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On the Cover: Electron micrograph of a yeast prion protein, called Sup35. Protein fibrils similar to these can aggregate and tangle in many degenerative brain diseases, including Alzheimer’s and mad cow disease. Image by Tony Kowal and Susan Lindquist
Six HHMI investigators were elected to the American Academy of Arts and Sciences: Pietro De Camilli, Yale University School of Medicine; Brigid L. M. Hogan, Vanderbilt University School of Medicine; Richard L. Huganir, The Johns Hopkins University School of Medicine; Michael A. Marletta, University of Michigan Medical School; Roel Nusse, Stanford University School of Medicine; and Charles S. Zuker, University of California, San Diego, School of Medicine.

Graeme I. Bell, an HHMI investigator at The University of Chicago, won the 2000 Naomi Berrie Award from Columbia University for diabetes research achievement.

Two HHMI international research scholars, B. Brett Finlay, University of British Columbia, and Roderick McInnes, the Hospital for Sick Children in Toronto, were elected fellows of the Royal Society of Canada.

Sergio Grinstein, an HHMI international research scholar at the Hospital for Sick Children in Toronto, received the 2001 Malcolm Brown Award from the Canadian Federation of Biological Societies. The award is given once every three years for health sciences research in Canada.

Arthur L. Horwich, an HHMI investigator at Yale University School of Medicine, won the 2001 Hans Neurath Award from the Hans Neurath Foundation and the Protein Society for contributions to protein science.

Richard P. Lifton, an HHMI investigator at Yale University School of Medicine, won the 2001 Robert J. and Claire Pasarow Medical Research Award for his cardiovascular research. He shared the award with Pasko Rakic, a Yale University neuropsychiatrist, and cancer researcher Alexander Varahvsky of the California Institute of Technology.

Roderick MacKinnon, an HHMI investigator at The Rockefeller University, shared the 2001 Gairdner International Award for medical research with Clay Armstrong and Bertil Hille (see story, page 4).

Sergio Mosialos of Greece and Laszlo Nagy of Hungary, both HHMI international research scholars, were selected by the European Molecular Biology Organization to be EMBO young investigators, scientists in member countries whose early research has been distinguished.

Thomas A. Steitz, an HHMI investigator at Yale University, was named one of three winners of the 2001 Rosenstiel Award from Brandeis University for distinguished work in basic medical sciences.

Joseph S. Takahashi, an HHMI investigator at Northwestern University, received the 2001 W. Alden Spencer Award from the College of Physicians and Surgeons of Columbia University. The award honors young scientists who have made original contributions to neurobiology.

Two HHMI investigators, Marc Tessier-Lavigne, University of California, San Francisco, and Brigid L. M. Hogan, Vanderbilt University School of Medicine, were elected fellows of the Royal Society of London.

Bert Vogelstein, an HHMI investigator at The Johns Hopkins University School of Medicine, won the 2001 International Chiron Award for Biomedical Research and Training, given by the Italian National Academy of Medicine.

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Putting Patients Back into Biomedical Research

Mention “biomedical research” to people outside the scientific world and they may well envision a physician testing a new drug. They may not realize that most biomedical researchers study biological processes rather than specific diseases, and never interact with patients. In recent decades, in fact, many of the most important discoveries in biomedical research have resulted from the study of fundamental biological problems, such as how organisms develop, how genes function and how cells communicate. These studies, in all likelihood, were conducted using fruit flies, mice, yeast and other organisms—not human patients. That’s the kind of research we’ve emphasized at the Howard Hughes Medical Institute (HHMI), knowing that some fraction of it inevitably contributes to advances in clinical medicine that save people’s lives.

For all of the discoveries that scientists around the world have made about oncogenes, tumor-suppressor genes, the cell cycle and programmed cell death, however, fundamentally new treatments for cancer patients have been slow to appear. We know far more about the immune system and retroviruses than we did when AIDS appeared 20 years ago, yet that disease remains a growing scourge that is claiming untold millions of lives, particularly in the developing world. Researchers have identified more than a thousand genetic flaws involved in illnesses ranging from cystic fibrosis to Alzheimer’s disease, but physicians generally remain unable to fix these flaws. Advances in basic science have been breathtaking, in other words, but translating them into therapies has been difficult.

Ironically, our success in basic science now compels us to look back to the days when biomedical research almost always meant working with patients. After all, what is seen in a test tube or a fruit fly, for example, does not necessarily occur in a human being, and only a small percentage of promising discoveries ends up having a direct impact on medicine. Fortunately, as we deepen our understanding of how the human body operates at the cellular and molecular levels, it is becoming possible to carry out new kinds of “patient-oriented research” to learn which insights might pay off.

The experience of HHMI investigators who do work directly with human patients demonstrates that such a patient-focused approach can yield unique and potentially valuable medical insights. Recent issues of the Bulletin, for instance, have described Huda Zoghbi’s research at Baylor on mental retardation, Rick Lifton’s work at Yale on hypertension and Andy Chan’s work at Washington University on rheumatoid arthritis. Similarly, Bert Vogelstein at Johns Hopkins has worked closely with patients for many years as he helped uncover the genetic secrets of colon cancer, as have other HHMI investigators who specialize in heart disease, diabetes and other disorders, combining the latest techniques of molecular biology with their special perspectives as physicians.

These “physician-scientists” work closely with patients, which is not the case with all physicians engaged in research. Indeed, many M.D. and M.D./Ph.D. researchers pursue the same kinds of research as Ph.D.s, focusing on basic biological questions; although they may have an interest in certain diseases, they do not integrate their research with the medical problems of the patients they treat. These scientists have contributed tremendously to biology’s bounty, to be sure, but the system should encourage physician-scientists to take full advantage of their special knowledge and experience.

Wanting to make an impact on this situation, we recently announced an initiative at HHMI to encourage the support of patient-based biomedical research. In June, we sent letters to 119 medical schools and schools of public health, inviting them to nominate physician-scientists to become HHMI investigators. We expect to appoint as many as 10 new investigators—a modest number, but one that builds on the Institute’s existing cadre of patient-oriented investigators. Hopefully, other organizations may be stimulated to increase their investments in this area as well.

At the same time, HHMI is contributing to keeping the pipeline of such scientists flowing through its research training fellowships for medical students and the HHMI-NIH Research Scholars Program, which enables medical school students to join research teams for a year or two on the campus of the National Institutes of Health. We are also considering additional ways to promote this kind of research in the future. Having seen our patience in basic science pay off so handsomely, we believe it’s time to give “patient research” a broader meaning.

Thomas R. Cech
President
Howard Hughes Medical Institute
A Crystal-Clear Focus on Ion Channels

Rod MacKinnon forges his own path to study potassium gateways.

Isaac Newton acknowledged that his scientific vision was sharper because he was “standing on the shoulders of giants.” Science historian Gerald Holton, commenting on the accelerated pace of research, gave Newton’s famous line a modern twist: “We are now uniquely privileged to sit side-by-side with the giants on whose shoulders we stand.” Holton’s tongue-in-cheek comment certainly describes the seating arrangement at the 1999 Albert Lasker Basic Medical Research Awards ceremony—at least from HHMI investigator Roderick MacKinnon’s point of view. MacKinnon had the privilege of sharing the prestigious basic medical research prize with a personal giant—Clay M. Armstrong, of the University of Pennsylvania School of Medicine—whose publications had an enormous influence on MacKinnon’s development as a scientist.

MacKinnon, Armstrong and Bertil Hille, of the University of Washington (and a member of the HHMI scientific review board, for neuroscience), were honored for “elucidating the functional and structural architecture of ion channel proteins.” MacKinnon’s particular contribution was the determination of the three-dimensional structure of a potassium ion channel, using x-ray crystallography. Simply attempting to examine the channel via this uncharted route was deemed highly questionable by many and foolhardy by some. Great risk, however, can bring great reward—and his ultimate success was judged by Armstrong, writing in the journal Science, to be “a remarkable accomplishment” and “a dream come true for biophysicists.”

A great deal was at stake in MacKinnon’s quest to understand the as-yet-unseen ion channel proteins, as the Lasker proclamation attests: “ion channel proteins … govern the electrical potential of membranes throughout nature, thereby generating nerve impulses and controlling muscle contraction, cardiac rhythm and hormone secretion.”

Intimate knowledge of the proteins is expected to lead to the synthesis of pharmaceutical compounds that can affect conditions directly or indirectly related to ion flow. Although MacKinnon toyed with microscopes as a youth, his serious interest in science was bestowed on him by his greatest scientific influence—his undergraduate adviser at Brandeis University, Christopher Miller, also an HHMI investigator. Miller, just starting his laboratory in the mid-1970s, was looking at a number of processes involving ion transport, including calcium pumping in the sarcoplasmic reticulum, a mechanism in muscle cells that is critical for nervous excitation. MacKinnon joined the effort, becoming Miller’s first student. Both scientists like to point out that Miller’s dog Gribet was already a lab member, but one can still safely say that MacKinnon was Miller’s first research assistant who had the handy attribute of opposable thumbs.

MacKinnon went on to medical school—against Miller’s advice—and then practiced medicine for four years. Realizing then that he yearned to return to basic research, he made a pilgrimage to Miller’s lab to talk about his assumption that such a move would require additional training and even a Ph.D. Miller bluntly informed his former student that the acquisition of a doctorate was redundant, as the M.D. already fulfilled that qualification. MacKinnon thus rejoined the Miller lab, as a postdoctoral fellow investigating potassium channels. “I had a sense I had a lot of catching up to do,” MacKinnon recalls. “And the only way to really do that was, I thought, to knuckle down, and read and study and do as much as I could to learn on my own. I learned a lot from books and I learned a lot by just trying things out myself. That made me very confident about learning on my own. And that stuck with me.”

In 1989, MacKinnon started his own laboratory at Harvard to study ion channels using a technique, called mutagenesis, that introduces variations in single amino acids in the protein sequence. Alterations in the protein’s behavior resulting from a change in a lone amino acid reveal those regions of the protein that are critical for its function. But the going is slow, like feeling one’s way through a dark room. “It became clear that in order to understand the chemistry of the
thing, we would have to see it,” MacKinnon says, “because ultimately it is a structural issue. And it was clear that mutagenesis could never answer those questions.” He resolved to attempt x-ray analysis of ion channels, which, being membrane proteins, are extremely difficult to crystallize.

Miller advised him to start the project slowly, on the side, while continuing to direct his bustling lab at Harvard in tried-and-true mutagenesis work. MacKinnon again considered and then declined his mentor’s advice. “I felt once again I could teach myself and talk to people to make sure I was on the right path,” he recalls.

To make the transition to x-ray crystallography, MacKinnon accepted an offer from The Rockefeller University, and in 1996 moved to New York City. There, his wife and a lone postdoc stood by him as he cranked up his research. “Rockefeller gave me this big lab,” he recalls, laughing. “And I was embarrassed to have people visit me. I thought, ‘How am I going to explain there are only three of us? They’re going to take the lab away.”

The quiet, however, was apparently good for MacKinnon’s concentration. In only two years—during which time he became an HHMI investigator and painstakingly developed his new methodology—he succeeded in deducing the three-dimensional structure of the potassium ion channel protein. The structure revealed, for example, that the channel coaxed potassium ions with a portal that includes an array of oxygen atoms that surround the ion like a cage. The resulting chemical climate is similar to the oxygen-rich, watery environment that the ions ordinarily prefer.

The structure revealed why the potassium ion channel is selective, encouraging the flow of charged potassium while discouraging sodium ions. Both types of ions have the same charge (+1), and the sodium ion is significantly smaller, thus a simple sieve would accept both sodium and potassium ions. However, the large size of the oxygen cages—perfect fits for potassium ions—prevents the smaller sodium ions from ever falling under the electrostatic influence of enough individual oxygens to be compelled to make the trip through the pore. Nature’s clever structure thus solves multiple problems simultaneously.

Meanwhile, the accolades keep coming: MacKinnon won this year’s Gairdner Foundation International Award, which recognizes achievement in medical science. He once again rubbed shoulders with Armstrong, who shared the Gairdner, along with Hille and Harvard cell biologist Marc Kirschner. MacKinnon is now focused on determining the structure of another species of potassium ion channel, one with a voltage-sensitive gating system. This channel’s ion portal should be quite similar to that of the channel already elucidated. But an additional structure that straddles the membrane acts as a voltage meter, reading the voltage difference between the inside and outside of the cell and opening or closing the gate to control the flow of ions. “When we see that structure,” MacKinnon says, “I think we’ll understand how the channel works.”

MacKinnon’s scientific reputation may be assured, but his research focus could shift once again. “Right now I’m thrilled with what I’m working on,” he says. “But I think I’ll reach a point where I want to think about something new. I’m not ready for it yet, but I’ll probably do it at least once more before I’m too old.” Don’t bother telling him he can’t. —STEVE MIRSKY

MacKinnon is probing the structure of a potassium channel that controls ion flow by reading the voltage difference between the inside and outside of the cell.
Memorable Mouse

Ask a pro ballplayer about a home run he hit 30 years ago and he may say, "Runner on first, two outs, two strikes, Seaver fastball up and inside, I pulled it down the line and into the second row." Ask the same man the date of his wedding anniversary and the response may come in the form of a wrinkled forehead. Such is the slippery stuff of memory.

HHMI investigator Eric Kandel was awarded the Nobel Prize last October for his discoveries concerning the molecular nature of memory. In studies on invertebrates, Kandel, of New York's Columbia University, showed that memory storage depends on the coordinated expression of specific genes that code for proteins involved in making new synaptic connections. (The part of a ballplayer’s brain in which game situations are stored must be a synaptic thicket.) There is a flip side, however, as Kandel reported in the March 9, 2001, issue of the journal Cell: Working with a transgenic mouse, he and his colleagues announced the first direct evidence in a mammal for genes involved in actually suppressing memory. (This discovery does not serve as an excuse for anniversary amnesia.)

In a previous mouse study, Kandel demonstrated that overexpression of the enzyme calcineurin interfered with memory, providing damning circumstantial evidence that calcineurin is a memory suppressor. "But the really definitive evidence is when you remove it and the animal gets smarter," Kandel says of the strategy used in the Cell study. Indeed, the animal did get smarter—in terms of memory of objects and locations.

Removing calcineurin from the memory-storage mechanism required the creation of a transgenic mouse with a gene for a calcineurin inhibitor that was controllable—it could be switched on and off by administration of the antibiotic doxycycline. This system allowed the researchers to conclude that their transgenic mouse was normal in all other respects when the inserted gene was inactive and that no other systems had been affected during development.

"Why do we have a brake on memory?" Kandel asks. "There are probably several reasons. One is that you probably don’t want to remember everything that you encounter. A lot of things that happen to you are trivial, and getting rid of that information fairly rapidly is probably a good thing. We don’t know what the limits of the storage capabilities of the brain are, but there probably is, for each major category of learning, a limit as to how much you can put in there."

The assumption that similar memory-suppression systems exist in human brains brings up the issue of filtering: We are no doubt constantly making judgments as to what is worthy of inclusion in our collection of mental memorabilia. "The amazing thing about the mind is that it’s just filled with prejudice," Kandel notes. "The mind is prepared to learn certain things and to remember certain things, and not others." Evolution has probably ensured that certain memories be strongly stored—for example, the location of an abundant food source. Individual memory strengths, however, like those of our hypothetical ballplayer, may be more idiosyncratic.

With an aging population, the detailed understanding of the mechanisms of memory is of obvious interest in pharmaceutical development. "Clearly, there are two approaches," Kandel says of any future memory drugs. "You act on positive regulators and make them stronger, or you work on inhibitory regulators and make them weaker. So calcineurin is a perfectly reasonable candidate." The enzyme is not an easy one, though, as Kandel points out: Existing calcineurin inhibitors would also suppress the immune system because of the enzyme’s roles in other pathways in the body. Nevertheless, the search for techniques to impede memory-suppression genes is only in its infancy—and researchers will quite likely remember to follow in Kandel’s first footsteps.

—STEVES MIRSKY
My colleagues and I were intrigued recently by something that happened at several meetings of biomedical researchers that we attended—something clearly so common in the culture of basic science that the researchers themselves probably didn’t even notice. At the beginning or end of their talks, the scientists showed slides naming every person who contributed to their research. They listed not only their faculty colleagues, but also postdocs, grad students, undergraduates, and technicians and, in some cases, the administrative and glass-washing staff. Typically, the scientists read each name and carefully delineated each person’s achievement—some even showed photos of their team members. Throughout their presentations, they noted where they had built on the research of others and which colleagues had assisted them, often across scientific disciplines.

We were also struck by how seriously the scientists viewed their roles as mentors. Not only did they publicly credit their junior colleagues and staff in their talks, but many brought postdocs or others to the conference and included them in their conversations and meals. The junior colleagues, in turn, routinely and proudly identified themselves in conversation and on their name badges as being in the laboratory of their mentors. It was obvious, in other words, that everyone was taking responsibility for making these mentoring relationships work.

For someone from another discipline—in my own case, religious studies and ethics—this was an impressive set of “cultural performances” that exemplified important operative values of the scientific community. Now I recognize that scientific research feeds as much on competition and drive as it does on collaboration and credit. But the spirit of collegiality I witnessed at these meetings spurred me to take a fresh look at the norms of my own community.

This situation is ironic because the practice of providing robust, public citation has a long tradition in the world of religious studies. In the Talmud, it is noted that failing to credit your insights, in the name of the one who has taught you, is akin to linguistically “killing the teacher,” who is thereby “erased” in the textual sense.

Some may argue that, of course, biomedical research differs from the humanities in some important ways, because, for example, it is experimental or it requires teams—but I think these differences are not as great as they might seem. In reality, much of our work in any university department would also be impossible without a team effort.

My experience attending scientific meetings has caused me to wonder what might happen if bioethicists and others in the humanities adopted practices like those I observed at the biomedical research meetings. What would it be like if we fully credited everyone who helped us think through “our” ideas? What if we routinely recognized the teachers who had brought us along? How might we begin to implement such norms? I have begun to discuss these ideas with colleagues and will be curious to see where our discussions lead.

Usually, when scientists interact with bioethicists, the expectation is that those of us on the “ethics” side will help the scientists think through the moral dimensions of their research. As my recent experience illustrates, however, the lessons actually flow in both directions. Personally, I have already learned two ethical lessons from watching scientists in action and observing their culture. First, all of us should identify with and take responsibility for the “shops” we work in, honoring our mentors and mentoring our students. Second, we should remember that honor for our work is never a personal matter, but rather a collective effort and a collective triumph.
For decades of pessimism about the chances of ever finding effective treatments for Alzheimer’s disease, Huntington’s disease, Lou Gehrig’s disease and other progressive killers of the brain such as mad cow disease, scientists have produced a flood of new discoveries that link these outwardly unrelated ailments and suggest ways in which they might be reversed or prevented.

What these diseases have in common is a plague of abnormally shaped proteins that stick together and destroy brain cells. Different proteins are at fault in each disease. They affect different parts of the brain, and they produce diverse symptoms. Yet all these proteins are “mishapened,” meaning they have strayed from their proper three-dimensional shapes; either they never reached these shapes as they emerged from tiny protein factories inside the cell, or they became corrupted. So, instead of doing their normal jobs, these proteins form aggregates of insoluble gunk, and in this process they devastate the brain. Some of them—“prions”—are even infectious: they cause mad cow disease and its human counterpart, new-variant Creutzfeldt-Jakob disease.

The big question now is how to clear up—or prevent—protein.

New discoveries link seemingly unrelated, fatal illnesses such as Alzheimer’s disease and Huntington’s disease to misshapen proteins, providing hope for new treatments.

BY MAYA PINES
Prion proteins (red) aggregate in a mouse neuroblastoma cell that is infected with the prion disease called scrapie. The cell’s nucleus is shown in blue.
Prospects for Treatment

Susan L. Lindquist can imagine several possible strategies for treating diseases caused by misfolded proteins. Scientists might find new ways to design proteins or drugs that would bind to sticky surfaces and prevent other molecules from getting trapped there. They might design proteins that could insert themselves between the aggregates and help break them up. They might alter the chaperone balance of the cell to help ensure that the proteins attain their correct shape. Or they could try to increase the activity of the cell’s proteasome, a sort of garbage can in the cytoplasm that chews up misfolded proteins and gets rid of them.

A wide range of diseases might be treated with these approaches, she says. In addition to the 20 or so amyloid diseases and at least eight CAG-repeat diseases, Parkinson’s disease is a candidate. There are some helpful treatments for Parkinson’s today, but they do not get to the root of the disease, which involves aggregates of the alpha-synuclein protein. Amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig’s disease, too, has been shown to involve protein aggregates—in this case, the protein superoxide dismutase.

There is even hope of treating or stopping mad cow disease—bovine spongiform encephalitis, or BSE—before the disease spreads to large numbers of humans in the form of new-variant Creutzfeldt-Jakob disease. "I really do believe that most of these neurodegenerative diseases can be attacked," Lindquist says. "It may be five or ten years away, but we will be able to make a real difference." —AMP

clumps. Coming from several different directions, researchers have uncovered a variety of potential targets for drugs. Equally important, they have learned how to try out their new remedies on yeast, flies, worms, or mice. "Things have really changed in the past few years," says Susan L. Lindquist, newly elected director of the Whitehead Institute for Biomedical Research and former HHMI investigator at the University of Chicago, who works mostly with yeast cells. "The first meetings I attended about these diseases were so depressing…. But now we have several different kinds of strategies that look as if they might work, so everyone shares an optimism that just wasn’t there before."

Amyloids in Alzheimer’s

Some of the most promising research involves the dreaded Alzheimer’s disease, which robs so many older people of their ability to think or to remember, and then kills them. Alzheimer’s affects an astounding large number of people—10 percent of those over age 62 and roughly half the population over age 85.

The brains of Alzheimer’s patients are typically riddled with strange, insoluble “plaques,” which consist of amyloid (small protein fibers that form a hard mass). For a long time, there seemed no way to get at the amyloid—or the disease.

The "defining moment," according to Sangram Siadla, a researcher on Alzheimer’s at the University of Chicago, came with the discovery of specific mutations in the DNA of certain unusual families. Not only is Alzheimer’s hereditary in these families, but it also occurs very early in life. Members may develop the disease in their forties or fifties.

Certain families had errors in the gene that codes for amyloid precursor protein (APP), a large molecule that is cut up by various enzymes to release peptides of amyloid-beta—including the type that accumulates in Alzheimer’s plaques. In other families, two different genes, presenilin-1 and presenilin-2, had mutations that also produce an increase in amyloid-beta.

With these genes in hand, researchers charged ahead, creating transgenic mice and other animals in which the genes’ effects could be studied rapidly. One of their first approaches showed that amyloid plaques were produced in the brains of transgenic mice with mutated APP genes, just like in those of Alzheimer’s patients. This experiment and others opened the door to the possibility of finding drugs that counteract the effects of the mutated genes. Several drug companies, including Bristol-Myers Squibb Co. and Amygen, Inc., are now racing to develop compounds that might prevent the enzymes from snipping the precursor protein and thereby stop the release of amyloid-beta.

At the National Institute on Aging, in Baltimore, researchers developed an experimental drug called phenserine that simply decreases the production of the precursor protein, thereby lowering the level of amyloid-beta; the drug is now in clinical trials.

In 1999, researchers at Eli Lilly Pharmaceuticals in South San Francisco announced that they had made a vaccine against Alzheimer’s disease—and that it worked in transgenic mice. The vaccine contains bits of amyloid-beta, prompting them to make antibodies against this substance that apparently prevent Alzheimer’s plaques from forming in the animals’ brains. Human trials of this vaccine began last year and demonstrated its safety. Now the company will test the vaccine’s efficacy.

Believing the vaccine too good to be true, two independent teams of scientists—one led by Peter St. George-Hyslop, an HHMI international research scholar at the University of Toronto, and the other by David Morgan of the University of South Florida—recently set out to challenge its effectiveness. Instead, they ended up supplying evidence in its favor. After mice with the equivalent of Alzheimer’s disease received the vaccine, their performance on memory tests clearly improved.

Another group at Tel Aviv University in Israel is betting on a different vaccine, AN-1792, to prevent or treat Alzheimer’s. Though nothing is yet certain, several researchers—including Lindquist—think that at the current rate of scientific progress there is a good chance of seeing treatments to slow down or prevent Alzheimer’s disease within 10 to 20 years.

A Clearance Mechanism

Another area where there’s suddenly a lot of optimism,” according to Lindquist, is Huntington’s disease (HD), a rare inherited disorder that is best known for having killed the folk singer Woody Guthrie. People with this disease slowly deteriorate both mentally and physically for more than a decade, suffering uncontrollable writhing movements along the way. Though the huntingtin gene was identified in 1993, after a long search, its normal function is still unknown and the mechanism of the disease remains a mystery. Nevertheless, the gene’s discovery has led to some interesting findings—and new approaches to treatment.

The key to whether the huntingtin gene is normal or defective has turned out to lie in a kind of genetic stutter: a repetitive sequence of the DNA triplet CAG, which codes for the amino acid glutamine. Stretches of CAG “repeats” appear in every human being’s huntingtin gene, but in varying lengths. Whereas the normal gene has a sequence of between 6 and 34 CAG repeats, the abnormal gene contains many more. In fact,
versible—that the gunk in the brain cells cannot be dissolved and that decreases misfolded proteins, which then stick together in toxic clumps and aggregate formation and progress motor decline.

This was tremendously good news—not only for Huntington’s patients and their families but for people concerned with any of the other diseases caused by misfolded proteins. “It proves that mammals have a clearance mechanism that normally removes this junk,” says Arthur L. Horwich, an HHMI investigator at Yale University who studies how proteins fold. He points out that HD and other diseases might be reversible if one could find ways to shut off the production of the abnormal proteins. The cells that are dead could not be revived, of course, but those that are sick might be cured. “It could happen,” he says, “if one could intervene rapidly enough.”

Prodding Proteins into Line
One of the greatest puzzles in biology is precisely how the body’s billions of proteins fold into their correct three-dimensional shapes. When amino acids are first strung together to make new proteins, they flop around inside the cell like cooked spaghetti. Then they rapidly contort into various partially folded states before adopting their final, active form.

Because scientists knew that a special class of “chaperone” proteins guide nascent proteins toward their proper structure, they wondered if an extra supply of chaperones would help to prevent protein misfolding. For instance, could it prod emerging huntingtin proteins sufficiently into line to prevent them from becoming toxic to neurons?

Nancy M. Bonini, an HHMI investigator at the University of Pennsylvania, decided to try this idea out in Drosophila because, as she explained, “late-onset, progressive diseases such as Alzheimer’s or Parkinson’s can take months or years to develop in mouse models, but in fruit flies they take only 10 days.” Instead of working directly with Huntington’s, however, she focused on spinocerebellar ataxia type 3 (SCA3, also known as Machado-Joseph disease), one of at least eight diseases caused by too many CAG repeats.

After Bonini and her colleagues inserted the human SCA3 gene into fruit flies, they found that the flies’ retina, which contain nerve cells, rapidly degenerated. The researchers then produced a new strain of flies that had both the SCA3 gene and a gene for an human chaperone protein, Hsp70, in the hope the chaperones would come to the cells’ rescue. They did. The chaperones suppressed the disease, and the flies’ eyes remained normal.

Other researchers, such as Huda Zoghbi, an HHMI investigator at Baylor College of Medicine in Houston, are working with mice as well. Zoghbi is working to find molecules that help suppress the damage caused by CAG repeats in the fly, then use the mouse model to examine how these molecules produce their effects.

The Workhorse: Yeast
Lindquist’s favorite model organism, however, is Saccharomyces cerevisiae, or baker’s yeast, which can be manipulated easily and grows rapidly. Eventually, she hopes, models of HD in yeast will provide a route for “first-level screens for pharmacological agents that might reverse some of the damage” from CAG-repeat diseases. “Obviously, something that works in yeast might not work in mammalian cells,” she says, “but you can screen through many, many more compounds much...
The epidemic of mad cow disease that erupted in British herds in 1986 has slowed down recently, probably because the country’s meat industry changed its methods of recycling animal byproducts into cattle feed. Yet an unknown number of apparently healthy people who ate infected meat in Britain long ago may be incubating a fatal brain disorder, new-variant Creutzfeldt-Jakob disease (vCJD), which seems to be caused by the same type of infectious proteins, or prions, as mad cow disease. At least 105 people have been infected, mostly in Britain, and 98 have already died.

Mad cow disease and vCJD kill so many brain cells that they leave holes in the victim’s brain, making it look like a sponge—which is why these disorders are called “spongiform” diseases. In sheep, the equivalent disease has been known for about 300 years as scrapie, a fatal illness that makes its victims tremble and wobble frantically, often rubbing themselves raw against the fences of their pens as they try to stay upright. Their brains, too, are riddled with holes.

Was it scrapie that infected British cows? Maybe. But how could infectious prions overcome the usual barrier between species? Recent studies by Jonathan S. Weissman, an HHMI investigator at the University of California, San Francisco (UCSF), and graduate student Peter Chien provide a possible answer. Working with two different species of yeast, they showed that a yeast prion, Sup35, can misfold into several “dramatically different” infectious shapes; this property enables abnormal prions from one yeast strain to interact with normal prion proteins from other strains, inducing them to adopt similarly abnormal shapes. In yeast, abnormal prion proteins clump together and lose their normal activity. In mammals, clumps of abnormal prion proteins may damage the brain.

“Other aggregation diseases are either sporadic, like most cases of Alzheimer’s, or inherited, like Huntington’s,” says Weissman. “What makes mad cow disease so frightening and unusual is that it’s infectious. But that also gives you a chance to eliminate it.”

All mammals, including humans, carry the prion gene PrP, which was discovered and named by Stanley Prusiner of UCSF in the 1980s. Prusiner and others showed that transgenic mice lacking the prion gene were totally resistant to infection with scrapie. One of these experiments in the prion hypothesis was to delete the prion gene from mice and show that now they weren’t capable of acquiring the disease, comments Arthur L. Horwich, an HHMI investigator at Yale University. When these mice were given a normal prion gene, they became susceptible to scrapie again.

Several research teams have been looking for ways to eliminate PrP-scrapie aggregates or to prevent them from forming in the first place. “We work with molecules that denature PrP protein,” says Fred Cohen, at UCSF, where he collaborates with Prusiner. “We learned that branched polyamines work well in cell culture. But they don’t cross the blood-brain barrier and don’t get into the brain, so they cannot be used on animals. However, they could still be quite useful as disinfectants.” There are no good disinfectants against abnormal prions, and cases of people contracting Creutzfeldt-Jakob disease from surgical instruments or from corneal transplants have been reported.

“We also found that some antibodies actually clear prions from mouse cells infected with scrapie,” Cohen says. “This argues that prion diseases may be treatable with antibodies.” Most recently, Prusiner’s team examined a large number of compounds that are known to cross the blood-brain barrier and discovered that two older drugs—chlorpromazine, an antipsychotic, and quinacrine, an antimalarial agent—prevent the formation of PrP scrapie. They are encouraged by this finding that they suggest the drugs are “immediate candidates” for treating Creutzfeldt-Jakob disease and other prion diseases, and have begun testing them in people dying from CJD.

Still, the best approach would be prevention, Weissman points out. The new-variant CJD is “a very aggressive disease,” he says. “Once you have the symptoms of vCJD, it will be difficult to treat.” Because there’s no blood test for the disease, the American Red Cross announced in May that it would stop accepting blood from anyone who has spent as little as three months in the United Kingdom or six months elsewhere in Europe during the past two decades.

Weissman would like to know what makes cows or people susceptible to these diseases. Since some sheep are naturally resistant to scrapie, it might be possible to find bulls that are naturally resistant to prion diseases and use them to breed more-resistant cattle. “If we can learn where mad cow disease came from and how it is transmitted,” he says, “we may be able to ensure that the cattle supply is completely free of mad cow disease—and to prevent future outbreaks.”

Jonathan S. Weissman (right) and grad student Peter Chien determined how prions can jump from species to species.

The Mad Cow Connection

Photo: Jonathan Weissman/HHMI

h h m i  b u l l e t i n | s e p t e m b e r 2 0 0 1
more rapidly and much more cheaply in yeast than you could in mammalian neuronal systems."

Even more important, perhaps, research on yeast may lead to some basic insights: "The problem of why proteins misfold—and why that is associated with toxicity—is very complex," Lindquist says. "It's such a complex problem that I think it's really important for lots of people to be working on it, and to be approaching it from different angles."

One reason for the complexity is that "there seem to be a variety of different ways in which proteins can misfold," she explains. "In addition, there are different kinds of aggregates. To make matters worse, 'aggregated proteins are really miserable to work with,' she says. "You can't crystallize something that's an aggregate, so you can't use x-ray crystallography. You can't use any of the typical tools for the study of protein structure, which require the protein to be either in solution or free. So we're reduced to using some fairly primitive tools, and when you see a big blob inside a cell you can't tell whether it's the same as another blob. Yet one blob might be toxic and the other not. One might provide a surface for other proteins to bind on, while others don't."

"It's not even clear," she adds, "whether it's the aggregate per se that's toxic. Could it be some earlier misfolded intermediate? The large aggregates might be the cell's way of sequestering material to protect itself."

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The Influence of Prions

Yeast may in fact provide the key to understanding not only amyloid diseases and CAG-repeat diseases, but also "spongiform encephalopathies" such as mad cow disease, which have been attributed to prions. The idea of prions makes many scientists uneasy because it violates the fundamental principle that the presence of nucleic acids, such as DNA, is essential both to inheritance and infection. Yet prions produce clumps in the brain that are infectious even though no nucleic acid seems to be involved. In addition, prions can pass their traits across generations.

Lindquist came to prions by accident. "We just happened to be working on a protein called Hsp104, which is a heat-shock protein—it's very important for thermal tolerance in yeast," she says. "Other chap-

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A little later, Lindquist discovered that Hsp104 also controls the aggregation state of the huntingtin protein, at least in yeast. "So now we're using Hsp104 in yeast to change the aggregation state of huntingtin and to test some models of how its toxicity might arise," she says. Next, she plans to look for "agents that might interfere with the toxicity" first in yeast, then in mammals. Lindquist believes prions arise when certain normal proteins accidentally produce folding intermediates that have a sticky surface. "That surface provides a template for other partially unfolded proteins, which bind with it and wind up getting trapped," she explains. "Little aggregates of protein are then passed on from mother cell to daughter cell through the cytoplasm, and when the daughter cell starts making her own proteins, these have the same capacity to get trapped on larger aggregates."

"It's very heritable. It's very reproducible," Lindquist says. "If you cross a cell that has a prion trait with a cell that doesn't, the prion trait is always dominant because it's got that sticky surface, and the other proteins join up to it. Then all the cell's progeny will have that trait in them."

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In mid-March, when the British epidemic of hoof-and-mouth disease (hmd) appeared to be spiraling out of control, the government appealed to the country’s scientists for help. Among those who answered the call was Neil Ferguson at the Imperial College School of Medicine in London, an hml international research scholar who develops mathematical models of infectious diseases.

Ferguson’s models are informed by the biology of diseases— from the molecular-level action of pathogens and host immunity to the environmental, social and behavioral factors that work at the population level. His models of hmd led him to draw some stark conclusions: The existing controls weren’t working and the long delays between diagnosis and slaughter of infected animals were fueling the epidemic. A more aggressive eradication program was needed. This would involve the culling of animals on farms suspected of infection within 24 hours, without waiting for confirmation from the lab; all animals on neighboring farms had to be culled within 48 hours.

The other three modeling teams that advised the government came to the same conclusions. The military was called in, and at the peak of the outbreak, some 2000 troops were involved in the eradication nationwide, supported by up to 1000 police officers. Almost 2.5 million animals were slaughtered in 11 weeks, requiring burial pits equivalent to 200 Olympic-size swimming pools.

During a visit to Cumbria, one of the counties hardest hit by the disease (see map, page 16), Ferguson participated in one of the army’s daily operations meetings. While listening to the soldiers talk about the logistics of the operation, the ramifications of his research became clear. On a separate occasion, he spoke to a group of farmers and came face-to-face with their concerns. “Half the farmers in that room had lost their farms already because of hoof-and-mouth,” he says. “I estimated that by the end of the epidemic, up to 70 percent of Cumbrian farms might be affected. That number shocked them, but it is turning out to be about right.”

Another member of the Imperial team, Christl Donnelly, found herself confronted by a group of angry, vocal farmers in Devon, another badly hit county in the southwest part of the country. She described feeling “out on a limb.” Still, motivated by a desire to offer practical help in a desperate situation, Ferguson and his colleagues defend their recommendations vigorously. “The hmd epidemic has significant economic consequences for the country, which I hope my work might help to minimize,” he says.

As soon as the government released its data on infected cases to the Imperial team in March, Ferguson and his colleagues spent an intensive 10 days feeding critical numbers into their models. By calculating the likelihood that one farm would infect another in a...
Uncertainty
particular length of time, given the separation between farms and the dynamics of the nationwide agricultural network, they were able to predict the future course of the epidemic and to rank the potential effects of different interventions.

**REducing R₀**

Specifically, they measured the impact of those interventions on $R_0$, the case reproduction ratio, or average number of secondary cases generated by one primary case of infection. By definition, when this figure drops below 1.0, the epidemic can no longer sustain itself. “What control measures do, whether it’s culling or vaccination or a whole range of other things, is to reduce that quantity, make the disease less infectious, give it less chance to spread to other farms,” says Ferguson. He and his team were simply looking for the quickest and most effective way to bring $R_0$ down.

Publishing their results in the May 11, 2001, issue of Science, they argued that vaccination would be less effective than culling as an emergency response. Although vaccination reduces the population of animals susceptible to the disease, it does not reduce the infectiousness of those animals already contaminated, and so, does not reduce transmission. Similarly, culling of infected farms alone, leaving their seemingly healthy neighbors untouched, would be insufficient. By failing to stem newly acquired though not-yet-apparent infections, such restricted culling would leave $R_0$ at or around the critical threshold, resulting in a larger epidemic that tailed off more slowly. “Extensive culling is sadly the only option for controlling the current British epidemic,” the Imperial team concluded.

The policy has been largely successful. By the end of May, the number of infected farms was dropping by half each fortnight and $R_0$ was under 1.0. Ferguson’s advice was nevertheless to maintain the aggressive cull until the disease was completely eradicated. The second serious outbreak in previously unaffected Yorkshire in mid-May could, he suggests, have been an indirect result of the government’s decision to relax the policy, allowing veterinarians more discretion as to which animals were slaughtered on farms that neighbored infected ones. Even taking that outbreak into account, the epidemic has declined in line with the team’s predictions.

**OVERsimplifying RÉALITY?**

Still, some leading HIV experts have described the policy as excessive. Alex Donaldson, head of the Institute for Animal Health laboratory in Pirbright, Surrey, and a government adviser himself, has criticized the mathematical models for oversimplifying reality. In a study published in the Veterinary Record on May 19, 2001, he argued that the models were based on an average animal, and did not allow for differences in infectivity, immunity and transmission routes among cows, pigs and sheep.

Fred Brown of the U.S. Department of Agriculture’s Plum Island Animal Disease Center in Greenport, New York, who was asked by

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**Modeling Common Human Diseases**

The same techniques that Neil Ferguson has used to model hmd in animals are shedding light on some of the most common childhood infections, as well as killers such as hiv/aids. The Imperial group is involved in an international collaboration with the joint United Nations Programme on hiv/aids (un aids) in Geneva to map this disease, which presents an enormous challenge to modelers.

There are uncertainties about the disease process itself—how the virus interacts with its host—and about the behaviors that will shape the epidemic. As Bernard Schwartlander, head of epidemiology at un aids, notes: People’s sexual proclivities “are not stamped on their foreheads.”

Ferguson’s group is also working on measles, partly because the biology of the disease is relatively well known and detailed historical records of its patterns of incidence are available. He is trying to predict future incidence trends in the post-vaccination era, as well as how health scares about vaccines—particularly the controversial combined measles-mumps-rubella vaccine—will affect those trends.

Similarly, Ferguson is analyzing how mass immunization against chickenpox and the resulting reduction in natural immunity to it is leading to a rise in cases of shingles, a closely related (and more serious) adult disease that is caused by the same virus. “Neither exercise would be possible without the sort of macroanalytical tool provided by mathematical models,” he says.

He also intends to study how diseases evolve under selection pressures, the two main ones being how a pathogen evolves through interaction with the host’s immune system and how it evolves resistance to drugs. In addition to the obvious clinical implications of this research, it will have broader scientific consequences.

As Ferguson explains, “I am fundamentally interested in the population biology of pathogen evolution, because it’s a microcosm for evolution as a whole. But since [pathogen evolution] happens on a much faster time scale than in other organisms, you can actually observe it and the processes shaping it directly.” —LS
Ferguson says such criticisms show a lack of understanding of modeling. Infection grows geometrically in a population, giving an epidemic the characteristic shape of an exponential curve. Based on this principle, a mathematical model divides a population into three classes: those who are susceptible, those who are infected and those who have recovered. It consists of a set of equations that represents the epidemic process as a feedback loop where the rate at which susceptible individuals become infected is proportional to the number of those already infected.

At that level, a model is indeed a simplification of reality. The complexities come in with the diverse behaviors of different diseases—the immunity generated by the pathogen, the infectivity and routes of transmission will vary. When any of these parameters are unknown, says Ferguson, or when the relevant data are not available, the skill is to factor them into the equations, with alternative scenarios weighted according to their probabilities. Each alternative generates a different outcome, providing policymakers with a worst-case scenario, a best-case scenario and a spectrum in-between from which to make their decisions. As more hard data come in, the equations can be adjusted to give a better fit and more precise projections.

Inevitably, says Roy Anderson, head of the Imperial group and one of the pioneers of infectious disease modeling, when you are dealing with an ongoing epidemic the most current data are less precise than you would like. Given the urgency, however, “there is a scientific compromise to be made between detail and something that is sufficiently robust to give a qualitative guidance,” he says. One of the reasons for studying animal diseases such as mad cow, adds Ferguson, is to “offer the opportunity for much more complete data to be collected easily and for experimental and epidemiological studies to be carried out that are not possible in humans.”

MERGING MODELS

When it comes to understanding how a disease behaves, modelers are constantly deluged with new information from well-established fields such as immunology—the discovery of new immunological markers of disease, for instance—as well as relatively young fields such as molecular biology. At the moment, different aspects of disease tend to be modeled separately, and the modeling community divides roughly into those who model the spread of a disease within an individual and those who model it within a population. The problem with these partial models, however, is that they tend to overlook interactions among the many different factors that shape an epidemic.

New-variant Creutzfeldt-Jakob Disease (vCJD), the human form of so-called mad cow disease (see story, page 8), is a good example of the difficulty of modeling interactions. In the August 2000 issue of Nature, the Imperial team estimated that the predicted British epidemic would likely affect no more than 136,000 people. That was a preliminary projection, based on data relating to the 70 or so cases that had been recorded at that time. But all of those early cases came from the 40 percent of the population that shares a certain identifiable genetic makeup, or genotype. There was a hypothesis that the other 60 percent might be immune to vCJD.

Since then, molecular biological evidence collected by John Collinge of Imperial College and University College London has indicated that, rather than being immune, people with different genotypes might just incubate vCJD for longer periods. The evidence comes from Collinge’s studies of kuru, a similar disease that is still affecting elderly members of the Fore tribe of Papua New Guinea more than 40 years after their practice of eating the brains of dead relatives was banned.

His findings raised fears that the Imperial team had vastly underestimated the size of the epidemic. But Ferguson points out that they never excluded the possibility that the rest of the population might be susceptible. The only assumption they made, and one he thinks is justified, was that the distribution of incubation periods is likely to be similar to that of other prion diseases. In the case of kuru, for instance, the incubation period varies from 2 years to 35 years, rising to a single peak at around 15 years. By definition, the vCJD cases that have already come to light are those with the shortest incubation periods. It may be 20 years before we see the cases with longer incubations, he says.

The molecular biological evidence is therefore not at odds with the models, Ferguson maintains, or the worst-case estimate his team generated. Still, one thing he may have to correct for as the epidemic unfolds is how those genetic susceptibilities interact with behavior. In vCJD, the incubation period is not determined solely by the underlying genetics but also by the amount of infected material ingested. The more infected meat a person eats, the sooner he or she succumbs. “We don’t have any idea of the distribution of doses, but it was probably quite wide, and that will make a lot of the additional variation you might get from the genetics,” says Ferguson.

Martin Nowak of the Institute for Advanced Study in Princeton, New Jersey, who models the spread of viruses within an individual, believes the main challenge facing the field now is to establish a single theoretical framework that will accommodate all the available information and its possible interactions. “In the end, one will build models where a virus spreads within an infected individual and within a population,” he says.

Ferguson hopes to start developing the methodology to build these comprehensive models over the next five years to answer basic science questions about evolution as well as public health (see box, page 16). He believes this next generation of models will make possible more precise predictions, and that modeling will play an increasingly important role in disease control. Even now, he says, more and more scientists are realizing that the value of modeling lies in quantifying uncertainty, in making it manageable for policymakers.

Ask him if there is any disease that can’t be modeled, and he smiles: “There is nothing that can’t be modeled, but there are lots of things that can’t be modeled easily.”
Rohit Varma heads a $6 million eye study. He works with leading scientists. He can lecture off the top of his head. So shouldn’t teaching a class of kindergartners be a snap for him?

Not at all. Two years ago, Varma, an ophthalmologist at the University of Southern California, carried a skeleton—dubbed Peter—to his son’s kindergarten class. He quickly launched into the basics of bones, making it all the way down to the rib cage before a girl pointedly raised her hand. She wanted to know one thing: Where did the skeleton come from? “Then the dam broke,” Varma recalls. Suddenly, another child—and then another—joined in the chorus of questions. Was this a dead person? What happened? How did Varma get hold of the body? Varma shot a look at the teacher. She smiled—and stood back.

Speaking to a room full of scientists is one thing. Standing before a class of kids—whether kindergartners or high-school seniors—is something else. With kids, Q-and-A isn’t just an after-talk interval; it’s a way of life.

If you have an hour to share with a class, how can you make the time count?

After plenty of trial-and-error, science educators and savvy volunteers have some hard-earned tips to offer. “Talking to kids can be a great boost for any scientist,” says Nancy Moreno, head of the Himi-funded Science Education Leadership Fellows Program (SELF) at Baylor College of Medicine in Houston. “And these are skills you can learn.”

**Tip 1: Know Your Audience**

To give a great talk, study up on your students. You could probably guess that fourth graders aren’t ready to run gels—but did you know that even eighth graders have a hard time grasping the complexities of DNA?
Scientists often overestimate a class's general sophistication. During one recent project, for instance, Moreno and colleagues developed lesson plans for elementary-school students. They were particularly pleased with a model that used different kinds of popcorn—butter, cheese and caramel—to show that air is a mix of gases, with each variety representing a different gas. The teachers who used the model reported that the kids were certainly fascinated, but some took home an unexpected lesson. "Most of the first-grade children confidently reported that air was made out of popcorn," Moreno says. "You have to learn to be humble!"

So before you painstakingly mold raspberry Jell-O into a replica of a cell membrane, make a phone call. "The teacher knows the students best," says Laura Streichert, head of the speaker's bureau at the Washington Association for Biomedical Research in Seattle. "If you make the teacher your partner, your talk has a much better chance of hitting the target." Researchers can check out the National Science Education Standards to see what's typically taught at each grade level. Keep in mind, however, that the standards are general benchmarks—and schools vary widely in meeting them. "Even if you take third or fourth grade as your level and gear your talk to that, it will not be universally understandable kids of that age," cautions Jon Levitt, a postdoctoral fellow in the Department of Immunology at Baylor College of Medicine and a frequent grade-school visitor. "There's a big difference between schools, particularly those with students from different socioeconomic backgrounds." Again, a teacher's insight is key.

**Tip 2: Bring Props**

Whenever David Schneider, a molecular biologist at the Whitehead Institute for Biomedical Research in Cambridge, Massachusetts, climbs the steps to a local grade school, he brings along extra visitors: bugs. "I call them 'extreme insects,'" Schneider says. "Scary ones, huge ones, really beautiful ones." Shopping the Internet, Schneider buys dried beetles and butterflies for kids to hold. "It's a way of breaking into bug biology," he says, and it works. "I've been amazed by how quickly young kids can pick things up. They're curious about everything!"

Alive or dead, real or pretend, props are a great way to reach kids. Just ask Eric Chudler, a neuroscientist at the University of Washington in Seattle, who has been volunteering monthly at local schools for about five years. By now, he's got props down to a science. Chudler now in a class, he's holding the brain of a different animal—from a cow to a cat. He describes the differences—in brain size and patterns of folds, for instance—between species, and then asks kids to identify the brain in each jar. "Some kids say 'it's gross,'" Chudler says, "but most of them think it's really cool."

Even simple props can jazz up a talk. What do the brain do? To tackle this question, Chudler juggles plastic brains while he leads the kids through a guessing game on muscle coordination, balance and sight. What is the brain made of? For this one, students become giant neurons, linked to each other with rope, plastic and ping-pong balls. When Levitt teaches about friction, he asks students to pull a child in a wagon with—and then without—sandpaper beneath the wheels.

The same approach works with older crowds. High-school kids don't play with wagons, but they usually do like experimenting with the quick-freeze properties of liquid nitrogen, watching flowers curl up, or pennies shatter after a dip in the stuff. "Skip the PowerPoint presentations," advises Mary Margaret Welch, a biology teacher at Mercer Island High School in Washington. "Bring something to do instead."

**Tip 3: Lighten Up**

No matter what gizmos you may bring in your backpack, volunteers say, come to a classroom with the right attitude. "Kids can really sense whether or not you are into what you are doing, and they will immediately pick up on your vibes," says Harry Orf, director of Harvard University's molecular biology labs at Massachusetts General Hospital. "If you have fun, the kids will have fun."

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**Different Strokes for Different Ages**

![Different Strokes for Different Ages](image)

**GRADE-SCHOOL KIDS**
- Like nature
- Identify with family
- Need frequent physical activity

**MIDDLE-SCHOOL KIDS**
- Challenge rules
- Think in the abstract
- Need positive reinforcement

**HIGH-SCHOOL KIDS**
- Identify with peers
- Consider careers
- Need to be inspired
you're tentative, they'll be tentative. If you're having fun, so will they."

Among younger crowds, in particular, enthusiasm is contagious. "All it takes for a young child to get interested in science is some sort of special moment," Varma says. "Kids want to be baseball players because we pay so much attention to them. They don't see a whole lot of excitement in science, but there's real thrill in discovering something new—and it's easy to share."

Even at the middle-school level, kids can often overcome their inhibitions and really enjoy learning about science from a stranger. "Middle-school students still tend to have lots of enthusiasm, and they're often willing to accept you just on face value," says Larry Ann Ott, a biology teacher at Northglenn High School in Denver. "Their emotions are close to the surface. High-school students, Ott says, require a different touch. "Older students have been through a lot more, and they tend to be more cynical or subdued," says Ott. "It takes more to capture their imagination."

One solution, Ott says, is to keep the science relevant. High-school students get swept up into social conflicts, with changing friendships, dating and plans for the future. "If you can bring any of this—gender differences, social interactions—into your discussion, it can make a major difference in what they remember," Ott says. Catch their attention, and their curiosity will follow.

**Tip 4: Get Moving**

At meetings scientists often listen to 50-minute lectures. At school, 50 minutes is an eternity. Kids move around a lot. If you want to keep their attention, get moving, too. "The more you move around, the more they have to keep watching you," Levitt says. "Whatever you do, don't stand at a lectern and rave on." A couple of years ago, Levitt was five minutes into his first talk to a grade-school class when he realized that nothing was sinking in. Kids were elbowing each other, looking around, playing with their sneakers. He quickly jumped up to change gears—and he hasn't stopped moving since.

David Schneider uses "extreme insects" to spark children's curiosity about bug biology.

David Schneider uses "extreme insects" to spark children's curiosity about bug biology.

If you're moving around, and the kids get a turn handling props, what's the message? What's more, Schneider adds, the teacher can keep kids on task. "With the little kids, in particular, I just don't have the skills to control them," he says ruefully. "I wouldn't want to go in cold, alone. It's important to have the teacher close by."

**Tip 5: Follow Up**

Spending an hour with a class can bring smiles all around—but following up can do even more. Teachers may build on your talk, doing lessons afterward to reinforce whatever you’ve taught. Chances are, they will also have questions along the way. "If you really want to make a difference, make a commitment," says Keith Verner, chief of the division of developmental pediatrics and learning at Pennsylvania State University College of Medicine. "Don't wait to hear back from the teacher. Instead, send an e-mail. Say, Hey, I enjoyed that. I have any questions come up that I could answer?"

Many teachers would welcome the input. "A real partner is not just about having someone come in and give this presentation, but having someone who's willing to be on call," says Welch. "It's someone I can call if there's a kid who got really excited by something or had a question I couldn't answer. That's the kind of partnership we need."

That sort of partnership is not very hard to create, adds Harvey Lodish, a molecular biologist at the Whitehead Institute. "All research institutes can do something. A junior scientist can give one talk a year to third graders, or make a special presentation to high-school students. "We can't change the world, but we can change a little piece of it."

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**Classroom and Online Education Resources**

Some scientists go back to school themselves before stepping foot in a classroom full of children. At the University of California, San Francisco, more than 150 scientists have completed six hours of Scientist Orientation Workshops, part of an HHMI-supported school outreach program there. Several Web sites offer information for scientists interested in speaking to schools:

- University of California, San Francisco, Science and Health Education Partnership
  www.ucsf.edu/toap/index.html
- Resources for Involving Scientists in Education (RISE)
  www.nru.ca/riise/
- Sharing Science with Children: A Survival Guide for Scientists and Engineers
  www.noaa.edu/education/tipsheets/scitext.html
- HHMI's Precollege Science Education Program
  www.hhmi.org/grants/precollege/
H
is students tend to freak out at first, says Presley Martin, describing the introductory biology course he teaches at Hamline University in St. Paul, Minnesota. When they walk into the course's laboratory section for the first time, the students find themselves face-to-screen with the Genetics Construction Kit (gck)—a computer simulation of Mendelian inheritance that will compel them to do some real science.

To begin an experiment, the gck generates a “field collection” of, say, fruit flies, each with a combination of traits—white eyes or red eyes, bent wings or stubby wings or straight wings and so on. The program also provides the tools for performing genetic crosses, plus a spreadsheet to analyze the outcomes statistically. It does not explain the hidden genetic mechanisms that produced those outcomes, nor does it offer a traditional lab manual that tells the student how to find out. Instead, the student is expected to decide what traits to look at, what crosses to try, what hypotheses to consider and, perhaps most important, when to be satisfied that a hypothesis is correct, just as a scientist faced with a real field collection must do.

“They’re really uncomfortable” says Martin, who is chairman of the Hamline biology department. “They’re used to problems where they’re expected to get the right answer, so it’s hard for them to deal with the fact that the program isn’t going to tell them when they get the right answer.” Instead it confronts them with the task of learning firsthand the most fundamental principles of science—that hypotheses have to be tested, alternatives have to be ruled out, objections have to be satisfied and a conclusion requires evidence. “Ask for supportive evidence,” says Martin, “and at first they’re just puzzled.” As the exercises progress, however, at least some of the students really do begin to get it.

Stories like Martin’s are being heard more and more often. Thanks to the proliferation of high-powered personal computers on campus and the rapid growth of the Internet, colleges and universities are experimenting with computer-based learning as never before—frequently with biologists among the leaders. Indeed, many of those biologists believe that online learning is the best hope for maintaining high-quality, individualized education in the face of undergraduate enrollments that have surged dramatically during the past decade. Some biology educators would use online resources to help change the method of learning itself, regardless of class size. They find that the gck and similar software programs can be powerful tools for giving students an experience as close as possible to real scientific research—what curriculum reformers call “inquiry-based” learning. Students are encouraged to ask their own questions, struggle toward the answers and, in effect, teach themselves.

RAISING SKILLS AND EXPECTATIONS
Certainly that was the intent of the kit’s co-creator, biologist John R. Jungck of Beloit College in Wisconsin, who wrote the program in 1985.
with biologist John N. Calliey, then at the University of Arizona. In a 1988 article, Jungck and Nils S. Peterson of Washington State University explained that the teaching and the software work together to reinforce the “3 Ps” of research: problem-posing, problem-solving and peer persuasion—the same in this case being the other students.

That 3-Ps approach has, in turn, been the guiding principle of the BioQUEST consortium, which Jungck and a group of like-minded software authors founded in 1986. The consortium, which is located at Beloit College and funded partly with hhm grants, maintains a library of some 70 tools, simulations, databases and other resources developed for undergraduate biology. Each resource is peer-reviewed, available on cd-rom and enhanced by data readily retrieved from the Internet. Among the offerings are the original Genetics Construction Kit, Sequence It! (a simulated protein-sequencing lab) and Bird It!—Beagle Investigation Returns with Darwinian Data (a tool for exploring evolution through a database of taxonomy, song recordings, DNA sequences and measurements on some 650 specimens of Galápagos finches).

Jungck is especially taken with how such tools, complemented by e-mail, discussion groups and chat rooms, have raised the skills and expectations of students to a whole new level. “You see them engaged in collaborative problem-solving, looking at multiple hypotheses, sharing data.” A teacher in one of our workshops told me recently that their worst project this year is better than their best project three years ago. Another said, “we never knew our students were that creative.”

He admits that this kind of science teaching is never going to be as easy as the traditional approach, Internet or no Internet. “For teachers, it’s more intense,” he says. “With oodles of projects going on all the time, and with students accessing all these complex tools, you have to be willing to let the students teach you things. And that's being designed at Stanford to give large introductory physiology classes hands-on, lab-like experiences without going to a lab. Other virtual labs will focus on human gastrointestinal, cardiovascular, respiratory and neurobiological systems.

“This is more than a digital textbook,” says Camillian Huang, virtual labs project manager. “It is fun, and it helps students understand difficult concepts and relate what they are learning to their everyday lives.” In a preliminary comparison of student achievement, students who used the virtual lab scored higher than those who only attended lectures and read the text, Huang reports.

More information and demonstration labs can be found online at: summit.stanford.edu/hhm/
a huge change in the social contract of the classroom.”

Meanwhile, Jungck says, “for the students this is a lot more work than just passively sitting in front of an instructor, taking notes. But even so, from all of our studies, the students who go through this process retain more. They stay in the courses longer. They more often go on and take additional science courses. They are better at applying what they’ve learned to social and legal issues. And they seem to have a conversant, speaking knowledge of science for a long time after they finish.”

FIRST-YEAR BIOLOGY ONLINE

None of the software in the BioQUEST library was specifically designed to help teachers cope with overcrowded classes, but that is definitely an issue at Michigan State University, where an interdisciplinary team of biologists and education specialists is attempting to put the school’s entire first-year biology curriculum online. After all, notes microbiologist John Merrill, one of the leaders in that effort, “unless the students suddenly throws a huge amount of money at us so that we can have everybody in small classes, I still have to teach these huge courses with 400 students.”

The project, called “First Year Online,” began in 1998 as part of a five-year, $3.6 million grant from HHMI, says project director Estelle McGourt, and it soon proved to be an even more daunting task than the team had imagined. “It took us most of a year after we were funded just to figure out how to approach online biology,” she says. “Early on, for example, we made the decision that we would not provide a complete virtual course. Biologists, more so than the physicists, feel that there has to be a face-to-face component in teaching.”

Materials are presented using I O L , the Lecture Online platform that had just been developed at Michigan State by physics research associate Gerd Kortemeyer. Like commercial course-management software, I O L offers tools for keeping track of administrative details such as enrollment and grades, and, most importantly, it allows instructors to customize the online content to suit their particular needs.

HOW TO HELP STUDENTS LEARN

“There is a pretty strong body of evidence that students don’t learn much by just being told about science, as in being lectured to, or just reading about it,” says team member Joyce Parker of the vision of science and mathematics education. “They first have to be engaged in some sort of problem, so that they can see a purpose. ‘Here’s something intriguing, let’s try to understand it.’

The online modules are designed to start by piquing the students’ interest—something that can be done with animation. Photosynthesis, for example is presented as an animated play in eight acts, with the water molecule anthropomorphized as a tragic hero who sacrifices himself for the good of the cell. Cellular respiration and the electron transport chain are presented in comic-book style, complete with a capped crusader: “The Story of Electron Man.”

“We use what works,” laughs Merrill, who particularly enjoys the large biomolecules module. “We start each subtopic with a picture of a nice juicy hamburger with a side of French fries, and then we have arrows pointing to, say, protein in the meat.”

Once you’ve got the students’ attention, then what? “The student has to wrestle with the material,” says plant ecologist Diane Ebert-May, director of Michigan State’s Lyman Briggs School—a residential community for students in the natural sciences—and a frequent consultant to the First Year Online project. “You can tell them, tell them and tell them again—and if they have a different mental model, they won’t get it. Most incoming freshmen think that only animals respire; they have trouble with the concept that plants do too. They think that plants get their food from the soil, and forget that there is this diffused carbon dioxide in their air. In fact, the whole notion of the carbon cycle and its connection to global warming is a hard concept. So in the HHMI project we try to give them modules on concepts that we know are hard to understand.”

Ultimately, the project’s goal is to produce 20 to 30 such modules covering the content found in most introductory biology textbooks. In developing the modules intended for the first semester of introductory biology (“Cells and Molecules”), Merrill says, the group has been learning a lot of lessons. “One is that developing online educational materials is a huge undertaking. In the way that we’ve done it, it’s a lot like writing a textbook—and I don’t think we were prepared to write a textbook. Plus it requires all the same skills as developing a complex Web page. It’s quite a challenge for a faculty member to learn the graphical design tools you need for that.”

A second lesson, says Merrill, is that online teaching is really an art form. “The best pieces we’ve produced have an individual voice and sensibility. There’s no formula for that; he says, “except to recognize when it happens.”
Repairing the Disconnect Between Research and Teaching

By Peter J. Bruns

Jane just started her freshman year at a top-ranked state university. John is a freshman at an Ivy League school. Both were outstanding high-school students interested in pursuing careers in science and medicine, so they chose those institutions precisely because of their reputations for research excellence.

John and Jane may be in for a shock. They could find themselves in packed lecture halls, listening to instructors who would rather be almost anywhere else. Their labs and seminars may be taught by graduate students who often are doing it not for the love of teaching, but to pay for their Ph.D.s. Meanwhile, the research leaders with whom John and Jane hoped to study may be tucked away in their labs, supervising their research teams, writing grants and avoiding undergraduates whenever possible.

Unfortunately, we have evolved a built-in disconnect between research and teaching at many of our biggest and best universities. While undergraduates go to research institutions to get an outstanding baccalaureate education, the faculty at those same universities seek (and need) to do cutting-edge research that often depends on peer-reviewed funding. To move important research forward, faculty attention is diverted from local teaching needs to a sometimes overwhelming concern about the attitudes of review panels in Washington. Although faculty value and for the most part enjoy teaching, it is research that tends to yield the rewards of tenure, rank and pay—in other words, professional respect—while teaching usually winds up low on the totem pole.

Yet good research and teaching can coexist, and actually reinforce and invigorate each other in provocative ways. Science education must involve more than facts and concepts; students need to learn how we do research and be exposed enough to the excitement of discovery to be inspired to learn more about science. In a world increasingly dominated by science and technology, even those who will not become science majors need to learn enough about the content and process of science to be informed decision-makers and rational, critical thinkers throughout their lives.

Research scientists and their institutions sometimes say that teaching takes valuable time and attention away from research, but this is a short-sighted view. Teaching adds value to research by providing the fresh insights that flow from creative interaction among undergraduates, graduate students, postdoctoral fellows and senior scientists. It also provides apprenticeship experiences in science education for graduate students and postdoctoral fellows—the scientist-educators of the future.

In my years at Cornell, I watched with joy as undergraduates became fully integrated in my research group and those of many of my colleagues. They clearly brought fresh ideas and wonderfully challenging, if naïve, questions to lab meetings and daily interactions. Still, individual research projects by the top few students at research universities, although desirable, are not enough. The synergy of research and teaching needs to extend beyond the few and be part of the standard fabric of science education in research universities.

In that spirit, HHMI has launched a new initiative to help bridge the gap between lab and classroom. The Institute has committed $20 million to support 20 "HHMI Professors" for four years at...
research universities across the nation. The program’s goal is simple: to encourage faculty members who are very creative scientists to apply some of that creativity to undergraduate education.

The HHMI Professors program is designed to legitimize and reward great teaching, encouraging science departments at research institutions to place a higher value on undergraduate teaching. By supporting the development of innovative, crossdisciplinary and multiyear lab courses, the Institute hopes to enhance the alliance between research and education and to generate new undergraduate curriculum materials that can serve the entire science community.

At HHMI, a gap has tended to separate investigators who conduct research in universities and medical centers from their peers who receive support through the Institute’s science education grants programs. I hope that by participating in both research and science-education meetings at the Institute, the HHMI professors will create synergy between those groups, a goal to which the Institute’s leadership is committed.

Nominations for HHMI professors have been invited from 84 institutions and will be selected by an expert panel of scientists and educators. Nominees will each have a proven track record in research, as well as some teaching experience. They will also have two other assets of special importance: innovative ideas on how to change the fundamental ways in which science is presented to undergraduates, and an ardent desire to try out these ideas.

In the tradition of HHMI’s appointment of investigators, the awards to HHMI Professors will support promising individuals rather than projects; the awardees will be given the freedom to try innovative ideas, which includes the liberty to change direction. We hope to empower imaginative people to direct their skills and energies to undergraduate science teaching, and then share the results.

The baseline for this experiment is not zero. I certainly have colleagues all over the nation who have worked hard to bring innovative science education to undergraduates. But no individual or campus in isolation can change the center of gravity on this issue. The National Science Foundation has just begun a distinguished teaching scholars program and the Carnegie Foundation for the Advancement of Teaching is supporting initiatives such as Portland State University’s Center for Academic Excellence. We hope that putting the HHMI imprimatur on scientist-educator programs will further stimulate a cascade effect, motivating more science departments and their institutions to seek out and reward good undergraduate teaching. In any case, it will help form the beginnings of a cadre of scientist-educators that can be instrumental in improving the quality of undergraduate science education for generations to come.

Peter Bruns is HHMI’s vice president for grants and special programs.
An entire class of proteins has long resisted the best efforts of scientists to fathom its mysteries. These molecules—known as membrane proteins because they reside within the fatty membranes that encase the body’s cells (and certain internal parts of cells)—are involved in a vast range of vital functions. They regulate the flow of nutrients into cells, let waste products out and relay messages that support life or trigger cell death. By chaperoning microbes into cells or by failing to function properly, membrane proteins can also play a role in making us sick. They are basic to the improved understanding and treatment of depression, Alzheimer’s disease, cystic fibrosis, blindness, childhood diarrhea and a host of infectious diseases.

Despite their obvious importance, fewer than 30 of the estimated 20,000 membrane proteins that exist have been described structurally—atom by atom. They are notoriously difficult to purify and crystallize.

The University of Texas Medical Branch at Galveston (UTMB) has imported a possible solution from Europe, along with its codeveloper, Ehud Landau. He’s devised a way to quickly remove the proteins from their stable lipid-layered environment, purify them and insert them into a new material that imitates their native milieu. The proteins remain stable enough to crystallize, which is a prerequisite for solving their structures by using x-ray crystallography. Landau and colleagues first used this concept, the lipidic cubic phase, to crystallize a membrane protein found in bacteria called bacteriorhodopsin in 1997.

“It is terrific to see Ehud following up on his stunning success in bacteriorhodopsin crystallization with tests on other membrane proteins,” says HHMI investigator Wayne Hendrickson, a structural biologist at Columbia University. “Even if the applicability of lipidic cubic phase proves to be limited, I expect that what he learns about how membrane proteins interact with lipids will be highly instructive.”

In August, Landau and colleagues published the molecular architecture of a second bacterial membrane protein, called sensory rhodopsin II. Discerning its structure is important, says coauthor Javier Navarro, because “this bacterial protein is structurally and functionally related to a family of G protein-coupled receptors,” which, he notes, are the targets of some “60 percent of all drugs currently in use.” Knowing the structure of sensory rhodopsin II brings the researchers closer to understanding the G protein-coupled receptors, some of which mediate sight, smell, neurotransmission and the body’s recognition of the human immunodeficiency virus.

Even with the excitement of determining this new structure, Navarro admits that the road is slow going. “We’re working to crystallize 15 membrane proteins right now,” he says, including some G-protein-coupled receptors and a protein involved in cystic fibrosis. “If we get one a year, that would be fantastic.”

Landau and Navarro are codirectors of UTMB’s Membrane Protein Laboratory—one of three core facilities of a comprehensive new program built with support from an HHMI grant designed to help medical schools build facilities, hire faculty and create centers of excellence. The other core labs are devoted to the genetics of membrane proteins and the development of small molecules designed to activate or inhibit the function of these proteins.

With a thick beard and horn-rimmed glasses, Landau exudes an intense scientific work ethic. The Israeli researcher spent years as a physical chemist studying the nuances of how lipids—the main components of cellular membranes—behave under different conditions. Landau and Navarro became fast friends and colleagues in 1998 when Navarro, a clean-cut and high-spirited native of Peru, took a year-long sabbatical at the lab Landau was running at the University of Basel in Switzerland.

Landau and his collaborator, Jurg Rosenbusch, a pioneer in membrane-protein research, had recently developed a novel concept to stabilize membrane proteins in three-dimensional bilayers—the use of the “lipidic cubic phase.” Navarro, who, like Rosenbusch, knew the evasive
behavior of membrane proteins, was eager to learn the new technique.

The lipidic cubic phase stood out because it promised to speed the pace of research in a field in which progress had been terribly slow, mainly for two technical reasons. First, unlike other proteins, those residing within fatty layers of cellular membrane don’t dissolve in water. When researchers try to purify them—separate the proteins from their membranes—the water-loathing, fat-loving layers of the membrane uncoil, gelling into a useless mass like the white of a hard-boiled egg. To overcome this problem, researchers traditionally have turned to detergents, which remove fats the way soap removes dirt—by forming protective belts around the protein. But detergents also can damage proteins, and milder substitutes that accomplish the same task have been hard to find.

A second difficulty, related to the first, is that membrane proteins are difficult to crystallize—a necessary step for getting detailed, three-dimensional images of the molecules. For decades researchers have been growing nonmembrane proteins into well-ordered networks, or crystals, that can then be bombarded with x-rays. The resulting diffraction patterns are analyzed to produce pictures of the molecules’ architecture. It’s tough to crystallize membrane proteins, however, because this process, like purification, relies on detergents. Unfortunately, “what works for one doesn’t [necessarily] work for the other,” says Navarro. Researchers, he says, often have to screen many detergents and settle in the end for less than optimal results.

“You have to do an enormous amount of work,” agrees Richard Henderson, a structural biologist at the Medical Research Council in Cambridge, England. A pioneer in membrane-protein research, Henderson toiled for 17 years before publishing, in 1975, the very first structure of bacteriorhodopsin, which is found in the salt-loving bacterium Halobacterium salinarum. Henderson’s structure was groundbreaking—but crude by present-day standards because it showed only the protein’s general folding pattern. Scientists prefer the ultimate insight: an atom-by-atom picture of the molecule. No one succeeded until Landau and Rosenbusch, together with French crystallographer Eva Pebay-Peyroula, published their structure of bacteriorhodopsin in Science magazine 22 years later, in 1997.

Landau and Rosenbusch had devised a way to achieve their goal. They reasoned that the membranes’ own three-dimensional network of lipid bilayers would stabilize membrane proteins in a way that artificial detergent solutions never could. In essence, the team asked, why not try to replicate membrane proteins’ natural oil-and-water home?

“Lipids and water are in principle immiscible—they don’t mix,” says Landau, “but we can manipulate them into a new material—the lipidic cubic phase—that allows us to work with membrane proteins.” By rapidly dissociating these proteins from their native lipid containment, purifying them and then very rapidly incorporating restructured versions of them into the new bilayered material, says Landau, “they are much more stable because they are in a native-like environment.” This technique offers a great practical advantage, adds Navarro, because the onerous process of screening detergents has been eliminated.

Since Landau’s arrival at UTMB, scientists from around the world have come to Galveston to learn the new method, and others are sending protein samples to the lab for characterization. “Our method opens up possibilities to work with unstable membrane proteins that researchers haven’t been able to crystallize in the past,” explains Landau.

“Structural biology of membrane proteins is one of the most important frontiers in biology today,” he says. “It’s about time these proteins got their due.”

— STEVEN J. MARCUS & ALANA MIKKELSEN

Segments of this article were adapted with permission from the UTMB Quarterly, Winter 2001.
Neuroscience of Music

It's a cool spring evening at Allegheny College in Meadville, Pennsylvania. The Alexander String Quartet—professional chamber musicians who perform at the college every year—is tuning up on the stage of Ford Memorial Chapel. As the audience files in, a few students scurry around the balcony attaching electrodes to their classmates' heads and connecting the wires to large computers hauled across campus for the occasion. For tonight, the old stone church is converted into a living laboratory.

This combination concert-experiment was part of an interdisciplinary course, “Neuroscience of Music,” offered for the first time during the spring 2001 semester by faculty neuroscientist Jeff Cross and his colleagues—electrophysiologist Alexander Dale and concert pianist Alec Chien. “It is the participant model of science,” Dale says. “The subject participates in the research.” The pilot course was so successful that the scientists will soon team up with visual artists and dancers to provide new and unique learning experiences for the students, while further investigating the workings of the human brain. “Neuroscience has the wonderful advantage of being applicable to every human endeavor,” Dale explains.

Supported by a grant from HHMI, the music course involved a series of concerts in which electroencephalograms (EEGs) recorded alpha and beta brain waves of students as they listened to the music. Later, in the laboratory, the students measured the brain activity of the quartet members as they listened to the piece of music they had performed earlier. Comparisons showed that alpha-wave patterns—characteristic of relaxed wakefulness—were similar in both sets of listeners.

As expected, Cross says, beta-wave patterns—those indicating intense mental activity—appeared in both groups in the brain’s right frontal area in response to changes in key. However, the beta waves appeared an average of four measures earlier in the quartet members. Of course, Dale notes, the master musicians are more familiar with the music and can anticipate the key changes. Still, “being able to detect this expertise with EEG is truly exciting,” says the electrophysiologist.

Both science students and music majors say they benefited from the course. Jessica Hoge, a pianist who majored in music and neuroscience, used the data generated by the concert-experiment for her senior thesis and submitted a scientific paper for publication. She says the whole experience has influenced her music as well. “When I play now, I’m definitely aware of the mechanism working in the listeners’ brains.”

Chien adds that musicians have long suspected the effects of music on the brain, but “now we have proof.” For nonmusicians, the hands-on activity was critical to the learning of the science, Cross says. Music brings familiarity and relevance to the classroom. “It makes our job easier.”

A number of factors inspired Cross, Dale and Chien to create the course. The college encourages cross-disciplinary collaborations, students were showing interest in learning about music and the brain and the local Alexander String Quartet—having participated in an annual artists-in-residence program on the campus for 10 years—was a handy resource.

In next spring’s course, using vocal music as stimuli, new telemetry equipment will allow the researchers to leave the heavy computers in the lab. A new imaging system will enable them to map more regions of the brain.

In addition to the music course, other cross-disciplinary courses will include “Neuroscience of the Visual Arts,” “Neuroscience of Dance,” “History of Neuroscience” and a philosophy course called “Mind and Brain.” Dale says he is looking forward to these new collaborations. “The faculty gets so excited about these models,” he says, “and, when you get the faculty excited, that excitement is absorbed by the students.”

—CAMILLE MOJICA REY
Twenty-nine museums, aquariums, zoos and nature centers have won new HHMI grants totaling $12 million. A number of the programs focus on environmental stewardship in inner city, rural and other areas where there are high concentrations of disadvantaged children and families. The Fairchild Tropical Garden in Miami, for example, will receive a $290,000 grant to reach the local, largely Cuban, community. The program, called Green Treasures, involves schoolchildren, teachers, families and older people who emigrated from Cuba in hands-on study of the scientific, economic and cultural importance of plants. The objectives of the grants are to strengthen the science literacy of teachers, children and their families; to provide resources for improved science teaching; to engage families and communities in science education; to develop an interest in science-education and research careers; and to foster collaboration between informal science education centers and other community institutions.

A list of the new grantees follows. Profiles of some of the programs can be found on the HHMI Web site at: www.hhmi.org/news/071001.html.

- Arizona Science Center, Phoenix, Ariz.
- Bronx Zoo, New York, N.Y.
- Cable Natural History Museum, Cable, Wis.
- Chicago Botanic Garden, Glencoe, Ill.
- Children’s Discovery Museum, San Jose, Calif.
- Daliota Science Center, Grand Forks, N.D.
- Fairchild Tropical Garden, Miami, Fla.
- The Gulf Coast Exploreum, Mobile, Ala.
- The Imaginarium, Anchorage, Alaska
- Irvine Natural Science Center, Stevenson, Md.
- The Maritime Aquarium, Norfolk, Conn.
- Missouri Botanical Garden, St. Louis, Mo.
- Museum of Science, Boston, Mass.
- National Aquarium in Baltimore, Md.
- New Jersey State Aquarium, Camden, N.J.
- Rock Creek Nature Center, Washington, D.C.
- The Science Museum of Minnesota, St. Paul, Minn.
- The Seattle Aquarium, Seattle, Wash.
- Sedgwick County Zoo, Wichita, Kan.
- Staten Island Children’s Museum, Staten Island, NY.
- UC Berkeley Museum of Paleontology, Berkeley, Calif.
- University of California Botanical Garden, Berkeley, Calif.
- University of Wisconsin-Madison Arboretum

New Museum Grants Awarded

A mini-course on immunology and tumor immunology is routine—except when it involves two American scientists traveling to Moscow to lead the event. “It may be a seditious thing to say, but we actually don’t have serious education in immunology, and particularly in tumor immunology, in Russia,” says course organizer Sergei Nedospasov, an HHMI international research scholar at the Engelhardt Institute of Molecular Biology of the Russian Academy of Sciences. “The need for such lectures is vital.”

Philip Greenberg of the University of Washington and Robert Schreiber of the Washington University School of Medicine led the four-day course in May at Moscow University’s Center for Molecular Medicine. They are among more than 15 researchers, including several HHMI investigators, who comprise a “visiting faculty” that has begun traveling to Russia to discuss the latest achievements in immunology in general and tumor immunology in particular. Nedospasov launched the three-year educational program last September with support from the New York-based Cancer Research Institute and the Ludwig Institute for Cancer Research.

Nedospasov wants his colleagues, especially younger scientists, to have more contact with leaders in immunology research. On a competitive basis, he helps select groups of 10 to 15 trainees from Russia and other countries of the former Soviet Union to participate in “journal clubs” with the lecturers and attend the larger lectures.

Program organizers say they hope that if the program proves successful over its three years, colleagues will begin to participate in greater numbers, leading to more such efforts in Moscow and elsewhere. The program’s Web site is lmi.webzone.ru.

—ANDREI ALLAKHVERDOV
Reason to Stay Another Year

To travel the path of discovery, one had better be open to extending the adventure a little while longer. That’s exactly what medical student Tamiko Katsumoto found herself doing when her project dropped tantalizing results in her lap.

Originally scheduled to spend one year in the lab of Kevin Shannon at the University of California, San Francisco (UCSF), Katsumoto ended up adding another year to her stay in order to explore fundamental mechanisms of hematopoietic stem-cell engraftment—the means by which immature blood-forming cells take up residence in the fetal liver and then move on to the bone marrow. In the process, she uncovered a previously unknown role for the bone marrow’s stroma—the spongy mix of fat, fibroblasts, macrophages and other components that support blood-cell development.

“I realized around February of that first year that we had a really striking result,” Katsumoto says. “If I wanted to carry the project through, I needed another year.” Katsumoto, who was doing her research under an HHMI medical student research fellowship, decided to apply for a second year of support. She was among the very few who received it.

She was working with mice lacking the gene for granulocyte macrophage-colony stimulating factor (GM-CSF)—a substance that stimulates the growth of certain blood cells. After irradiating the mice lacking GM-CSF to destroy their bone marrow, she discovered that fetal liver cells, which contain hematopoietic stem cells, could not alone help the irradiated mice to recover. However, she could save them by transplanting bone marrow.

Both fetal liver and bone marrow contain stem cells that should be capable of restoring bone marrow. Why couldn’t the fetal liver cells alone manage it? Katsumoto began focusing on the potential role of accessory cells, which aren’t stem cells but somehow support the engraftment process. Accessory cells are prevalent in bone marrow, but exist at much lower concentrations in fetal liver.

When Katsumoto mixed fetal liver cells with accessory cells derived from bone marrow and injected them into irradiated mice lacking GM-CSF, the bone marrow regenerated and the mice were rescued.

“These accessory cells aren’t the immature precursor cells that reconstitute hematopoiesis,” Katsumoto says. “Still, these cells were somehow facilitating engraftment.”

However, enough accessory cells had to be present to compensate for the injury to the stroma that occurs in response to irradiation. Will adding GM-CSF protect and nurture sufficient numbers of accessory cells to improve engraftment? Katsumoto hopes to find out.

“What we can start thinking about doing,” Katsumoto says, “is using GM-CSF to improve engraftment. This might be especially important when umbilical-cord blood or other sources of stem cells that contain few accessory cells are used.”

Her project mentor, Kevin Shannon, noted that his lab, which mainly focuses on leukemia, would not normally have pursued this line of research. With Katsumoto preparing to complete her last year of medical school, however, he says the lab will do so, at least for the short term.

When she graduates from UCSF, Katsumoto is sure she will pursue internal medicine, although she admits she is also fascinated by hematology/oncology. “I really just love the practice of medicine,” she says. “It’s so wide open—there are so many opportunities.”

—Lisa Chiu
A River Runs Through Us

The Texas town of McAllen shares more than a border with its Mexican neighbor, Reynosa, in the state of Tamaulipas. The Rio Grande/Rio Bravo Watershed is the region’s primary water source, and it is one of North America’s most endangered river systems. In May, the McAllen International Museum brought a mobile, hands-on exhibit—Our Watershed—to the Universidad Autonoma de Tamaulipas. It is part of a bilingual environmental education project called “A River Runs Through Us,” supported in part by a science education grant from HHMI. Children from six Reynosa area high schools were trained by museum staff to serve as guides to the 4,200 elementary school students from 30 schools who visited the exhibit.

Above: Sixth graders from Colegio Reforma, a Reynosa elementary school, use a model of the Rio Grande/Rio Bravo Watershed to see how dams change the flow of a river.

Lower Left: Carlos Alberto Pérez Abrego, left, and Raimon David Pérez Hernandez, students at CETIS 71, a Reynosa high school, operate small hand pumps to cause “rain” to fall from clouds in a model of the water cycle.

Lower Right: A visiting student plays the role of “watermaster,” whose task is to distribute fairly—among cities, industry, agriculture and wildlife—the water that McAllen and Reynosa share.
If You Can Name That Tone, Thank Your Parents—and Your Music Teacher

A conversation with Jane Gitschier

Jane Gitschier, h h m i investigator at the University of California, San Francisco (u c s f ), studies the genetic basis of childhood disorders. One of her latest explorations, inspired by her training as a classical singer, is the genetics of perfect pitch—less a disorder than a rare musical gift. With colleagues at u c s f , including Nelson Freimer, now at the University of California, Los Angeles, Gitschier has found that this ability to name a note immediately and effortlessly, when it is sounded tends to run in families. The researchers don’t yet know which gene or genes are responsible, but they’ve begun the linkage studies to find out. They do know, however, that the trait requires early musical training to bloom.

How rare is perfect pitch, really?

Jane Gitschier: I gave a talk on perfect pitch at h h m i last year. The staff had the Steinway tuned for the occasion. I gave the audience of about 100 people our operating definition of perfect pitch: If I played a tone without an external reference, a person with perfect pitch could identify that tone. Then I played four notes on the piano. Just one person, a postdoc, quickly raised his hand and correctly named the four notes. The audience applauded. It’s very clear that this is an ability the average person does not have.

Do people with perfect pitch know they have it?

JG: Yes, and they give the same answers to three basic questions. How long does it take you to tell what a tone is? They respond, “Immediately.” How long have you known you have perfect pitch? “My whole life!” How accurate are you? “I never miss.”

Is this a case of nature needs nurture?

JG: Exactly. You need to have some kind of training to develop perfect pitch. It makes sense. You clearly need to be exposed to the definition of a note—this is a D-flat, this is an A-sharp. If you don’t get that musical input by a certain age, around age six, you’ll lose the chance to have perfect pitch even if you have the right allele.

Can a person develop perfect pitch without the genetic predisposition?

JG: People claim you can, but I’m dubious about it. You can develop very good relative pitch—get to know what an A feels like on a violin, for example. You might seem to have perfect pitch. But you may not have it on other instruments.

How will this research benefit people in music?

JG: (Laughing) I don’t think there is any application for people in music. I think there’s a lot of application for science—in the study of brain development and neuronal plasticity, and in educational issues as well. For example, it could help us decide whether to expose our children to certain things, like new languages. I tried to give my daughter piano lessons by the time she was six years old. It became obvious to me that she does not have perfect pitch, so I didn’t push it. On the other hand, she’s doing a beautiful job learning Chinese.

—CORI VANCHIERI

Think you’ve got that magical ability to name that tune in one note? Test your inborn skill with Gitschier’s pitch test online at: www.hhmi.org/bulletin

If You Can Name That Tone, Thank Your Parents—and Your Music Teacher

A conversation with Jane Gitschier

Jane Gitschier explores the genetics of perfect pitch. She and daughter Annie Steinberg enjoy playing music together.
A Science Connection in Roxbury

Located in the heart of Roxbury, a largely minority, inner-city neighborhood of Boston, the James P. Timilty Middle School shines in science education. In the rigorous statewide achievement tests for the eighth grade, Timilty’s students outscored most of Boston’s schools in science and technology and in a combined measure of achievement in four broad subject areas. The school has been singled out with several national and statewide awards for its overall high student performance.

Timilty’s success, administrators say, reflects several factors, including its skilled and dedicated staff; its adoption of Project Promise—a program featuring an extended school day, team teaching, shared decision making and smaller classes; its inspired students and a little help from its friends. Since 1989, a partnership with nearby Massachusetts General Hospital (MGH) has enabled the school to tap the hospital’s resources. Each year, some 250 hospital employees spend time as mentors, occasional classroom lecturers and hosts to young visitors. Science Connection’s longest-running activity—in this spirit—its “cornerstone,” says Prince—is the Science Fair Mentoring Program. Each MGH volunteer is paired with a Timilty student for the six months leading up to the school’s annual science fair. Students are chosen not so much for their grades as for their motivation, says Timilty science teacher Robert Cho, the program’s former manager. They are “kids who really wanted to be in the program.”

In 2001, Timilty sent more student projects to the citywide science fair than any of Boston’s 26 other middle schools, and many won awards. The Science Connection program has additional components. “Science in the Classroom” features teaching stints by MGH employees ranging from one-time visits to continuing relationships with a class. Twice a year, the students’ family members join in for “Science Family Activity Night.” “We expose these young men and women, who often live in a very small circle, to science,” says mentor Guillermo Banchiere, director of environmental services at MGH. “By showing them lots of things they probably didn’t know existed, we expand the universe for them.”

—STEVEN J. MARCUS

NEW UNDERGRADUATE COMPETITION

HHMI has invited 200 research and doctoral universities to apply for a new round of undergraduate biological sciences education grants. An estimated 50 to 60 four-year grants ranging from $1.2 million to $2.2 million will be awarded in 2002.

In addition to the existing objectives, such as preparing students for careers in biomedicine and providing engaging science curricula for nonscientists, new program objectives include:

- Enable graduate students and postdoctoral fellows to supplement their research training with teaching and mentoring experiences that prepare them for roles as scientist-educators.
- Develop models for overcoming the traditional dichotomy between research and teaching.
- Foster a team approach to research among faculty, undergraduates, fellows and graduate students.
- Explore the interactions of biology and other disciplines, including mathematics and computer science.
- Share university educational resources with other institutions, including colleges and secondary and elementary schools.
- Provide increasingly challenging science experiences to undergraduates during their four-year college stay.

—JENNIFER BOETH DONOVAN
Fault the ion channel  Genetic mutations that yield flaws in a specific ion channel have been tied to a rare disorder characterized by muscle paralysis, irregular heartbeat and growth problems. The finding offers a new perspective on how faulty ion channels—pore-like proteins that poke through cell membranes and control the flow of potassium, sodium and other ions into and out of the cells—can cause disease in humans. Researcher: Louis J. Ptáček. www.hhmi.org/news/ptacek3.html

Motor neurons need vitamins  Spinal muscular atrophy (SMA), the most common genetic cause of infant mortality, may be exacerbated by insufficient amounts of folic acid and vitamin B12 in the diet. The HHMI investigators who made this discovery plan to collaborate with clinical scientists to explore whether vitamin therapy might offer some relief from the muscle weakness and wasting experienced by SMA patients. Researcher: Gideon Dreyfuss. www.hhmi.org/news/dreyfuss2.html

Genes and benign tumors  Researchers have determined the normal role of two genes that are mutated in the inherited disorder tuberous sclerosis complex. Ordinarily, these genes, Tsc1 and Tsc2, help regulate cell growth and organ size; their protein products are likely part of the insulin-signaling pathway. These genes may offer a novel target for treatment of type 2 diabetes, as well as tuberous sclerosis complex, which causes widespread benign tumors in the brain, skin, lungs and kidneys. Researcher: Tian Xu. www.hhmi.org/news/xu2.html

Tracking forward motion  Researchers have distinguished some of the cues that the human visual system uses to estimate the speed of an approaching object. As the object gets closer, the visual system extracts information about its motion by estimating the rate of change in its size. Researcher: Eero P. Simoncelli. www.hhmi.org/news/simoncelli.html

Room for Improvement in Statin Drugs  Researchers have provided the first molecular look at how a popular family of cholesterol-lowering drugs does its work. They’ve captured images of the widely prescribed statin drugs, including Lipitor and Zocor, in the process of blocking cholesterol synthesis—and they see room for improvement.

Statins block the enzyme HMG-CoA reductase (HMGR) from grabbing hold of a molecule called HMG-CoA to begin cholesterol production. As a result, the cell suffers a shortage of cholesterol and compensates by importing ready-made cholesterol from the bloodstream. This, in turn, lowers cholesterol levels in the blood.

The scientists used x-ray crystallography to produce images of six different statins binding with HMGR. Although the statins have different shapes, they all imitate part of the HMG-CoA molecule, and trick HMGR into grabbing hold of the statin. This coupling twists the enzyme slightly out of shape, preventing it from forming its active site—the business end of the enzyme that binds with HMG-CoA. HMGR investigator Johann Deisenhofer at the University of Texas Southwestern Medical Center in Dallas and Eva S. Istvan, now an HHMI postdoctoral fellow at Washington University in St. Louis, published their findings in the May 11, 2001, issue of Science.

“This finding is important because it shows that the statins work by attaching themselves to an inactive form of HMGR,” says Deisenhofer. “That suggests that you can’t assume that a drug will have its effect by attacking the active form of an enzyme. You may have to design a drug that attacks the inactive form of the enzyme and prevents the enzyme from becoming active.”

The researchers also noticed that existing statins fail to block an additional region of HMGR, suggesting that the drugs might be improved to more tightly bind to the enzyme and further reduce its activity. Deisenhofer emphasizes, however, that tight binding to the enzyme may not be the whole story. Statins appear also to interact with other proteins, as evidenced by their effects on blood-vessel growth, bone formation and the immune system. www.hhmi.org/news/deisenhofer.html

—MARC KUSINITZ

A representation of part of the surface of HMG-CoA reductase (yellow and green) shows how one statin drug, simvastatin (purple), binds to the enzyme. The drug blocks the enzyme from becoming active and instigating cholesterol synthesis.
First-Line Virus Fighters

Researchers have discovered a sensing molecule on the surface of natural killer (NK) cells that enables them to battle viral infections. The finding is an important step in understanding innate immunity—how the body rapidly launches its first strike against invading pathogens before other components of the immune system can take action.

NK cells are lymphocytes best known for their ability to kill developing tumor cells. They have also been thought to count for their ability to kill developing tumor cells. They have also been thought to count—herpesvirus that infects mice). The researchers then studied the immune response of the BXD-8 strain of mouse, which lacks only the Ly-49H receptor on NK cell surfaces. Without this receptor, the mice were susceptible to murine cytomegalovirus. In addition, when Ly-49H was inactivated in mice that possessed the receptor, the mice died, unable to control the virus. These studies provided key evidence that the Ly-49H receptor sparks the NK cells’ attack against the virus.

“These findings strongly suggest that NK cells have a specific role in immunity that was not previously known,” says Yokoyama. “NK cells apparently use Ly-49H to recognize something on the membranes of cells infected with murine cytomegalovirus and initiate an immune response that destroys those cells. This further implies that NK cells may use this receptor or others to recognize and attack other infections.”

Basic understanding of NK cell activation could lead to better treatments, especially for people with AIDS and others with weakened immune systems who are highly susceptible to viral infections.

—MARC KUSINITZ
May I Take Your Mouse Order, Please?

It’s not quite as routine as ordering a magazine or a bouquet of flowers, but the process of buying specialized mice for experiments in genetics and related fields has become commonplace. The Jackson Laboratory, which runs the world’s largest mouse repository, supplies approximately 2 million mice each year to universities, medical schools and research laboratories.

The not-for-profit institution in Bar Harbor, Maine, also has its own research program, whose investigations range from diabetes to sleep disorders, and it offers a variety of training programs for visiting scientists. It remains best known, however, as the place that researchers call to get mice bred with a vast array of genetic variations—more than 2,500 strains. Already the most widely studied research model for human diseases and disorders, the mouse has become even more essential since scientists developed techniques to “knock out” or otherwise modify specific mouse genes, most of which have close human counterparts.

Researchers interested in genes connected with cancer, for instance, can find hundreds of mouse strains that might be useful. Stock number 002265 is a mouse that lacks the Bcl2 gene involved in leukemia and other cancers, a characteristic that makes it useful in the study of cancer itself or in learning about underlying biological processes such as programmed cell death. Other mouse strains related to cancer are so numerous that the lab’s 535-page catalog lists them under “Oncogenes,” “Growth Factors” and similar categories. The catalog also offers mouse models for numerous other disorders. Scientists at the Jackson Lab, like Simon John, an HHMI investigator who studies the genetics of glaucoma, and at numerous other institutions supplied the strains to the laboratory for breeding and distribution to the scientific community.

The lab distributes mouse DNA as well as live mice, and it is assessing the feasibility of shipping frozen mouse embryos or sperm that researchers could use to build their own mouse colonies. All materials undergo rigorous quality-control testing to ensure health and genetic purity. The lab also maintains a comprehensive database about mouse genetics, which is available through its Web site, www.jax.org. HHMI has provided more than $5 million to help the Jackson Laboratory meet the growing demand by researchers for genetically altered mice.

Scientists from around the world can order mice by phone, fax or mail, or online at jaxmice.jax.org. They can use credit cards and other forms of payment but encounter some interesting restrictions. Some mutant mice, for instance, must travel with harder mice, called shipping companions, to survive the stress of shipment. Scientists also need to provide advance notice if they want pregnant females, which do best if shipped between the 11th and 15th days of pregnancy.
Inventory control is a challenge for the lab, which provides colonies to match demand whenever possible but sometimes must restrict quantities of certain strains. Many factors affect the availability of a strain, especially when it is first released for distribution. These include how well the strain breeds, the size and viability of typical litters and whether one gender is preferred as a research model. For example, both of these mouse strains are useful in cancer research. Scientists can order only as many as 10 of each sex per month of the first strain, but they can order 25 or more per month of each sex of the second strain.

Some mice, like the first one described here, have genetic mutations that occurred spontaneously in nature. Others, like the second entry, have mutations that researchers created deliberately.
"Home-Grown" Proteins Build Synaptic Strength

Many neuroscientists believe that synaptic strength—the ease with which a signal traverses the synapse, which is the gap between two neurons—plays a central role in learning and memory. When a music student first reads “C major 7 chord” on a score, for example, it takes considerable effort to strike the keys correctly on the piano. After reading and playing the chord 500 times, however, the neural pathway that translates a visual image into a musical concept and then into a fingering pattern becomes established, enabling the fingers to strike the keys faster and more accurately. At the molecular level, the “wearing in” of this neural pathway translates into the building-up of synaptic strength and a more powerful signal.

The cell biology of this process has posed a paradox, however. To build synaptic strength, new proteins are needed immediately at the dendrites, the synapse-forming branches emerging from the body of the neuron. These proteins must be transported from elsewhere because, according to conventional wisdom, they are made in ribosomes inside the cell body, not in the dendrites. If so, how are the proteins transported to the correct synapse quickly enough to account for learning?

Erin M. Schuman, an HHMI investigator at the California Institute of Technology, has investigated this apparent anomaly and now offers another view. “Since we know that all synapses are individual, protein would have to be shipped to each, and that would be a traffic nightmare,” she says. Instead, Schuman concludes that dendrites use a “home-grown-protein” approach that is considerably swifter and surer than the problematic “manufacture-and-ship” tactic. Using a technique that she invented, she has shown that dendrites make the proteins themselves, when and where they’re needed, rather than import the proteins from the cell body.

Proving this hypothesis required considerable experimental dexterity. Schuman’s studies used green fluorescent protein (GFP), derived from jellyfish, to signal that protein synthesis was occurring. Her team built a “reporter” molecule containing the GFP messenger RNA (mRNA), which carries the DNA’s instructions for synthesizing proteins in the ribosomes. The team flanked the GFP with two key elements: one that causes the reporter mRNA to travel from the cell body (where it is made) to the dendrite, and another that responds to the neuron’s signal to “make protein” by regulating the synthesis of GFP on the mRNA template.

To start the protein synthesis, Schuman used a growth factor called BDNF. After a few minutes, reporter protein levels in many parts of the dendrites did rise, as shown by the increased brightness of GFP under a light microscope.

To prove that the proteins were being synthesized in the dendrites, Schuman and her graduate students Bryan Smith and Girish Aakalu tried several hundred times to keep dendrites alive after being severed from the cell body. The neurons came from the rat hippocampus—a part of the brain that is essential for learning and memory. Roughly a dozen dendrites survived, and each showed protein synthesis after stimulation with BDNF, indicating that the synthesis must have occurred in the dendrite rather than the cell body.

The data were intriguing. For one thing, throughout the experiment, protein synthesis occurred at the same spots within the dendrite, suggesting that locally synthesized proteins might be delivered to only a few synapses. These experiments, Schuman stresses, show the simplicity of a process that’s essential to learning and memory. “Our data show that protein is made right in the dendrite. This means that an activated synapse need not send a signal to the cell body to make new protein and ship it back. There is a local control mechanism. The events at the synapse are in very close proxim- ity to the protein-synthesis machinery.”

In practical terms, Schuman notes that the protein involved in fragile X syndrome, a genetic abnormality that causes mental retardation, is an RNA-binding protein found in dendrites. “Understanding dendritic protein synthesis may help us understand, somewhere down the line, what goes wrong with fragile X syndrome,” Schuman says. If that hope is not realized, there is still a broader benefit: Every step toward understanding the transmission of nerve signals across synapses produces a clearer picture of learning and memory.

— DAVID TENENBAUM
Protein synthesis along dendrites, seen at high magnification. Upper: part of a dendrite before stimulation with BDNF. Lower: same dendrite after stimulation. The location of synthesis does not change, but it intensifies after stimulation, as shown by the transition from blue to red and the appearance of blue in the dendritic spines.

On a single, severed dendrite, protein synthesis lasts hours after the BDNF stimulus. The five colored trails indicate protein synthesis at 30-minute intervals after stimulation. Distance from the cell body (bottom scale) shows synthesis taking place in the same locations—possibly at synapses.

Dendrites before (left) and 120 minutes after (right) BDNF treatment. Arrow shows where the dendrite was severed from the cell body.
In a molecular choreography of great precision and timing, young neurons are alternately attracted and repelled by different molecules as they wend their way toward targets in the brain and spinal cord. Disruption of this delicate process and the consequent misrouting of neurons can have catastrophic consequences—schizophrenia and autism, for example.

Despite the daunting nature of the task, researchers are making remarkable progress in understanding how trillions of neural circuits are formed in the mammalian brain, especially how different types of molecules alter the trajectory of axons. Located at the tip of neurons, axons contain all of the “hardware” needed to pilot growing neurons through the nervous system. Axons are stippled with receptors that enable them to sense and respond to molecular guidance cues. If a receptor binds to an attractant molecule, for example, the axon is pulled toward a target. Alternately, if the receptor binds to a repellent molecule, the axon is pushed away.

Understanding how neurons are pushed and pulled toward their final destinations is time-consuming work. In addition to being tedious, the assays and experiments used to discover axon guidance factors in mammals are costly.

In an effort to speed things up and reduce expenses, a team of researchers has developed a faster screening method to identify genes that guide neural wiring in the mammalian brain. HHMI investigator Marc Tessier-Lavigne at the University of California, San Francisco, William C. Skarnes at the University of California, Berkeley, and their colleagues unveiled their new technique and discussed some of its early applications in an article published in the March 8, 2001, issue of the journal Nature.

“Until now, we’ve gone about trying to identify brain-wiring mechanisms one guidance event at a time,” says Tessier-Lavigne. It took him and his colleagues more than four years, for example, to identify the netrins, a small family of axon-guidance molecules. With the team’s new “gene-trapping” technique, however, researchers can cast a much wider net to study many genes simultaneously and then determine the effects of mutations in those genes.

The improved gene-trapping technique described in Nature was built on two generations of gene-trap technology. In the original method developed in the 1980s, genes in mouse embryonic stem cells were mutated by randomly inserting a genetic marker with two components: the first, a gene that produces a blue color in cells carrying it; and the second, a drug-resistance gene. Thus, the embryonic stem cells with insertions in genes (rather than insertions in the non-gene components of the cell’s DNA) could be isolated by applying a drug to weed out those cells that did not take up the drug-resistance gene. The desired cells could also be distinguished by their blue color.

In 1995, Skarnes refined the gene-trap technology by including a gene segment that would activate the blue marker only if the DNA had fused itself into a gene for a secreted protein or membrane protein, such as a receptor. This refinement, called a secretory trap, enabled the researchers to narrow the list of trapped genes to those coding for signals or receptors involved in axon guidance.

“The secretory trap is a nice bonus,” says Tessier-Lavigne, “because we can focus on exactly the kinds of molecules we’re interested in—mainly receptors and ligands (the molecules that bind to receptors). These genes represent a small fraction of the genome, and this trap concentrates on just that fraction.”

Even with Skarnes’s improvements, the gene trap needed additional modifications before it was ready to fish out axon-guidance molecules. “In early studies, we found that mice with ‘trapped’ neuronal genes didn’t show proper axon staining because the blue marker got trapped in the neuron’s cell body,” Tessier-Lavigne says. This poor staining made it more difficult to explore the effects that specific gene mutations had on brain wiring.

In the work published in Nature, Tessier-Lavigne and his colleagues fixed the staining problem by inserting an additional marker, PLAP (placental alkaline phosphatase), in the gene-trap system. If PLAP is present, axons are stained purple. “This modified gene-trap strategy enabled us to...
mutate a gene for a guidance-molecule receptor, and by including the PLAP marker, we were able to see the purple-stained, altered neuronal wiring and rapidly assess what had gone wrong with the wiring process,” says Tessier-Lavigne.

Using the modified technique, the researchers produced 46 lines of mice with defined defects in axon-guidance molecules. “With these mice, we have proven that we can trap genes that are specifically expressed in the nervous system,” he says. “We can also see discrete patterns of axonal labeling, and we can uncover mutant phenotypes.”

Studies on two of the genes—Sema6A and EphA4, known to be involved in neural development—demonstrated that the trapping method could also identify axon-guidance mutants. “With EphA4, we showed that we could reconstruct a known mutant and use it to learn additional information about where the gene is expressed and how the mutation alters brain wiring,” says Tessier-Lavigne. “And with Sema6A, we showed that we could use the technique to discover a new mutant that affects only a small subset of axons in an otherwise normal nervous system.”

These results suggest that the new gene-trapping method may enable rapid progress in understanding how neurons wire the brain. “Neurons that project their axons to a particular area follow a code of transcription-factor activation that presumably activates genes for surface receptors that, in turn, dictate what the axon does,” says Tessier-Lavigne. “We’re hoping that gene trapping can help identify an underlying receptor code by focusing very specifically on receptors involved in axon guidance and finding their expression patterns as well as their mutant phenotypes.”

To make these advances widely available to researchers studying the normal wiring pattern of the brain, Tessier-Lavigne and his colleagues are putting their gene-trap data on the Web at www.genetrap.org. The mutant mouse lines produced by this technique should also be of use to fellow researchers. “These mouse lines have very specific populations of axons that are labeled purple,” Tessier-Lavigne says. “In some cases it’s the first time that a marker has been identified for those axons, and those markers provide a valuable resource.”
How to ZAP the Signals that Lead to Rheumatoid Arthritis

For decades, physicians tended to treat rheumatoid arthritis conservatively, progressing carefully to the most powerful therapies. During the past several years, however, several new drugs have emerged that permit physicians to treat patients quickly and aggressively to help avoid crippling illness. They are using these new drugs, singly and in combination, to greatly ease the pain, swelling and stiffness that once seemed inescapable in a disease that affects more than 2 million Americans.

Andrew C. Chan, a rheumatologist who recently completed eight years as an HHMI investigator at Washington University School of Medicine in St. Louis, has treated many arthritis patients and thinks these advances are only the beginning. Chan and other researchers have determined in remarkable detail how a complex cascade of molecular events enables the immune system to recognize and attack foreign invaders. In rheumatoid arthritis and other autoimmune diseases, such as multiple sclerosis and lupus, the immune system mistakenly launches an attack against the body it is supposed to protect. By learning precisely how the process works, with one molecular event triggering the next, Chan hopes to find ways of shutting it down in these autoimmune disorders.

These illustrations—part of a new animation at HHMI’s BioInteractive.org—show some of what Chan and others have discovered about this signaling cascade, which starts with a T cell recognizing what seems to be a foreign antigen and ends with the T cell replicating in huge numbers. At each step along the way, there’s a flurry of activity. In the beginning, for example, enzymes in the T cell’s cytoplasm move to docking sites near the cell’s membrane, where they start interacting in a precise pattern. Chan and his colleagues have shown that one enzyme, ZAP-70, plays an especially important role in this process. Blocking the action of ZAP-70 with new drugs, they hope, may prevent the proliferation of T cells that causes the joint inflammation and other debilitating effects of rheumatoid arthritis.
The green circles, or IP3, shown in the last drawing of the previous sequence have now made their way to the T cell's endoplasmic reticulum, which they signal to begin releasing calcium. Along with calmodulin and calcineurin, the calcium triggers a transcription factor, NF-AT, to enter the cell's nucleus. NF-AT and other transcription factors induce a gene within the nucleus to produce the protein IL-2, which then leaves the T cell.

Multiple copies of the IL-2 protein, shown as blue ovals, bind to receptors on the T cell's surface, causing the cell to start replicating.

With the IL-2 proteins binding to its surface, the T cell begins reproducing in large numbers. The process is usually beneficial, enabling the immune system to build up its forces to fight deadly invaders. In the case of rheumatoid arthritis, however, the proliferating T cells harm the body itself—which is why Chan and others seek to block the signaling process.

A new animation at HHMI’s BioInteractive.org shows in detail the normal T-cell signaling cascade that is activated inappropriately in autoimmune diseases such as rheumatoid arthritis. The Web site also features “virtual laboratories,” click-and-learn demonstrations, scientific lectures and other online learning tools.
These images by Erin Schuman and colleagues show proteins being synthesized at dendrites separated from the cell body (at black squares). They indicate that neurons can produce proteins right where they’re needed for learning and memory, instead of ferrying them from the cell body to distant dendrites. The lower image shows increased protein production after addition of a growth factor. Story on page 40.