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Janelia Farm: A Progress Report
HHMI broke ground for its new research campus, Janelia Farm, last May. When completed in 2006, the facility will house a wide range of scientific programs in a world-class research environment. We’ll take a look at how construction is progressing and plans are proceeding.

Science and the Liberal Arts College
From the push toward hands-on undergraduate research to the building boom in new science facilities, many signs suggest that science at liberal arts colleges is stronger than ever. And liberal arts colleges still produce a disproportionate share of next-generation Ph.D. scientists and engineers. What’s the story behind these trends?

DNA Repair
Damage to DNA occurs all the time. Keeping the genome in top shape requires a network of genes and enzymes to sense and repair that damage. As investigators begin to understand how DNA repair machinery works, they are also gaining insight into fundamental mechanisms that contribute to disease and aging.

Is there a formula for living a long life?
Genes, and Longevity

Howard Hughes Medical Institute Bulletin

Helen Hobbs || Brett Finlay || Science in Chile || Lessons from Lipids

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Cover photograph by Ed Kashi, from the project Aging in America.
Lab Management Demystified
Bridging a gap in young researchers’ training.

To most fledgling scientists, launching an independent research lab is an exhilarating—and daunting—prospect. It’s a lot like getting your first driver’s license, says HHMI President Thomas R. Cech. “Suddenly you have all this freedom to turn where you want to turn, go straight when you want to, and go as fast as you like.”

But along with the freedom comes responsibility, he adds. “On the other hand, you have to pay for the gas. And if you bump into someone, you have to deal with the consequences.”

To help smooth the way for new investigators, HHMI and the Burroughs Wellcome Fund (BWF) joined forces to publish a book—Making the Right Moves, A Practical Guide to Scientific Management for Postdocs and New Faculty. The new resource is designed to demystify pertinent issues not typically addressed in formal graduate and post-graduate education.

The book grew out of presentations and discussions at a course developed and sponsored by both institutions and held at HHMI in July 2002. The five-day course had 128 participants who were current or former recipients of grants from HHMI or BWF. All were either newly appointed academic faculty members or senior postdoctoral researchers hoping to benefit from the wisdom of experienced investigators who were once in a similar position.

“As investigators, we don’t teach graduate students and postdocs the kind of lab management skills they need when they become, essentially, the manager of a small business,” says Peter J. Bruns, HHMI’s vice president for grants and special programs who was also on the faculty at Cornell University for more than 30 years.

Considerable time and effort went into designing the course curriculum. HHMI and BWF staff, with assistance from colleagues at the American Association for the Advancement of Science, convened focus groups of advanced postdocs and newly appointed faculty—physician and nonphysician scientists alike. They also sought input from the sponsoring organizations’ senior researchers and other professionals, including executive coaches.

The book details the broad range of topics covered in the course—negotiating a faculty position, hiring and firing staff, mentoring, time management, and more. Such challenges as establishing research collaborations and sorting through the technical nuts and bolts of university administrative policy are also addressed.

“This stuff seems like it’s a big secret, but it’s not,” insists Maryrose Franko, a senior program officer in Bruns’s department who was instrumental in developing the course. “We’re interested in the long-term success of our awardees,” she says. “Making the Right Moves will help them hit the ground running.”

“Usually these things are learned haphazardly,” adds Martin Ionescu-Pioggia, Franko’s counterpart at BWF, who shared responsibility with her for the content of the course and the book. “We wanted to create a more formal means of providing this information.”

Course participants and other grant recipients will be given a copy of the book to keep handy as a lab resource. In the interest of reaching a broader audience, the publication has also been made freely available for downloading from the HHMI Web site (www.hhmi.org/labmanagement). The Web version features videos of course keynote presentations as well as live links to other informative sites.

The book “is not meant to be comprehensive or prescriptive,” Bruns points out, “but we think it’s a good starting point from which we are planning follow-up activities.” The two institutions are now in the midst of organizing a similar course, to be held in 2005, which will have a new slant. In addition to training newly minted scientists, invitations will be extended to several institutions, societies, and associations that are interested in organizing similar courses for their own constituents. Lessons learned through this “train the trainers” approach will be published as a supplement to the current guidebook.

“The ultimate solution is for such a course to be offered by home institutions,” says Bruns. “It should become part of the standard education for scientists.”

— MARY BETH GARDINER
Global Science

As the recent crisis involving transmission of the SARS virus demonstrated so vividly, today’s health problems have no respect for national boundaries. They require an immediate global response—and a biomedical research infrastructure capable of generating the knowledge necessary to address them. The challenge is greatest in the developing world, where AIDS has become endemic and where long-established infectious diseases, such as malaria and tuberculosis, affect millions.

Earlier this year, representatives of science academies from all over the world gathered at the United Nations to assess global science and technology in developing countries. The InterAcademy Council, which includes the U.S. National Academy of Sciences, highlighted the critical need for investments to create the physical, human, regulatory, and financial infrastructure necessary for scientific research and technological innovation. Recommendations made in the Council’s report, “Inventing a Better Future,” focused on the importance of training and retaining young scientists and engineers, fostering public-private partnerships, providing science and technology education at all levels, and building regional networks of collaboration.

Building a strong foundation of scientific knowledge and capability beyond the United States is a cornerstone of our three international programs at the Institute. Since 1991, HHMI has invested more than $100 million in a global network of scientists in 32 countries who make important contributions outside the U.S. research establishment. In that time, we have often seen how a research grant to a single scientist can benefit nearby researchers, whether through training opportunities for students, shared electronic access to top journals, or equipment made available to colleagues.

Our programs now include scientists around the globe, with an emphasis on diseases that disproportionately affect the world’s poor populations. This issue of the HHMI Bulletin profiles one such scientist, Canadian microbiologist Dr. B. Brett Finlay, who conducts research on a strain of *Escherichia coli* implicated in a deadly form of diarrhea.

Over time, the international scholars supported by HHMI have become part of a productive and dynamic scientific community. One way we leverage individual efforts to achieve even greater impact is through our annual meeting of international research scholars—in 2004 we will convene in Tallinn, Estonia. Such meetings lead to collaborative research projects and educational programs that cut across national boundaries. For example, two scholars who share a research interest in tuberculosis are now collaborating between their respective home countries of South Africa and Australia. In South and Central America, where a parasitic infection called Chagas disease affects more than 18 million people, HHMI-supported scientists are collaborating in the development of potential antiparasitic agents.

HHMI is also looking at a variety of other ways to leverage its support for international biomedical research. For example, young scientists traveled to Bangladesh last year from as far away as Guatemala, Malawi, Peru, and Thailand for a course sponsored jointly by HHMI and Britain’s Wellcome Trust. They worked for two weeks with an international faculty to learn advanced techniques that would help their research in infectious disease. Equipment purchased for the program by HHMI was donated afterwards to the International Centre for Diarrhoeal Disease Research, based in Dhaka. We will support comparable programs this year in Argentina and Uruguay.

This year, HHMI is seeking applicants for two international programs—one for scientists whose work focuses on infectious disease and parasitology and the second for biomedical researchers in the Baltics, Central and Eastern Europe, Russia, and Ukraine. The 80 recipients, who will receive $50,000 to $100,000 a year for five years, will be announced in 2005.

These are not, of course, the only ways in which HHMI participates as a member of the international community of science. Indeed, many HHMI investigators devote considerable energy to enhancing the research infrastructure of their home countries. For example, Dr. Tian Xu has been working to strengthen the ties between Yale University and his alma mater, Fudan University in Shanghai. Dr. Bruce Walker, whose work is highlighted in this issue, is helping to create a research center dedicated to studying HIV at the Nelson R. Mandela School of Medicine of the University of KwaZulu-Natal in South Africa.

These efforts, whether undertaken by HHMI as an institution or by its individual scientists, represent a significant commitment to supporting the research of talented scientists in their own countries. In sustaining an international scientific tradition—or in helping to create one—the Institute fulfills an important dimension of that part of its mission that speaks to biomedical research “for the benefit of mankind.”

Thomas R. Cech
President
Howard Hughes Medical Institute
Fatty acids are intriguing molecules,” says researcher Marina Kniazeva. “We know that DNA stores information and proteins carry out specific functions, but what do fatty acids do in this scheme?” Kniazeva grapples with that question as a senior research specialist in the lab of Min Han, an HHMI investigator at the University of Colorado at Boulder.

Although his lab has focused on many other cell and developmental biology problems, Han and his colleagues recently backed their way into research on fatty acids, the building blocks of lipids. Searching for a gene mutation that causes a form of retinal degeneration in humans, Kniazeva, Han, and colleagues at other institutions collaborated to identify an enzyme that elongates fatty acid chains. The finding is the first to link a disruption in a fatty acid elongase directly to a disease state.

Kniazeva and Han realized that determining how a defect in this enzyme led to the retinal disease would take extensive molecular and genetic studies. They decided to apply the tools they know the best, genetics, to investigate how fatty acids are made and their functions regulated. “Little is known about why there are so many various fatty acids and why their proper levels are important. This is still a wide-open area,” he says. “We decided to take a look.”

A Different Breed

Fatty acids are made up of carbon chain backbones, which can be saturated (with no double bonds) or unsaturated (with double bonds that cause kinks in the chain)—traits that make them a different breed from, say, proteins. For one thing, the study of the oily, uncharged properties of fatty acids requires a special set of biochemistry skills and instruments. Lipids have different structures than proteins, and, unlike proteins, lipid structures do not necessarily hold information about their function.

Scientists know that some lipid molecules like cholesterol circulate throughout the body; others get incorporated into the zipper-like molecules of the cell membrane. One famous group, the omega-3 fatty acids found in certain kinds of fish, are thought to help prevent heart disease. Changes in fatty acid profiles have been linked to diseases such as cancer. And because lipids make up more than half the weight of our brains, the balance of various fatty acid levels is likely to be important in the central nervous system. For the most part, though, researchers still don’t understand how the fatty acid composition of cells affects daily operations or how it might cause disease if that profile gets out of whack. And because fatty acids are not synthesized directly from DNA, as proteins are, studying them requires indirect genetic manipulation: Han’s lab can exploit the genes that make the enzymes that direct the synthesis of fatty acids, but not the fatty acids themselves.

“It’s a difficult field to start with,” says
Han, “and because we are not lipid people we need to learn a lot. And we will get a lot of scrutiny. So it’s a risky area for us to get into.”

But Han is a betting man. After middle school, he worked on a farm for four years in China. He crammed three years of high school into seven months of self-tutoring to get into Beijing University. He was later selected through an examination to come to the United States for graduate study in molecular biology. But like any good betting man, Han tries to play his cards to advantage; his lab studies not humans, but the much simpler system of the transparent, 959-cell, 1-millimeter-long roundworm, *Caenorhabditis elegans*—their chosen lab model for the last 12 years.

“Fatty acid profiles are pretty much the same for all worms,” he says. “We’ll use the worms to study how these enzymes are organized to maintain precise levels of fatty acids.”

**How Worms Respond**

To understand how worms respond to raising and lowering different fatty acids, Kniazeva and Han came up with an approach that blends classic genetics and biochemistry with cutting-edge genomic technology.

In the first round of their approach, the team knocked out eight of the predicted elongase enzyme genes in worms using RNA interference (RNAi). The technique causes worm cells to destroy the RNA message that would normally direct a cell to make a specific elongase. The RNAi effectively shuts down production of the enzyme, thereby dramatically reducing the level of the fatty acids it generates. Having this kind of control allowed Han’s lab to begin to characterize the elongases and their corresponding products.

Results of the first round of studies, published in the January 2003 issue of *Genetics*, showed that the ELO-2 enzyme acts to elongate palmitate, a 16-carbon fatty acid, into longer chains with 18 and 20 carbons. If the enzyme is knocked out using RNAi, then palmitate piles up and the longer-chain fatty acids decrease. The upset in the fatty acid profile causes multiple problems for the worms, which grow slowly, lay fewer eggs, and change their rhythmic digestive pattern.

Such diverse and serious disruptions hint at the importance of having just the right balance of fatty acids. Two other elongase knockouts, ELO-5 and ELO-6, led to lower levels of branched fatty acids whose functions in animal cells are not clearly understood. These worms stopped growing abruptly at the first larval stage, indicating that these fatty acids must be crucial to worm growth and development. (This work has recently been submitted for publication.)

The second round of the approach involved running a DNA microarray analysis on two elongase knockout worm strains. By surveying the whole worm genome, the microarray tells Kniazeva which genes’ expression levels go up or down in response to the missing enzyme and fatty acid. From those results, she picked a number of candidates that seemed most likely to be involved in regulating fatty acid production. Now, she has made RNAi knockouts for 25 genes and used gas chromatography to get the fatty acid readout from each one. From the analysis, they have identified genes that are likely to be involved in branched fatty acid production. If need be, the team will go back and do a microarray analysis for knockouts of these regulatory genes as well, repeating the process until each gene and its corresponding enzyme or protein is placed in the correct spot of the fatty acid synthesis pathway. The group has learned a great deal from the previous work of other lipid researchers, including Michael S. Brown, HHMI Trustee Joseph L. Goldstein, and HHMI investigator David J. Mangelsdorf, all at the University of Texas Southwestern Medical Center at Dallas.

These days, Han says, you have to look at the whole genome to get the complete picture. “And as a worm geneticist,” he says, “it makes it easy to go after functions.” Observing the RNAi-treated worms should quickly reveal any problems in muscle, nerve, feeding, or reproductive systems that the disrupted fatty acid metabolism may cause.

Han explains why he thought the problem of fatty acid regulation was worth taking the lab down a new path: “Since not many people are working in this area, our contribution to science as a whole can be bigger.” And besides, he says with a gambler’s grin, “As a scientist, I have to have the attitude that I have nothing to lose.”

—KENDALL POWELL
When it comes to getting a start in this world, flies don’t dillydally. After fertilization, a one-celled egg in the fruit fly (Drosophila melanogaster) takes but three hours to develop into a hollow oval containing some 8,000 cells. Ten minutes later, sheets of cells from the edge of the sphere stream into the center, establishing what will become Drosophila’s internal tissues and organs. In less than a day, the tiny fly larva works its way out from its eggshell. Youth lasts just four days, by which time the larva has outgrown two stages of skin and burst into adolescence as a pupa. Then, over another four days, multitudes of larval cells die while select clusters of cells multiply within the darkness of the pupal shell. What had been a pale fleshy worm emerges, reincarnated as a glistening adult fly.

Carl S. Thummel, an HHMI investigator at the University of Utah School of Medicine, recently found that a particular chemical plays several key roles throughout the beginning stages of Drosophila’s life. And that finding may offer scientists clues about how humans develop.

**Mysterious Pulse**

The key chemical that punctuates each milestone in a fruit fly’s life—molting, pupa formation, metamorphosis—is ecdysone. Ordinarily, Thummel says, the standard approach to the problem would be to use mutants: isolate a line of flies in which one of the genes for ecdysone signaling is so disrupted that it no longer functions. The thinking is that if ecdysone is necessary for proper embryonic development, then ecdysone-signaling mutants should suffer embryonic defects. But the problem with this strategy is that mother flies deposit ecdysone precursors and ecdysone receptors in the egg; to completely erase ecdysone signaling in the embryo, maternal ecdysone would have to be disabled as well. Unfortunately, researchers are unable to do that—as in vertebrates, the steroid is needed for female fertility. A female fly without ecdysone signaling would be unable to produce the embryos that scientists need for their experiments.

Thummel challenged postdocs in his laboratory to come up with a clever way around this quandary, but none succeeded. An off-campus meeting in November 1998 brought an enlightening revelation. Thummel met with fellow HHMI investigator and fruit fly enthusiast Michael B. O’Connor at the University of Minnesota Medical School. O’Connor’s group had discovered a gene that encodes a critical biosynthetic enzyme for making ecdysone during embryonic stages. The name of the gene, disembodied, hints at what happens to flies with a mutation in the gene. They die even before completing embryogenesis, failing in a number of key developmental processes. This effect was the first concrete evidence that ecdysone is required for embryogenesis, consistent with the high levels of ecdysone seen in embryos. But what was the hormone doing, and where did it come from?

**Rigging Genes**

In the era of Watergate, “Deep Throat” told...
Carl Thummel sees intriguing parallels between the fruit fly and mammals.

reporters Woodward and Bernstein to “follow the money.” Tatiana Kozlova, Thummel’s postdoctoral associate, pursued a parallel strategy: Follow the ecdysone. Kozlova reasoned that if she could determine exactly where the hormone was located within the embryo, she might be able to infer how it got there and what purpose it was serving. The researcher ultimately did so by exploiting ecdysone’s ability to turn on specific genes. Adapting a tool devised by molecular biologists some 40 years ago, Kozlova transferred a gene called lacZ—which encodes an enzyme that can stain cells a deep blue—from bacteria to flies. And she rigged the gene so that it could be turned on only in the presence of ecdysone.

To Kozlova’s surprise, the blue staining was concentrated in one region of the embryo, the amnioserosa, providing evidence that this tissue was the primary source of active ecdysone in the early embryo. Though little was known about the amnioserosa, which doesn’t become part of the fly but somehow supports embryonic development, it was known that the amnioserosa is essential for a critical developmental event called germ-band retraction—a coordinated movement of a set of cells that gives rise to the internal organs and nervous system, among other key body parts. The staining indeed occurred during the time when germ-band retraction took place, suggesting to Kozlova and Thummel that ecdysone from the amnioserosa might have a role in coordinating this event. The researchers also noticed other developmental defects, similar to those seen in O’Connor’s ecdysone-deficient “disembodied” mutants, adding further credence to their hypothesis.

Corroboration came when Kozlova and Thummel devised a way to inactivate ecdysone receptor proteins in fly embryos by forcing them to produce “dominant negative” receptors, containing mutant versions of the proteins that interfere with the normal function of the receptors. Almost every embryo died, and most showed signs that they had failed to undergo proper germ-band retraction, arresting development before the larva could be formed. The findings were reported in the September 26, 2003, issue of Science.

Kozlova and Thummel realized that, taken together, these ecdysone-dependent events represented a sort of metamorphosis within the embryo—linking the hormone to a series of changes that converts the developing entity from a nondescript ball of embryonic cells into a young larva.

Thummel says the discovery is important on two levels. First, it shows that there are two stages—one in the embryo and one in the pupa—during which ecdysone directs major coordinated cell movements that form an entirely different body plan for the fruit fly. Second, the work provides an unexpected and intriguing parallel between the insect amnioserosa and the mammalian placenta, both tissues serving alongside the embryo to supply the steroid hormones critical to ensuring proper growth and development into a viable creature.

—PAUL MUHLRAD
Walter E. “Skip” Bollenbacher had the best of intentions. In 1989, brimming with ideas for improving science education at North Carolina’s historically minority universities, he won a grant from HHMI’s undergraduate science education program to go out and do it.

But Bollenbacher, a professor of biology at the flagship University of North Carolina at Chapel Hill, had forgotten to do one thing: to find out what the historically minority institutions themselves wanted and needed.

“I was very skeptical” when Bollenbacher came calling, recalls Ronald Blackmon, dean of the school of mathematics, science, and technology at Elizabeth City State University. “I had seen this kind of thing before. A big institution with few previous ties to minority universities thinks it has the prescription for improving science education, and they try to give us that medicine. Usually they just pay lip service and go away when things don’t work.”

That’s probably what would have happened, Bollenbacher admits, if he hadn’t stopped talking and started listening.

“We learned very quickly not to prescribe and not to assume that what we thought they needed was what they actually wanted,” says Nancy T. Barnes, one of the first staff members Bollenbacher hired. Instead, they began to talk with science faculty at historically minority institutions—an ongoing dialogue that evolved into a successful consortium, the Partnership for Minority Advancement in the Biomolecular Sciences (PMABS). Barnes, now one of PMABS’ associate directors, collaborates with university partners to advance underrepresented students into science careers.

Variations in the Message

PMABS began to offer summer research fellowships at Chapel Hill for science faculty from the historically minority universities. The program was later expanded to include students from those institutions as well. To help transfer what the professors had learned back into their institutions, PMABS developed a cornerstone course, “Frontiers in the Biomolecular Sciences,” which focuses on advances in cell, molecular, and developmental biology. And when program participants suggested that labs would complement the course’s seminars, PMABS secured a second grant from HHMI to provide the needed equipment.

Here, too, the key was to listen to the message—and to make note of its variations. “Science departments in these colleges had different curricular emphases, so it made no sense to give everyone the same box of tools,” says Barnes. Johnson C. Smith University in Charlotte, for example, needed inverted microscopes to pursue that school’s focus on cell biology, while other institutions needed research-grade equipment for new molecular biology courses.

Marilyn Sutton-Haywood, associate vice president for academic affairs at Johnson C. Smith, was impressed by PMABS’ openness and restraint. She expected the scientists from Chapel Hill “to tell me what to do. But PMABS acts as a real facilitator to all of us.”

When PMABS found that some of the lab equipment wasn’t being used due to time constraints on faculty, the staff learned that the universities needed additional skilled hands in order to be able to deliver engaging labs. Only two partners—North Carolina Agricultural & Technical State University and North Carolina Central University—had graduate students to assist with teaching undergraduate labs. So PMABS established research assistantships to train undergraduates to play that role.

This program has been as rewarding to the research assistants as it has been to the partner universities. For Jan Lee Santos, the time spent as an undergraduate research fellow at the University of North Carolina at Pembroke changed his life. UNCP was originally a teachers’ college for the Lumbee tribe.
(and to this day, one in five students there is Native American; another 22 percent are African American). Thanks in large part to his PMABS fellowship, Santos became hooked on research. He’s now pursuing a Ph.D. in molecular biology and genetics at Texas A&M University.

The PMABS consortium has also been working to provide stronger science teaching to ensure that new fields are taught at the minority universities. Through a National Institutes of Health–supported program called Seeding Postdoctoral Innovators in Research and Education (SPIRE), PMABS began training postdoctoral scientists to be top-notch researchers and teachers, placing them for a third of their training on the historically minority campuses to teach and be mentored by outstanding teaching faculty. So far, 21 SPIRE postdocs have spent at least a year each teaching at these institutions, and many plan to stay; two have already accepted tenure-track faculty positions.

C. Dinitra White, a SPIRE postdoc, is coming full circle from her career as an undergraduate at Johnson C. Smith. She had decided to become a researcher while taking lab classes at the university, and went on to Michigan’s Wayne State University for a Ph.D. in microbiology. Now she is heading back to Johnson C. Smith, intent on teaching there in a full-time position. “I want to teach in a small historically minority university,” she says, “because I know that is where I can have the greatest impact on students.”

SPIRE alumnus Brian Rybarczyk, now one of PMABS’ Ph.D. scientists, is developing and teaching videoconferencing courses, bringing such Chapel Hill classes as “Molecular Basis of Disease” to students at three partner campuses so far.

Another PMABS innovation is what Bollenbacher calls “change agents”—Ph.D. scientists who specifically want to contribute to providing historically minority university students a comprehensive science education. Again, PMABS turned to NIH for support in hiring seven scientists, having one at each partner institution to teach courses, mentor students, integrate technology into the respective learning cultures, and help attract students into bioscience research careers.

Change agents, SPIRE postdocs, and other PMABS-supported initiatives have brought 53 courses to approximately 1,200 students across North Carolina, in subjects that otherwise would have been unavailable to them. In the next five years, Bollenbacher expects PMABS courses to reach triple that number of students. “In essence, we will have one huge, interconnected, statewide biology department that can offer any student any subject, either on their campus or through our electronic distributed-learning network,” he predicts.

A Bus Named Destiny
While the PMABS consortium was busy fortifying college-science learning, it also realized the extent of the changes needed to help high schools in North Carolina to prepare students for college level science. “We need to do more than reform science education,” Bollenbacher explains. “We need to transform it. That language is very important. Would you collaborate with me if I said I was going to reform you? But we can transform together.”

He described a pilot transformation project in Caswell County, a rural area with a high population of minority students. To bolster low student performance (as characterized by the state), PMABS provided educational specialists to work with teachers, parents, school administrators, and community leaders. “We helped them examine the realities of life in their community and their schools,” Bollenbacher explains. “Do the teachers have classes of 25 or 45? Do they teach 50-minute periods or 90-minute blocks? Do they have labs? Whose expectations are they trying to meet, and what are those expectations?”

PMABS brought Destiny to Caswell County. Funded by the pharmaceutical giant GlaxoSmithKline, whose operations are based in North Carolina, Destiny is a mobile lab—a 40-foot bus—that accommodates 24 students at 12 lab stations. The program has trained almost 1,000 teachers in 95 of the state’s 100 counties. Almost 9,000 high school students have conducted experiments on the bus, which is so popular that it will be joined in May by another bus, Discovery, funded by NASA.

“The only thing wrong with Destiny is that it doesn’t visit us often enough,” says Ophelia Willis, a director of instruction for the Caswell County schools. “It provides instruction and equipment that rural school systems cannot afford. If we need anything else, I feel we can just call on UNC Chapel Hill. They are there for us 100 percent.” Bollenbacher agrees: “The goal of the program is to provide a powerful visual image of what science education must be, and we are here to support schools’ efforts to put that science in the classroom.”

PMABS may soon become a national model for science education. Robert N. Shelton, executive vice chancellor and provost at UNC Chapel Hill, wants to establish an institute of science learning to help scientists and professors in other disciplines use some of the most successful teaching models, including Bollenbacher’s. “A lot of the problems we have in higher education are so big, it will take this kind of collaborative model to solve them,” says Shelton.

Although pleased by the praise for PMABS’ program, Bollenbacher makes one thing clear. “We don’t provide solutions,” he explains. “We provide opportunities, resources, and a perspective that empowers people to do it the way it works best for them. The only way to do this is to ask, listen, and learn.”

—RENEE TWOMBLY
s South American revolutions go, it was a quiet one. Not a drop of blood was shed. But when HHMI international research scholar Pedro Labarca and a handful of other Chilean biologists and physicists moved the Centro de Estudios Científicos (Center for Scientific Studies, or CECS) to a remote southern town, it was a revolution the likes of which Chile had never seen.

In a nation where science had been done only at the universities, physicist Claudio Teitelboim and biophysicist Ramón Latorre established an independent research center in 1984 with the support of the Tinker Foundation. Labarca joined the team in 1987. Then, in 2000, they had the audacity to move the center to Valdivia, a town in the foothills of the Andes Mountains, 500 miles south of Santiago. They set up shop there in a renovated historic hotel. “It was a crazy thing to do,” says Labarca, “and the crazy thing is, it’s working.”

**Dictators and Angels**

Labarca, a neuroscientist, and Latorre were working at the Universidad de Chile but were growing dissatisfied with the stifling conditions for research there. Teitelboim, who is now director of CECS, came up with the idea of moving to Valdivia.

“We wanted to work together, and we couldn’t do it at the university,” Labarca recalls. So they jumped ship. “We thought that when democracy came, the center would simply move into the university.”

Democracy did come in 1990. A freely elected president replaced military dictator Augusto Pinochet, but the scientists soon realized that their kind of free-flowing interdisciplinary research was still not welcome on campus. “We found that we had a lot of differences with the university that had nothing to do with dictatorship or democracy,” Labarca explains. “There were too many rules, too much rigid structure.”

So CECS remained independent, struggling along on the scientists’ own savings and whatever grants they could get. Labarca became an HHMI international research scholar in 1997, bringing the Institute’s support to his lab.

Felipe Barros and Pablo Cid were working at the University of Chile after doing postdoctoral fellowships in England and the United States when CECS invited them to join the center. “It was a bit scary, because they didn’t have funding,” recalls Barros, an M.D.-Ph.D. who studies the mechanism of cell death. “But the University of Chile wasn’t paying enough to live and do science, so we took a chance. And we were rewarded.”

In 2000, an angel appeared in the form of the World Bank’s Millennium Science Initiative, offering five years of funding to help countries establish research centers. Eager to bring Millennium Initiative support into Chile, the Chilean government also contributed to CECS.

Barros and Cid, together with former HHMI international research scholar Francisco Sepúlveda and Icha Niemeyer, are researching potassium and chloride channels—proteins in cell membranes that play key roles in molecular transport and communication among cells. “Channels seem to be very important in cell death,” says Barros. “Sometimes they kill by opening, sometimes they kill by closing.”

“We would like to be able to control the channels,” Barros explains, “to close them in stroke and open them in cancer.”

To track the movement of ions across cell membranes and study cell death, the researchers use electrophysiological techniques and a confocal microscope, one of two at CECS and one of only a handful in all of Latin America. Its microscopes and other state-of-the-art equipment are actually turning CECS into a training center for Latin American scientists. For example, a two-week course in 2002 organized by the U.S. National Academies with support from HHMI brought graduate students, postdoctoral fellows, and young investigators from eight countries to Valdivia, where they
received hands-on instruction in techniques such as intracellular calcium imaging and cysteine scanning.

Although CECS doesn’t grant degrees, the center has had little trouble attracting students such as Timothy Ryan, an American with a bachelor’s degree in physics from Harvard University. Ryan is studying and working in Labarca’s lab, where the research team studies the memory centers in *Drosophila* brains. “In the future, we hope to establish a joint graduate degree program with a university outside of Chile,” Labarca says.

Meanwhile, CECS is expanding, currently renovating another historic building next door that will more than double Labarca’s lab space. “My flies will have their own room,” he says with a smile.

**Ways of Looking**

Other than their irrepressible self-confidence and willingness to take risks, what makes the CECS researchers different from many scientists elsewhere? It may be the way they work together, bringing the word “interdisciplinary” to life.

“There is value in talking with people who view things differently,” Labarca explains. “Biologists try to make everything fit to Darwin. But a physicist says, ‘Forget Darwin; why not look at it this way?’ A physicist here showed the biologists how to approach a problem with an equation instead of empirically.”

Latorre, head of biophysics and molecular physiology at CECS, describes the center’s distinctiveness this way: “When we get together, good ideas are recognized and approved very quickly, and bad ideas are recognized and rejected just as quickly. We spend very little time in meetings.”

CECS’s devotion to interdisciplinary research enables its investigators to forge alliances with scientific front-runners all over the world. Latorre has collaborated with HHMI investigators Christopher Miller and Roderick MacKinnon, a 2003 Nobel laureate. Latorre and University of California, Los Angeles, researchers Enrico Stefani and Francisco Bezanilla are investigating voltage-dependent ion channels. Labarca and Alberto Draszon, a Mexican biologist, are studying the physiological mechanisms that underlie behavior in sea urchins and microscopic animals from the highland lakes of northern Chile. A new laboratory was formed to study glaciology and climate changes, after CECS moved to Valdivia, concentrating on international collaborative research in the Patagonian ice fields. In 2002, the program was expanded to study global ice masses in the Antarctic. Now HHMI international research scholar Marcelo Rubinstein, a biologist from Argentina, is establishing a transgenic animal lab at CECS.

The center also works with scientists and students at Valdivia’s Universidad Austral de Chile, and it has made a commitment to share science with schoolchildren as well. The father of six-year-old Miranda and four-year-old Tomas, Barros knows how important it is to expose children to science. As part of a Chilean government program called “1,000 Scientists, 1,000 Schools,” he and Cid went to speak at Valdivia primary and secondary schools. “The students and teachers wanted more,” Barros recalls. So he brought the high school students to CECS to see the labs and look through the microscopes. He continues to visit the schools.

Is CECS a model for a new kind of science? Labarca and Latorre hope so. “We are not trying to replace the university, just to provide an alternative,” says Labarca. “We hope this will be a model for Chile and other countries,” Latorre adds.

But Teitelboim sounds a note of caution. “We don’t want to be a model,” he says, “because as soon as models are formed, they become institutionalized and obsolete. We want to demonstrate that at any time, something drastically different is possible. We are a useful irritant to the establishment.”

What will happen to CECS when Millennium Initiative support ends in 2005? “The modest answer is, we don’t know,” says Latorre. “The other answer is, we are so good that the money will find us.” Whatever the future brings, Latorre says, for now “we are free, we are doing good science, and we are having fun.”

—JENNIFER BOETH DONOVAN
TO YOUR HEALTH!
Guests toast San Franciscan Isaac Donner in celebration of his 100th birthday.
IS THERE A FORMULA FOR LIVING TO the age of 100 or beyond? HHMI investigator Louis M. Kunkel believes there is, and he’s working hard to define it.

Besides a healthy dose of good luck (Kunkel says it helps to not be killed in a war or a traffic accident), one key to longevity is a highly unusual combination of gene variants that protects against the customary diseases of old age. Several research teams are now in the process of uncovering these genes.

Kunkel, director of the Genomics Program at Children’s Hospital in Boston, and his associates recently identified a genetic variant that is particularly prominent among sibling pairs in the New England Centenarian Study, perhaps the world’s largest pool of centenarians. They are seeking additional genetic variants that might retard—or perhaps even prevent—many of the diseases that debilitate the old. “People with this rare combination of genes clearly age more slowly,” Kunkel says. “When they reach 90, they don’t look any older than 70.”

Hundreds of centenarians around the world are now contributing their blood and medical histories to the search for these precious genes. They have become a key resource for researchers who hope that as these genes are revealed, their good effects may be reproduced in other people with the help of new drugs.

CLUSTERED IN FAMILIES

Kunkel was drawn to the hunt for longevity genes about six years ago, through a chance encounter with Thomas T. Perls, a Boston University Medical School geriatrician who had enrolled a large group of centenarians for his New England Centenarian Study. Kunkel’s own research was focused on a deadly genetic disorder called Duchenne muscular dystrophy, which affects mostly boys. In 1986, he discovered a mutation that causes this muscle-wasting disease, and he is still working on a therapy for it (see box on p. 16). But he could not resist the opportunity to also apply his knowledge of genetics to what he heard from Perls.

The two men were acquainted through Perls’s wife, Leslie Smoot, who happened to be a postdoc in Kunkel’s lab. When they met on a street in Cambridge, Massachusetts, in 1997 and started talking about their work, “Tom told me that many of the centenarians whose lineage he was examining were clustered in families,” Kunkel recalls. “I realized that’s just got to be genetics. We soon started a collaboration.”

For his part, Perls remembers that at the

Photographs by Ed Kashi

The black-and-white photographs that accompany this article are from the book Aging in America: The Years Ahead, which explores in photos and text the social impact of longevity. Photojournalist Ed Kashi and his wife, writer Julie Winokur, worked eight years on the project. Their book was published last year by PowerHouse Books.
beginning of his study he thought the centenarians had little in common except for their age. But he soon realized that many of them had an unusually large number of equally aged relatives. “We had a 108-year-old man who blew out his birthday candles next to his 102-year-old sister,” Perls recalls. “They told us they had another sibling who was 103, and yet another who was only 99. Two other siblings—also centenarians—had passed away. Four siblings had died in childhood. So here was an incredible clustering, 5 or maybe 6 siblings out of 10! We’ve since found about 7 families like that.” This implied that all these families carried especially protective genes. Shortly after the two scientists met, a new postdoc arrived in Kunkel’s lab—Annibale A. Puca, a young Italian neurologist who wanted to work in genetics—and Kunkel suggested he take on this new project. “I warned him it was going to be a lot of work and high risk, but he said okay,” Kunkel says, “and he spearheaded the whole program.”

Puca and Perls rapidly expanded the group of centenarians, recruiting them through alumni associations, newspaper clippings, and state census lists. After taking samples of the centenarians’ blood, the researchers extracted DNA from it and started looking for genetic markers—specific stretches of DNA that might occur more frequently among these extremely old men and women than among a group of younger people who were the study’s controls. Most scientists believed that human longevity is far too complicated a trait to be influenced by only a few genes. There are so many independent mechanisms of aging that “the chance that only a few major genes control longevity in man is highly unlikely,” wrote a self-styled “pessimist” on this issue, George M. Martin of the University of Washington in Seattle, in the journal *Mechanisms of Ageing and Development* in 2002. But Kunkel’s lab took a different view. “In lower organisms, such as nematodes, fruit flies, and yeast, there are only a few genes that need to be altered to give a longer life span,” Kunkel says. “My feeling was that there were only a few genes, perhaps four to six, in humans that would do the same.”

The team proceeded to examine genetic markers for the entire genomes of 308 people, selected because they belonged to 137 sibships (sets of siblings) in which at least one member was over 98 and the others were over 90. “From early on, we saw a blip of a peak on chromosome 4,” says Kunkel. “Eventually, in 2001, we found a linkage between one region of this chromosome and longevity.”

**SEARCH FOR A SNP**

It was “phenomenal” to get a real linkage from such a slight hint in the original data, Kunkel declares. But that didn’t mean further research would be easy. This stretch of DNA was so large—12 million DNA base pairs long—that it seemed it could contain as many as 200 genes. Furthermore, the researchers knew that within...
these genes they would have to look for variations in single bases of DNA—“single-nucleotide polymorphisms,” or SNPs (pronounced “snips”). “SNPs really represent the difference between individuals,” Kunkel explains. “Everybody’s DNA is 99.9 percent identical—it’s the SNPs that make us unique and allow certain people to live longer. Even though most of our DNA is alike, the 0.1 percent variation means that we have more than 10 million SNPs across the genome. And we’re on the verge of being able to map them.” For Kunkel, the critical question was “how would we find the one SNP in a single gene that might help a person to live much longer than average?”

The groundbreaking work of the Human Genome Project had not yet been completed at that time, and Kunkel realized that finding this particular SNP would be both expensive and time-consuming. It would also be quite different from zeroing in on a missing or severely garbled gene, as had been done for cystic fibrosis, muscular dystrophy, and other single-gene disorders. The widespread diseases of aging—heart disease, stroke, diabetes, cancer, and Alzheimer’s disease—are much more complex and are triggered by subtle gene variations that produce only slightly altered proteins, Kunkel says. These proteins may either work a little better or be less active than those in the normal population, and several of them may work in concert. Searching for a single SNP would require doing thousands of genetic analyses on each of his subjects (now numbering 653) and comparing the results with the control group. “We estimated it would cost at least $5 million,” Kunkel said. “It finally cost $8 million and took one-and-a-half years.”

Ultimately, all that painstaking work paid off. The paper announcing the discovery of a SNP...
that contributes to longevity was published in the November 25, 2003, issue of the Proceedings of the National Academy of Sciences.

NOW FOR THE OTHERS
The long-sought SNP turned out to lie within the gene for microsomal transfer protein, or MTP, which had been known since the mid-1980s to be involved in cholesterol metabolism.

“It’s quite clear that to live to be 100, you’ve got to maintain your cholesterol at a healthy level,” says Kunkel. “It makes perfect sense. We know that increased LDL (the ‘bad’ cholesterol) and lowered HDL (the ‘good’ cholesterol) raise your cardiovascular risk and that cardiovascular diseases account for a large percentage of human mortality. So variations in the genes involved in cholesterol packaging will influence your life span. It’s as if these centenarians had been on Lipitor [a cholesterol-lowering drug] from birth!”

This discovery might lead to drugs that are tailored to intervene in the cholesterol pathway. Because the MTP gene was already in the public domain, however, it could not be patented, much to the disappointment of the former Centagenetix Corporation (founded by Puca, Perls, and Kunkel and now a part of Elixir Pharmaceuticals of Cambridge, Massachusetts), which had bankrolled most of the study. In any event, this SNP “cannot be the whole story,” Kunkel declares. “There must be other gene variations that enable people to avoid age-related diseases. Some of our original families did not show linkages to chromosome 4.” Nor did a group of centenarians who were tested in France.

Cures for Muscle Diseases?

Ever since Louis M. Kunkel discovered the cause of Duchenne muscular dystrophy (DMD) in 1986, he has been laboring to find a cure for this muscle-wasting disease. DMD—the result of an error in a single gene—attacks 1 out of every 4,000 newborn boys, progressively crippling and then killing them at an early age.

Kunkel saw that patients with DMD lacked a protein, dystrophin, which this gene would have produced if it were functioning normally. So he knew he had to replace the protein somehow. He and others tried many methods—gene therapy to deliver a normal gene to the defective muscle cell, drugs to help restore the missing protein, and cell therapy to inject normal cells into muscle or blood—but despite some partial successes in animals, nothing really worked.

Kunkel’s lab worked mostly with mdx mice, a naturally mutant strain that lack dystrophin. When he and his colleagues attempted to cure these crippled mice with injections of muscle stem cells from normal mice, “some of the donor cells did go into the damaged muscles,” he recalls, “but we never got more than 1 to 2 percent of the muscles repaired. Part of the problem was that when you inject cells into a mouse’s tail vein, which is the most accessible part of its circulation, the donor cells go through all the organs—the lungs, liver, heart, and so on—and out through the arterial system. Most of the cells get filtered and lost, and don’t contribute to the therapy.”

Today, however, Kunkel feels he is on the verge of success. The big breakthrough came last summer when a team of Italian scientists headed by Giulio Cossu of Milan’s Stem Cell Research Institute announced it had found a new route for the injection of stem cells into dystrophic mice directly into an artery. The cells seemed to lodge within the capillary system near the injection site. From there, about 30 percent of them migrated to the diseased muscles. “Not only did the cells get there,” he says, “but at later time points, you could see a larger number of donor cells than at the earliest point, as if they were trying to divide.”

“Can we improve on this?” asks Kunkel with a glint in his eye. “If we can get the stem cells into 50 percent of the dystrophic muscles, that’s basically a cure.”

They had trouble at first because “the mouse artery was 10 times smaller than our smallest injection needles—it was like trying to hit it with a hammer!” Kunkel says. “Though a tail vein is even smaller than an artery, it can be hit much more easily because it is right under the surface of the skin and can be made to swell up by warming it. In the new system, the mouse had to be anesthetized and opened up to expose its artery, which was lifted out—a complex procedure.

“It wasn’t until we started collaborating with some vascular surgeons who had been doing heart transplants in mice that we were able to get the stem cells into the mouse arteries efficiently,” he says. In humans, of course, reaching an artery would not be a problem given that human arteries are so much larger.

Getting the stem cells into the muscles was just the first step. Unless these cells supplied enough dystrophin, the diseased muscles would not be repaired. So Kunkel also tried to find different stem cells that could do the job more effectively. In 1999 his lab and that of his colleague Richard Mulligan announced they could restore some of the missing dystrophin in mdx mice with the aid of a new kind of stem cells called “side population” (SP) cells, which seemed to work much better. These SP cells had to be taken from muscle tissue, however. Last year Kunkel’s lab succeeded in deriving similar SP cells from adult skin, which is easier to obtain. Since they originate in adult tissue, both kinds of SP cells will be much less controversial than embryonic stem cells.

“It’s my belief that you can do a lot of therapeutic intervention with adult-derived cells,” says Kunkel. He notes that the new stem cells seem ready to differentiate into every type of muscle tissue, which implies that they have the potential to treat many forms of muscle disease.

The combination of a new cell type and a new delivery system “may revolutionize how one does therapy for muscle diseases,” Kunkel suggests. “When we get it perfected in mice, we’ll go to humans.” He thinks this might happen “in a couple of years.”
Determined to find some of the other SNPs that produce longevity, Kunkel says he’s going back to his sample and will redo the whole study. “We now have 310 sibships,” he says. “Our genetic markers are much denser. I believe we can get 10 times the power in our next screen than we had in the first.”

Moreover, the work can be done much more rapidly and inexpensively than last time, he notes, given the giant strides that have been made recently in human genetics. Not only has the entire human genome been sequenced, but many of the errors in the original draft have been corrected. Equally important, all the known genes in the genome are now available on a single Affymetrix DNA chip, allowing researchers to promptly identify which genes are activated and which are damped down in any given situation. In addition, as many as 10,000 different human SNPs have been placed on a single chip.

Similar tools have already turned up new gene variants in yeast, worms, and flies. But Kunkel will use the chips to analyze the DNA of humans. Once his lab gets started on the new longevity project, he believes, it will not take very long to get some definitive answers. He hopes these will lead to drugs that could mimic the protective effects of the centenarians’ genes.

**GOLD STANDARD**

In fact, these studies foreshadow a far-reaching attack on all complex diseases—not just those of the aged but others, such as autism and hypertension. None of these ills could be tackled efficiently in the past. “The centenarians are the ideal control group for such research,” Kunkel says. “To reach 100, you must have good alleles [versions of the genes] at all points. So if one wants to find the genes that are connected with hypertension, for instance, one can look across the genome for genes that are highly active in the hypertensive population but down-regulated in centenarians. Ultimately, that’s what the centenarians’ genes will be used for.”

He believes that in the future, “every person who comes to our genetic clinic—or goes through any type of care system—with what appears to be a complex disease should be analyzed in detail. I mean that we should gather all the information we can about each patient’s symptoms, the family history of these symptoms, any environmental insults the patient suffered, any learning disability—anything that would allow us to categorize the patient and [the patient’s] family into subtypes of the disease which could be more related to one another and thus more likely to involve the same gene.” To make this happen, Kunkel has just appointed a director of phenotyping (the Greek roots of this word mean “classifying phenomena into specific types”) who will collect, categorize, and catalogue such patient information.

“We will also analyze the patients’ genes but only in the context of the category of symptoms they exhibit,” he says. “The samples we collect—under appropriate protocols—will be available to the national groups of patients and researchers that are organizing to find the underlying genetic bases of specific diseases.” Eventually, he hopes, many complex disorders such as heart disease, diabetes, and autism will be broken down into more specific categories, which in turn may lead to more precise treatments or ways of preventing the disorder. Kunkel expects this process to accelerate in the near future as more patients’ genes are compared with those of the gold standard for humans—the centenarians.
Nobel Prize laureates Michael S. Brown and Joseph L. Goldstein still remember their reactions when they heard that Helen H. Hobbs was coming to work in their lab some 20 years ago. “We were very skeptical,” Brown recalls. It wasn’t that Hobbs, who was then wrapping up a residency in internal medicine, was inept, difficult, or dull-witted. On the contrary, she had already distinguished herself as a skilled chief resident in the pressure-cooker atmosphere of Dallas’s Parkland Hospital. “She became famous during that time for her ability to function in a crisis and treat very sick people, and she also had the ability to inspire and lead the others around her,” says Brown, a molecular geneticist at the University of Texas Southwestern Medical Center at Dallas (UT Southwestern). ♥ But laboratory research was an altogether different realm, and her mentors-to-be weren’t sure Hobbs was a good fit. “She didn’t even know what a pipette was!” recalls Goldstein, who is now an HHMI Trustee. Hobbs herself wasn’t convinced that a stint in the lab would work out, though the idea intrigued her. “I’d always been attracted to people who did science—I loved to hear their stories,” she says. “But I really had no experience in the lab at all.” Gregarious and outdoorsy, she also feared that the life of a research scientist would be too confining. “It seemed like such a singular, lonely pursuit that I didn’t think it would be appropriate for my personality.” ♥ But someone else—a very influential someone whose opinion was respected by Brown, Goldstein, and Hobbs alike—thought otherwise. Donald W. Seldin, then Hobbs’s boss as head of medicine at UT Southwestern, sat her down toward the end of her
residency and asked about her plans. When she told him she intended to practice endocrinology, he offered the promising young physician a bit of advice. As Hobbs tells it, Seldin said “I think you’d like that for about five years, and then you’d wither on the vine. I think you should do research.” Hobbs didn’t argue. “I trusted his intuitions about me,” she says. “He’s a very bright and insightful man, and I knew that he knew all my strengths. But more important, he knew all my weaknesses, and he felt strongly that I should do this.” Brown and Goldstein, despite their doubts, didn’t argue with Seldin either when he asked them to take Hobbs on as a postdoctoral fellow.

Seldin’s instincts, it turned out, were right on the mark. Today, colleagues use words such as “brilliant,” “outstanding,” and “highly regarded” to describe HHMI investigator Hobbs and the work she continues to do at UT Southwestern. Focusing on the genetics of cholesterol metabolism, she and her research team have discovered the genes responsible for two disorders that produce extremely high levels of low-density lipoprotein (LDL)—the fat-and-protein complex that carries about 70 percent of circulating cholesterol. At present, they are studying the defective proteins behind these disorders. That knowledge, says Hobbs, could help reveal the details of how the body normally keeps cholesterol in check by regulating its uptake from food, shuttling it from the bloodstream into the liver, and excreting it into the bile.

In addition to overseeing her laboratory research groups, Hobbs runs the Dallas Heart Study. This intricate and innovative examination of risk factors and cardiovascular health in Dallas-area residents is aimed at tailoring treatment and prevention efforts for an ethnically diverse population (see sidebar).

**EVEN DYNAMOS GET THE BLUES**

It’s a whirlwind of a professional life, which she combines with a 23-year marriage and motherhood. (Hobbs’s husband, Dennis Stone, is vice president for technology development at UT Southwestern, where he is also a professor of internal medicine; the couple has two teenage sons.) But colleagues say that if anyone can handle it all with skill, finesse, and a touch of humor, Hobbs can. “Helen is total energy,” says HHMI investigator David J. Mangelsdorf, a biochemist at UT Southwestern. “She’s a dynamo.”

But even for a dynamo—maybe especially for a dynamo—the path to this point was no sure thing. Hobbs’s career was tough going at times, particularly during those early years in Brown and Goldstein’s lab when she struggled to make the shift from bedside to bench. “It was especially hard to change pace,” she recalls. “In medicine, everything happens very quickly. You make a diagnosis, and if it’s right, the patient gets well. If the diagnosis is wrong, the patient doesn’t get well and you have to

**True Translational Research**

H oleding the population-based Dallas Heart Study—an examination of the biological and social foundations of the widening ethnic gap in cardiovascular disease—presents Helen Hobbs with a set of challenges different from those she encounters in her lab work. There are patient-recruitment and privacy issues, specific concerns of the ethnically and economically diverse population, and matters of managing an enormous database. But the payoffs are well worth the effort, says Hobbs. “It’s a different kind of science, but it complements the work that I do in the lab very well.”

The study, initiated in 1999 with funding from the Donald W. Reynolds Foundation, involves some 3,000 Dallas County residents—half of them African American—who have been extensively interviewed on their medical and family histories; health-care access, practices, and beliefs; environmental exposures; and other details related to socioeconomic status. During home visits, the subjects’ blood pressure, heart rate, and weight are recorded, and blood and urine samples are collected for analysis. They also come to the University of Texas Southwestern Medical Center for detailed physiological and imaging studies to assess heart function, body fat distribution, signs of atherosclerosis, and other measures of cardiovascular health. Meanwhile, of course, their DNA sequences are recorded.

“Never has such a large and ethnically diverse population undergone such detailed phenotyping,” says Hobbs. “That’s what makes the study unique and very valuable in terms of trying to define the genetic underpinnings, along with the nongenetic components, of complex traits.” In particular, researchers can begin looking for DNA-sequence variations associated with specific cardiovascular risk factors.

While population-based studies can uncover only the associations between genetic and environmental factors and health—not the underlying mechanisms—they have some advantages over lab-based studies, says Hobbs. For one thing, “they’re large and they’re random, so they’re more representative of the population at large.” The ultimate goal—and challenge—is using the information to understand what contributes to premature heart disease and higher cardiovascular death rates among African Americans and to design education, prevention, and treatment strategies to address the problem.

Her focus in the Dallas Heart Study is to probe ethnic differences in lipid and glucose metabolism and discover what these differences mean in terms of heart disease. For example, plasma levels of Lp(a), a lipoprotein known to contribute to the buildup of cholesterol on arterial walls, are 2- to 3-fold higher in African Americans than those in Caucasians and Asians. However, Hobbs has shown in the Dallas Heart Study that high plasma levels of Lp(a) are not associated with increased coronary atherosclerosis in African Americans, for reasons that remain unclear.

In addition, the prevalence of insulin resistance is higher in African Americans than in Caucasians, yet plasma levels of triglycerides—which are usually elevated in people with insulin resistance—are lower in African Americans. The researchers also have uncovered two intriguing differences in lipid metabolism between African American and Caucasian participants, and “we’re now trying to identify the genetic basis for these ethnic differences,” says Hobbs.

The heart study “is true translational research,” Hobbs says. “It’s clinical investigation tied to basic science, it brings people from different disciplines together, and it focuses on the community that we care for clinically.”
of cells that snatches LDL cholesterol from the bloodstream and helps it into the cell. They went on to identify and clone the LDL-receptor gene, and when Hobbs arrived in their lab, they were trying to learn how mutations in the gene destroy the receptor’s normal function. One of Hobbs’s earliest successes was finding a mutation that alters the binding specificity of the LDL receptor—the first demonstration of such an effect.

Through the FH work, Hobbs was also introduced to population genetics and the scientific sleuthing it entails. FH can be a tricky subject for geneticists to study; although mutations in the FH gene are common, occurring at the rate of 1 in 500 people, many different versions—more than 900 at last count—can cause the disorder. So except in families, it’s hard to find groups of people with the same mutation. But certain populations—French Canadians, for instance—make the tracking job easier. “French Canadians are descended from between 5,000 and 7,000 immigrants who came from France to Quebec Province in the 1600s and 1700s and stayed very genetically isolated,” Hobbs explains. By studying samples collected from large numbers of French Canadian families with FH, she found that a whopping 60 percent of the patients had the particular mutation she was seeking, making it possible to track its route reassess.” That no-time-to-waste aspect perfectly suited the energetic Hobbs, who still busses down corridors with the forward-leaning stride of a cross-country skier and often positions herself between two banks of elevators to make sure she catches the first one—only to get impatient and bound up the stairs instead.

But things moved much more slowly in the lab, especially for a rookie who was still learning the language and techniques. “I wasn’t a natural,” Hobbs admits. “Some people come into the lab—I see it with students—and they just have ‘the hands.’ They have an easy time concentrating and getting their experiments done without making mistakes. I had to learn that, and it was frustrating.”

What’s more, the persistent inquisitiveness that colleagues now appreciate in Hobbs wasn’t always seen as an asset—in fact, she had a reputation for being a pest in those early days. “When an experiment didn’t work, she would hunt down the one person who knew how to make it work, corner them, and make sure that they explained exactly how to do it properly,” says Brown. “Whenever Helen walked down the hall, everybody else would run the other way.”

No wonder Hobbs seemed glum when, a year or so into her lab training, she ran into a clinician she had worked with in her residency. He asked how things were going, and when she mumbled, “Well...OK,” he was taken aback. “That doesn’t sound like the Helen Hobbs I used to know,” he said. “Well, you know,” Hobbs confided, “every day that goes by, I feel like I’m becoming a worse clinician—because I get farther away from the clinical work—and I’m not even a very good scientist.”

But then, just as Hobbs was reaching her lowest point, something changed. “I started to have results,” she says, beaming. For the first time, she saw beyond the frustrations to the fun of doing science, and before long, recalls Brown, everyone else was tracking her down for technical advice.

**SCIENTIFIC SLEUTHING**

Hobbs’s early work built on the research that earned Brown and Goldstein the 1985 Nobel Prize in Physiology or Medicine. For more than a decade before Hobbs joined their lab in the early 1980s, the two scientists had been studying familial hypercholesterolemia (FH), an inherited condition in which blood levels of LDL cholesterol are not only stratospheric but also resist any attempts at control through diet, medication, or lifestyle changes. People who carry two copies of the FH-causing gene can have LDL levels 6 to 10 times higher than normal and often die of heart attacks in childhood.

In the early 1970s, Brown and Goldstein had discovered that the disease stems from a defect in the LDL receptor—a protein on the surface of cells that snatches LDL cholesterol from the bloodstream and helps it into the cell. They went on to identify and clone the LDL-receptor gene, and when Hobbs arrived in their lab, they were trying to learn how mutations in the gene destroy the receptor’s normal function. One of Hobbs’s earliest successes was finding a mutation that alters the binding specificity of the LDL receptor—the first demonstration of such an effect.

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through the lineage. "We were able to trace it back to the person who brought the mutation to the New World," says Hobbs. "That really hooked me."

Though she still interacts with Brown and Goldstein several times a week, Hobbs veered off in her own direction after a few years under their wings. Any early worries about losing her touch as a clinician or becoming a research recluse dissipated as she developed her own unique scientific style. Hobbs retains her clinical skills by seeing patients one afternoon a week. Most of these patients have unusually high or low levels of cholesterol or have had heart attacks in the absence of any known cardiovascular risk factors. With her outgoing personality, patients "love her and trust her," observes HHMI postdoctoral fellow Christine K. Garcia, who works in Hobbs’s lab. And the extroverted nature that makes her patients smile turns out to be just as big an advantage in research, where a knack for assembling talented teams and motivating them to do their best pays off in high-quality results.

"I get a lot of pleasure out of running a laboratory and seeing people grow and develop as scientists," says Hobbs. "It’s much like the pleasure I used to get in the wards."

Striding into the lab, Hobbs rallies the troops with her exuberance. "What’re you up to?" she calls to a technician. "What’d you find out about the DNAs from Italy?" Later, in a lab meeting, she leans forward "What’re you up to?" she calls to a technician. "What’d you find out about the DNAs from Italy?" Later, in a lab meeting, she leans forward “This is interesting,” she says, her chin in her hands, scrutinizing data on a projection screen. “What is this?” she asks. “What’s the problem?”

"This about the DNAs from Italy?" Later, in a lab meeting, she leans forward “What’re you up to?” she calls to a technician. “What’d you find out about the DNAs from Italy?”

Hobbs and her team are trying to identify and better understand proteins that may work to help ferry LDL cholesterol out of the blood and into cells.

A second project focuses on proteins involved in clearing cholesterol from the blood. In 2001, Hobbs’s team identified a gene that, when defective, causes a rare type of high-cholesterol disorder called autosomal recessive hypercholesterolemia (ARH). People with the disease have perfectly normal LDL receptors, but they are unable to clear LDL cholesterol from the bloodstream. The problem, it turns out, is that these patients lack an adaptor protein that likely tethers LDL receptors to the machinery that pulls them and their LDL-cholesterol cargo out of the blood and into liver cells. Hobbs and her team are trying to better understand this ARH protein’s normal role and to identify other proteins that may work with it to help ferry LDL cholesterol out of the blood and into cells.

In the third line of research, Garcia is following up on one of Hobbs’s early projects. While working with Brown and Goldstein, Hobbs studied a family in which some members with FH had high cholesterol levels as expected, while others with FH had surprisingly normal cholesterol levels. "It seemed that these people had also inherited a genetic modifier that normalized their cholesterol," Garcia explains. So "the big question is, what gene is behind this modifier effect?" The original data, which Hobbs collected in 1988, were insufficient to answer it, but by studying additional family members, along with other families in which some members have unusually low LDL-cholesterol levels, Garcia and Hobbs hope to close in on the gene.

Also exciting is the prospect of using genes as biological crystal balls to predict future health—a quest that has so far proven elusive. "Despite what you read in the newspaper about genetic profiles, there really are very few examples where one can take a blood sample from a person, do a DNA test, and make any really competent prediction about their risks over the next 10 to 15 years," says Goldstein. "Yet, heart disease is a condition that one should be able to do this for, because it boils down to things like LDL cholesterol being bad and HDL cholesterol being good. If one can understand all the genes that control these two lipoproteins, then one should be able to make more precise predictions. “If such questions are answerable,” he concludes, “Helen’s research is poised to answer them.”

Brown, the other early skeptic, couldn’t agree more with Goldstein’s assessment. "There seems to be no limit to what she can do," he says. And not just do, but also accomplish with that infectious enthusiasm her colleagues now find so endearing. "With Helen," says Brown, "there’s no such thing as a toe in the water."
**INTERVIEW**

**A Big Voice for Science**

*An interview with Leonard Zon.*

With his enthusiasm and booming voice, Leonard I. Zon, an HHMI investigator at Children’s Hospital in Boston and Harvard Medical School, can be persuasive. Those traits are useful in his roles as leader and advocate.

Zon helped turn a tiny tropical fish—the zebrafish—into one of the key model organisms for geneticists. And last year, Zon became the founding president of the International Society for Stem Cell Research (ISSCR).

When we met with him in December at Children’s, he had just moved into a new zebrafish facility.

**What are you and your colleagues doing with zebrafish?**

**Zon:** Many things. [HHMI investigator] Mark T. Keating and his associates are studying how damaged organs regenerate, which the limbs of zebrafish do very quickly. Other scientists are looking at angiogenesis—the growth of blood vessels—which is important in cancer. Some people from [HHMI investigator] Louis M. Kunkel’s lab are doing research on muscle disorders such as muscular dystrophy.

In my own work, I use zebrafish in lots of ways, but what got me started was my search for the genes that control the gene GATA-1, which directs the development of red blood cells. This was around 1992, and I had heard through the grapevine that Janni [Christian Nüsslein-Volhard, a German geneticist and recipient of the 1995 Nobel Prize for Physiology or Medicine] had started to work with zebrafish, which are fantastic models for developmental studies because they are fertilized externally and their embryos are completely transparent. You can see all the organs in the zebrafish blood system, which forms within 24 hours. We used this system to study the genes required for blood formation.

**1992 was still a prehistoric era with respect to zebrafish in research, wasn’t it?**

**Zon:** Yes, almost nothing was known about these fish at the time. In 1996, I began a collaboration with Janni, who had found 50 zebrafish that had independent mutations affecting their blood. I sent a postdoctoral fellow and a graduate student to her lab to work on these blood mutants. Ultimately, they found that 17 genes were involved, because in some cases the same gene had been mutated in several different places. A lot of critics said it would be impossible to isolate the genes that were responsible for these mutants. We had no physical map of the zebrafish, no gene libraries, no reagents, and very few gene markers for a genome roughly the size of the mouse genome. So I took a role in getting the zebrafish community to think about tackling the zebrafish genome, and we finally got a genome initiative. By the end of 1998, we had fantastic resources for zebrafish that actually made our system go very fast!

**So that took care of the doubts?**

**Zon:** No, not even when we developed the first animal model of a human disease—congenital sideroblastic anemia, in which patients have trouble making hemoglobin. The critics said, “We already knew about this gene. Can zebrafish be used to define something new?” Well, in 2000, we published a paper on a gene, weissherbst—that’s the name of a wine—which encodes a novel iron transporter protein, ferroportin, a key regulator of iron biology. Janni and I had a few glasses of weissherbst to celebrate. For years, people had been looking for an iron transporter gene in the gut of humans. It turned out to be the weissherbst gene product. Humans diverged from fish about 300 million years ago, but the process of iron metabolism is conserved in vertebrates. Two years ago, we and others found human patients with problems in iron metabolism and mutations in ferroportin.

**Did you ever find the gene you were originally looking for that regulates GATA-1?**

**Zon:** We did find a gene upstream of GATA-1, just recently. It’s cdx-4, and it participates in the generation of blood stem cells during embryogenesis. That’s very exciting because it may lead to ways of regulating blood stem cell development in the treatment of patients.

**What prompted you to become a stem cell activist?**

**Zon:** Well, I needed to study how stem cells become blood. And people who are trying to understand the biology of stem cells clearly need to band together. Four years ago, at a Keystone meeting on stem cells, people who don’t usually interact with each other—they work on different organisms, for example, or different problems—realized they had a lot in common. So Irving Weissman, Douglas Melton, and I decided it would be a good idea to start a society. [An HHMI alumni investigator, Weissman is at Stanford University School of Medicine. HHMI investigator Melton is based at Harvard University.] Our group, the ISSCR, is now 700 members strong and will hold its second annual meeting in Boston in June. We just launched a Web site (www.isscr.org).

In the past, stem cell biologists didn’t have a voice; now we do. Stem cell biology is in its infancy. We hope the ISSCR will help to move the field at a faster pace.

—MAYA PINES
Science in Overdrive

The energetic Brett Finlay works hard to help solve global health problems but still finds time to be a husband, dad, boss, athlete, musician, cook, and grocery shopper. By William Dietrich

In May 2000, spring floods washed cattle manure into the water wells of Walkerton, Ontario, a farming community of 5,000 people about 90 miles west of Toronto, thereby contaminating the town’s water supply. An epidemic of diarrhea followed, sickening half of the population and leaving seven dead. The culprit was Escherichia coli O157:H7, a strain of the common intestinal bacterium that was first detected from cases of severe bloody diarrhea in the late 1970s.

E. coli is now a significant health problem worldwide. According to the U.S. Centers for Disease Control and Prevention, for example, the microbe causes some 76,000 infections a year and kills an average of 61 people in the United States alone. Yet, this is just the tip of the iceberg. In developing countries, as many as 2 million people die annually from diarrhea-related dehydration.

Canada and the United States have developed four different approaches to preventing such tragedies, both at home and abroad, but what’s remarkable is that a single Canadian scientist—B. Brett Finlay, a microbiologist at the University of British Columbia (UBC) and an HHMI international research scholar—is helping to lead all four:

■ Reform of water and health systems. Finlay helped establish the Canadian Research Coalition for Safe Food and Water, a $13 million effort that supports research to increase food and water safety. Finlay is also a member of the advisory board for the Institute of Infection and Immunity, a group working to establish national priorities in that field and improve communication and coordination between Canadian health, food, and water agencies.

■ Vaccination of cattle that carry the bacteria. The vaccine will help banish “hamburger disease” (as infection from O157:H7 is commonly called) by keeping it out of the meat supply in the first place. In a paper published in the January 2, 2004, edition of the journal Vaccine, Finlay and colleagues reported results of a clini-
Kayaking on English Bay off Vancouver’s shoreline is just one of the ways Brett Finlay channels his boundless energy.
It’s time to close the book on infectious diseases. By 1969, the U.S. surgeon general declared, “It’s time to close the book on infectious diseases.” Antibiotic drugs such as penicillin as well as vaccines against a long list of infectious diseases helped boost average American life expectancy by about 30 years. But the optimism was premature. While human generations are about 20 years apart, bacterial generations are an hour or less apart. Bacteria trade and share genetic information, and this constant throw of the genetic dice means mutant strains rapidly arise that are resistant to our arsenal of antibiotics. In addition, new challenges—such as AIDS, Ebola, legionnaires’ disease, and SARS—continue to appear.

Meanwhile, only one new class of antibiotics, the oxazolidinones, has reached the market in the past 30 years, and finding drugs to combat each form of infection is difficult to justify. It can cost upward of $500 million and take 10 years to commercialize a new drug, but bacteria mutate so swiftly in response that drug-resistant strains can appear within a year and the new drug can be obsolete in three years.

Hospitals are breeding grounds for such resistance. For his 14-year-old daughter’s recent science project, Finlay helped her analyze bacterial contamination of coins collected from hospital cafeteria vendors compared to coins from an outside grocery store. Those that had passed through the hospital carried a far higher percentage of drug-resistant strains of microbes, demonstrating that these institutions’ heavy use of antibiotics has helped create superbugs.

“We need to rethink this,” he says. We are in a constant “arms race” with microbes and viruses that, he warns, “we will never completely win.” Because the germs mutate against every defense we throw at them, we need to develop other strategies.

Bacteria evolved on the planet first, long before plants and animals, and are found in almost every environment, from boiling hot springs to shafts thousands of feet below the ground. “They live everywhere,” Finlay observes, “and humans just represent another nice place for them to live.” We’re warm, wet, full of nutrients, and, in some ways, Finlay says, “more microbe than we are human.”

The human body has 10 times more microbes than cells, or an estimated 1,000 trillion bacteria for each one of us. A square centimeter of skin can have up to a million bacteria, and a gram of feces contains approximately 2 billion. The vast majority of these microbes are benign, helping digest food in our gut and crowding out their disease-causing brethren. But some of these bacteria develop parasitical strategies that make us sick.

Until recently, the two major counterstrategies were either to kill them with antibiotic wonder drugs or trick the body into beefing up its own defenses with the aid of vaccines. But given the current wealth of information on how cells, bacteria, genes, and biochemical pathways work in a complex microscopic ecosystem of mutual dependency and attack, researchers such as Finlay seek new approaches. They don’t try to kill the bacteria, thereby destroying our friends in the bacteriological ecosystem, but rather interfere with the processes that specifically cause illness.

SABOTAGING THE CELL

A key breakthrough of the Finlay lab was the discovery, in 1997, that disease-causing E. coli have a clever way of sabotaging human cells to create a place where they can anchor themselves. Each bacterium exudes a tube, like a syringe, into the cell surface and injects a protein called Tir that serves as a receptor, plus at least a dozen others that disrupt the host cell. The injections trigger rearrangement of the cytoskeleton, which underlies the cell wall like scaffolding under a tarp, and cause it to swell upward, forming a pedestal on which the bacterium can comfortably nest.

This insidious adhesion actually offers researchers an opportunity, Finlay says. If science could find a way to snip or block that syringe, bad actors such as O157:H7 would be unable to link to a cell and cause damage. Instead, they would be flushed out of the body. His lab, in fact, is working on this approach. “We tell pharmaceutical companies that you don’t have to kill the bugs, you just knock out the mechanism that causes the disease,” he explains.

Similarly creative thinking informs the Finlay lab’s development of the cattle vaccine against E. coli O157:H7, which is sure to attract a great deal of interest. Relatively simple to prepare and economical, the vaccine shows that it may be feasible to decrease human infections by vaccinating an animal population.

The lab is also working on Salmonella, a bacterium that sickens some 1.4 million people in the United States per year. In some ways, it is even craftier than E. coli, tricking the cell into opening up and absorbing it by chemically “ringing the doorbell.” Once it is inside, Finlay has discovered, it forms a protective coating to avoid being destroyed by cell defenses and starts feeding and multiplying until it explodes the cell. Is there a way to teach the cell not to open the door? If there is, Finlay is determined to find it.

Still another tactic is to improve sanitation. The town of Walkerton, Ontario, had plenty of chloride on hand but didn’t use it to treat its water supply. If it had, the E. coli outbreak there might never have happened.

SUPER SCIENTIST

Finlay is one of those rare super scientists who somehow seems to have twice the energy and three...
Despite Finlay’s fast pace and unwavering focus, his approach to science is also refreshingly down-to-earth.

microscopic world. His laboratory’s Web site (www.biotech.ubc.ca/faculty/finlay/homepage.html) uses cartoons of bacteria besieging castles—an analogy for cells—to explain the lab’s research.

Despite Finlay’s fast pace and unwavering focus, his approach to science is also refreshingly down-to-earth.

If science is complex in its details, the questions it asks and problems it tackles are fundamentally simple, he says. “If you can’t explain to your mom what you’re working on, you shouldn’t be working on it.”

GREAT EXPECTATIONS

In fact, it was Finlay’s parents who explained much to him. A lot of his energy and seriousness of purpose comes from a relentless curiosity fostered during childhood by scientist-parents. His father, Cam, was an ornithologist who worked at Elk Island National Park of Canada, near Edmonton. His mother, Joy, was an accomplished botanist. Finlay’s parents gave him the opportunity when growing up to, for example, clean dinosaur bones, build bird shelters, and measure the contents of a dissolved magpie nest.

“They attitude was to expose us to many things and let us do what we wanted,” he recalls, but there was also an expectation to excel. His mother once disconnected the doorbell so that Finlay had the time to complete projects instead of being tempted to go out and play. His parents taught him to start keeping detailed scientific notebooks. And when his parents were working, Finlay cooked the family’s meals.

Finlay found his calling when he first looked into a microscope. “Once I stuck my face in the microscope, it was a whole new world. You’re an explorer. You’re after what no one has found before. The North Pole has been conquered, but microbial science is uncharted territory.”

Ask Finlay today about his work and he’ll describe it as “playing in the lab” while trying to solve problems that can help people lead better lives. Much of his inspiration came from touring labs and seeing sick children in Vancouver, Brazil, and Indonesia and noting the real human agony that can come from our constant struggles with the microbial world. “I can see the utility of it,” he says. “I want to do science of use to humanity.”

The scientist is also helping to streamline the process of science itself. When British Columbia’s government asked him to oversee the crash effort to find a vaccine for SARS, it was not just the problem but the approach that intrigued him. Instead of confining the research to individual labs, each of them often operating not just the problem but the approach that intrigued him. Instead of confining the research to individual labs, each of them often operating

leap at the opportunity,” says Finlay. “This has been a chance to put in rapid research in response to a real threat—a ‘commando science’ attitude—and it’s incredibly refreshing because the enthusiasm [of researchers] is unbounded. It breaks down barriers. You leave your ego at the door. You leave money concerns at the door.”

Leaping at opportunity. Rapid response. Unbounded enthusiasm. That’s how it is, day in and day out, in Finlay’s supercharged world. To the casual observer of Finlay’s brand of science in overdrive, it’s clear that he wouldn’t have it any other way.
P ublic understanding of science," a catchphrase among
scientists, is definitely a worthy goal. But the converse
should apply as well: Science needs to have a better
understanding of the public if the two worlds hope to
communicate and work together effectively.

Over the decades that I’ve been talking to researchers, usually
for the purpose of interpreting their work for the public, I’ve
noticed remarkable misconceptions among scientists about how
people think. It is nearly dogma among some researchers that the
public is antiscience, ignorant of elementary science facts, and vir-
tually hopeless with regard to changing those states.

Such beliefs are widespread even though they fly in the face of research that the
National Science Foundation (NSF) has been
doing since 1979. For example, every two
years, NSF conducts a nationwide survey of
U.S. adults to gauge their opinions about sci-
ence and knowledge of science facts. According
to the 2002 edition of Science and Engineering
Indicators, 86 percent of Americans agree with
the statement "science and technology are
making our lives healthier, easier, and more
comfortable." Some 89 percent agree that
"most scientists want to work on things that
will make life better for the average person."

It’s one thing to have a high opinion of
science and scientists, but is the average person
interested in science? NSF’s study, of nearly
2,000 adults chosen to be a nationally repre-
sentative sample, found that 58 percent of
American adults expressed a “high” level of interest in general
science. With medical science in particular, even more—two out
of three—give that rating. In fact, another study (by the Pew
Research Center for the People and the Press) found that among
all news topics that Americans say they “follow closely,” health
ranks second—a hair behind crime and way ahead of sports.
Science and technology score in the middle of the range for all
subjects, but still well above entertainment, business, and con-
sumer news.

If we assume that the polls are representative, can we also
assume that the average person knows any science facts? The bienni-
ual NSF polls show that although the answer basically amounts to
"not really," the situation is steadily improving. In 1995, for exam-
ple, only 21 percent could passably define DNA. That number has
ticked upward every two years, and in 2001, it stood at 45 percent—
still not a majority, of course, but a clear improvement. The increase
is credited to two things—a change in how responses were tallied
and pervasive coverage in the mass media of the subject, including
such widely watched events as the O.J. Simpson trial.

Other questions tell us that 70 percent of respondents know
that plants produce oxygen and that 75 percent know that some
radiation is natural. Slightly more than half realize that electrons are
smaller than atoms, and a surprising 80 percent are aware that the
continents are moving.

But what about the concerns Carl Sagan
expressed in his 1996 book The Demon-
Haunted World? The late astronomer described
widespread popular belief in pseudoscience—
astrology, for example. He argued that if peo-
ple believe in that stuff, they cannot believe in
science.

I challenge that view. Many people believe in both science and pseudoscience simply
because they can’t tell the difference. The NSF
surveys suggest an explanation. When people
were asked about the nature of scientific
inquiry—questions about, for example, what
an experiment or a hypothesis is—only 27 per-
cent gave acceptable answers. In other words,
many more people are interested in science
than grasp what makes it different from pseu-
doscience. They don’t understand the nature of
evidence. So instead of dismissing such folks as hopelessly beyond
the pale, scientists—and journalists—need to find better ways of
teaching them how to think more rigorously.

First, whether they routinely cover science or not, journalists
need to learn more about scientific methods and ways of thinking.
These days, practically all reporters do stories with science content,
at least once in a while. My own community of science writers and
editors has much work to do to educate nonspecialist colleagues.

Second, when scientists talk to the public—including jour-
lists—they should move beyond their findings and explain their
methods. Unless the ordinary person sees that the new finding is
founded on a plausible base of evidence, he or she has no way of
knowing how science trumps pseudoscience or of moving beyond
an interest in science into genuine comprehension of science. For
that to happen—for achieving true “public understanding of sci-
ence”—the researcher needs to have a better understanding, and
greater appreciation, of the public.

Boyce Rensberger directs the Knight Science Journalism Fellowships program at the
Massachusetts Institute of Technology. A science writer and editor for more than 30
years, including stints at the New York Times and the Washington Post, Rensberger is
also the author of four science books. This essay was adapted from a presentation made
at HHMI last fall.
Designer Protein

In an end-run around nature, researchers build an artificial protein.

We don’t know whether evolution has sampled everything that’s possible or only a subset of what’s possible,” says David Baker, an HHMI investigator at the University of Washington School of Medicine. “One way of testing that is to try to make something new.”

The remarkable “something new” that Baker and his colleagues Brian Kuhlman, now an assistant professor at the University of North Carolina, Chapel Hill, and graduate student Gautam Dantas accomplished was to design and produce Top7, the world’s first artificial globular protein. Their work demonstrates for the first time the feasibility of designing and building a protein from scratch.

With the ability to design functional proteins that are not found in nature, researchers open the way to engineer artificial protein enzymes for use in medicines and in other practical applications. Moreover, the Baker lab’s achievement should contribute to our understanding of larger questions about how proteins work and how they evolved.

The feat, which the researchers described in the November 21, 2003, issue of Science, also shows that nature has not exhausted the set of all possible protein folds. Proteins are initially synthesized as long chains of amino acids. They cannot function properly until they fold into intricate globular structures. Understanding and predicting the rules that govern this complex folding process—involving the folding of the main backbone and the packing of the molecular side chains of the amino acids—is one of the central problems of biology.

Previous attempts to design a completely novel protein, a process called ab initio protein design, have met with mixed results at best, says Robert Russell, a structural biologist at the European Molecular Biology Laboratory in Heidelberg, Germany. Russell says that Baker and colleagues “have made very detailed attempts to compare their designed protein in every possible way to real proteins of roughly the same size and composition.” Through this strategy, he adds, “they seem to have avoided many of the pitfalls that have plagued previous attempts.”

Baker’s team began by searching the Topology of Protein Structure server at the Worldwide Protein Data Bank (www.wwpdb.org/pdb) to identify a folding pattern that had not been previously reported. They selected a fold that included the two most common structural elements of proteins—an alpha helix and a beta sheet—but put together in an entirely new configuration.

Once the scientists had defined the protein’s overall shape, says Baker, they sought the combination of amino acid “three-dimensional jigsaw-puzzle” pieces that would fill in the shape, using protein-design software called RosettaDesign (now freely available to academic groups at www.unc.edu/kuhlmanpg/rosettadesign.htm).

Because it was possible that the arbitrarily selected three-dimensional structure would not fold stably, the scientists knew it would be necessary not only to optimize the amino acid sequence but also to fine-tune the structure. Proteins tend to adopt the lowest-energy conformation, Baker explains, and the energy levels of the sequences generated for the starting protein conformation were much higher than those of naturally occurring counterparts. To achieve a more stable structure, the scientists used a method they had previously developed to predict protein structure from a sequence that identifies the lowest-energy structure for a given amino
Hunting Proteins the Nanotech Way

A medical student helps develop a supersensitive new screen for prostate cancer.

Shad Thaxton, a medical student at Northwestern University, aimed to do nothing that afternoon but study at a Borders bookstore in Chicago. But feeling restless, he wandered down to the magazine racks, where the lime-green cover of the September 2001 Scientific American caught his eye. A headline blared: “NANOTECH: The Science of the Small Gets Down to Business.” Thaxton thumbed through the magazine and was consumed, reading eagerly about the hot new field devoted to creating and manipulating tiny specks of matter measured on the nanometer scale. (One nanometer is a billionth of a meter, or just 10 times the diameter of a hydrogen atom.) “I got all fired up about it,” he recalls.

From one article, Thaxton learned that a prominent nanotechnology investigator, chemist Chad A. Mirkin, ran a laboratory right on the Northwestern campus. Thaxton sent an e-mail to Mirkin that very night—a contact that led him to spend last year working in the scientist’s lab, supported by a medical student fellowship from HHMI. In the Mirkin lab, Thaxton played a key role in developing an assay to detect proteins in minuscule amounts.

The assay, which targets prostate-specific antigen (PSA)—a protein marker for prostate cancer—is up to 6 levels of magnitude more sensitive than methods now used in medical laboratories. In general, detecting cancer markers at very low levels may allow clinicians to diagnose cancer early, when treatments are more likely to succeed. Additionally, an ultrasensitive test for PSA would help clinicians diagnose any recurrence of cancer following prostate surgery.

Some studies suggest that PSA levels may also indicate breast-cancer risk, but the test’s usefulness goes beyond detecting PSA alone; it can be modified to search for any of thousands of human proteins, providing a broad spectrum of information about cellular function and dysfunction. In theory, it could be used to flag those thousands of proteins simultaneously, and the technique works fast. Potentially, Thaxton says, “you could assay for every known human protein—the entire proteome—in the same time you now need to do one assay [about seven hours].”

Thaxton, Mirkin, and co-author Jwa-Min Nam published a report on the assay in the September 26, 2003, issue of Science. Thaxton had begun working on an assay for HIV when a chat with his medical-school adviser, Anthony J. Schaeffer, chairman of Northwestern’s urology department, prompted a change of direction. Schaeffer said, “Since you are detecting things so sensitively, how about detecting PSA?” The student was intrigued, wondering if he could create a technique for identifying and quantifying proteins using an approach analogous to PCR (polymerase chain reaction, which allows molecular biologists to analyze even a short strand of genetic material by generating enough copies of the original sequence to make it easily detectable).

Proteins don’t replicate like DNA, however. So the Mirkin lab had been using a tech-
nique, developed before Thaxton arrived, to identify proteins by means of DNA tags, dubbed "bio bar codes," that Thaxton says are "a kind of surrogate—a marker for a protein target." Instead of amplifying the protein itself, "you just pop off the corresponding DNA sequence and amplify that."

Combining the bio bar code method and several other detection techniques devised by the Mirkin group, Thaxton brainstormed with his new colleagues to formulate a novel strategy: In order to fish out the PSA protein floating in a thumb-sized Eppendorf tube, the researchers use magnetic iron microparticles and gold nanoparticles as probes.

The iron probes stick to the protein because they carry antibodies specific to PSA. Then the vial is placed against a magnet, which draws the iron probes (and bound PSA) to one side. When the rest of the "biological soup" is washed away, only the protein bound to probes remains.

In the next step, they add the gold probes, which are linked to antibodies that bind to other sites on the PSA molecule. These probes attach to the iron-bound PSA to form what Thaxton calls "little PSA sandwiches." The researchers again place the vial next to a magnet, which yanks the iron-PSA-gold "sandwiches" over to the side. Another wash removes unbound gold probes.

Each bound gold probe carries hundreds of DNA hitchhikers: very short, tightly attached, single-stranded DNA molecules. These "capture strands," in turn, have grabbed complementary sequences of DNA—the bio bar codes. A simple wash releases the bio bar code DNA from the capture strands. Any of several standard DNA-detection methods may then be applied to confirm the presence of PSA and make a rough measure of its concentration in the liquid—and in the original sample.

The assay is potentially very useful, Thaxton says, because of its excellent ability to seek many proteins at once. For each protein sought, researchers can construct a probe with an antibody specific to the protein target that carries a unique bio bar code to signal that protein.

Proteins have 20 building blocks, in contrast to 4 for DNA, and do not create predictable pairs. Consequently, detecting proteins "presents a much harder analytical problem" than does detecting genes, observes University of Florida chemist Charles R. Martin. "The exciting thing about this latest work, Martin says, "is that Mirkin's team has taken a technique that works for gene sensing—in a way, the easier problem—and applied it to protein sensing, the much more difficult problem."

One recent afternoon, Thaxton was at work in the second-floor lab at Northwestern's newly built Institute for Nanotechnology. During a break between medical school rotations, surrounded even on a Sunday by a half-dozen graduate students, he was clearly delighted to be back at the bench. For now, Thaxton is sticking with the plan he made before reading that issue of Scientific American. He and his wife, first-grade teacher Maggie Thaxton, are talking over where to go for his urology residency.

In addition to securing his M.D., Thaxton also plans to work toward a Ph.D., combining his interest in clinical medicine with his yen for "banging beakers." Urology remains appealing, he says, because he enjoys seeing the broad range of patients that urologists treat. "And I like doing surgery—or the idea of doing surgery: I've done the occasional retracting and sewing already," he says with a laugh. "So all those things kind of draw me to medicine. But I really have a passion for doing research as well."

Meanwhile, a Chicago company called Nanosphere, co-founded by Mirkin, is working on a commercial version of the assay that it hopes to market in a couple of years.

"This will be exciting to watch and be part of," says Thaxton. —CATHY SHUFRO

Science in Bangladesh

Eighteen infectious-disease specialists from developing countries, researchers and graduate students alike, gathered in Dhaka, Bangladesh, in September 2003 to enhance their knowledge of molecular and immunological laboratory techniques and bioinformatics. Working in the parasitology lab are (from the left) Phuangthip Phoophong, Thailand; lab assistant Shantanu Roy, Bangladesh; Shamsun Nahar, Bangladesh; Giang Lien Ngo, Vietnam; and Kea Parker, Peru. HHMI international research scholar Rashidul Haque of the International Centre for Diarrhoeal Disease Research in Bangladesh assembled faculty from India, Thailand, and his own country, as well as from Canada and the United States. As part of its international program, HHMI supports such courses to enable the Institute's competitively funded international research scholars, in partnership with their home institutions, to help build the science infrastructure of their countries. —CATHY SHUFRO
Coming to a school like Northwestern University is intimidating for any freshman, but for some, the adjustment can be overwhelming. Minority students, students from small towns and rural areas, and students from foreign countries are more likely to founder, especially in the sciences.

“A lot of freshmen come in with misconceptions from high school chemistry, and they are easily demoralized by not doing well on the first general-chemistry midterm,” says HHMI professor Hilary A. Godwin, an associate professor of chemistry at Northwestern. “We lose a significant number in the middle of the first quarter, right after that midterm.”

So Godwin decided to do something about the situation; she established a program called Undergraduate Success in Science (USS), which began in 2003. Godwin invited entering freshmen who intended to take general chemistry to spend the summer with her on the Northwestern campus, in the Chicago suburb of Evanston, Illinois, before starting college. There, they would do research and acquire skills—such as time management, communication, and use of the library and other educational resources—needed for success in their studies.

From the 24 incoming students who applied, Godwin chose 12. Some were minorities, others were from rural communities, and one was from France. Statistically, many were at risk of dropping out of science at Northwestern, even though each of them graduated near the top of his or her high school class. The first order of business was academic: Program participants took a renowned leadership class considered instrumental in raising the minority graduation rate at Northwestern’s Robert R. McCormick School of Engineering and Applied Science to twice the national average. Godwin’s group, together with 20 entering engineering students, learned about team building and conflict management as well as how to communicate and interact in a work setting. They shared a dorm, got to know each other, and learned their way around campus.

Next came some “Real World 101” based on Godwin’s own research, which focuses on naturally occurring interactions between metals and proteins—in particular, on environmental contamination by heavy metals such as lead. Her lab seeks to understand how the binding properties of proteins make heavy metals so toxic to living organisms. Godwin put her students to work in the nearby Chicago neighborhood of Rogers Park, where she serves on a lead task force. In that way, she reasoned, the students would not only experience an actual research project, but would also see how science connects to people and the world they live in.

Community-clinic nurses in Rogers Park asked if the students would produce some eye-catching, creative educational materials about lead poisoning for the clinics’ monthly health fair. You’ve come to the right place, Godwin told them. “There’s nothing greater than 18-year-olds for creativity.”

While half of her group designed and built a health-fair booth to educate parents and other community residents on the dangers of lead poisoning and how to prevent it, the others met with the Rogers Park Builders’ Group to consider ways to get the word out on lead poisoning—specifically to contractors and landlords.

“At first, it was pretty intimidating,” 18-year-old Sharon Calderwood recalls. But Godwin’s students held their own. “There were these important businesspeople firing questions at them, and they were answering with quiet confidence,” recalls John Addison, 20, a junior premedical student and mentor in the USS program. “I was so proud of them.”

The builders wanted a PowerPoint presentation for their Web site and to use when they gave talks, so the students developed Lead-Safe Home Improvement. The presentation’s 34 slides spell out the sources and hazards of lead poisoning; common myths about lead; prevention, abatement, and control techniques;
and the legal liabilities of builders, home-improvement contractors, and landlords.

While they worked with neighborhood nurses and builders, the incoming freshmen also spent time in the lab doing research. Godwin, Addison, Molly Grovak, a graduate student at Northwestern and a program mentor, and Scott Baker, assistant professor at Chicago State University and a visiting scholar in the program, taught them the basics of lab safety and procedure, and directed them to the community garden in Rogers Park to collect soil samples to analyze for lead.

In Chicago, 10 percent of children have elevated lead levels in their blood. That can cause nerve disorders, brain-development problems, and kidney damage, and result in coma, seizures, and even death. In some neighborhoods, more than 25 percent of the children have elevated blood-lead levels. But Rogers Park’s soil contamination by lead turned out to be less than the citywide average. To their surprise, while practicing their techniques at Godwin’s older suburban home, the students discovered higher lead levels there than they did in the urban neighborhood.

There was a lesson in that discovery too. “Lead poisoning isn’t just a problem in poor neighborhoods,” says USS participant Daniel Crowder, 18, “and it doesn’t just come from lead paint or lead pipes.” The students learned that there is lead in dust, especially around windows, and in the soil outside. It can be found in some imported products—vinyl miniblinds, pottery, ceramic bathtubs and doorknobs, furniture, and toys. It was used in gasoline for decades, and the residue doesn’t degrade.

As they learned—and shared what they had learned—the entering freshmen’s self-confidence grew. “We realized that we could make a real difference,” Calderwood explains. And in September, seeing how the newly arrived freshmen struggled to acclimate, Calderwood says that she and the other USS students realized “we were at such an advantage; it was almost as though we were sophomores.”

Addison, an African American, recalls the stress of taking tests when he was a freshman. “I felt as though I was passing or failing for my whole race,” he says. “I really would have benefitted from a program like this.”

—Jennifer Boeth Donovan

The Value of Evaluation

HHMI grantees build capacity by assessing how peers measure success.

Evaluation has long been the stuff of grantee nightmares. “I always thought evaluation was something to be dreaded and just gotten through,” says Sandra Shmookler, head of HHMI-supported programs in the Montgomery County (Maryland) Public Schools. Yet, after she and 11 other directors of HHMI precollege science education programs participated in a 2002 peer-assessment experiment underwritten by the Institute, they came to see evaluation in a new light—in part because they helped to improve it.

Divided into teams of four, the directors didn’t judge one another’s programs per se. They were assessing each institution’s evaluation processes by visiting them one by one, observing their programs, and exploring how they evaluated their own effectiveness. An evaluator hired by HHMI went along on the site visits and was available for consultation.

An early decision point in this pilot project involved HHMI’s two types of precollege science education programs—one for community science organizations such as museums and zoos and another for biomedical research institutions. The question was whether each type of program should evaluate only other similar programs or whether both types should evaluate each other.

Participants opted to include both kinds of programs on each team—a decision that contributed strongly to the pilot project’s success. “We generally don’t have the opportunity to cross-pollinate among such diverse programs and institutions on a national scale,” notes Libby McCann, a team member from the University of Wisconsin–Madison Arboretum. This new approach, she says, was “an exciting and essential component of the learning process and the generation of new ideas.”

Robin W. Rockhold, of the University of Mississippi Medical Center, was pleasantly surprised to see “the very fundamental similarities that exist among our apparently very diverse projects, especially the passion of the people and their dedication to making science education a living, evolving fascination with the fundamental processes of life itself rather than a dry, fact-based grind.”

The interactions of such diverse but like-minded individuals helped realize the project’s main long-term goal—to help grantees improve their ability to assess what is and is not effective and to build their capacity for sustaining the work, especially when grant dollars are no longer available.

As a result, HHMI has mandated peer evaluation in its most recent competition for precollege science education programs. And four new teams are now planning visits to one another’s programs. Meanwhile, members of the original teams are busy preaching the gospel of peer evaluation to meetings of science educators and grant makers such as the Council on Foundations, Grantmakers for Education, and the Association of Science-Technology Centers.

They’ve discovered a new way of operating—“Everyone in our programs, including me, stays constantly in evaluation mode,” says Shmookler—and a new and valued resource: each other. “We now have a circle of critical friends,” says McCann, “who have a sense of our varied programs, share a common language of evaluation, and are willing to provide support and advice to each other.” Adds Bill Watson, education director of the Gulf Coast Exploreum Science Center in Mobile, Alabama: “We’re all in this together.”

—Jennifer Boeth Donovan
Life Studies in Clay

Exploring physical-chemical mechanisms for how it all began.

Researchers have identified conditions that possibly led to the development of living cells on Earth, though they are quick to note it isn’t the definitive word on the origins of life. HHMI investigator Jack W. Szostak and colleagues Martin M. Hanczyc and Shelly M. Fujikawa at Massachusetts General Hospital discovered that montmorillonite, a type of absorbent clay, could have catalyzed the assembly of tiny fatty acid particles, called micelles, into sacs that ultimately evolved into the first living cells.

Under simulated conditions in the laboratory, the researchers also demonstrated that such sacs, known as vesicles, could be induced to grow in size and to split into separate vesicles. They reported their studies in the October 24, 2003, issue of Science.

Szostak and his colleagues were prompted to perform their experiments by other scientists’ discovery that montmorillonite could catalyze the chemical reactions needed to construct RNA from building blocks called nucleotides. If the clay could also foster the formation of vesicles, they thought, it would not be inconceivable that clay particles with RNA on their surface could end up inside such vesicles. And if that were true, the resulting conditions might be amenable to self-replication.

The researchers knew that micelles are stable under conditions of basic pH but spontaneously assemble into vesicles when exposed to more acidic conditions, though the process takes some time. “We reasoned that if the right kind of mineral surface was present, this lag phase would be eliminated,” says Szostak. Indeed, he and his colleagues found that adding small quantities of the clay to micelles greatly accelerated the initial rate of vesicle formation. They also discovered that many other substances with negatively charged surfaces catalyzed formation of vesicles as well.

When the researchers loaded montmorillonite particles with fluorescently labeled RNA and then added them to micelles, they were able to detect the RNA-loaded particles inside the resulting vesicles. Going a step further, they showed that when they encapsulated labeled RNA alone inside vesicles, it did not leak out.

“Thus, we have demonstrated that not only can clay and other mineral surfaces accelerate vesicle assembly, but assuming that the clay ends up inside at least some of the time, this provides a pathway by which RNA could get into vesicles,” Szostak says.

However, Szostak notes, even primitive, nonliving cell-like structures need a mechanism to grow and divide. So the scientists explored the behavior of vesicles to which micelles were slowly added. Using tracking dyes and quantitative methods, they confirmed that the added micelles were, in fact, being incorporated into preformed vesicles and increasing in size, rather than congregating and forming new vesicles.

“After we showed that efficient growth was possible, the next problem was how to complete the cycle by persuading these vesicles to divide,” Szostak recalls. The scientists discovered that if they extruded larger dye-containing vesicles through small-pore filters, the result was a proliferation of smaller vesicles that still contained dye.

They aren’t sure exactly how the proliferation occurs, though they are developing different models to explain the process. “The important thing is that it all works. You end up with small vesicles in which the contents have stayed mostly inside,” says Szostak. “This is important if the process is to be vaguely analogous to biological cell division. Now that we have proof of principle that growth and division are possible in a purely physical-chemical system, we are trying to get this cycle to function in a way that is more natural,” he says.

Meanwhile, the investigators are keeping their findings in perspective. “We are not claiming that this is how life started,” Szostak maintains. “We are saying that we have demonstrated growth and division without any biochemical machinery. If we can now demonstrate more natural ways in which this might have happened, it may begin to give us clues about how life could have actually gotten started on the primitive Earth.”

In addition, he suggests, further research should aim to demonstrate that the formation of RNA—a related polymer molecule—could take place concurrently with vesicle replication. “If we could demonstrate both processes under arbitrary laboratory conditions,” says Szostak, “we could begin to make them work under more natural conditions.”

—DENNIS MEREDITH
Exploring Bioethical Choices

At HHMI’s 2003 Holiday Lectures, students use improvisational play to confront tough issues.

Three genetic counselors, two lawyers, a married couple, their blind daughter, their normal son, and their unborn child (yes, their unborn child) take their places on the auditorium stage at HHMI headquarters in Chevy Chase, Maryland. Until this moment, the actors had been Washington, D.C.-area high school students attending the Institute’s 11th annual Holiday Lectures on Science, in December 2003. Now, having volunteered to play roles in an improvised dramatization of ethical issues raised by genetic testing and counseling, they are wrestling with some of the thorny problems that accompany the miracles of modern biology.

The role-playing complements lessons learned from four lectures by HHMI investigators Bert Vogelstein from the Sidney Kimmel Comprehensive Cancer Center at the Johns Hopkins University School of Medicine, and Huda Y. Zoghbi at the Baylor College of Medicine. Their topic: “Learning from Patients: The Science of Medicine.”

In the scenario developed by Vogelstein and Zoghbi, a mother and father have two children: a 3-year-old girl with retinoblastoma (a rare eye cancer that is usually inherited) and a 12-year-old boy who does not. The father’s mother also had retinoblastoma, the only treatment for which is removal of the eyes. Half of all offspring of a parent with the retinoblastoma mutation will also carry it, and 9 out of 10 of those will develop the disease.

Now expecting another child, the couple seeks advice from genetic counselors. “What are the chances that this baby will have retinoblastoma?” they ask. “Should we even have it?”

In the spirited discussion that follows, the students on stage and their classmates in the audience explore what genetic counselors can and should advise. For example, when a counselor tells the couple what they “should” do, one of the lawyers pops up shouting “lawsuit, lawsuit.” The role of counselors is to educate, not instruct, Zoghbi explains.

The role-play includes a frank discussion of abortion issues. “I think you should have me,” says the fetus. “Even if I’m disabled, who’s to say that my life is not worth living?” And when the mother describes her blind daughter as “a burden,” the girl protests. “I aspire to be a Braille teacher for blind children in underdeveloped countries,” she says. “I am a gift from God, both a burden and a blessing.”

“What if we had the skill to fix this gene?” asks Laurie Zoloth, a Northwestern University bioethicist who chairs HHMI’s bioethics advisory board. “Should we do it?”

Caution prevails. “If you start changing one gene, it might set a precedent,” one of the genetic counselors remarks. A student in the audience calls it “like going online and ordering a child.” Another comments, “Evolution is based on genetic diversity for a reason.”

The role-playing students confront a final twist in the tale. The counselors recommend that the father be tested for the retinoblastoma mutation. He doesn’t have it. The baby is born, and she develops retinoblastoma. So the mother is tested. She doesn’t carry the mutation either.

“How could this be?” Vogelstein asks the audience. “The ‘father’ isn’t the father of the child,” several students suggest. “Exactly,” says Vogelstein. “Genetic counselors, what are you going to do now? Should the mother be asked to identify the baby’s father? Should he be told? If so, by whom? Should the mother’s husband be told?”

In real genetic counseling, “this does happen,” Zoloth tells the students.

Geneticists have learned to discreetly probe the medical and social history if a person presumed to be an “obligate carrier” (an individual who must carry a gene mutation based on analysis of family history) does not show signs of the disease in question, even though statistics show, for example, that some 90 percent of people with the mutation would be expected to exhibit symptoms.

“We know a lot more than we used to know, a lot less than we want to know, and we can’t do as much as we’d like with the information we do have,” says Zoloth.

Vogelstein points out that 15 years ago “this whole conversation would have been deemed science fiction. Today, we can test—and tell with certainty—whether someone does or does not carry a specific genetic mutation. That’s the science. Now we are faced with the ethical choices.”

—JENNIFER BOETH DONOVAN
Food for Thought

Why do chocolate lovers salivate when they see a candy-bar wrapper? The answer lies in the way the brain connects food and food-related images.

Any scientist studying people’s relationship to food is likely to arouse the curiosity of the popular press, and HHMI physician postdoctoral fellow Jay A. Gottfried is no exception. His research showing how the state of one’s appetite modulates the brain’s responses to food-associated images triggered a frenzy of phone calls from women’s and health magazines. “They billed it as ‘why there is always room for dessert,’” says Gottfried, “but our findings are more subtle than that. I think they tell us something about learning in general.”

Gottfried, who came to the Wellcome Department of Imaging Neuroscience at University College London in 2001 after completing a neurology residency at the University of Pennsylvania, set out to identify the brain regions that enable us to make associations between certain foods and the images representing them—why chocolate lovers, say, salivate at the sight of a candy-bar wrapper. He then asked how the brain modulates those associations in accordance with a person’s state of hunger. Why does the sight of the wrapper become less attractive after one has eaten one’s fill, and what are the brain pathways involved in altering that attractiveness judgment?

Gottfried and his colleagues trained 13 people to associate abstract images with two distinctive food smells they found pleasant—vanilla and peanut butter. While the volunteers were hungry, the researchers scanned their brains (using functional magnetic resonance imaging) as they manifested the various learned responses to image and odor.

Among the brain structures that were active during this “hungry phase” of the experiment were the amygdala and the orbitofrontal cortex (OFC)—regions that have been linked with learning in animal and human studies. The volunteers then ate—indulging in either vanilla ice cream or peanut butter sandwiches until they were full but not uncomfortably so—and were returned to the scanner to be presented with the image-odor combinations for a second time. In this “sated phase,” the researchers saw a dampening of the responses of the amygdala and OFC to the image associated with the food the subjects had eaten, but not to the image related to the other food.

What this suggests, says Gottfried, is that the amygdala and OFC are able to track the current reward value of a predictive stimulus and modulate their activity as that reward value changes. “While the brain is very efficient at establishing meaningful associations between items in the environment, it’s not a rigid system,” he explains. “It’s very flexible and plastic and can be updated according to one’s motivational or appetite circumstance.”

It follows that when this plasticity breaks down, eating disorders may result. Patients with the rare neurological disorder Klüver-Bucy syndrome, for instance, who have suffered damage to the amygdala and OFC, regularly eat to excess and even occasionally attempt to eat nonfood items. It could be, says Gottfried, that they lack the ability to update those reward circuits so as to put a brake on their appetites. And the underlying mechanism, or the lack thereof, is not limited to rare conditions. “You could step from the land of Klüver-Bucy,” he suggests, “into more generic eating disorders such as food cravings.”

Deanne Jade, principal of the UK’s National Centre for Eating Disorders in Esher, Surrey, warns against singling out one cause of eating disorders, and she points to evidence that distorted body image is also a major contributor to conditions such as anorexia nervosa. But she welcomes Gottfried’s findings as a “very positive” step in the right direction. “We know that anorexics will have very heightened activities in their brain’s reward systems just by looking at food,” Jade says, “which is why they seem to resist [therapeutic] diets and go around supermarkets feeding themselves on the look of food alone.”

Gottfried readily admits that his study, which was published in the August 22, 2003, issue of Science, raises more questions than it answers. For example, he says, it remains to be determined how the myriad hunger and satiety signals generated by the brain and digestive system converge to modulate the brain’s reward networks.

—LAURA SPINNEY
On Martian Time
A teacher and her students help NASA scientists explore the red planet.

Marilou Bebak remembers the thrill of watching astronaut John Glenn become the first American to orbit Earth. “Just put me on the next rocket,” she recalls quipping.

This year, Bebak, now a biology teacher at Nardin Academy in Buffalo, New York, got to do the next best thing. She and two of her students flew to the Jet Propulsion Laboratory (JPL) in Pasadena, California, to work with science payload project director Steven W. Squyres on the landings of Spirit and Opportunity, NASA’s latest Mars-exploration robotic rovers. They were among only 13 teacher-student teams chosen nationwide to provide that kind of assistance.

Kristen Curtis, a 17-year-old Nardin senior, had heard about NASA’s Athena Student Interns Program and turned to Bebak, a teacher known not only for her interest in space but also for her hands-on, real-world approach to learning science. At first, Bebak misunderstood the nature of Curtis’s request. “I thought she needed a letter of recommendation,” the teacher recalls. Instead, Bebak found herself applying to the competitive program with Curtis, who wants to be an aerospace engineer, and Katie Reedy, a junior at Nardin.

The contest drew some 100 applications. Given the heavy competition, “we didn’t expect to be chosen,” Curtis says. “When we found out we were one of the teams, we were as shocked as we were excited.”

The team joined scientists at JPL in October 2003 for a dry run based on a simulated Mars environment. That’s when Squyres, a planetary astronomer at Cornell University, tapped Curtis to run the project’s Collaborative Information Portal, a computer-based master scheduler for the entire mission. “He was confident that she could handle it because she remembered every step in sequence after seeing it just one time,” says Bebak.

On New Year’s Eve, the Buffalo team returned to JPL for the first landing, scheduled for January 3. Scientists and engineers were working around the clock, and keeping Martian time—Mars’s day is 40 minutes longer than Earth’s. And the team kept pace with them. “When we slept, and how much, really depended on what was going on with the rovers,” Curtis says.

Squyres asked Reedy, 17, a writer and editor for her school paper, to handle press arrangements. “I had never been involved in a large-scale media event like this, with so many people clamoring to get their stories and interviews,” she remarks. But when the time came, she managed it like a pro.

As Spirit entered Mars’s atmosphere, Bebak, Curtis, and Reedy joined a crowd of scientists and engineers in a room near Mission Control to watch a live video feed of the rover’s landing on wall-sized screens. “During its six-minute descent, you could hear a pin drop,” Bebak recalls. “The parachute opened, the heat shield held, and everyone applauded. The next 12 minutes—until we got the first signal—went on forever. Some people were pacing, some were crying, others were praying.”

Finally, a signal arrived from Gusev Crater. Spirit was safe on the surface of Mars. When the first images from the little robot explorer appeared two hours later, “it was exhilarating,” says Curtis. “When everything worked, there was a sense of ‘Wow!’ among the engineers and scientists.”

In fact, they seemed like “space tourists,” Bebak says, “as they ran around with cameras and video recorders, taking pictures of the pictures on the wall.”

The teacher-student team stayed at JPL for another week, working with the scientists as they started to analyze data coming in from Mars. They attended brainstorming sessions where hypotheses flew, assessment meetings to discuss what had been learned, and planning meetings to decide what the rover should do next.

“The girls saw how science really works—how scientists operate when no one knows exactly what the data mean or what will happen next,” says Bebak. “And they saw the camaraderie, the teamwork, the respect for each other’s ideas.”

Bebak’s team was invited back to work on the landing of Opportunity, the second rover, on January 25.

Now that the internship is over, the team has been sharing their adventure with classmates, teacher-colleagues, and the world at large. They have presented a program at the Buffalo Museum of Science, and Reedy has written an article for Natural History magazine. Although the experience of actually working on the Mars landings can’t be duplicated in a classroom, Bebak believes that all her students will benefit. “It definitely energized my teaching,” she explains.

Some would say that Bebak’s teaching was fairly energized already. For one thing, she has been inspired and informed by participating in the Cornell Institute for Biology Teachers—a workshop program, supported by an HHMI science education grant, to keep science teachers in touch with the latest research advances and with each other. Bebak returns to Cornell regularly for updates, and she shares tricks of the trade with fellow teachers throughout the year via the institute’s alumni network.

For another thing, Bebak is basically someone with a taste for learning by doing. “My philosophy of teaching science,” she says, “has become: ‘Let’s try this and see what happens.’”

—JENNIFER BOETH DONOVAN
Its Name Is Noggin

An aptly named molecule may help at-risk children avoid craniofacial surgery.

On October morning in 1995, Stephen M. Warren, then a medical student at the University of California, Los Angeles, stayed behind after participating in an operation to remove a chest tumor. He wanted to watch a team of plastic surgeons reconstruct the patient’s chest wall.

“It was so inventive,” he says. “Unlike the cancer surgery, the plastic surgeons put everything back together again.” Their dexterity in fitting a piece of mesh to rebuild the gaping hole resonated strongly with Warren’s puzzle-solving personality. So much so that later that day he switched all of his fourth-year electives to plastic surgery, leaving surgical oncology behind. That pivotal moment would eventually lead Warren to make a key discovery that could render reconstruction of deformities affecting the skull and face less traumatic and, ironically, less surgical.

At the time of his epiphany, Warren had just returned to medical school after two years at the National Cancer Institute (NCI) at the National Institutes of Health (NIH) under the sponsorship of the HHMI-NIH Research Scholars Program (also known as the Cloister Program). After receiving his degree, he went on to spend three years as a general surgery resident at Oregon Health & Science University in Portland. He then returned to the laboratory in 1999, working with Michael T. Longaker at New York University Medical Center in New York City. Warren moved with Longaker when he relocated his craniofacial development lab to Stanford University in 2000. Longaker, who considers Warren “a natural scientific leader,” notes that the young researcher took on a project to discern how cranial sutures in the skull fuse properly—a problem that had been puzzling the field since Rudolph Virchow’s seminal work in the mid-19th century.

Cranial sutures are the “seams” between the skull plates where new bone is added. They eventually seal when the brain and skull have reached full size. However, if the sutures fuse prematurely—a condition called craniosynostosis—they can cause disfigurement, blindness, mental retardation, seizures, and devastating pain. Children with this condition—it occurs in about 1 in 2,500—must undergo extensive operations to restructure the skull and give the brain room to grow.

Researchers knew that genetic mutations that turn on a particular growth factor receptor cause two different forms of the condition—Apert and Crouzon syndromes. For years, they had been looking for a connection to that bone-forming factor, reasoning that in affected children, too much bone is produced in the seam too fast, which results in fusion.

In a meeting with other self-described “boneheads,” Warren recalls hearing how a colleague had discovered that a molecule called “Noggin,” secreted from the Spemann organizer region of the frog embryo, directed brain development. “I came away from that meeting,” he says, “wondering if the tissue within a suture could be functioning like the Spemann organizer and directing fusion.” What he now refers to as “a fanciful speculation” led to the idea that inhibitors of bone formation might normally act at the suture site to hold it open and keep it from fusing prematurely.

Warren and his colleagues went on to test sutures for the presence of inhibitors, and they found Noggin present in open sutures but absent from fused ones. The team also showed that boosting Noggin levels prevented the fusing of sutures that had been cultured in a lab dish or grown in mice.

The next question, Warren recalls, was whether Noggin could be turned off or suppressed in a way that would cause a normally open suture to fuse prematurely. Connecting back to the mutations that turn on a growth factor receptor in affected children, the group showed that the growth factor FGF2 could indeed turn off Noggin expression. In fact, when the researchers gave cells grown in a lab dish the same mutations found in the syndromes, they observed that Noggin production dramatically dropped off. Their work was published in the April 10, 2003, issue of Nature.

Warren admits that getting people to think about suture fusion as the inhibition of an inhibitor was a bit challenging. His mentor Longaker compares the phenomenon to driving. “It’s a nice example,” he says, “of regulation at the brake level as opposed to the accelerator.”

Jill A. Helms, a developmental biologist and dentist at the University of California, San Francisco, says the finding provided much-needed direction in a field confused by a large number of genes that, when mutated, could each lead to premature fusion. “Imagine looking down from a stadium and seeing too many players,” she says. “You wouldn’t have any idea who’s directing the game or how it works; this paper helped clarify how some of these molecular players were directing suture fusion.” She also notes that the work suggests a future in which children at risk for developing craniosynostosis are treated with medicine—such as the right combination of molecules to keep sutures open—instead of having to undergo the risky surgery done now.

Warren gives some of the credit for his discovery to the time he spent almost a decade earlier in the Cloister Program, which he says instilled an open-minded approach to research questions. He was in a different
field at the time, but he saw how it was possible to “work both sides of the coin.” In Steven Rosenberg’s group at NCI, Warren was working on tumor-invading lymphocytes, trying not only to make them better tumor killers, but also to make the tumors themselves more susceptible to killing. In a similar spirit, Warren says he later “looked on both the bone-forming and bone-inhibiting sides of the coin.”

Warren now has one more year as a clinical fellow in plastic and reconstructive surgery at Brigham and Women’s Hospital in Boston. Then the physician-researcher must decide, he says, whether to pursue clinical work or research, as he believes it’s nearly impossible to do both of these more-than-full-time jobs simultaneously.

Longaker respectfully disagrees: “Steve could be one of those rare people who could do both. But I believe if he had to choose, he is as likely as anyone I know to make contributions in research that could help thousands or millions of children.” —KENDALL POWELL

When she wasn’t in the lab, Nisha David took time to get to know Australia’s unique fauna, including these approachable marsupials.

G’Day, Lab Mates
A New England undergrad art major tackles malaria down under.

What was an art major from an American liberal-arts college doing in an immunology research lab in Australia? Contributing to the fight against malaria, discovering her own career interest in medical research, and inspiring others—contemporaries and elders alike.

Nisha David, now a junior at Williams College in Williamstown, Massachusetts, spent the summer of 2003 at Melbourne’s Austin Research Institute, where she was the youngest member of the laboratory of HHMI international research scholar Magdalena Plebanski, a specialist in vaccine development for infectious diseases. David learned of the summer-internship opportunity from biology professor Steven J. Zottoli, the HHMI undergraduate program director at Williams. Although her science experience to that point had been confined to chemistry, the description on the HHMI Web site of Plebanski’s malaria-vaccine work caught her interest. “She wasn’t daunted by going into a situation with very little background,” says Zottoli. “She took the bull by the horns and went.”

“I began by wandering around the lab and asking people about their projects,” David recalls. “Most of their explanations were soadvanced that I found it difficult to ask pertinent questions. But I took notes on as many different terms and processes as possible so that I could return to them later after I’d read more. As time passed, I adjusted to the complexity and breadth of the material as well as to the fast pace of the lab.”

The researchers had developed a vaccine against the malaria parasite Plasmodium falciparum that was highly effective in mice, but they weren’t sure why it worked so well. The team was in the midst of studying the animals’ immune responses to the vaccine when David arrived, so they put her to work on that effort. Doctoral student Dodie Pouniotis taught her how to do ELISAs—enzyme-linked immunosorbent assays—to aid in the analysis of the antibodies that the mice manufactured post-vaccination. Her project culminated with a PowerPoint presentation to the group.

David’s visit down under wasn’t all work—she made time to relax and observe Australia’s famed fauna, including kangaroos grazing on golf courses and penguins strolling on moonlit beaches. And she picked up some of the lingo as well, dotting her conversation with an occasional “mate” and “good on you.”

In her emails to Zottoli throughout the summer, David’s evolving confidence was evident. She wrote early on, “It’s all very exciting. I am learning a ton, and although a lot of the presentations each morning are still way over my head, I am at least able to understand the basics of the research, which is great.” Her later messages echo the pride of scientific discovery: “It’s pretty amazing to compile all my data—I hadn’t realized all that I had accomplished. And it’s also fun to realize that I completely understand what I am presenting, while only a few months ago I didn’t know anything about immunology!”

David contributed more to the lab than performing some- tedious assays. “It was a delight having Nisha with us,” says Plebanski. “Her very basic immunology questions made all of us question our own preconceptions. And having somebody so young, so clearly curious to understand new concepts and motivated by discovery, made us remember why we got onto the science path ourselves.”

Back at Williams, David has a new view of her future—having glimpsed the trials and tribulations of research, she wants more. She plans to study biology and immunology, and will likely go on to medical school. “My Australian experience influenced my academic life in ways I had not foreseen and that are still unfolding,” she reports.

Zottoli adds that the early timing—when career options had not yet crystallized—was particularly important for David, as it is for others who participate in such internships. “The program is not only an opportunity for students who are already committed to research,” he says, “but also for students to see what it’s like.”

—RICKI LEWIS
Identity Crisis

Researchers have discovered some of the basic control signals involved in organizing the spinal cord in the developing embryo. These signals help decide the fate of newborn motor neurons by allowing them to form columns of neurons that are grouped according to function. Such a columnar arrangement ensures that the right set of motor neurons from the spinal cord send axons—and messages—to the appropriate muscle group.

In earlier studies, HHMI investigator Thomas M. Jessell at Columbia University and his co-workers found that transcription factors—proteins that regulate gene expression—control how motor neurons acquire a generic identity that distinguishes them from nearby neurons through a signaling process that operates from front to back in the spinal cord. The concentration of a particular signaling molecule, Sonic hedgehog, was key.

The researchers decided to see whether a similar system was at work along the front-to-rear (or anterior-to-posterior) length of the developing spinal cord. They focused their attention on a family of genes called homeo-, or Hox genes, which they showed help choreograph spinal cord development. Previous evidence indicated that a subgroup of Hox genes, Hox-c genes, were expressed at various locations along the length of the spinal cord. In addition, various motor neuron column subtypes had been known to reside at different anterior and posterior positions in the spinal cord.

In subsequent experiments, Jessell and collaborator Jeremy S. Dasen, an HHMI research associate at Columbia, and Jeh-Ping Liu, at the University of Virginia School of Medicine, showed that Hox-c gene expression along the length of the developing spinal cord is controlled by a gradient of a secreted protein, fibroblast growth factor (FGF). Changing FGF levels in the embryo dramatically altered Hox-c expres-

Sweet Genes

Is the craving for sweets in our genes? Researchers led by HHMI investigator Charles S. Zuker at the University of California, San Diego, conducted a series of experiments to nail down the identity of taste receptors for sweet and umami, or “savory,” in humans. As part of that research, they inserted the gene for a human sweet-taste receptor protein into mice. The animals showed the same preference for sweets as do humans, making it likely that such preferences are indeed genetically encoded. They also showed that knockout mice lacking either one or both protein receptor subunits for sweet and umami failed to respond, or showed a lessened response, to such chemicals.

The researchers reported their findings in the October 31, 2003, issue of Cell.

Inflammation Toggle

Researchers have discovered that a protein called PPARδ acts as a genetic switch that can drastically reduce fatty deposits in the coronary arteries of mice. Ronald M. Evans, an HHMI investigator at the Salk Institute for Biological Studies in La Jolla, California, and his colleagues fed normal and PPARδ-deficient mice a fatty diet and compared the formation of atherosclerotic plaques. To their surprise, the PPARδ-deficient mice had clean arteries. “The lesions almost failed to develop at all” in the PPARδ knockouts, says Evans. Further research suggests that PPARδ regulates plaque-promoting inflammation in arteries through a unique pathway that increases the availability of inflammatory suppressors.

The findings were published in the October 17, 2003, issue of Science.

Mutations Abet Metastasis

Cancer is deadliest when it spreads, but the reasons that make one type of cancer more likely to spread than another have been a mystery. HHMI investigator Tian Xu and graduate student Raymond A. Pagliarini at Yale University School of Medicine have recently used the fruit fly Drosophila melanogaster to systematically screen the genome for cancer genes, revealing unexpected combinations of genetic mistakes required for metastasis.

Xu and Pagliarini showed that a mutated version of the cancer gene Ros, which plays a central role in human cancer development, is also crucial to promoting metastasis in the fly when combined with mutations in a variety of genes, such as a gene called scribble (scri), which normally maintain epithelial cell polarity. Neither mutation alone was enough to cause metastasis.

The findings imply that different benign tumors have their own individual potentials to become metastatic cancers, depending on the kinds of mutations that initiated early tumor growth. Thus, it may one day be possible, Xu suggests, to predict an early noninvasive tumor’s likelihood to spread, based on identifying which genetic mutations initiated the disease. The researchers reported their studies in the November 14, 2003, issue of Science.

Hirschsprung Help

Researchers have found that Hirschsprung disease, a potentially...
Promiscuous Prions

Scientists have taken a step toward understanding the behavior of misfolded and infectious proteins, called prions, that appear to propagate by prompting their normal counterparts to misfold as well. Prion infections can be lethal, triggering protein clumping that causes fatal brain disorders such as Creutzfeldt-Jakob disease in humans and bovine spongiform encephalopathy, or mad cow disease, in livestock.

Jonathan S. Weissman, an HHMI investigator at the University of California, San Francisco, and his colleagues knew that mutations in only a few amino acids in a prion could cause “transmission barriers” that prevent one species of prion from infecting another species. But they wanted to know how and why species barriers arise.

To find out, they turned to a prion they had previously created by stitching together pieces of prions known to infect either of two yeast strains—Saccharomyces cerevisiae (Sc) and Candida albicans (Ca). This chimeric prion was “promiscuous”—that is, capable of creating two different protein shapes, each of which could infect either strain.

When Weissman’s team introduced “point” mutations into the chimeric prion, however, it found that the mutations would favor the formation of one shape over another, thereby changing the transmission barriers of the chimeric prion. They showed, for example, that prions mutated to favor the Sc-infesting form could no longer infect the Ca yeast strain. The researchers reported their findings in the August 21, 2003, issue of Nature.

“It’s not just changes in the amino acids in the protein when going from one species to another that determines the species barrier,” concludes Weissman. “Changes in the prion protein sequence change the shape of the infectious protein—it is this change in shape that causes species barriers.”

Understanding protein misfolding might have application someday for treating such illnesses as Alzheimer’s and Parkinson’s diseases, says Weissman. Misfolded amyloid proteins clump into pathological plaques in both disorders. Rather than completely preventing protein misfolding, drugs might direct amyloid proteins to fold into less toxic products.
Tsien Wins Wolf Prize

Roger Y. Tsien, an HHMI investigator at the University of California, San Diego, was named winner of the 2004 Wolf Prize in Medicine, to be shared jointly with Robert A. Weinberg of the Massachusetts Institute of Technology. Considered Israel’s Nobel Prize, the award will be presented by the president of Israel at the Knesset (parliament) in Jerusalem on May 9, 2004.

The Wolf Foundation honored Tsien for his “seminal contribution to the design and biological application of novel fluorescent and photo-labile molecules to analyze and perturb cell signal transduction.” By virtue of these uniquely informative markers, Tsien and his lab have helped to expand knowledge in areas as diverse as chemical biology, cell biology, and neurobiology.

Researchers around the world now use Tsien’s probes to study changes in calcium levels in living cells. The series of modified green fluorescent protein probes engineered in his lab are widely used for studies of intracellular protein localization and interaction. Tsien’s lab has also delved into the design and synthesis of alternatives to fluorescent proteins, resulting in successes such as his nimble arsenic-based dyes. These discoveries did not arise from a vacuum—each was born out of a need to answer biological questions that were impossible to address using currently available methods. Hence, in applying these innovative tools to their own research, Tsien and his lab have also deepened our understanding of cellular signaling.

—MARY BETH GARDINER

Südhof Receives MetLife Honor

Thomas C. Südhof, an HHMI investigator at the University of Texas Southwestern Medical Center at Dallas, has received the 2004 MetLife Foundation’s Award for Medical Research in Alzheimer’s Disease. He shares the award, which recognizes scientists whose work has contributed significantly to understanding Alzheimer’s disease, with Roberto Malinow from the Cold Spring Harbor Laboratory. The award was presented in January at a ceremony in Washington, D.C.

Südhof has long been interested in how neurons communicate at the synapse between two nerve cells. His lab focuses on how a
presynaptic nerve terminal forms a precisely targeted junction with a postsynaptic neuron, how the terminal tightly regulates the release of chemical messages (neurotransmitters), and how these functions become abnormal in neurodegenerative diseases.

Recently, Südhof’s lab has turned its attention to examining the role of amyloid-β precursor protein (APP)—a molecule believed central to the development of Alzheimer’s disease—in synaptic activities. Their work has led to a greater understanding of the protein’s normal function and has laid the groundwork for future studies in the underlying causes of the disease.

—MARY BETH GARDINER

Advancing Research in South Africa

Bruce D. Walker, an HHMI investigator at Massachusetts General Hospital, is helping to establish the physician-researcher model at the Nelson R. Mandela School of Medicine of the University of KwaZulu-Natal in South Africa, where he has a faculty appointment.

For 15 years, Walker has studied the HIV strains of Africa, which has the world’s highest burden of HIV infection but whose medical schools do little of their own research on the subject. To remedy that situation, he sought funding for a center at the Mandela School that would study HIV at the heart of the epidemic and that would help retrain local physicians and repatriate physicians trained in research elsewhere. Funding for the $5.17 million institute came from the Doris Duke Charitable Foundation and the University of Natal; it has the distinction of being the first dedicated research facility at a medical school in sub-Saharan Africa and the first new building on campus in almost 50 years. It employs 20 principal investigators and offers training workshops for researchers from across the continent.

Walker and his African collaborators also established a clinical cohort at the rural St. Mary’s Hospital in KwaZulu-Natal, where 70 percent of admissions are HIV-related and 50 percent of pregnant women are HIV-positive. —CATHERYN M. DELUDE

The fellowships are awarded to artists, scholars, and scientists by the John Simon Guggenheim Memorial Foundation.

B. Brett Finlay, a two-time HHMI international research scholar at the University of British Columbia, received the 2003 National Merit Award from the Ottawa Life Sciences Council (OLSC). The award recognizes individuals for contributions to Canada’s life sciences sector. The OLSC awarded the 2003 Career Achievement Award to another two-time HHMI international research scholar, Robert G. Korneluk, currently at Children’s Hospital of Eastern Ontario Research Institute.

D. Gary Gilliland, an HHMI investigator at Brigham and Women’s Hospital and Harvard Medical School, won the 2003 William Dameshek Prize from the American Society of Hematology. The award recognizes recent outstanding contributions in the field of hematology.

David Ginsburg, an HHMI investigator at the University of Michigan Medical School, received the 2003 American Heart Association Basic Research Prize, which recognizes significant advances in cardiovascular science. He shared the award with Shaun R. Coughlin of the University of California, San Francisco.

One HHMI investigator and three current or former HHMI physician postdoctoral fellows and/or mentors are recipients of the 2003 Richard and Susan Smith Family Foundation Pinnacle Program Project Award. The investigator is Todd R. Golub, at Dana-Farber Cancer Institute.

Joel Hirschhorn, Children’s Hospital Boston, is a postdoctoral fellow; David Altschuler, Massachusetts General Hospital, is a former postdoctoral fellow and mentor; and Gary Ruvkun, Massachusetts General Hospital, is a mentor. The fifth recipient in the group award is Mark Daly of the Whitehead Institute for Biological Research. Given by the American Diabetes Association Research Foundation, the award supports independent but complementary research projects in diabetes.

A. James Hudspeth, an HHMI investigator at the Rockefeller University, won the 2003 Ralph W. Gerard Prize in Neuroscience from the Society for Neuroscience.

Richard P. Lifton, an HHMI investigator at Yale University School of Medicine, received the 2003 Roy O. Greep Award for his work dissecting the molecular physiology of human cardiovascular and renal function. The Endocrine Society presents the annual award in recognition of exceptional contributions to research in endocrinology.

Roderick MacKinnon, an HHMI investigator at the Rockefeller University, was awarded the 2003 Louisa Gross Horwitz Prize by Columbia University. The award honors outstanding research in biology or biochemistry.

Philippa Marrack, an HHMI investigator at National Jewish Medical and Research Center in Denver, received the 2004 L’OREAL-UNESCO “For Women in...
Science” Award for her “dedication and outstanding contribution to scientific progress.” Marrack, one of five women from around the world to receive the award, was honored for her research on T cells and their roles in the body’s immune system.

- **Randall T. Moon**, an HHMI investigator at the University of Washington School of Medicine, won the 2003 T.L.L. Temple Foundation Discovery Award for Alzheimer’s Disease Research.

- **Joseph R. Nevins**, an HHMI investigator at Duke University Medical Center, was named director of the Center for Genome Technology, a center of the Duke Institute for Genome Sciences & Policy.

- **Tom A. Rapoport**, an HHMI investigator at Harvard Medical School, was elected to the German Academy of Natural Scientists Leopoldina. Founded in 1652, the limited-membership academy elects scientists distinguished by their scientific excellence.

- **Stephen W. Scherer**, an HHMI international research scholar at the Hospital for Sick Children in Toronto, won the 2003 E.W.R. Steacie Award in Chemistry from the Canadian Society for Chemistry. The prize goes to a scientist residing in Canada who has made a distinguished contribution to chemistry while working in Canada.

- **John D. Scott**, an HHMI investigator at Oregon Health & Science University, received a 2003 Medical Research Foundation of Oregon Discovery Award for his work on the family of molecules called AKAPs, which has greatly advanced knowledge of cellular communication.

- **Jack W. Szostak**, an HHMI investigator at Massachusetts General Hospital, won the 2003 Harrison Howe Award from the Rochester section of the American Chemical Society. The award is given to honor an individual for outstanding contributions to research in chemistry.

- **Christopher A. Walsh**, an HHMI investigator at Beth Israel Deaconess Medical Center, has been named director of the Harvard Medical School (HMS) M.D.-Ph.D. program, which combines medical training at HMS with graduate studies at Harvard University or the Massachusetts Institute of Technology.

- **Huda Y. Zoghbi**, an HHMI investigator at Baylor College of Medicine, received the W. Alden Spencer Award from the College of Physicians and Surgeons at Columbia University in October 2003. The award recognizes outstanding research in neural science.

### Institute Appoints Two Senior Scientific Officers

HHMI has appointed two new senior scientific officers to support the research of HHMI investigators in more than 300 laboratories across the nation.

**Denis A. Baylor**, M.D., who assumed his new role on February 1, 2004, will oversee investigator-based research activities in the western United States, principally on the West Coast.

**Philip S. Perlman**, Ph.D., will come on board full time by July 1, 2004, taking on a diverse portfolio of responsibilities, including oversight of investigator-based research activities on the East Coast. Both positions will be based at HHMI headquarters.

Baylor joins HHMI with a distinguished record of achievement as a neuroscientist and mentor, principally during his nearly thirty years as a faculty member at Stanford University.

“We are delighted to be able to benefit from Denis’s experiences in an academic medical center,” said David A. Clayton, HHMI vice president and chief scientific officer.

“His ability to advise us on emerging opportunities in the neurosciences will be invaluable.” Currently a professor of molecular biology at the University of Texas Southwestern Medical Center at Dallas (UT Southwestern), Perlman has been on the faculty there since 1990. Before that, he was a professor of genetics at the Ohio State University for more than 19 years.

“Philip has been responsible for many activities relevant to HHMI’s missions, including graduate training as well as his productive research program in molecular genetics,” said Clayton.

Perlman recently ended a three-year stint as John P. Perkins Distinguished Professor for Graduate Studies at UT Southwestern and currently holds the Roy and Christine Sturgis Chair in Biomedical Research.

**HHMI Scientific Officer**

**Carl D. Rhodes** will continue to manage investigator reviews and organize investigator science meetings. In addition, he will assume responsibilities for investigator-based research activities in the Midwest.
Beantown Team Helps the Science Happen

It has been a while since the Red Sox won the World Series, but as far as HHMI is concerned, another Boston-based team is a perennial champion. Captained by Jan Scranton, this group of administrators supports, solves problems, and generally smooths out the wrinkles for the region’s many HHMI investigators, and its winning strategy has been replicated nationwide.

All HHMI laboratories are served by a manager of administrative services (MAS). They handle human resources, procurements, budgeting, asset management, facilities issues, what-if strategies, and the complex interfaces with host institutions. In the late 1980s, all of the Boston-area offices were reorganized under Scranton, who joined HHMI in 1986, and he thus became the first regional MAS (RMAS). Before then, each MAS reported directly to headquarters, as other areas continued to do until recently—when the entire field was reorganized into regional structures.

Some people refer to Boston as the “pioneer” of the regional concept, but Scranton demurs. “It was no revolutionary insight,” he says. “We just recognized what was there.”

Several events converged to help the model emerge in Boston, he recalls. In 1985, HHMI was rapidly adding investigators. In the Boston/Cambridge area, already dense with investigators, new offices were regularly coming online.

“Getting bigger does not just add volume,” says Scranton. “It also adds complexity.” In addition, new management theories were in the air. “Everyone talked about ‘empowering employees’ and putting decision making as close to the field operations as possible,” he recalls. “I realized we could make some of those decisions here.”

Scranton proposed to HHMI headquarters that all the area’s offices report to one regional manager, thereby giving headquarters a single point of contact. The Institute’s leaders agreed, made Scranton that manager, and gave him a mandate: “Serve the investigators!” And by all accounts, he seems to have done just that, though Scranton readily acknowledges that he was by no means alone. “I was fortunate to have a staff of talented administrators,” he says, “including Mary Ellen Morency, Steven Barbour, and Judi O’Connor, who eagerly responded to the challenge.”

Mary Ellen Morency had also joined HHMI in 1986 as a lab administrator, and she knew the importance of “letting the science happen,” as she describes her role. She later became MAS for Brigham and Women’s Hospital and associated institutions.

Morency makes regular rounds in the labs and maintains personal contact with 15 HHMI investigators and 117 employees. Scranton’s office backs her up during emergencies. “If the CO2 or liquid nitrogen runs out in a lab Friday afternoon, we’re working until it’s delivered that night,” he says.

In a like manner, Morency and the four other MASs in Boston have worked seamlessly and interchangeably with standardized and consistent procedures. “If someone is away, others fill in like clockwork,” Scranton says. “There’s no directive; it’s just understood. As a result, you don’t come back to a foot-high inbox.” And the investigators don’t have to wait for requests to be handled, Morency adds.

But although geography seems like a key ingredient of Boston’s success—Harvard and MIT are a fairly short hop from lab sites across the Charles River—the Boston regional office gladly covers the Jackson Laboratory in Maine, an eight-hour drive up the coast, when needed.

Two years ago, Pamela A. Phillips, HHMI’s director of research operations, saw an opportunity to regionalize the HHMI labs in Southern and Northern California. Those experiments, proving that the model could succeed beyond Boston, prompted HHMI to commission a full field-assessment study, with the result that all the sites across the nation were ultimately organized into regions.

“Now, I can ensure that the regional managers thoroughly understand the issues, knowing they will communicate in turn with their local managers. Previously, I had to communicate directly with 27 managers,” Phillips says. “It was too many to do a reasonable job.”

“Five is a good number,” Scranton says, referring to the current number of RMASs: New York, Baltimore, San Francisco, San Diego, and Boston/Chicago. Yes, the Chicago office, which includes Iowa, Wisconsin, and Minnesota, reports to Scranton in Boston. At last, the Red Sox and Cubs nations meet...not in the World Series, but under the auspices of HHMI.

—CATHRYN M. DELUDE
Janelia Farm: A Progress Report
HHMI broke ground for its new research campus, Janelia Farm, last May. When completed in 2006, the facility will house a wide range of scientific programs in a world-class research environment. We’ll take a look at how construction is progressing and plans are proceeding.

Science and the Liberal Arts College
From the push toward hands-on undergraduate research to the building boom in new science facilities, many signs suggest that science at liberal arts colleges is stronger than ever. And liberal arts colleges still produce a disproportionate share of next-generation Ph.D. scientists and engineers. What’s the story behind these trends?

DNA Repair
Damage to DNA occurs all the time. Keeping the genome in top shape requires a network of genes and enzymes to sense and repair that damage. As investigators begin to understand how DNA repair machinery works, they are also gaining insight into fundamental mechanisms that contribute to disease and aging.