhere: The old introductory courses that were basically surveys of the animal and plant kingdoms have disappeared. "There has been a tremendous movement to get away from those survey classes and to focus more on cellular, molecular and biochemical issues," Wienhausen says. "But it comes at a price." Whereas old-style survey courses might make students mere "stamp collectors" of species, with no insight into molecular fundamentals, modern classes may lay out their own stamp collections of molecules and biochemical pathways, without the context of actual, living organisms.

Lazarowitz points out that historical details are often the first items sacrificed to make room for new material, again potentially removing context from biology education. "One answer to this dilemma has been to create a one-credit 'Readings in X' seminar/discussion course in a given area—for example, microbiology or genetics—in which students read and discuss landmark papers that were truly groundbreaking in a particular discipline," she says.

Meanwhile, an obvious need in biology curricula is interdisciplinary education to accommodate the emerging fields of genomics, proteomics and bioinformatics. To ultimately work in those areas—to understand, and perhaps transcend, topics such as protein folding or statistical analyses in epidemiology—students need training in biology, mathematics and computer science. Although much of the interdisciplinary melding takes place at the graduate level, some campuses are attempting to foster undergraduate departmental crossbreeding as well. At Virginia's College of William and Mary, the mathematics and biology depart-
Sixty-five years of living may separate Marta Valdes from seventh-graders Victoria Karr and Phoenix Gonzales, but a middle school science project has brought them together. The two students from George Washington Carver Middle School in Miami are interviewing 78-year-old Valdes at a community senior center. Their immediate goal: to learn how Hispanic immigrants like Valdes used plants in their native countries. Hers: to help the girls choose a plant to research.

"Did you ever use foods or other plants as medicine?" Karr asks. "In Cuba, where I was born, we used sábila (aloe vera) to lower cholesterol," Valdes replies. Another Cuban immigrant, 80-year-old Matilde Merino, tells Katherine Lopez and Yadira Perez, both 13, that her mother gave her mint or chamomile tea for stomach aches. "We ate garlic so we wouldn’t get sick," she adds. Hoydee Lorrreate-gae, born in Ecuador in 1932, recommends lemon grass for fever and cactus for a swollen foot, to seventh-graders Tamara Trotz and Jordan Shockett. Much of what the teenagers hear is a revelation. "I just never thought about the plants, how they grew and how they used them," 13-year-old Gonzales remarks.

From these discussions, the middle school students choose a plant to study, and during the rest of the school term, they investigate their plant’s scientific name, family, place of origin, ecology and distribution. They study the plant’s reproductive biology and compare its traditional uses to its modern applications as a food, medicine, fiber or component in industrial or manufacturing processes. They look up scientific studies on the useful properties of the plant, and they design an experiment such as a test for sugar or starch content. Aloe vera, anise, garlic, sour orange and a score of other edible or medicinal plants come under scrutiny. The students ultimately present their findings to the seniors they interviewed at an intergenerational ethnobotany symposium at Miami’s Fairchild Tropical Garden.

What can different generations gain from Learning from Their Elders

Programs cross generations to bolster children’s curiosity.

Sixty-five years of living may separate Marta Valdes from seventh-graders Victoria Karr and Phoenix Gonzales, but a middle school science project has brought them together. The two students from George Washington Carver Middle School in Miami are interviewing 78-year-old Valdes at a community senior center. Their immediate goal: to learn how Hispanic immigrants like Valdes used plants in their native countries. Hers: to help the girls choose a plant to research.

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What can different generations gain from

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STEVE MIRSKY
Up Front

studying science together? “They can enrich each other’s understanding,” says Patti J. Anderson, former science-education coordinator at the Fairchild Tropical Garden. With support from HHMI, the garden developed this project that pairs middle school students with neighborhood seniors to study plants so that young and old alike will reap personal satisfaction from the experience. “For the kids, it’s an opportunity to relate to people from a different generation without having to deal with the dynamics of family relationships,” Anderson says. “They enjoy the role of interviewer and researcher, and they seem to take the job seriously. The seniors enjoy talking with younger people, and the ones who do have some knowledge of their native plants feel appreciated for what they know.”

There are cultural benefits as well. Caribbean immigrants make up a significant segment of Miami’s population and cultural heritage. But while many of the students at Carver Middle School have an immigrant parent or grandparents, more than a few confess little knowledge of their families’ native lands. Interviews with the seniors seem to awaken for many of the teenagers a new interest in, and respect for, the places where their parents or grandparents were born. “Sometimes kids are simply more open to talking with strangers than with their own parents,” explains Anderson. “Yet some of the seniors are from the same Caribbean island or town that the kids’ parents came from, and that makes a connection; it stimulates the children’s curiosity about their own culture.”

Interest in projects that pair “the book-end generations”—children and seniors—is growing in education and among those who work with the aging, says Donna Butts, executive director of Generations United, a national coalition of more than 100 organizations with intergenerational programs. The federal Older Americans Act includes provisions for intergenerational programs, and several universities, including the University of Pittsburgh and Ohio’s University of Findlay, now offer degrees in intergenerational studies.

Sometimes when science crosses the generation gap, it does so within families. In Chicago, preschoolers and their parents are studying science together. One physics primer begins with a trip to see Disney’s Little Mermaid on Ice. Afterward, back in school, the children try “skating” across a carpet on squares of slippery waxed paper, thus learning about friction and balance. They discover the principles of density, viscosity and flow by filling bottles with baby oil, food coloring and water and then agitating them. Together they examine shells and sponges under a magnifying glass and hunt with magnets for metal objects hidden in sand.

The preschoolers and their relatives are part of a hands-on science-education program—the Science and Math Excellence Network (SAME)—run at 18 Chicago schools by Rush-Presbyterian-St. Luke’s Medical Center in collaboration with the Chicago public schools, independent schools and businesses. SAME is supported in part by HHMI. Parents are an integral part of the program and are encouraged to participate in workshops to help reinforce for the children the excitement and importance of learning. “Parents are kids’ first teachers,” says Kati Gilson, an early-childhood science-education specialist with SAME’s preschool education program. “What happens in the early years is an essential stepping stone to what they are going to achieve in the future. Parents and teachers are the ones providing the foundation.”

Janice Thompson, whose 4-year-old daughter Janishia Calhoun attends preschool at Chicago’s Medill Elementary School, volunteers in the classroom and goes to parent workshops. “Science was boring back when I was in school. We just worked from a book. But every science project we do here is fun for me and fun for the kids.” At home, she and Janishia have planted watermelon seeds and watched them germinate and grow. They put mealworms in a jar of oatmeal and watched them turn into beetles. “My daughter loves science, and now so do I,” she says.

Elsewhere, the older generation may not be directly related to the students, but they often share a cultural heritage. At a summer science camp in Grand Forks, North Dakota, tribal elders kick off each day of camp and later wrap it up, helping the Native American schoolchildren connect what they’re learning with the tribe’s culture. “The elders serve as the heart of the camp,” says Mary Beth Kelley-Lowe, director of the HHMI-supported program run by the Dakota Science Center. “They talk with the kids about how they can be good scientists, yet respect traditional knowledge and ancient ways.”

In remote villages of rural Alaska, with support from an HHMI grant, an Anchor- age science museum called The Imaginari- um is working with elders and local experts familiar with cultural traditions to develop science programs that incorporate examples relevant to the children’s lives and culture—the speed of a kayak paddled with or against the current, for example, or the life cycle of a familiar bird or fish. Community science festivals put on by the museum enable elders to share their knowledge, bringing tradi- tional and modern science to village resi- dents of all ages.

“We work with local elders to integrate traditional native knowledge,” explains Christopher Cable, The Imaginari- um’s executive director. “It helps make the content of our programs relevant and meaningful to the entire community.”

—JENNIFER BOETH DONOVAN and CATHERINE KRISTIANSEN

FOR MORE INFORMATION:
Fairchild Tropical Garden, www.ftg.org
Science and Math Excellence Network, fisheredu.com/SAME
Dakota Science Center, www.dakota-science.org
The Imaginarium, www.imaginarium.org
With a Little Help from Our Friends

The genomes of chimps, chickens, bees and others may tell us much about ourselves.

HMI researcher A. James Hudspeth, who studies the causes of human deafness, can barely wait to get hold of the genome sequences of two small animals that seem quite remote from humans—zebrafish and chickens.

"Nearly all human hearing problems are due to the loss of hair cells in the cochlea," Hudspeth explains. Such losses are permanent in mammals but not in other vertebrates. "If you expose a chicken to loud noises or otherwise injure its delicate hair cells, it will lose its ability to hear, as a human would. But within a few days, the chicken's hair cells will begin to regenerate," he says. "Within a few weeks, the cells have grown to maturity and reconnected to nerve fibers, and the chicken has largely recovered its hearing."

Hudspeth, who heads the Laboratory of Sensory Neuroscience at The Rockefeller University in New York City, hopes to identify the chicken and fish genes that control this regeneration. Having them in hand might lead to ways of stimulating the corresponding genes in human ears, he says, thereby improving the hearing of deaf people. His lab has painstakingly cloned some of the genes related to hearing in zebrafish, which are economical to work with. But if the zebrafish genome were already sequenced, he says, "we could do in weeks what now takes us a year."

And the winners are . . .

Hudspeth may soon have his wish. England's Wellcome Trust Sanger Institute is sequencing the zebrafish genome, and the chicken genome has just received a "high priority" rating by the National Human Genome Research Institute (NHGRI) as one of the next organisms that may be sequenced with National Institutes of Health (NIH) funding.

This is just the start of a flood of new genome sequences that are expected within the next few years.

Comparative genomics, in which the DNA sequences of two or more species are closely compared, is becoming a key tool for scientists who want to understand the functions of human genes. Dozens of research groups have been clamoring to get their favorite animal's genome sequenced ever since the first draft of the human genome was announced two years ago. The cat, dog, cow and other familiar species have their partisans, while other scientists support the rhesus monkey, the platypus or various strange birds, fish or fungi. To bring some order to this free-for-all, NHGRI drew up guidelines for setting priorities and asked some questions: How valuable would the new genome sequence be to researchers? How would it be used, and how soon? How would it advance human health?

In the first round of replies, 13 groups submitted "white papers" backing their particular organisms, and a panel of scientists chose six organisms that varied enormously in size, type and evolutionary distance from humans. Approved in May by the NHGRI’s advisory council, the winners were the chicken, the chimpanzee, a group of fungi, the honeybee, the sea urchin and Tetrahymena (a freshwater protozoan).

"The chicken fulfilled all our requirements, so giving it high priority was easy," recalls Sean R. Eddy, an HHMI investigator at Washington University in St. Louis, who served on the panel (see Q&A, page 13). "We took only one minute to decide." The chicken, he explains, is a model system for studies of embryonic development, which is easier to observe in an egg than in a uterus. In addition, although the chicken genome is only about one-third the size of mammalian genomes, there is a remarkable level of conservation between the two.

Scientists throughout the world are awaiting this sequence for a variety of surprising reasons. While Hudspeth looks forward to finding the genes and proteins involved in deafness, David C. Page, an HHMI investigator at the Massachusetts Institute of Technology, expects the chicken genome to help him search for the causes of infertility in humans.

"We could do a tremendous amount with this sequence," Page says. "I’d be especially interested in the sex chromosomes because in the chicken, the female has two different sex chromosomes, a W and a Z, while the male has two Zs. Given that we’ve learned a great deal about sperm production and male infertility from studying the human Y [chromosome], one might speculate that the best way to study infertility in women is to sequence the chicken’s sex chromosomes."

Hastily made-over apes

Although the chicken genome had smooth sailing in the NHGRI panel, the chimpanzee, "our closest living relative," aroused a great deal of controversy. Among the arguments: Deciphering the chimp’s genome sequence will be
very time-consuming and expensive, costing about $100 million. (“The good thing about the other genomes is that they’re smaller,” said one scientist. “We can do 5 to 10 of them for the price of only one primate.”) Furthermore, chimps are now so rare and valuable that they cannot be used for genetic experiments—and many scientists believe it would be unethical to do so because of the chimp’s closeness to humans. The rhesus macaque, which has proved valuable in many medical experiments, offered tough competition; the panel wavered between the two primates.

Yet the chimp won, partly because of a rousing white paper whose first author is Maynard V. Olson, director of the University of Washington Genome Center in Seattle. Paul W. Sternberg, an HHMI investigator at the California Institute of Technology, in Pasadena, who was also on the panel, supported the chimp enthusiastically. “In some ways, we didn’t need to put a person on the moon and bring him back, either,” Sternberg says, “but it was a magnificent achievement. Sequencing the chimp genome will give us an inkling of what it means to be human.”

According to the Olson white paper, the chimp is genetically so similar to humans that only 1.2 percent of its nucleotides diverge from the human ones. However, because both genomes contain more than 2.5 billion base pairs of DNA, this comes to about 30 million differences—“a lot of differences between the two, and well worth studying,” says Sternberg. These differences may shed light on “how the human brain acquired its extraordinary capabilities,” the white paper points out. They may help explain humans’ long periods of maturation and helplessness during infancy relative to apes.

Some of the major contributions of sequencing the primate genome may be medical. A few years ago, Olson developed the theory that in any rapid evolution, it is much more common for a species to lose some of its old genes than to acquire brand-new ones. As our species broke out of the rain forest and gained access to the entire ecosystem, he says, it changed so speedily that humans may be called “hastily made-over apes.” And our loss of the ape-like genes, he suggests, may be directly responsible for the human propensity to obesity, diabetes, cardiovascular disease, epithelial cancers and neurodegenerative disease. Therefore the genes we lost might provide “a direct biochemical model of how to remedy…human defects,” according to the Olson white paper, and the chimp might serve as “a presently unexploited source of ideas” on how to improve human health.

**Picking favorites**

Each of the other four genomes to which the NHGRI panel gave high priority has its own set of advantages for researchers. The honeybee’s genome sequence, for example, may prove to be a gold mine for scientists who study the genetic basis of humans’ social traits and ability to learn. “Honeybees live in societies that rival our own in complexity,” says Gene E. Robinson, director of the neuroscience program at the University of Illinois, Urbana-Champaign, and lead author of the bee white paper. With their famous dances, which tell other bees where the flowers are, bees have developed “the only nonprimate symbolic language,” he says. Like humans, bees have an intricate system of division of labor, highly organized defense and warfare, complex architecture and even a well-developed system of personal sacrifice. The genes that play a role in these activities can now be analyzed rapidly with the help of genetics and new genomic technologies.

Bees also have much to offer from a medical point of view. Bee hives present ideal conditions for bacterial growth because of their high temperature, humidity, overcrowding (the equivalent of 15 adult humans living in a 12- by 18-foot apartment) and the bees’ constant food-sharing. Given their ability to thrive in these environments, bees must have evolved powerful antibiotic peptides, some of which might lead to novel therapies. Bee venom is another promising source of active compounds. In addition, bees may be very useful to researchers who study the aging process: Queen bees live twenty times longer than their workers, despite identical genes.

The panel gave high priority to three other organisms for specific reasons. Sea urchins are expected to be of particular value to scientists who study early embryonic development, genetic mutations in cancer and evolution. *Tetrahymena* could be useful in advancing research on telomeres, the tips of chromosomes that play a major role in aging and cancer. And the fungi should help researchers solve problems related to fungal infections, for which very few therapies exist.

Now that the panel has made its first selections, scientists in the three major sequencing centers funded by NIH—the Washington University Genome Sequencing Center in St. Louis; the Whitehead Institute/MIT Center for Genome Research in Cambridge, Massachusetts; and Baylor College of Medicine in Houston—will be free to pick any organism out of the high-priority bin and sequence it.

Meanwhile, an intricate network of sequencing collaborations has been established between private companies, universities and government agencies around the world. The Department of Energy is funding the genome sequence of *Fugu rubripes* (the Japanese pufferfish), the frog, the sea squirt, 41 microbes and the poplar tree, which may be used to produce liquid fuel. The Institute for Genomic Research (TIGR) is sequencing a variety of bacteria and viruses. Baylor College of Medicine and others are sequencing the rat genome with NIH funds. The Welcome Trust Sanger Institute recently completed a draft sequence of *Anopheles gambiense*, the malaria mosquito. Japan’s National Institute of Agrobiological Sciences is sequencing the silk moth. Germany’s Bayer AG chemical conglomerate and Exelixis, of South San Francisco, have just announced an incomplete version of the tobacco budworm genome.

Mark Guyer, assistant director for scientific coordination at the NHGRI, has been nurturing the selection process but claims to have no favorite animal of his own. “I like ‘em all,” he says diplomatically. He points out that more white papers arrived in June, another set is expected in October and eventually many more genomes will get done.

—Maya Pines
Genome Insider

A conversation with Sean Eddy

Having helped build the rough draft of the human genome, the U.S. genome-sequencing centers are starting to make inroads into the genetics of other animals as well. Determining which animal genomes are most worthy of sequencing, though, is the task of a panel of scientists convened by the National Human Genome Research Institute (NHGRI) of the National Institutes of Health (NIH). Sean R. Eddy, an HHMI investigator and computational biologist who studies the evolution of genomes at Washington University in St. Louis, is on the panel.

Why is the panel necessary? Why can’t the genome-sequencing centers decide for themselves?

Eddy: If the genome centers had to plan which organisms to sequence next, they’d spend too much time reading zoology literature and not enough time sequencing. NHGRI’s idea was an “open public contract” mechanism: If you think your dog should be sequenced as a service to the community, you can submit a 10-page white paper and explain why. If the panel agrees, the dog genome gets placed on NHGRI’s list of high-priority items. Then a genome center can look at the list and say “Ah! The dog! We can do the dog.” The idea is to use this constant amount of sequencing capacity and fill the pipeline.

What are your criteria for selection?

Eddy: One criterion is whether the organism has long served as a model system for molecular-genetics research. Some of these, like Drosophila, C. elegans and E. coli, were no-brainers, and those genomes got done early. A second criterion involves comparative genomics. Once I have, say, the C. elegans sequence, I want to find features in that sequence that are important. One of the best ways to do that is to find another nematode sequence that’s closely related. And a third criterion is “weird biology,” so to speak, where the genome is inherently interesting in its own right. An example, which didn’t get approved but probably will be for long, is the Oxytricha genome sequence. It’s a ciliate—distantly related to paramecium. The weird thing about Oxytricha is that each gene is basically its own little chromosome. If we had the Oxytricha genome, we would have one in which a lot of the gene finding had already been done for us, since the ends of the chromosomal DNA pretty much define the ends of the genes.

Is there much lobbying from researchers or other groups to get something placed on the high-priority list?

Eddy: As the genome project expands outward to cover more animals, no one wants to be in a backwater that doesn’t have a genome yet. You want your genome to be up at the top of the list, or at least part of the club. Everyone is pushing an agenda, but not particularly strongly. You’ll be at a pub or a meeting and someone will say, “I think we should do the platypus.” And someone else will say, “Oh no, the platypus is a stupid genome. We should do the koala.” So there’s that level of buzz or arguing, but there actually isn’t a lot of serious lobbying.

Has the panel seen anything that caused members to laugh?

Eddy: Sure, but I’d hesitate to name names. For instance, we’ll see an out-of-left-field white paper written on an organism that no one has thought hard about—they don’t even know the genome size. This is an immediate killer because there are genomes out there that are big—much bigger than the human genome, like the lily genome, which is about 100 gigabases (Gb), 30 times the size of the human.

There’s no way we would sequence something whose proposers hadn’t asked the basic how-heavy, how-much-DNA questions.

You’re a self-professed “cat person.” How soon should the cat genome be sequenced?

Eddy: Well, clearly, cats are much more important than dogs [chuckling], so cats have priority. We haven’t seen a white paper for the cat yet, but it’s perfectly justifiable. Still, the dog’s behavioral characteristics are extremely well-studied; if we had a dog genome, the rate at which people could clone genes involved in behavioral traits might be accelerated. So even though I’m a cat person, I’m leaning toward the dog project. I want to see the dog people put in a white paper.

How many genomes can the centers get through?

Eddy: If you do everything as rough draft, you’d have the ability to do maybe 5 Gb of assembled sequence per year at the three main NHGRI centers combined, not counting the capacity of other large genome centers, such as the Wellcome Trust Sanger Institute in England or the Department of Energy’s Joint Genome Institute. That means the NHGRI centers can do one or two large mammalian genomes a year, plus many other smaller genomes.

—BRIAN B. REID
NE DAY IN 1994, A MAN APPEARED at the Massachusetts General Hospital infectious-diseases clinic and offered himself up for research. A hemophiliac, he had been infected with HIV since 1978, but, remarkably, he had never shown any signs of AIDS. “I feel great,” he told the doctors. “You might want to study me.”

Indeed, Bruce D. Walker recalls, “We started studying him like crazy.” The encounter ultimately produced a wealth of results, chief among them the discovery of a unique immune-system response that’s missing in patients who suffer from progressive HIV disease. The findings, published in 1997 in the journal *Science*, represented “the first indication that people could mount a successful cellular immune response against HIV,” says Walker.

Just as important was another outcome: The episode was a striking example of how those who labor at the intersection of two worlds—clinical medicine and laboratory research—can achieve critical biomedical advances that might not emerge from one or the other arena alone. These physician-scientists—also called patient-oriented researchers or clinical investigators—spend their professional lives crossing the boundaries between the bench and the bedside, convinced that the best science cannot be conducted in the absence of patient contact.

“Mice are not humans,” says Walker, one of a dozen physician-scientists recently chosen for appointment as new HHMI investigators (see page 18). “That’s the crux of the issue. All of our work on this immune response came from a clinical observation that never would
have happened if someone doing basic lab research didn’t have a chance to interact with a patient.”

**DIFFICULT CHOICES**

Yet despite the potential payoff, the number of physician-scientists in the United States is dwindling, according to a 2000 report of the Federation of American Societies for Experimental Biology. Young scientists and physicians are choosing more traditional career paths.

“Only about 11 percent of medical school graduates plan careers that are exclusively or significantly devoted to research,” says David G. Nathan, president emeritus of the Dana-Farber Cancer Institute and a member of HHMI’s medical advisory board. “These 1,600 graduates hold the future of medical research in their hands because some of them will be trained to translate the fruits of basic research into better care of patients and into prevention of disease. We must do everything we can to encourage them.”

Being both a physician and a scientist, by definition, requires expertise in two areas, meaning a hefty time commitment in both fields. This places a tremendous burden on many medical students, who often incur large debts while attending school and feel pressured to pay them off as quickly as possible. Medical school debt, however, is far from the only factor that discourages physicians from doing patient-oriented research.

Harold E. Varmus, who served as director of the National Institutes of Health (NIH) during the Clinton administration and is also an HHMI medical advisory board member, says that when discussing the plight of physician-scientists it is important to distinguish between two categories of researchers: those who treat patients and perform lab work, and those who primarily conduct patient-oriented research—that is, research that intimately and specifically involves the patients they see. Varmus, now president of Memorial Sloan-Kettering Cancer Center in New York City, worries more about the latter than the former.

“The patient-oriented types are a source of concern,” he says. “Clinical science is difficult, slow and underappreciated, [and] the rising demands on academic health centers for clinical revenue from patient care cut into research time.” Although significant people are doing first-rate studies with patients, Varmus asserts, “their numbers are suboptimal.”

Initiatives such as NIH’s Medical Scientist Training Program—a medical school curriculum established in 1964 that leads to a combined M.D., Ph.D. degree—has been “hugely successful in creating a powerful cohort doing great laboratory science,” says Varmus. Similarly, the HHMI–NIH Research Scholars Program encourages medical students to become physician-scientists by bringing them to the NIH campus to spend a year working alongside NIH scientists in the lab. Two-thirds of the physicians who participated in the late 1980s are actively engaged in research today.

“Many of us think that this is the most important issue we can address, that of encouraging bright young people to enter the field of physician-scientist,” says David A. Clayton, HHMI’s vice president and chief scientific officer. “We are looking at everything we do along those lines, asking whether we can add to what we already do.”

Apart from these training successes, however, physician-scientists encounter increasing demands, mostly economic, to spend more time in the clinic than in the lab, which makes it hard for them to compete for funding against Ph.D. researchers who are not encumbered by patient care. And often they receive little if any support from their institutions for “protected” lab time, which diminishes their ability to conduct basic science.

Observers generally agree that time is a key factor for those who opt for the lab over the clinic: Lab experiments can be conducted much more quickly than human studies. Recruiting subjects takes time—including approval by institutional review boards and informed consent from research candidates—and daunting amounts of paperwork. Moreover, trying to care for patients with certain diseases, such as cancer, can be unpredictable; they may take focus and energy away from the bench, often at inconvenient times.

“Research is very competitive, and it’s very difficult,” says Bert Vogelstein, an HHMI investigator who studies the molecular basis of colon cancer at The Johns Hopkins University School of Medicine. “It requires a supreme focus. Any other activities distract.”

As a result, researchers often are forced to make difficult choices. Vogelstein, trained as both a physician and a scientist, made the decision to devote his time to the lab. “My research is centered on patients, but I don’t see them,” he says. “Oncology is one of those disciplines where it is difficult to combine the two, because patients [can be] so sick and require constant attention. It’s easier for physician-scientists in other fields, like genetics or endocrinology, because they can see patients on a scheduled basis.

“Being a good physician is a full-time job; being a good scientist is a full-time job,” Vogelstein notes. “It’s extremely difficult to do both. It’s like trying to carry out two full-time careers. I didn’t feel I could do justice to my research or to my patients if I tried to do both, so I stopped seeing patients. However, the experience of being educated in both science and medicine has been enormously helpful, and I believe that such joint training will prove essential for those interested in disease-oriented research in the future.”

Yet there are some medical areas where the two mesh beautifully, says Katherine A. High, who conducts hematology research at The Children’s Hospital in Philadelphia, in explaining why she keeps a foot in each world. “If you have a firm grounding in the science, you

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A **Physician-Scientist by Any Other Name**

The term physician-scientist can mean different things to different people and covers a relatively wide range of researchers. There are those with medical degrees who work exclusively in the lab, never seeing patients. Others may see patients once a week in a clinic or monthly on rounds, but they don’t necessarily study patients as an integral part of their research. The final group conducts research—which includes lab work—specific to patients, and their contact with the patients often stimulates the research questions they ask. The majority of the 12 new HHMI investigators fall into this latter group of clinical investigators, or patient-oriented researchers. More often than not, however, distinctions among the three groups can be blurred and imprecise.
can approach clinical problems clearly.” She recalls a patient treated with the blood thinner coumadin after heart surgery. Bleeding problems led to several hospital visits and lab tests, none of which implicated the drug. Finally, High used an assay that showed very low levels of factor IX, a blood-clotting factor—only when the patient took coumadin. She eventually showed that the patient had a mutation in the gene for factor IX that made him extraordinarily sensitive to the blood thinner. The patient is now kept on low levels of coumadin and the bleeding has stopped. Additional lab experiments indicated just how the mutation caused sensitivity to the drug. The same mutation has since been observed in other patients with sensitivity to coumadin.

A SATISFYING BALANCE

Patient-oriented researchers need encouragements, such as HHMI’s new program to appoint clinical investigators, to “send a signal to medical schools and other places that clinical research has respect and warrants support, including more time to do the studies,” says Varmus. These programs will in turn “encourage others—M.D.s, mainly, but some Ph.D.s too—to enter the field. The many promises made about moving new discoveries about genes and signaling pathways and new chemical methods and the immune system into clinical practice will be met only if we train adequate numbers of people to do clinical studies and then find opportunities and resources for them to do what they are trained to do.”

Meanwhile, those who have managed to straddle both worlds speak overwhelmingly of having struck a satisfying balance in their professional lives. They dismiss the hurdles, which they see as being more than offset by the rewards of translating their scientific efforts into human terms.

“I love what I do,” says HHMI investigator Gerald I. Shulman, and in both arenas. He enjoys his time in the lab, he says, but would never abandon patient care.

Shulman, a diabetes specialist at Yale University School of Medicine, attributes much of his attitude to the childhood experience of watching his physician father interact with his patients. “I followed him on his rounds and loved the
connections—the wonderful relationships—he had with his patients,” Shulman recalls.

Repeatedly, physician-scientists emphasize that neither discipline can be pursued in isolation and that lab studies are not sufficient to extrapolate to humans—and at times can even be misleading. “If I study a mouse or a particular cell line, what I find there might not be applicable to the patient,” says Shulman, who is investigating the relationship of insulin resistance to the development of type 2 diabetes.

For example, he cites the work of Sir Philip Randle and his colleagues at the University of Bristol of nearly four decades ago. “They showed—in a classic series of in vitro studies—that insulin resistance could be induced in heart cells from rats by incubating them with fatty acids,” Shulman notes. “Randle and colleagues came up with a biochemical explanation that showed the fatty acids caused insulin resistance by inhibiting an enzyme involved in glucose metabolism. The question was: Does this same process happen in humans?”

In studying humans, however, “we discovered that a very different mechanism was responsible for fat-induced insulin resistance in skeletal muscle,” he says. “Therefore, there is a whole different set of therapeutic targets to pursue. So if you aren’t studying the human, you may be studying something that isn’t applicable. As powerful as animal studies are, without studying patients, you could be led astray.

“I think it’s important to be studying the patient with the disease,” he adds. “I go back and forth between patient studies in the clinical research center and studies at the bench involving transgenic and knockout mouse models of the disease. What I do in the clinical research center is about 10 times harder than what I do at the bench, but it’s the most important because it involves the actual patient. That’s what matters.”

Moreover, exposure to both disciplines gives physician-
antiretroviral therapy. They hope to understand how it manages to do so, and thereby design a means to eradicate the virus.

EDWIN M. STONE, M.D., PH.D.,
University of Iowa Roy J. and Lucille A. Carver College of Medicine, Iowa City.
Stone’s research interests are in inherited eye diseases. He collaborated with HHMI investigator Val C. Sheffield at the University of Iowa to identify the chromosomal location of genes that cause 14 different eye diseases. Stone and colleagues have also created the first international center for molecular diagnosis of eye diseases.

BRUCE D. WALKER, M.D., Harvard Medical School, Massachusetts General Hospital, Charlestown.
Walker’s group is studying patients in the earliest stages of HIV infection to determine how the immune system fights the virus during the initial encounter. They hope to learn how to boost immunity to viruses. Walker is also helping several institutions in South Africa expand their immunology programs and support training in virology.

CHRISTOPHER A. WALSH, M.D., PH.D.,
Harvard Medical School, Beth Israel Deaconess Medical Center, Boston.
Walsh’s lab is interested in the causes of mental retardation and epilepsy in children. He collaborates with clinical geneticists and pediatric neurologists around the world to improve diagnosis of childhood brain disorders, and through a pioneering “Internet Clinic,” he has described more than a dozen new neurological syndromes whose genetic bases are being investigated.

For more details on the investigators’ work, visit www.hhmi.org/news/052802.html.

免疫系统与病毒的战斗以及在最早的患者研究中

“为了接受医学观念不能被科学的医学观念所同化，对于每个患者，都需要采取相同的处理方式。”他说。

Robert B. Darnell, at The Rockefeller University, discovered this clinic-lab connection early in his career, in 1987, when he was the young neurology resident at Memorial Sloan-Kettering Cancer Center. An outwardly healthy woman in her mid-30s had woken up dizzy one morning. “Over the course of the next three days, she couldn’t read or watch TV; she became completely uncoordinated and couldn’t stand up without falling over. She couldn’t feed herself. Finally, she couldn’t take a step.” Her cerebellum, the part of the brain that coordinates muscle movement, had been destroyed in a matter of days. Lab tests showed high levels of an antibody to a new protein in that part of her brain. This was an immune response to a breast cancer that had gone undetected—a response that had been successfully suppressing the cancer at the expense of her cerebellum.

In the ensuing years, using blood from patients with similar ailments, Darnell’s research team has cloned a series of genes that encode for these previously undiscovered neuron-specific proteins. “We are using these rare disorders as a Rosetta stone for reading out new principles of tumor immunity and basic neuroscience,” he says. “The power of taking one disease apart and dissecting it is something that is not doable without the clinical interest and insight that comes from seeing patients.”

Charles L. Sawyers, a leukemia specialist at the University of California, Los Angeles, Geffen School of Medicine, has a similar view. His collaborative work led to the development of Gleevec, a drug that has reversed the course of chronic myelogenous leukemia (see Bulletin, December 2001). “To take the principle of understanding a cancer at the molecular level, come up with a treatment that exploits that molecular abnormality, test it and find out, amazingly, that it works,” he says, “you can’t imagine how motivated it makes you feel.”

Indeed, such an attitude goes to the very heart of the qualities common to those researchers who choose to practice their craft within these two disciplines. “The first is a great curiosity for understanding why something happens,” says Baylor’s Lee. “The second is a great need to use this information to make a difference in the lives of people.”
Adam Arkin sees the cell as a mechanical system. He hopes to transform molecular biology into a kind of cellular engineering and in the process, learn how to move cells from sickness to health. By M. Mitchell Waldrop

“WHEN I WAS VERY YOUNG,” SAYS ADAM ARKIN, thinking back to the 1970s and his childhood in New York City. “I used to get up early in the morning and go rooting through the neighbors’ trash, looking for mechanical items, or things like old calculators with those Nixie-tube displays—stuff with cool electronic widgets and readouts. I’d bring them back to my room, and over time I’d build these massive things I called ‘machines.’ There was always this feeling that everything was fitting together in some fashion.

“I still look for that feeling,” says Arkin, a 35-year-old HHMI investigator at the University of California, Berkeley. The difference is that today, he’s working on “machines” called organisms.

Pointing to a pair of charts that fill up most of one wall in his tiny, crowded office in Berkeley’s Melvin Calvin Laboratory, he says, “I want to know about that!” “That” is a tangle of lines and nodes that might almost be a circuit diagram for the latest Intel microprocessor. In fact, each chart depicts a bewilderingly complex universe of everything that’s known about the regulatory pathways of bacterial cells.

“I want to know the how and the why,” declares Arkin. “I want to know how the cell’s behavior emerges, how the cell survives and evolves and how life developed from a control perspective.” In short, he says, he wants to know how everything in the cell fits together.

**THINKING LIKE AN ENGINEER**

Although Arkin is certainly not the only biologist trying to understand the cell as a system—as opposed to looking at it gene by gene or protein by protein—he is tackling the problem with a broad range of tools and techniques. Mathematical modeling, network analysis, computer simulation, laboratory experiments—he and the 20-plus postdocs and students in his laboratory are using anything that seems to work.

How else, he asks, can you see the underlying phenomena? Consider the neutrophil, a type of white blood cell that’s critical to the body’s defense against disease. This organism lacks eyes, hands and a brain, yet through chemotaxis—the ability to follow subtle chemical traces in the environment—a neutrophil can lock on to an invading pathogenic bacterium, track it down as it darts among the surrounding red blood cells and destroy it with the accuracy of a heat-seeking missile. “This is an incredible navigation system,” says Arkin. “But the number of proteins involved in that system is huge—in the hundreds, at least. We’re not going to understand that cell until we get some way of ordering this information. We need a theory to encompass it all. We need the data structures to hold it. And we need the knowledge representation that allows us to query it in clever ways and help us learn how it fits together.”

One way to pursue this goal, he says, is to use a wide variety of organizing principles. He embraces fields such as electrical engineering and communications theory, in which practitioners have long since evolved ways of analyzing complex networks.

Arkin holds up a printout: “Here is a network diagram for sporulation in Bacillus subtilis”—a harmless bacterium that, like its deadly cousin B. anthracis, the cause of anthrax, will sometimes turn itself into a hardy spore under conditions of stress. How does it make that decision? “Look at this, this and this,” he says, pointing to clusters of interactions that seem to have a similar structure. These clusters are examples of what he and his group have dubbed a regulatory “motif.” They all have a promoter to guide the expression of two genes: one is the activator for a process and the other is the inhibitor. If you think like an electrical engineer about such a system, he says, you can analyze how its overall behavior will arise from the push and pull of those two genes.

“It turns out that this regulatory motif has the ability to be a switch, a pulse generator or an oscillator,” he says, depending on how the push and pull are balanced. Furthermore, he adds, “You get the same pattern of regulation from evolutionarily unrelated proteins. So it’s the structure of the network that’s important, not the identity of the proteins.”

With that insight, you can model these subnetworks as components in an electrical circuit, or perhaps as active nodes in a communications web. “When you put those oscillators and switches back into the network,” Arkin says, “you can determine what its possible dynamics are at a higher level of abstraction. So if I were to perturb the cell by a change in the outside environment, I can begin to analyze how the signal is processed through the network to trigger sporulation or any other change in behavior. Though the same results could be derived from a full physical model, he adds, this high level of abstraction, if done correctly, could give us a much clearer pic-
tute of how cell behavior arises.

Of course, admits Arkin, this high-level, functional approach to cell behavior has plenty of skeptics, who wonder if electrical engineering bears anything more than a vague resemblance to biology. Nonetheless, he says, he and his students have already used the technique to produce some interesting preliminary models of B. subtilis and several other organisms. In addition, he and his group are collaborating with many other laboratories on a related approach to organizing knowledge of the cell: a kind of online biology network library and cell-simulation tool known as BioSPICE.

Arkin doesn’t claim to be the originator of BioSPICE, just one of its earliest and most vocal proponents—although he does take credit for the name. That came from an electrical-engineering tool called SPICE, the Simulation Program for Integrated Circuit Evaluation, which does pretty much what its name suggests. He says, “when I first started pushing the idea, there were already a couple of simple programs out there for cell simulation. But I meant BioSPICE to be more than that.” Indeed, he and his allies argued that the system should integrate every form of molecular data available, from DNA sequences to protein structures and beyond—and then provide a seamless interface for any cell simulation or network analysis a researcher wants to write.

That’s obviously a huge undertaking, says Arkin, which is why “it’s now DARPA BioSPICE, not just my BioSPICE.” In September 2001, when the Defense Advanced Research Projects Agency started funding multiple laboratories to work on various pieces of the project, Arkin became one of 19 or so principal investigators. Nonetheless, he says, BioSPICE remains “a major core” of his lab in Berkeley.

He calls up a portion of the program on his laptop. “At the heart of BioSPICE is this pathway diagramming tool, which is our interface with working biologists.” He shows the “cartooning” view, in which a stretch of DNA is a simple straight line, the various genes of interest are yellow ovals embedded in the line, proteins are free-floating blobs and various processes among these components are specialized lines. “But even in a cartoon there are issues of what you want to include,” says Arkin. “For example, the central dogma of biology is that DNA gets transcribed into messenger RNA (mRNA), which gets translated into a protein. But if you’re not going to be talking about the RNA in this experiment, you don’t want to show it.”

Indeed, in this particular view, the complex process of gene expression has been collapsed into a simple arrow connecting each gene to the appropriate protein. “But the software has to know that there is still an RNA in there somewhere,” says Arkin. If need be, in fact, the software allows the user to drill down and show not just mRNA, but its binding sites, cleavage sites, terminators and all the rest. It can go even further than that. “For example,” says Arkin, pulling up another display, “here’s where someone has drawn two proteins binding to DNA. But what does that mean? It could be that this guy binds first, then that guy. It could be the other way around. It could be that that guy binds, and he prevents this guy from binding. And so on. We

Supercomputers Appeal to Biology Undergrads

While the pioneering work of Adam Arkin’s team at the University of California, Berkeley, relies on a remarkably broad range of tools and techniques, such versatility may soon become standard operating procedure in biology labs.

Consider the University of Pittsburgh’s undergraduate course on computational biology, which apparently has no trouble luring biology students. They’re already computer-savvy, so what might have seemed overly technical, complex or irrelevant to their predecessors is challenging and downright exciting to this next generation of researchers.

“The idea that they can apply their interest in computers to biology is very appealing to them,” says Lewis Jacobson, associate professor of biological sciences and project director for the grant from HHMI that supports the course. The goal, he says, is to enhance the undergraduates’ research skills through the use of sophisticated programs and Web sites.

A prime attraction is access to the Pittsburgh Supercomputing Center—a joint effort of the University of Pittsburgh and Carnegie Mellon University—that enables the students to work on some of the world’s fastest machines. “Their sheer power is enormous,” Jacobson says. “The kind of stuff that would take your desktop [computer] hundreds of years to do, these computers can do in a second.”

The supercomputing center also has a large selection of software and databases, says Hugh B. Nicholas, Jr., one of its senior scientific specialists. “In the neurosciences, we have programs that simulate neurotransmitters going back and forth between nerve cells and muscle cells,” he says. “That is invaluable if you’re trying to study how the brain functions.” Throughout the course, students hear guest lecturers—from at least a dozen biological disciplines—who discuss the creative ways they’ve been integrating computers and biology. The undergrads take a shot at it themselves; at the beginning of the course, each student chooses a specific gene or protein and uses computers to learn more about it, explains course coordinator Eric Polinko.

One student studied a protein kinase that is associated with Alzheimer’s disease. He compared versions of the protein in everything from cows to fruit flies, finding that only portions of the protein remained identical in them all. These portions should represent the most important parts of the protein, and thus, the most interesting to study, Polinko says. “The computational tools will never replace experimental research, but they can point you in the right experimental directions.”

“These students get hands-on experience and come out with computer skills that will make them highly employable,” Nicholas adds.

—MARLENE CIMONS
have to allow users to put that kind of information down—even if it’s just to say that we don’t know how these proteins interact.

“So that’s one of the issues we’re really struggling with,” Arkin says: “How do we represent all that information? And how do we do it so that biologists who don’t know anything about computer models can navigate around this information with ease?”

A SOCIAL EXPERIMENT

Along the way, Arkin and his team have also been struggling with an unusually complex social dynamic. Between the programmers and the various flavors of scientists and engineers, his group spans 10 different disciplines: chemistry, chemical engineering, molecular cell biology, mathematics, physics, computer science, electrical engineering, bioengineering, mechanical engineering and bioinformatics. His lab has expanded from fewer than half a dozen members to more than 20 within the past two years.

Everyone is still working through the culture clash. “You can imagine that a student coming in gets very disconcerted,” says Arkin, “because the guy next to her is from a different field and looks like he knows infinitely more than she does. But he’s thinking the same thing about her. So they both look at each other and say, ‘My God, I’m unqualified for this job,’ and there’s that uncomfortable period of learning.”

It probably doesn’t help that members’ offices are scattered over all four floors of Berkeley’s Calvin building while their new lab space is being constructed. Nonetheless, they generally give Arkin high marks for his ability to build team spirit. He does it partly through his weekly group meetings and discussion sections, they say, but mostly through his rapid-fire personality.

“Adam just creates an intellectually stimulating environment,” says postdoc Christopher Rao, who is doing a comparative analysis of how chemotaxis is controlled in Escherichia coli and B. subtilis. “It’s not especially well-oiled, but this is exactly the kind of multidisciplinary research group that everybody says we need in biology.”

Arkin’s background is uncommonly eclectic. During his high school years, for example, the one-time trash collector became interested in the brain. “It seemed like a natural progression,” he explains, “the brain being an organic kind of machine. I found my way into a programming job in the neurosurgery department of a hospital in New York, where I learned my first laboratory skills. I had told them I knew all these computer languages—even to tailor the drugs to individuals.

“When I began to look at the endogenous pathways to control this entire process, I was just captured. And I started thinking, ‘That’s how it actually works! And I’m studying one protein!’ ” He wanted to understand it all, how it actually works! And I’m studying only one protein?” “The numerous pathways to control this entire process, I was just captured. And I started thinking, ‘That’s how it actually works! And I’m studying one protein!’ ”

Then, as an undergraduate at Carleton College in Minnesota, Arkin switched to physical chemistry—a field that he pursued through his early graduate-student years at the Massachusetts Institute of Technology (MIT)—until he found himself working with a biologist on a study of one of the proteins involved in photosynthesis. That was interesting enough, he says, “but when I began to look at the endogenous pathways to control this entire process, I was just captured. And I started thinking, ‘That’s how it actually works! And I’m studying only one protein!’ ”

“Being a geeky kind of guy,” says Arkin, “my hypothesis was that there had to be some form of control and computation inside a cell.” So in 1992, Ph.D. in hand, he left MIT for a postdoc with Stanford University chemist John Ross, who was studying how to make chemical reactions carry out computer-like operations. Just as he was finishing up his postdoc in 1995, he noticed a new paper about lambda phage (a virus that infects E. coli) by Stanford’s Harley McAdams and Lucy Shapiro. “It was actually a very, very nice paper,” he says, “but, young upstart that I was, I found lots of faults with it—most of which were beside the point of the paper. So I called them up and started an argument with Harley. It was a great argument! We had so much fun that we decided I should migrate to do a postdoc in their lab.”

“Harley was an amazing mentor,” says Arkin, “and so was Lucy. Harley was working very, very hard to pin down everything he possibly could about lambda phage. Together we came up with this theory that genes have to be expressed stochastically (that is, with lots of statistical fluctuation in the rate of expression), given the low number of molecules that control them.”

That finding was an eye-opener for many biologists, and it may well have been what got Arkin his next job at the Lawrence Berkeley Laboratory, located on the hillside just above the University of California campus. He arrived there in January 1998, joined the university’s faculty in July 1999 and became an HHMI investigator in October 2000. Perhaps more important, however, the finding crystallized his current commitment to systems biology: “What came of working with lambda phage,” he says, “was a renewed understanding that everything was connected—that there is order and principles to cellular control.”

His hope, Arkin says, is that this kind of systems work will eventually transform molecular biology into a kind of cellular engineering—a discipline in which practitioners can predict, control and design cellular materials as confidently as traditional engineers create, say, a new aircraft.

“Just look at the following Holy Grail problem,” he says. “Given a known genetic predisposition of human beings, and the network that controls a cell, predict the best place for a drug, or a combination of drugs, to move that cell from sickness to health. You want to be able to use cellular engineering to cut down the time to find drug combinations—or perhaps even to tailor the drugs to individuals.”

“There are other practical applications,” he adds, “for example, designing an organism that will metabolize, say, a dangerous heavy metal like mercury into a compound that we can immobilize, extract and put someplace safe.”

“It’s an interesting quest, in a knightly sort of way,” says Arkin, “and I think I want to take that on.”
EFFECTS TO UNDERMINE EVOLUTION
EDUCATION—MOST RECENTLY IN THE FORM OF A
CONCEPT CALLED “INTELLIGENT DESIGN”—HAVE EVOLVED
INTO A 21ST-CENTURY MARKETING CAMPAIGN THAT
RELIRES ON LEGAL ACUMEN, MANIPULATION OF SCIENTIFIC
LITERATURE AND GRASSROOTS TACTICS.

BY TRISHA GURA
ing it optional for high school students. The move is meant to ease pressure on the country’s children, according to a report in the April 25, 2002, Nature, but scientists are concerned about the impact on students’ understanding of biology.

Planting the Seed

The hullabaloo about intelligent design, says evolutionary biologist David R. Lindberg, director of the Museum of Paleontology at the University of California, Berkeley, “is all really a smokescreen to get back to basic ‘creation science.’”

This self-styled science sprung from creationism, which became a legal reality when John T. Scopes was convicted by the state of Tennessee in 1925 of the crime of teaching evolution. It wasn’t until 1957 that evolution made a classroom comeback, spurred in large part by Sputnik, which generated a competitive zest in Americans to be scientifically literate. Law solidified the turnaround in 1968 when, in Epperson v. Arkansas, the Supreme Court ruled that states cannot ban the teaching of evolution on religious grounds.

In response, creationists reframed their doctrine as creation science. During the 1970s, 22 states proposed that creation science and evolution be given equal time in classrooms, and two states—Arkansas and Louisiana—adopted the idea. Then in 1987, the U.S. Supreme Court struck anti-evolutionists down again, reaffirming a federal district court decision that creation science was, in fact, religion and therefore couldn’t be taught in schools.

While the decision appeared to be a victory for science, Justice Antonin Scalia left a loophole. “Teachers could still teach ‘evidence against evolution,’” he wrote. That tiny phrase, part of a larger opinion, became a seed that anti-evolutionists readily planted. They scoured the scientific literature and attended scientific meetings, with the purpose of finding and pointing out evolutionary “controversy,” as if the practice of science proceeds any other way.

Scientists do of course disagree on some of the specifics of evolution. For example, they argue about the exact positions that whales and hippos occupy on the tree of life and about the exact sequence of genetic changes that cause tumor cells to develop resistance to chemotherapy. Darwin’s theory hasn’t explained all these details—at least not yet, say scientists. But the devil is in the details.

Meanwhile, anti-evolutionists claim that these disagreements cast doubt on whether evolution ever happened at all—a completely willful misinterpre-

Evolution Online

Meanwhile, adults and children can turn to the Web to learn about Darwinian evolution.

The Museum of Paleontology at the University of California, Berkeley, is developing a Web site that features interactive laboratories. Targeting primary, middle and high school students, the site, supported by a grant from HHMI, will show how evolution affects people’s daily lives. Examples such as the human-microbe “arms race” of antibiotic resistance form the basis of the lessons.

Evolutionary biologist David R. Lindberg, the museum’s director, calls the Web site’s approach “less esoteric than exploring evolution by discussing why Darwin’s finches all have different beak sizes.” He recalls hearing a public service announcement last fall that reminded people to get their flu shots because “last year’s shot won’t protect you from this year’s influenza strain.” Why doesn’t last year’s vaccine work this year? The answer is evolution, Lindberg points out. Because viruses and infectious microbes have short life cycles, the rapid development of new strains of flu is really an evolutionary event.

People don’t commonly think about evolution in the context of one year, nor is evolution part of their picture of disease and medical treatment. Yet such examples can bring difficult concepts home for students and adults alike. “Knowing that some people simply cannot get a penicillin shot to fight an infection because the bacterial strain they carry has evolved to resist the drug,” Lindberg says, “gives evolution real meaning.”

For more information: www.ucmp.berkeley.edu/history/evolution.html

For more information: www.ucmp.berkeley.edu/history/evolution.html

The Evolution of Intelligent Design

The intelligent-design concept stems from the work of English theologian William Paley, who in 1802 developed the idea in his book Natural Theology. He compared particular biological structures, such as the eye, to a watch. Just as this timepiece does not self-assemble, Paley wrote, the intricate designs of living things implicitly argue for the hand of a “watchmaker.”

In 1989, Percival Davis at the Hillsborough Community College in Tampa and Dean Kenyon at San Francisco State University resurrected the 200-year-old watchmaker argument. In their book Of Pandas and People, they maintain that classic Darwinism—which states that organisms evolve over long periods of time as a result of random change and mutation—cannot explain the structural complexity of life. Therefore, they conclude, life had to be created by an intelligent designer.
By the mid-1990s, the “scientific” component of intelligent design began to form. In 1996, for example, Michael J. Behe, a biochemist at Lehigh University, in Bethlehem, Pennsylvania, laid out his theory of “irreducible complexity.” In his book *Darwin’s Black Box: The Biochemical Challenge to Evolution*, Behe argues that systems like the bacterial flagellum—a whip-like appendage that propels the creature through biological fluids—has several parts that are necessary for its function. In the absence of any of those parts, the flagellum doesn’t work. If evolution moves stepwise from first conception to today’s version, intermediate forms should be able to function. Because they don’t, Behe argues, the fully made structure must be designed.

Not surprisingly, the intelligent-design concept has met with criticisms—the main one being, according to molecular geneticist Bruce T. Lahn, that “there is no evidence for it.” Lahn, an HHMI investigator at The University of Chicago, says that intelligent design, by scientific definition, cannot be a theory because it cannot be tested, only believed. What’s more, he notes, no account of intelligent design or its conceptual siblings has ever appeared in any peer-reviewed scientific journal.

The Discovery Institute’s Stephen C. Meyer says that intelligent design proponents haven’t published articles in peer-reviewed journals because the scientific community is “biased” against intelligent design and therefore won’t accept it. “They are excluding publication of a viable hypothesis,” Meyer asserts.

Amid the debates, intelligent-design proponents are making their mark, as evidenced by that Cleveland Plain Dealer poll. With its convoluted arguments and lack of evidence, how is intelligent design gaining such support?

“We’re dealing with emotional issues,” says board member Joseph D. Roman, who cochairs the subcommittee that will decide the issue in Ohio. There may be other factors as well, including the way intelligent design is being presented. One argument states that evolution is just a theory, intelligent design is also a theory; therefore, the two deserve the same time in classrooms. They “are exploiting Americans’ sense of fairness,” says Wisconsin’s Carroll.

The anti-evolution approach is being considered on the local level simply because that is where many educational decisions are made in this country, notes Lindberg. Board members are accountable to state legislators as well as to the community members who elect them. This produces incredible disparities between science curricula district-by-district and even school-by-school.

If intelligent design or some other “alternative” to evolution makes it into the state curriculum standards, it will likely dictate the content of textbooks, statewide proficiency exams and teacher certification. “Teachers are very much aware that they have to teach to tests,” says molecular biologist Joan L. Slonczewski at Kenyon College in Ohio, who runs an HHMI-funded outreach program for science teachers. They must also satisfy parents. If parents object to the teaching of evolution, for example, and teachers refuse to comply, their jobs are on the line, says Slonczewski. To skirt the problem, many teachers avoid evolution altogether—or wait until the last week of school, when no one has time to voice an objection.

This flight (as opposed to fight) approach is having an effect. Slonczewski and Carroll, both of whom teach biology, say that some students are arriving at college knowing little or nothing about evolution.

**Treading Lightly**

Teachers aren’t the only ones grappling with wide-ranging views about evolution. Similar disparity is playing out in zoos, museums and community programs, partly as a result of teacher actions (or inactions).

“I have been here for over eight years and I have not had one teacher ask us to cover evolution,” says Brad Batdorf, curator of education at the Sedgwick County Zoo in Wichita, Kansas. On the other hand, he reports, some teachers, parents and other visitors have asked not to be taught anything about evolution.

That puts Batdorf in a quandary. The zoo is receiving an HHMI grant to develop activities that boost scientific literacy. At the same time, community groups also provide funding to the zoo. His strategy is to tread lightly around the issue. Descriptive signs at the zoo often have subtle references to evolution, but Batdorf says he stresses respect for the creatures and their ecological relationships, rather than how they came to be.

Slonczewski is also trying to be sensitive. She is structuring her outreach program so that evolution is not a separate lecture for teachers but intricately woven into all of biology as an explanation for change—in everything from viral mutation to wing development in fruit flies to immunity in human beings.

Lindberg at the Museum of Paleontology, who last July received a grant from HHMI to develop an interactive Web site on evolution (see sidebar), is promoting evolution with no apologies. “K–12 science classes should reflect what scientists call science,” he explains.

Carroll agrees: “Love your religion, but don’t try to wrap it up and tell me it’s science. For the United States to remain a technological leader, we have to understand what science is—and teach it.”

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**FOR MORE INFORMATION:**

UC Museum of Paleontology:
www.ucmp.berkeley.edu/historyoflife/histoflife.html

Discovery Institute: www.discovery.org

National Center for Science Education—an organization that defends the teaching of evolution in public schools:
www.nccseweb.org

WGBH Boston Evolution project—a PBS miniseries with online teaching tools: www.pbs.org/wgbh/evolution

What do you think? Send us your comments:
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Call of the Wild

Could quirky, new animal models help scientists learn how to regenerate human limbs or avert the debilitating effects of a stroke?» » »

By Kathryn Brown

BAT EMBRYO
Differences in when and how identical genes are expressed mean humans have fingers and bats have wings.
Humans bear little resemblance to squirrels and even less to a bacterium that thrives in tins of irradiated horsemeat. But these and other far-flung creatures are offering new insights into the human condition. Although only a handful of organisms—notably fruit flies, nematodes and mice—have dominated comparative biology, scientists are casting a wider net for the biological lessons they say are lurking undiscovered in the wild.

HHMI investigator Sandra L. Wolin, at Yale University School of Medicine, and colleagues came across the bacterium *Deinococcus radiodurans*—the most radiation-resistant organism known—while studying proteins involved in two autoimmune diseases: systemic lupus erythematosus and Sjögren’s syndrome. Researchers have marveled at *D. radiodurans* since the 1950s, when they discovered it flourishing inside tins of meat that had been heavily irradiated during food-sterilization experiments.

A computer specialist working with Wolin, Anne Marie Quinn, was scanning a microbial genome database when she realized that *D. radiodurans* produces a protein strikingly similar to an RNA-binding protein found in humans, called Ro. People with lupus often make antibodies against their own Ro protein, though no one knows just how Ro functions.

To learn more about Ro’s role, a postdoctoral fellow in Wolin’s lab, Xinguo Chen, created a strain of *D. radiodurans* that lacked the protein. The resulting bacteria were no longer so hardy; they died when exposed to ultraviolet (UV) radiation.

“One fascinating thing is that lupus patients with antibodies against Ro often have serious sensitivity to sunlight,” Wolin says. Perhaps, she suggests, a lupus patient’s antibodies interfere with Ro in skin cells, leaving the patient sensitive to sunlight. Her team now hopes to unravel Ro’s precise role. Wolin suspects Ro binds RNAs damaged by UV radiation and targets them for destruction.

**Hints from Hibernation**

For some 50 years, a small group of researchers has studied hibernating animals such as the woodchuck and ground squirrel for clues to treating stroke. During a stroke, a person’s blood flow and oxygen in the brain plummet. Much the same occurs as animals begin hibernating, though these sleepers stay safe until spring, when they awaken unscathed. “Hibernation is nature’s solution to enduring in the face of very low oxygen and blood flow,” says John M. Hallenbeck, a senior investigator at the National Institute of Neurological Disorders and Stroke in Bethesda, Maryland.

How do hibernators do it? Over the past decade, researchers have shown that hibernating squirrels basically shift biochemical gears, suppressing metabolism and immune response while boosting antioxidant defenses, among other adjustments. “The key is that all these things happen at once,” Hallenbeck says, and this convergence yields potent results. “These ground squirrels have pretty dramatic protection against brain injury,” notes neurochemist Kelly Drew of the University of Alaska in Fairbanks.

More recently, Drew decided to see just how well hiber-
nation helps an animal resist brain injury. She and her colleagues inserted microdialysis probes into the brains of five Arctic ground squirrels, two hibernating and the others awake as usual. Several days later, the team compared the squirrels’ brains. Those that were hibernating at the time of the probe-induced injury fared well, with very little tissue damage. By contrast, the active squirrels showed clear signs of injury—significant cell damage and inflammation of the surrounding brain tissue. “These strikingly different responses do support the idea that hibernation is a good model of neuroprotection,” says Drew, whose team published the study in the June 2001 issue of the American Journal of Pathology.

If researchers can identify hibernation’s key biochemical steps, Hallenbeck suggests, it may be possible to induce a similar process in stroke patients. Emergency paramedics, for instance, could deliver drugs that minimize brain damage during, or immediately after, a stroke. “In a clinical setting, you’d want a patient’s metabolism to drop to some minimal level, while generating molecules that suppress inflammation and fight free radicals,” Hallenbeck says. Scientists still have much to learn about hibernation, and no one knows whether nature’s long winter nap will inspire realistic stroke therapies. Drew, for one, is optimistic.

Reviving Old Models
Some of the new creatures being studied are merely rediscoveries of some of science’s old models—such as the bat (see page 32)—that fell out of favor when biologists began training their microscopes on fewer organisms. “If you go back to the 1800s or earlier, you’ll find scientific sketches of bat embryos,” remarks Richard R. Behringer, a molecular geneticist at the M.D. Anderson Cancer Center in Houston. “In fact, there’s a heritage of reproductive biochemistry and molecular biophysics in diverse organisms, with a wealth of knowledge to be gained by doing comparative studies.”

About five years ago, Behringer decided to combine embryological studies of mice with research on bats. “We all say we’re studying this or that animal to learn more about human biology and disease,” says Behringer. “If that’s true, we should start questioning the relevance of our models. At some stages of development, human embryos are very different from mouse embryos. So you start thinking, why am I studying the mouse? How does it relate to humans?”

Bats may look like flying mice—but in many other ways, they distinctly differ. As the embryos develop, for instance, bats grow wings, with cape-like webbing between their digits. But mice, like chicks and humans, lose these “interdigital cells,” and their digits or fingers form with no webbing in between. All four creatures probably share the same limb-development genes—they just express those genes during different developmental windows, says molecular biologist Lee Niswander, an HHMI investigator at the Sloan-Kettering Institute in New York. “How do changes in gene expression give rise to these evolutionarily important differences in animals?” Niswander asks. “If we can understand how these limbs develop in bats, we’ll gain insight into the process in the chick, mouse and human.”

The flatworm is another old model with a new twist. At the University of Utah in Salt Lake City, biologist Alejandro Sánchez Alvarado decapitates freshwater planarians—only to watch those fragments regenerate into

A Living Biology Lesson
It’s a velvety green caterpillar. It’s a tough brown pupa. It’s a large, mottled gray moth.

*Manduca sexta*, or the tobacco hornworm, is all of the above, which is one reason (or three reasons) why the popular biology-lab animal has become a pet and living science lesson in the primary grade classrooms of Tucson, Arizona. The *Manduca* Project, run by the University of Arizona’s department of biochemistry and molecular biophysics with a grant from HHMI, helps teachers exploit the 40-day life cycle of the hornworm to capture the attention of first, second and third graders.

Although the young *Manduca* breeders don’t realize it, they’re also honing their powers of observation and expanding their knowledge of biological systems, diversity, metamorphosis and the relationship between structure and function—all elements of Arizona’s state science education standards. The project also addresses math standards as the children measure and graph the growth of their hornworms. Some classes have composed songs and poems about their multilegged pets.

More than 3,500 first, second and third graders so far have raised tobacco hornworms from egg to moth. University of Arizona undergraduates, who work with the teachers and children to study these insects, take what they learn back to their own labs for further exploration. Kim Keene, for example, did her senior research project on a digestive enzyme that helps *Manduca sexta* move through its many molts and rapid growth.

—JENNIFER BOETH DONOVAN

FOR MORE INFORMATION  
[www.manducaproject.com](http://www.manducaproject.com)
fully formed worms. “Flatworms have figured out how to access all their developmental processes at any given point during their lifetimes,” he says. “In this day of genome sequencing and developmental insight, it’s possible that we could learn a great deal about regeneration and stem cell biology from planarians.” For example, if scientists discovered the basis of nature’s regenerative talents, people who lost limbs to accidents or illness might ultimately be able to grow replacements.

When Sánchez Alvarado began working with flatworms six years ago, many of his colleagues derided his choice as “career suicide.” In developmental biology, after all, Caenorhabditis elegans was the worm to watch. But soon his lab began documenting genes found in planarians and humans, but not in C. elegans or fruit flies. “These may be missing pieces of evolution,” he says, “and it’s definitely a viable scientific endeavor.”

In fact, while some researchers debate whether adult-mouse stem cells can reliably turn into different tissues, others are uncovering the molecular-mechanics systems of naturally regenerating animals. These animal architects include hydra polyps, tadpoles, zebrafish, newts and planarians. So far, Sánchez Alvarado’s lab has found about 5,000 independent markers of gene expression, called expressed sequence tags (ESTs), in the flatworm Schmidtea mediterranea. His group and others are now crafting assays to profile gene expression during regeneration. The big task will be to pinpoint responsible genes—and their human homologs, if any, adds Sánchez Alvarado. “We don’t know whether regeneration is the same, molecularly, across organisms,” he concedes. “But the genetics could tell us.”

Even nature’s farthest corners—and tiniest creatures—may hold hints for humans. “Biology often makes progress by looking at extreme cases,” says Hhmi President Thomas R. Cech. Because all life is related through evolution, he says, scientists trust that biology’s extremes apply in more mundane settings as well. Cech speaks from experience. In the 1980s, his team at the University of Colorado, Boulder, discovered self-splicing RNA, or ribozymes, in a lowly pond organism, the ciliated protozoan Tetrahymena thermophila. Since then, scientists have recorded and sequenced 1,800 examples of this type of RNA spread across much of biological life.

While Cech advocates making the most of known animal models and their advanced tools, he also sounds the call for creative comparisons. “The best insights often come when you stop to compare vastly different species,” he says.
Intelligent Design Is a Cop-Out

This creationist ploy, if taught as science, could stop discovery in its tracks.

By Nipam H. Patel

I first became aware of the “intelligent design” movement a few years ago while doing research for an evolution textbook. Although we were designing the book for a college undergraduate course, I needed to know what was being taught at the elementary and high school levels in order to see the impact of various school-board decisions on curricula and to assess the likely effect of these curricula on students’ preparedness for college-level work. As I searched the Web for information, I was dismayed to come across sites describing this latest “evolution,” as it were, of the creationist movement.

Intelligent design proponents argue that many biological processes and structures are too complex to have evolved, and thus the only way to explain their existence is to suppose that they were constructed by an intelligent designer. This is not so much a theory in its own right as a vehicle to attack the scientific study of evolutionary biology, which creationists like to denigrate as “just a theory.” And they are quick to fall back on the tired old claim that scientific debate on the mechanisms of evolution somehow suggests that many scientists do not believe that evolution is a fact.

The intelligent design community has written several books that offer its views and “evidence.” In response, the science community has directly addressed, and rebutted, those arguments. In Abusing Science, Philip Kitcher provides examples of the kinds of evidence to support evolution that creationists claim is lacking. Robert Pennock in his book, The Tower of Babel, documents the confusions and inconsistencies that make up tenets, such as “irreducible complexity,” that are central to the intelligent design arguments.

In the end, arguments and counterarguments on intelligent design come down to a clash between faith and science and attempts to interject religion into science. While open debate is an essential component of our society, as is freedom of religion, the most troubling aspect of this movement for me is the notion that intelligent design should be taught alongside evolutionary biology in schools as an alternative “scientific” theory. This would send a wrong, even absurd, message about what science and scientific inquiry are all about.

Intelligent design implies that some “investigators”—those who’ve concluded that certain biochemical pathways or cellular structures, for example, are too complex to have evolved—have hit a wall in their “science” that they deem insurmountable. Is this what we tell our students is proper behavior when coming up against walls, or do we encourage them to have the creativity and tenacity to overcome such barriers?

I think that the majority of researchers enter science because they enjoy exploring the unknown, deciphering mysteries and feeling the thrill of solving one section of the puzzle at a time. To succeed, scientists must approach research with determination and resolve, because discoveries rarely come easily. Intelligent design, however, suggests that once a question becomes too complex, we should just throw up our hands and invoke supernatural intervention as an explanation, instead of continuing to explore deeper.

Scientists cannot claim to have all the answers, and we realize that currently well accepted theories may be overturned and replaced, but this happens because we continue to question, explore and test the world around us. And we do so while believing that we will find explanations and that questions—seemingly impossible to answer, or even address, today—eventually will be answered if we persevere. It is essential that we teach our students that this is the way science is done.

Where would our society be if an intelligent design-like approach had dominated our thinking in the past? We’d have very little of our current knowledge and treatments of diseases. We’d have scant understanding of the pull of gravity, the structure of the solar system, the constituents of matter, the uses of energy, the nature of living things, the science and technology that so improve the quality—and duration—of our lives. Worse yet, where would we be headed in the future if we taught our children this defeatist and backward approach to investigating the real world and its place in the universe?

While the intelligent design agenda is directed most specifically at evolutionary biology, we need to realize the effect that teaching such an approach would have on all areas of scientific inquiry. It is bad enough that students often enter college with a poor background in evolution, but if they harbor the more general idea that scientific advances—in whatever field—have distinct boundaries that can only be crossed by resorting to explanations outside the realm of science, we will be in serious trouble indeed.
It’s Friday afternoon, and Mario Godoy-Gonzalez’s science classroom at Royal High School in the rural Washington farming community of Royal City fills with the sweet smell of mint, cilantro and oregano. The aroma comes from the fresh herbs that Godoy-Gonzalez’s students diligently mash with mortars and pestles. Eventually, the leaves turn to lumps of damp paste, which will be refrigerated until Monday. That’s when the class will use a lineup of chemicals to check the plants’ liquid extracts for nutritional compounds: copper hydroxide and sodium citrate to test for sugar, 2,6-dichloroindophenol sodium salt for vitamin C and iodine for starch. They will also determine how much of each plant is water and how much is mineral.

Godoy-Gonzalez is not teaching a science class, per se. His is a unique English as a Second Language (ESL) program that uses hands-on science as a general educational tool. His students learn English—as well as history, geography and math—partly by wielding micropipettes, pouring gels, running polymerase chain reaction machines and participating in projects that one would normally expect to find only in advanced biology classes.

Most of Godoy-Gonzalez’s students are children of migrant farm workers who tend eastern Washington’s apple orchards. The students arrive speaking very little English; often they come from small rural villages in Mexico where formal education is limited. “Many of my students bring to this country the idea that they will get some education,” says Godoy-Gonzalez. “But most of them believe their future is just on the field picking apples. I want them to see that they have other options.”

This gutsy experiment began in 1994 when the Royal City school district, responding to a boom in the apple economy and an influx of migrant workers, hired Godoy-Gonzalez, an immigrant from Chile, to run the ESL program. Godoy-Gonzalez was given the tough task of developing a curriculum that would keep students in school and give them a fighting chance at graduating. He turned to science for several reasons. For one
thing, these students were culturally close to nature. For another, passing mainstream science was one of the toughest obstacles on their road to graduation. There was only one problem—Godoy-Gonzalez himself knew very little about science.

So he sought help wherever it was available. During his first year, he enrolled in the Summer Institute in Life Science, an HHMI-sponsored program at the University of Washington in Seattle, which introduced him to hands-on science instruction. Since then, he has participated in other enhancement programs, including the HHMI-supported Science Education Partnership at Seattle’s Fred Hutchinson Cancer Research Center, where secondary school teachers partner with faculty scientists for hands-on science workshops and research experiences. He even spent two summers assisting scientists who use DNA microarrays to study the genetics of plant-seed dormancy.

Like apple growers diverting water to their orchards, Godoy-Gonzalez has channeled this knowledge straight to his classroom with activities that bring lessons to life. When he taught about the stars and planets, members of the Yakima Astronomy Club accompanied his students and their families on a late-night stargazing session, bringing telescopes that were powerful enough to pick up vivid detail in the Moon’s craters. After learning about volcanoes, Godoy-Gonzalez gave his students shovels, and they began digging in a nearby roadside. Several inches down, they were amazed to find a layer of ash from the 1980 eruption of Mt. St. Helens.

In the past two years, 16 of Godoy-Gonzalez’s students have gone on to community college. One is studying agriculture at Washington State University. Another is en route to becoming a doctor. “Had we not had Mario and the program he has developed, these kids would have been lost,” says the school’s principal, Jack Hill. “They would have dropped out.”

In 2000, Godoy-Gonzalez was named the state’s migrant teacher of the year. His model is both simple and practical, says Sylvia Reyna, program supervisor at Washington’s Migrant Education Program. “He really is making some pathways for others to follow.”

**Lost on the Tip of the Tongue**

Memory loss is a common complaint among the elderly. In the early stages of Alzheimer’s disease, conjuring up a memory becomes an impossible chore. In both cases, according to HHMI investigator Susumu Tonegawa, the memories are sitting dormant in the brain; the challenge is retrieving them.

“As all of us age, we experience some memory impairment in which we have more trouble remembering, say, the name of a person we definitely know,” says Tonegawa, who directs the Picower Center for Learning and Memory at the Massachusetts Institute of Technology (MIT). “We feel like the name is just on the tip of the tongue, but it won’t quite come.”

Tonegawa led a team of researchers, including then HHMI postdoctoral fellow Kazu Nakazawa, in identifying a gene involved in the type of memory-retrieval process called pattern completion—the ability to recall complete memories from partial cues. Their hope is that this work, published May 30, 2002, in *Science Express*, the online version of *Science*, and in the July 12, 2002, issue of *Science*, may ultimately lead to new or better targets for drugs that help counter some of the deficits of Alzheimer’s disease and relieve those frustrating “senior moments” that begin to emerge in middle age. Tonegawa’s coauthors included colleagues at MIT and scientists at Baylor College of Medicine in Houston and Hokkaido University School of Medicine in Japan.

For these studies, the researchers generated and analyzed mice with a genetically altered hippocampus, a brain structure involved in learning and memory. They showed that the CA3 region of the hippocampus is responsible for the retrieval of complete memories from partial cues—and that age or disease might impair the functioning of this region.

Mathematical models of memory from the 1970s suggested that, based on its anatomy and wiring, the CA3 region of the hippocampus was a likely center for associative memory, says Tonegawa. Pattern completion was hypothesized to be a key function of such associative memory centers, he says. But, until now, researchers have not had a tool to test this hypothesis in live animals. Tonegawa and his colleagues developed a method called “spatial targeting” that enables them to knock out a gene in a specific area of the brain. For this study, they knocked out the gene for the NMDA receptors in the CA3 region. The neurons in the CA3 region are wired together in a characteristic way—each sends axons that synapse onto themselves or other cells of the same kind, forming a “recurrent network.” When the NMDA receptors are knocked out, the efficiency of the nerve-signal transmission throughout this network is drastically compromised, according to Tonegawa.

The researchers engineered the mutant mice so that the gene for the NMDA recep-

"Memories are sitting dormant in the brain; the challenge is retrieving them." —Susumu Tonegawa
N E W S & N O T E S

tor ceased functioning after the animals had matured—eliminating the possibility that knocking out the gene would affect development of the CA3 region. They were able to show that the CA3 region functioned normally except for the NMDA receptor.

To test the effect of disabling the NMDA receptor, the scientists studied how both normal and mutant mice behaved in the Morris water maze, which consists of a pool filled with murky water that has a small platform hidden just beneath the surface. A black curtain surrounds the dimly lit pool, and on the curtain in each of four directions the scientists placed visual cues consisting of distinctive spotlighted patterns.

In their experiments, they found that normal and mutant mice placed in the pool were equally capable of learning and remembering where the hidden platform was located. The researchers saw stark differences, however, when they removed three of the four visual cues and tested the animals’ ability to recall the platform’s location. “Normal animals had no problem remembering where the platform should be, based on only one cue,” says Tonegawa. “But the mutant animals showed a severe impairment in recalling the memory based on partial cues. It was a very specific deficit.”

In addition to the behavioral testing of the knockout mice, researchers in collaboration with coauthor Matthew A. Wilson of MIT studied the neurophysiological basis of the CA3 deficit. They used microelectrodes to measure the electrical activity of specific cells in the CA1, another region of the hippocampus (which affects its output and overall performance), as the animals explored an open arena surrounded by four visual cues. They found that when three of the four visual cues were removed, the knockout mice showed impaired ability to reactivate the hippocampal cells that had become active when the animals were first acquiring memory of that location.

“The combination of behavioral and neurophysiological studies of these knockout mice constitutes a very rigorous demonstration of the importance of the CA3 NMDA receptors in associative memory recall,” says Tonegawa.

—DENNIS MEREDITH

Biology by Numbers

The mapping and sequencing of tens of thousands of genes from humans, fruit flies, yeast and several other organisms has created a data windfall for research into the long-standing question of how the living world came to be so diverse. The interpretation of this trove of information requires a new breed of scientist.

Enter Carlos D. Bustamante, 27, who has assembled a formidable collection of skills for attacking questions about evolution. A recent Ph.D. from Harvard University, where he had an HHMI predoctoral fellowship, Bustamante has firm grounding in classical biology, population genetics and molecular biology and is well versed in computational and statistical methods of analysis.

Darwin of course focused on natural selection—the preservation of traits that enable organisms to adapt to specific environments—as the chief force propelling evolution. Even he, however, noted that natural selection wasn’t the only evolutionary force. In more recent times, scientists have argued that small, random changes in the frequency of genes in populations—known as genetic drift—can increase certain genes’ prevalence even when they don’t confer a selective advantage. The question of how much of the genetic differences between species is due to natural selection and how much to random processes is still hotly debated.

Sorting out the enormous number of molecular variations that occur within and between organisms in order to examine the effects of evolutionary forces poses a huge mathematical challenge. As lead author of an April 4 paper in Nature, Bustamante used advanced statistical tools to study this question in the fruit fly (Drosophila) and the mustard

Carlos D. Bustamante uses statistics to sort out questions about evolution.

weed (Arabidopsis). He and his colleagues deployed their statistical firepower, including a tool developed originally in statistical physics known as the Markov-chain Monte Carlo method.

“The novelty about the statistical approach used by Bustamante is that it allows the information from multiple different genes to be combined in a statistically rigorous way,” says Rasmus Nielsen, a population geneticist at Cornell University who was second author on the Nature paper. “This allows us to learn much more from large data sets,” such as those involved in the Drosophila and Arabidopsis research, says Nielsen.

The study revealed that both genetic drift and natural selection have been involved in the evolution of genes in the two species but that the process is not the same in both because Drosophila and Arabidopsis have different mating systems. In Arabidopsis, negative selection (selection against new variants) is dominant, presumably because of high levels of self-fertilization. In contrast, in Drosophila, which does not self-fertilize, positive selection (selection for new favorable variants) dominates.

Daniel L. Hartl of Harvard, a population geneticist who oversaw Bustamante’s Ph.D. work, hailed the Nature paper as “gorgeous. It opens the door to a genome-wide analysis of protein evolution in virtually any organism.”

While he was still in high school, after immigrating to the United States from his native Caracas, Venezuela, Bustamante was drawn to the work of evolutionary biologist Stephen Jay Gould and geneticist Richard C. Lewontin, who were both at Harvard. After
transferring to Harvard for his sophomore year of college, Bustamante got himself posted as an undergraduate researcher in Lewontin's lab and as a teaching assistant for Lewontin and Gould, who died in May 2002. Bustamante now looks back on both assignments as “incredibly formative experiences.” For his part, Lewontin calls Bustamante one of the best students he has ever had and a scientist who appears headed for great success and leadership in his field.

In his graduate work at Harvard, Bustamante developed statistical methods for using genetic data from any type of population to test evolutionary hypotheses. He immersed himself in graduate-level statistics courses, ending up with a master’s degree in statistics as well as a Ph.D. in biology. This training has set him apart; Lewontin comments that parts of the Nature paper are so arcane that “the number of people who can read it critically must be counted on the fingers of one hand.”

Bustamante’s interests are not only in the realm of theory. He is working on applying his method to human evolutionary issues. By identifying genes that have been especially important in human evolution, it may be possible to find genes that play a role in susceptibility to disease. Such genes could become targets for new drugs that would interact with these genes or their proteins.

Following a fellowship year at Oxford University with one of the world’s top groups studying theoretical population genetics, Bustamante will join Nielsen in Cornell’s new department of biological statistics and computational biology as an assistant professor.

“The biologist of the future may not have a ‘wet lab’ at all,” says Nielsen. “The generation of data is so cheap right now, what’s needed is someone like Bustamante who can sit down and make sense of it.”

“I don’t think there’s been a more exciting time” to be in the fields of evolution and genetics, says Bustamante. “Historically, population genetics has been theory-rich and data-poor. Not so today. ‘We have tons and tons of data.’”

—RICHARD SALTUS

Students Love the Details

An unscientific-looking instrument that resembles a small blow-dryer on a long cord is revealing life’s tiny details to school children. Students only have to touch the fat end of the device to a butterfly wing or to an embryonic fish, and instantly a finely focused image of a lacy wing scale or a developing organ flashes onto a television screen for all to see.

Kelly Riley, a 7th-grade life sciences teacher in East Baton Rouge, Louisiana, loves the device, known as the “Scope-on-a-Rope” video microscope (SOAR). “It is the best laboratory instrument I have ever had, and I apply it in every single unit I teach,” she says. “Kids break down the door in their eagerness to use it.”

Her sentiments are echoed in K–12 school systems across the country, as more teachers learn about the miniature, self-lit video camera with interchangeable magnifying lenses. The versatile, lightweight device—called the VL-7EX by its manufacturer, Scalar Corporation of Tokyo, Japan—can

Undergraduate Grants Foster Teaching, Interdisciplinary Courses

How can research universities encourage undergraduate students and postdoctoral fellows to develop their teaching skills?

What can universities do to bring disciplines such as genomics and computational biology into the undergraduate curriculum, and how can they best expose undergraduates to the interdisciplinary nature of modern biology?

How can institutions of higher learning encourage more minorities to pursue careers in science?

To support innovative answers to these questions, HHMI has awarded $80 million in four-year grants to 44 universities. Washington University in St. Louis, for example, will receive $2.2 million over four years to establish a science-education fellows program. After completing traditional summer-research fellowships, students who are interested in science education can spend another summer in science classrooms developing educational materials. These fellows will pursue a novel, five-year combined-degree program leading to a bachelor’s degree in science and a master’s degree in teaching.

A $2.2 million grant will enable the University of Colorado at Boulder to develop the Genomics Teaching Place, a combination laboratory and teaching facility where undergraduates and K–12 students and teachers can study genomics, bioinformatics and computational biology. Montana State University will use its $1.9 million grant to develop a six-week summer-research program for high school students and teachers from Montana’s seven Indian reservations. A $2 million grant to the University of Maryland, Baltimore County, will help the university develop an undergraduate academic and community-support program—targeting minorities underrepresented in the sciences—modeled after the university’s successful Meyerhoff Scholarship Program supporting minority achievement in science.

—JENNIFER BOETH DONOVAN

» For a list of new grant recipients: www.hhmi.org/news/070902.html
Robert Kao wondered at age 13, was in the yellowish liquid that his mother threw away after soaking soybeans in water to make soy milk? That simple question led Kao to work in a laboratory at the National Cancer Institute (NCI) before he graduated from high school, and to a research finding with potential applications in cancer prevention and treatment. The yellowish liquid, called soybean leachate, contains a mixture of water-soluble compounds. Kao remembered reading in a gardening handbook that it might benefit plant growth. Over the next several years, he carried out a series of school experiments that led to a contrary finding: Soybean leachate actually retarded the growth of corn plants. “I began thinking to myself, if it inhibits plant growth, maybe it would inhibit cancer cells,” he recalls. Kao got the opportunity to test his premise through an HHMI-supported program that each year enables up to 20 public high school juniors and seniors from Montgomery County, Maryland, to perform supervised research at the National Institutes of Health (NIH). “The students who succeed in the program are the ones who always want to know ‘why’—and who keep working to find an answer,” says Lesli Adler, one of Kao’s science teachers at Thomas S. Wootton High School in Rockville, Maryland, and leader of a two-week laboratory course that prepares students for their year of NIH research. Most teens in the program assist NIH scientists with ongoing institute research projects. But Kao persuaded cancer researcher Michael J. Birrer to allow him to pursue his own soybean-leachate investiga-
tion in Birrer’s NCI lab.

Many researchers have sought to isolate cancer-preventing agents from soybeans; epidemiological studies indicate that a diet rich in soy-based foods correlates with lower rates of some cancers in Asian countries. Yet Kao was surprised to find that no studies had been done on soybean leachate’s composition or its effects on cell growth.

Working with Virna D. Leaner in the Birrer lab, Kao tested soybean leachate and several proteins extracted from it on two ovarian cancer cell lines—one slow growing, one fast growing—as well as on normal ovarian cells and a line of breast cancer cells. The leachate had minimal effect on the breast cancer cells and the normal ovarian cells. But, stunningly, it stopped growth in breast cancer cells and the normal ovarian cancer cell lines. The leachate had minimal effect on the breast cancer cells and a line of breast cancer cells. The leachate had minimal effect on the breast cancer cells and the normal ovarian cancer cell lines. But, stunningly, it stopped growth in both ovarian cancer and breast cancer cell lines.

The findings proved so novel that NCI filed a provisional patent application on them. This gave the institute one year to do additional research and file a formal application—a rare if not unprecedented result from a high school student’s NIH research. The work also won Kao recognition in the 2001 Intel science awards.

Kao’s work has been backed by the strong support of his family. He is the son of Taiwanese parents who have encouraged his scientific endeavors. His father, Tzu-Cheg “David” Kao, is a biostatistician on the faculty of the Uniformed Services University of the Health Sciences, the military’s medical school in Bethesda, Maryland. His mother, Pheng-Fan, is a homemaker who took responsibility for making sure her son got to the laboratory on time. While doing his research at NCI, Kao lost an uncle to a malignant brain tumor, reinforcing the young scientist’s commitment to his study. “He taught me the human side of cancer,” Kao says.

In the fall of 2001, Kao entered Boston College in Chestnut Hill, Massachusetts, which he chose because it is close to a big city but is not an urban campus. While Kao focused on his studies as one of 50 freshmen in the university’s Emerging Leader Program, Birrer, his NIH mentor, was following up on his intriguing experiment.

Birrer sent a sample of the most active soybean-leachate extract to NCI’s labs in Frederick, Maryland, where it was tested against 60 different cancer cell lines.

“It didn’t show what they considered a robust activity,” Birrer reports. Kao took the news calmly. “Well, that’s a bummer,” he said to Birrer on hearing the disappointing result, “but where do we go from here, and what are your suggestions?” Kao later explained that he was “prepared for anything,” knowing that the lab in Frederick would use different testing methods than those he had used.

Birrer, meanwhile, doesn’t regard the Frederick lab results as final. “It may be that there are multiple factors in there that need to be used in concert,” he says. Last summer, NCI put its patent application on hold, and Kao was back in the Birrer lab, working to confirm his original findings and to isolate, identify and test some of the compounds in the leachate.

Although he plans a career in science, Kao hasn’t yet decided whether to pursue an M.D., Ph.D. or both. By any reckoning, he’s off to a flying start. “It is conceivable that he has identified an overlooked source of potentially active anticancer molecules,” Birrer says. “But whether or not the soybean leachate works out to be a cure for cancer, Bob is going to be a very good cancer researcher.”

—PATRICK YOUNG

HHMI Professors Promise to Break the Mold

HHMI has named 20 university scientists as the Institute’s first HHMI professors. Each will receive $1 million over four years to put his or her creativity, which is usually focused on research, to work in undergraduate classrooms. For example, one professor plans to create a “community of scholars,” enlisting undergraduates as early as their freshman year to partner in research teams with more advanced undergraduates, graduate students, postdoctoral fellows and faculty. Another will target non-science majors with a lecture and laboratory course on genetic engineering that addresses legal and social issues as well as the underlying molecular biology.

“We wish to empower scientists at research universities to become more involved in science education and come up with really innovative ideas that break the mold and take a fresh look,” explains Institute President Thomas R. Cech. “HHMI seeks to develop a cadre of scientist-educators who will become leaders in undergraduate teaching as well as research. The HHMI professors and their teaching strategies will serve as models for fundamental change both on their own campuses and elsewhere, helping to support and encourage research universities in their efforts to enhance undergraduate education.”

Manuel Ares, Jr. University of California, Santa Cruz
Uttaip Banerjee University of California, Los Angeles
Sarah Elgin Washington University in St. Louis
Ellen Fanning Vanderbilt University
Hillary Godwin Northwestern University
Bob Goldberg University of California, Los Angeles
Jo Handelsman University of Wisconsin–Madison
Graham Hatfull University of Pittsburgh
Ronald Hoy Cornell University
Elizabeth Jones Carnegie Mellon University
Darcy Kelley Columbia University
Mary Lidstrom University of Washington
Richard Losick Harvard University
Yi Lu University of Illinois, Urbana-Champaign
David Lynn Emory University
Rebecca Richards-Kortum University of Texas at Austin
Alanna Schepartz Yale University
Tim Stearns Stanford University
Graham Walker Massachusetts Institute of Technology
Isiah Warner Louisiana State University and A&M College
Viral Cousins

Three broad classes of viruses exhibit unexpected parallels in the way they reproduce. Although each type of virus copies its genes differently after commandeering the genetic machinery of the host it infects, researchers have found that the viruses all use similar structures to do so. This finding suggests that major groups of viruses may have similar evolutionary origins. If so, identifying such a connection may be the first step to devising new treatments for a wide range of viral diseases.

HHMI investigator Paul Ahlquist and colleagues at the University of Wisconsin–Madison engineered yeast to support the replication of brome mosaic virus—a well-characterized, positive-strand RNA virus—to better understand its behavior and replication. Positive-strand viruses are the largest class of viruses; they include the viruses that cause hepatitis C, polio and the common cold.

As the researchers were building a picture of the positive-strand replication process, they realized that many of its characteristics were similar to those of both double-stranded RNA viruses (such as rotavirus, which kills about 1 million children annually in developing countries) and retroviruses (a group that includes HIV). They found, among other discoveries, that two important positive-strand virus proteins, 1a and 2a polymerase, directly parallel the functions of two retrovirus proteins, Gag and Pol.

“We found detailed similarities involving multiple protein and RNA functions in central steps of replication,” says Ahlquist. He and his colleagues reported their findings in the March 2002 issue of the journal Molecular Cell.

These findings and others suggest that all three classes of viruses originated with a common ancestor. “One reason we are excited about these results,” says Ahlquist, “is that they suggest that common strategies might be developed against multiple types of viruses.”

www.hhmi.org/news/ahlquist.html
Guiding Blood Cells with VEGF

Researchers may have figured out how blood cells reach their final destinations in developing embryos. They’ve discovered that vascular endothelial growth factor, or VEGF, a protein better known for guiding the growth of new blood vessels, including those that nourish cancerous tumors, also helps to direct blood cells along specifically marked routes. In fact, evolutionarily speaking, this may have been VEGF’s original calling.

The movement of blood cells has been well documented in adult mammals, but the cells’ migration during development is not understood. To learn more about the molecular processes underlying cell migration, HHMI investigator Mark A. Krasnow at Stanford University and his team turned to Drosophila melanogaster, the common fruit fly. Because VEGF is vital to blood-vessel formation in adult mammals, the researchers thought it might have an analogous role in the fly. Instead, they saw that the VEGF pathway is directed at developing blood cells. VEGF proteins line many of the routes that blood cells travel, and the proteins’ function there is to activate the VEGF receptor on the blood cells, telling them when and where to migrate.

When the researchers inactivated the gene for the VEGF receptor, they found that blood cells never reached the posterior region of the body; they couldn’t find their way to their normal destination. “These results support a scenario in which chemical migration signals are placed at many positions along the migration pathway,” says Krasnow. “It’s a bit like attracting a duck by leaving a trail of bread crumbs.” He and colleagues at Stanford and the South San Francisco–based biotechnology company Exelixis reported their findings March 22, 2002, in the journal Cell.

The work suggests that blood vessels may have evolved from blood cells, according to Krasnow. Other researchers have shown that the VEGF pathway plays a critical role in hemangioblasts, a type of early stem cell that gives rise both to blood cells and the endothelial cells that become blood vessels. It had not been clear why these two major cell types are linked developmentally, but Krasnow believes his results provide an explanation.

“If during evolution of vertebrates a subset of blood cells acquired the ability to form tubes through which other blood cells can move, then endothelial cells are really just a highly specialized type of blood cell, all of which arise from a common stem cell and some of which continue to express VEGF receptors and use VEGF signaling for later steps in their development or function.”

HHMI Lab Book written by Steven I. Benowitz
Animal Magnetism
—and other creative ways to show kids, and teachers, the practical side of science

What makes physics and engineering essential to medical science? In Cleveland, a group of inner-city teens and secondary school science teachers know the answer. In fact, they know a number of answers.

In a program of school-year and summer workshops developed by biomedical engineering faculty at the Cleveland Clinic and supported by a grant from HHMI, students from John Hay High School and science teachers from all over Cleveland are learning that heart-valve and joint replacements—operations that have become almost commonplace—could not be saving lives and restoring mobility without the contributions of physics and engineering. Magnets, too, are proving useful in a variety of clinical and research settings, although it’s admittedly “a challenge to present magnets and magnetism in an attractive and stimulating way,” says Maciej Zborowski, a Cleveland Clinic researcher. He rises to the occasion, however, in a teachers seminar on physics in medicine by showing that indeed, as he puts it, “everything is magnetic.”

One of Zborowski’s favorite teaching tools is a levitating frog that’s featured on the Web site of the Nijmegen High-Field Magnet Laboratory in Amsterdam. Teachers and their students agree that one movie of a live frog floating upward—inside a magnetic-field system that exploits the ordinarily weak though inherent “molecular magnetism” of all living things—is worth much more than the proverbial thousand words. Students and teachers tend to be familiar with ferromagnetism; they’ve seen small magnets attract iron filings or nails. But they learn from Zborowski that there are other kinds of magnetism, as the frog graphically demonstrates; that magnetism of metal differs from magnetism in biological organisms; and that magnets can separate liquids as well as solids. In his research at the Cleveland Clinic, for example, Zborowski uses magnets to separate embryonic stem cells from their diffuse surroundings.

Concepts such as force at a distance, vector mechanics and calculus come to life for the students and teachers in the hands of Zborowski’s colleague William A. Smith. He shows them his work in progress: a magnetic screw that would make an artificial heart longer-lasting because it would pump with no friction and no wear. Force is transmitted magnetically rather than by the thread contact of a traditional nut-and-screw arrangement. Smith hopes his magnetic screws will last three times longer than today’s screws. Only additional research will tell. “We are 5 years away from clinical trials in humans and 10 years from this being a product on the shelf,” he says.

“Too often in schools and even in colleges, there is a failure to make any connection between what’s learned in the classroom and solving real-world problems,” Smith adds. “We must show teachers practical applications of scientific principles. We must help young people understand how what they are learning is directly involved in the development of better technologies.”

Brian Davis, another Cleveland Clinic researcher, heads the HHMI-supported community science education programs there. A biomedical engineer, he has a flair for the dramatic that quickly captures teens’ and teachers’ attention. “How do you make a dead foot walk?” he asks, proceeding to describe his research using a robotic device that attaches to the tibia or shinbone of a human cadaver and moves the eight leg tendons that are required for walking. Eventually, he hopes, the robot will help amputees move their prosthetic legs and feet more normally.

Next, Davis displays some failed joint replacements—real human knees and hips encased in cubes of epoxy. Examining them, teachers and students learn the anatomy of the joints and the kinds of materials that do and don’t work in replacements. Finally, all adjourn to the operating theater to watch a live joint-replacement operation.

Janeth Eby, a curriculum specialist at the Cleveland Clinic, has helped Davis and his colleagues turn their hands-on study of failed joint replacements into a Web-based lesson for high school students. She also helped develop a second unit, on heart valves; a third—one on the spine—is coming. The heart-valve unit, which uses a lasagna noodle as a model, teaches another valuable lesson: A model need not resemble the object or system it’s modeling. “In science,” Eby points out, “it is more important for a model to work the same way than it is for them to look alike.”

—JENNIFER BOETH DONOVAN
Science teacher Janeth Eby, at left, shows John Hay High School students Arielle Bell, Josephine Williams and Edy Hasrouni how to use cooked lasagna noodles to model the action of the heart valve opening and closing. A plastic bottle squirts water through the "valve" to model the pumping action of a ventricle. Students see the effects of calcification on heart valve function when parts of the noodles are left uncooked, hardened like a calcium deposit: The lasagna tears after just one or two pumps of water from the bottle.

About to enter 12th grade at John Hay High School in Cleveland, Leonard Curry is already skilled in tissue dissection. Here he prepares a sample of myocardial tissue for subsequent materials testing. Known stresses are applied to a material such as a heart valve, and the subsequent stretching or compression is measured. Curry is working on studies to determine the relative contributions of proteins such as elastin and collagen to the overall stiffness or flexibility of a heart valve.

Cleveland Clinic researcher William A. Smith is designing blood pumps using magnetic screws to reduce friction and wear. High school student Kemetta McBride watches him test an artificial heart in a fluid-filled chamber that mimics the blood pressures found in living patients.

Project director Brian Davis uses real, failed joint replacements encased in epoxy to show students how biology, physics, mathematics and medicine work together in designing artificial joints and understanding why they fail.

FOR MORE INFORMATION
The frog that learned to fly: www-hfml.sci.kun.nl/froglev.html
A study of failed replacement joints: www.lerner.ccf.org/education/k12/biomaterials/
H HMI international research scholars from 29 countries converged in June on Cairns, Queensland—the tropical north of Australia—for a unique set of face-to-face scientific exchanges.

Russian, South African and Mexican researchers compared notes on tuberculosis research while Argentine and Swiss scientists conferred on pathogen-survival mechanisms. Scientists from Canada, Hungary and the Czech Republic discussed their respective studies of signaling pathways. An Israeli who investigates trypanosomes learned about the work of a Venezuelan and a German directly from those scientists, who study similar parasites.

Hosting the meeting were HHMI’s 11 Australian research scholars: Deidre Carter, Ross Coppel, Alan Cowman, Brendan Crabb, Simon Foote, William Heath, Gunasegaran Karupiah, Malcolm McConville, Geoffrey McFadden, Magdalena Plebanski and Louis Schofield. Coppel, a professor at Monash University (Victoria), chaired the local organizing committee.

The international scholars also gave formal presentations on their latest work. Marcelo Rubinstein of Argentina, for example, described a novel mouse model for testing the role of dopamine D4 receptors in attention deficit and hyperactivity disorder. Australian Louis Schofield discussed his animal-model studies of a synthetic antitoxin vaccine that protects against the most severe effects of malaria.

While they were in Queensland, the research scholars also managed to see some of the locale’s exotic environment. They visited a rainforest habitat where they met kangaroos, crocodiles, pythons and other native creatures, and they spent an afternoon exploring the Great Barrier Reef.

To help maintain research efforts around the world—in many countries, under difficult economic circumstances—HHMI supports the research of competitively selected biomedical scientists in their home countries in the Baltics, Eastern and Central Europe, the former Soviet Union, Canada and selected countries of Latin America. The program also supports scientists throughout the world who are studying infectious diseases and parasitology.

—JENNIFER BOETH DONOVAN
On Stage and Off, This Lawyer Performs

When Joan S. Leonard was a full-time mother of two small children in the 1970s, she organized informal concerts at her home. A violinist and a cellist joined Leonard at the piano to entertain friends with renditions of Mozart and Schubert piano trios. Issues of scientific discovery and intellectual property were not on her radar screen.

Today, Leonard is vice president and general counsel of the Howard Hughes Medical Institute, responsible for all of HHMI’s legal affairs. She still enjoys being on stage—most recently accompanying James R. Gavin III as he crooned Sinatra favorites during his farewell to Institute staff. She contends that HHMI itself should move more squarely into the spotlight.

“We make enormous contributions through our research, and we can play a larger public role—in fact, I think we should,” she says. “As more and more public policy issues involve sophisticated scientific concepts that appear daunting to the person on the street, the Institute has the ability to be a trusted source of advice as to what the science is and what it means.”

Leonard has already helped HHMI stand out in public discussions about intellectual property—an increasingly hot issue as more corporate money flows into basic research and the lines blur between academic and commercial laboratories. In 1997–1998, she served on an advisory committee to the National Institutes of Health (NIH) that examined limitations on access to research tools and demands made by companies for “reach through” rights. The most publicized example among many was DuPont and its popular technique for developing genetically engineered mice, called cre-lox. The company began requiring users to give it rights to whatever discoveries were made using the technology. “Many scientists felt that it was the equivalent of Microsoft claiming rights to a book you wrote because you used Word to compose it,” Leonard says.

This was an area ripe for public confrontation. Academic scientists had assumed they could use whatever technologies they needed in the laboratory without worries of infringing patents. After all, their work was for the public good. When companies started becoming more aggressive about what scientists could do with their patented tools, the researchers balked.

Ultimately, DuPont responded to NIH concerns and developed a license for academic and nonprofit users with few restrictions. “A workable approach to difficult intellectual property issues has to acknowledge the realities of the marketplace as well as the research laboratory,” Leonard says. “In the NIH advisory group, I saw the valid, deeply held and often antagonistic perspectives of scientists, academic institutions, biotech companies and pharmaceutical concerns.”

Leonard’s participation in these debates grew out of the role her office plays in implementing HHMI’s strict rules on investigator relationships with industry. For example, investigators are limited to 36 days of consulting per year and must obtain Institute approval to consult. Institute lawyers carefully review every agreement and approve only if all terms are acceptable. In 2001, Leonard’s staff successfully negotiated more than 740 materials-transfer agreements, 12 collaborations with industry and another 200 or so consulting arrangements; they also reviewed more than 74 licenses of technologies developed by HHMI scientists.

When Leonard attended law school after 15 years at home, she was intent on becoming a tax attorney. Well on her way to building that career, a different door opened. She joined HHMI in 1992 as a general practice, in-house lawyer when she was hired by then General Counsel José Trias, who had worked with her at the Washington, D.C., law firm of Paul, Weiss, Rifkind, Wharton and Garrison.

Two years later, she became general counsel under horrific circumstances: Trias and his wife Julie Gilbert were murdered during a robbery of their home. HHMI staff were devastated, but Leonard soon had to decide whether to assume Trias’ role as general counsel. “José had mentored us to be good lawyers,” she said. “We had assembled a group on the strength of José’s vision for this office, and I felt a responsibility to pursue it.”

Leonard says she’s proud that Trias’ vision endures today. Each of her staff of six lawyers is a generalist first, handling all the legal issues—from personnel to intellectual property—facing HHMI scientists. Each lawyer also cultivates two or three specific subject areas, such as investment or immigration issues. “José wanted an office in which people had a real sense of what this institution does,” Leonard adds. “The lawyers come here because they’re interested in the mission, and they feel most effective in that mission if they’re engaged in a range of work that includes contact with investigators and their laboratories.”

Leonard considers herself very lucky to be where she is today. “Raising two children was the best job I’ve ever had,” she says. “This is a real close second.”

—CORI VANCHIERI
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Twenty years after scientists determined the cause of AIDS, a cure still evades us. What is it about this virus?

» Married to the work
Meet HHMI investigators whose partners at home are their best collaborators in the lab.

» When economies collapse
Researchers in Argentina and other Latin American countries are struggling to keep their laboratories afloat as their nations’ economies sink.

Let the Sun Shine How have humans, mice, plants and insects evolved to make the best use of light?