On Human Terms

» A small—some say too small—group of physician-scientists believes the best science requires patient contact. By Marlene Cimons

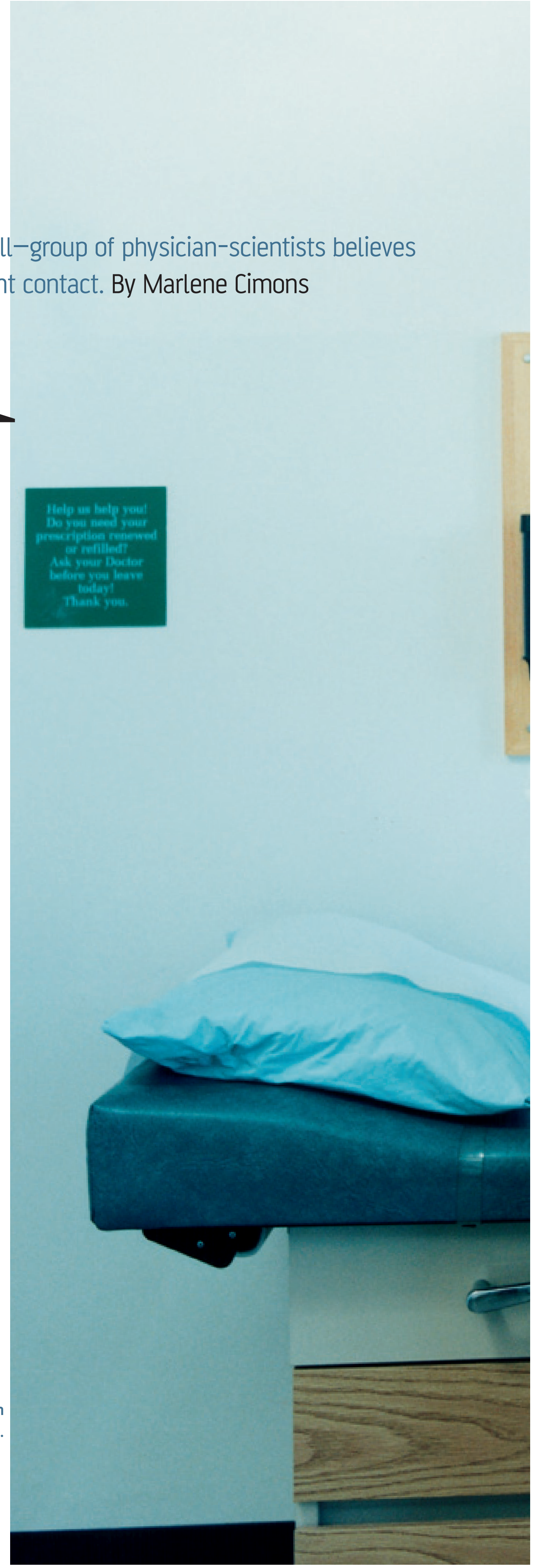
ONE DAY IN 1994, A MAN APPEARED at the Massachusetts General Hospital infectious-diseases clinic and offered himself up for research. A hemophiliac, he had been infected with HIV since 1978, but, remarkably, he had never shown any signs of AIDS. "I feel great," he told the doctors. "You might want to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

Indeed, Bruce D. Walker recalls, "We started studying him like crazy."

The encounter ultimately produced a wealth of results, chief among them the discovery of a unique immune-system response that's missing in patients who suffer from progressive HIV disease. The findings, published in 1997 in the journal *Science*, represented "the first indication that people could mount a successful cellular immune response against HIV," says Walker.

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

"Mice are not humans," says Walker, one of a dozen physician-scientists recently chosen for appointment as new HHMI investigators (see page 18). "That's the crux of the issue. All of our work on this immune response came from a clinical observation that never would



KATHLEEN DOOHER

» Interacting with patients has enabled Bruce Walker to ask research questions that probably wouldn't have come out of lab work alone.

have happened if someone doing basic lab research didn't have a chance to interact with a patient."

DIFFICULT CHOICES

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

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

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

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

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

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

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

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

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

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

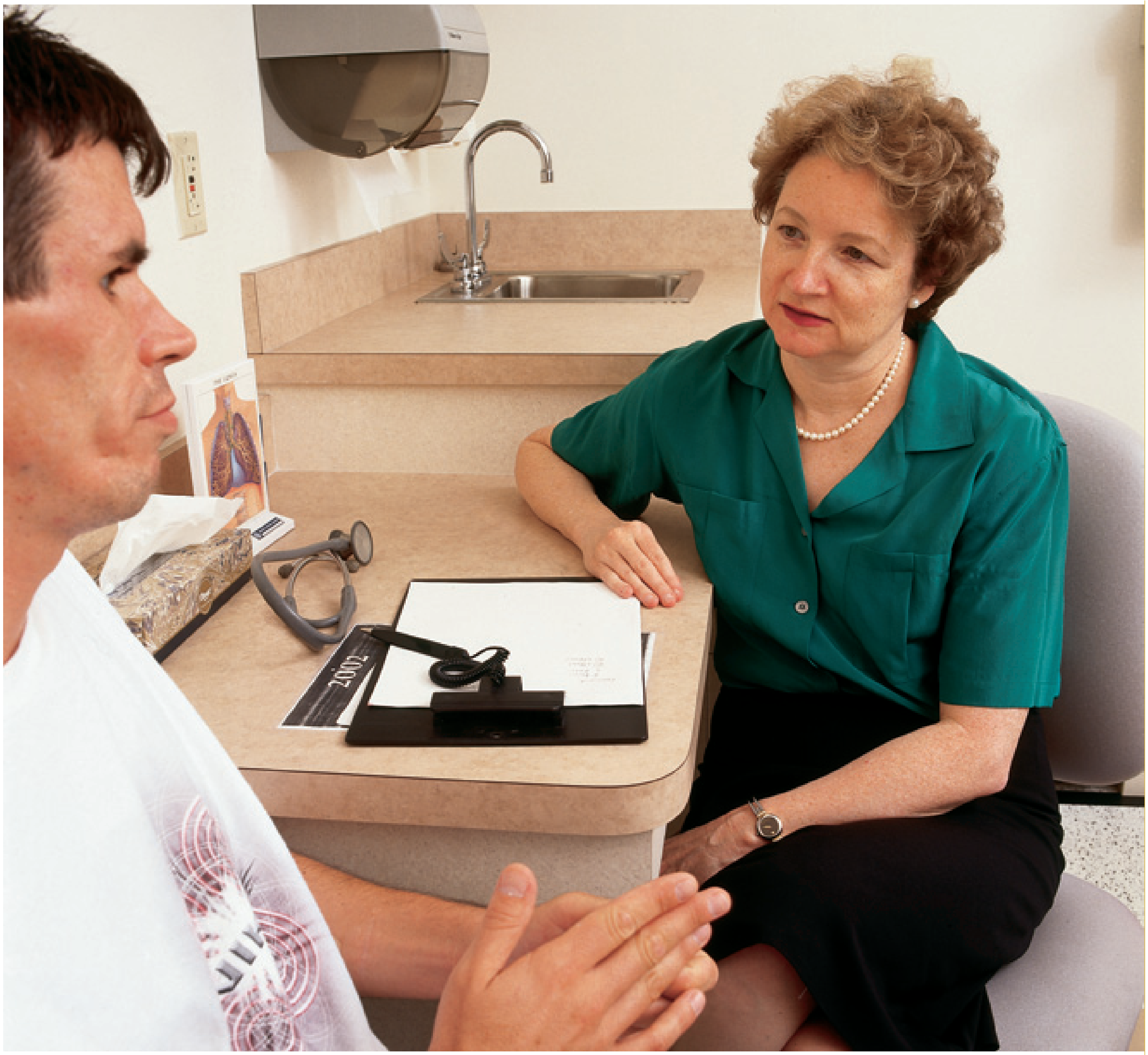
As a result, researchers often are forced to make difficult choices. Vogelstein, trained as both a physician and a scientist, made the decision to devote his time to the lab. "My research is centered on patients, but I don't see them," he says. "Oncology is one of those disciplines where it is difficult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

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

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

A Physician-Scientist by Any Other Name

The term physician-scientist can mean different things to different people and covers a relatively wide range of researchers. There are those with medical degrees who work exclusively in the lab, never seeing patients. Others may see patients once a week in a clinic or monthly on rounds, but they don't necessarily study patients as an integral part of their research. The final group conducts research—which includes lab work—specific to patients, and their contact with the patients often stimulates the research questions they ask. The majority of the 12 new HHMI investigators fall into this latter group of clinical investigators, or patient-oriented researchers. More often than not, however, distinctions among the three groups can be blurred and imprecise.



DAVID GRAHAM

» Katherine High, with hemophilia patient Leonard Selvoski, studies the molecular basis of blood coagulation.

can approach clinical problems clearly." She recalls a patient treated with the blood thinner coumadin after heart surgery. Bleeding problems led to several hospital visits and lab tests, none of which implicated the drug. Finally, High used an assay that showed very low levels of factor IX, a blood-clotting factor—only when the patient took coumadin. She eventually showed that the patient had a mutation in the gene for factor IX that made him extraordinarily sensitive to the blood thinner. The patient is now kept on low levels of coumadin and the bleeding has stopped. Additional lab experiments indicated just how the mutation caused sensitivity to the drug. The same mutation has since been observed in other patients with sensitivity to coumadin.

A SATISFYING BALANCE

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

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

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

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

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

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

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

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

Moreover, exposure to both disciplines gives physician-

Broadening the Research Base

HHMI has selected 12 new investigators who conduct patient-oriented research. These physician-scientists have made important contributions to understanding health problems such as cancer, AIDS and cardiovascular disease. President Thomas R. Cech says he hopes the group will "find new ways to translate basic science discoveries into useful therapies for patients."

They will join 324 HHMI investigators across the United States, the majority of whom focus on basic research directed toward understanding the genetic, molecular and cellular bases of human disease.

ROBERT B. DARNELL, M.D., PH.D., *The Rockefeller University, New York City.* Darnell studies degenerative brain disorders that are provoked by an autoimmune response to certain cancers.

BRIAN J. DRUKER, M.D., *Oregon Health and Science University, Portland.* Druker's search for a molecule that would block the action of a tyrosine kinase that promotes formation of chronic myelogenous leukemia and gastrointestinal stromal tumors led to STI-571, commonly known as Gleevec. Druker played a key role in shepherding the drug through clinical trials in patients.

TODD R. GOLUB, M.D., *Dana-Farber Cancer Institute, Boston.* Golub and colleagues are developing diagnostic and prognostic tests for childhood leukemia, devising strategies for predicting responses to chemotherapy based on gene expression patterns and exploring novel treatment strategies based on analyses of a patient's genome.

KATHERINE A. HIGH, M.D., *The Children's Hospital of Philadelphia.* High studies the molecular basis of blood coagulation and has showed that gene therapy can achieve long-term improvement in dogs with hemophilia. Her team has begun clinical studies in patients with severe hemophilia B.

HELEN H. HOBBS, M.D., *University of Texas Southwestern Medical Center at Dallas.* Hobbs and colleagues are studying how abnormalities in the processing of dietary lipids cause human diseases. She is also principal investigator for the Dallas Heart Disease Prevention Project, studying 3,000 randomly selected individuals and their behavioral, environmental, metabolic and genetic risk factors for cardiovascular disease.

BRENDAN H.L. LEE, M.D., PH.D., *Baylor College of Medicine, Houston.* Linking studies on mammalian tissue and organ development with clinical research in patients with skeletal malformations, Lee hopes to understand the consequences of gene mutations on craniofacial/limb development. He and colleagues are also investigating gene-nutrient interactions in patients who have disorders in the urea cycle, which can lead to brain damage and death.

EMMANUEL J. MIGNOT, M.D., PH.D., *Stanford University School of Medicine, Palo Alto, California.* Mignot and colleagues are studying narcolepsy, a severe sleep disorder that causes the afflicted to fall into a deep sleep with little or no warning. He is investigating whether narcolepsy is exacerbated by an autoimmune response against specific cells in the brain.

CHARLES L. SAWYERS, M.D., *Jonsson Comprehensive Cancer Center, David Geffen School of Medicine at the University of California, Los Angeles.* Sawyers collaborated with Brian Druker to design and conduct the clinical trials of STI-571 for treatment of chronic myelogenous leukemia and recently showed how resistance to STI-571 occurs. He is now working to identify the molecular changes that accompany a form of brain cancer called glioblastoma as well as prostate cancer.

ROBERT F. SILICIANO, M.D., PH.D., *The Johns Hopkins University School of Medicine, Baltimore.* Siliciano is searching for ways to prevent or treat HIV infection. He and colleagues have shown that HIV-1 can persist in a silent form, even in patients on effective scientists "a sense of how each world exists," says Matthew L. Warman, an HHMI investigator at Case Western Reserve University School of Medicine in Cleveland. "A lot of clinicians who never spend time in a basic science lab don't appreciate how experiments are performed—what types of samples are needed, what kind of information needs to accompany the samples," he adds. "And people who live entirely in a lab do not understand the time and effort that goes into explaining to a family affected by disease the nature of scientific research."

Warman continues, "I am driven to live in both worlds and make connections that would be more difficult for people who live in only one world to make."

CLINICAL INTEREST AND INSIGHT

Brendan H.L. Lee, who studies skeletal development and metabolic diseases at Baylor College of Medicine in Houston, says that almost all physician-scientists must make a similar decision: to accept the notion that the practice of medicine cannot be divorced from the science of medicine. "For a physician-scientist, the approach to each patient needs to be similar to the approach to a scientific problem," he says.

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

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

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

Indeed, such an attitude goes to the very heart of the qualities common to those researchers who choose to practice their craft within these two disciplines. "The first is a great curiosity for understanding why something happens," says Baylor's Lee. "The second is a great need to use this information to make a difference in the lives of people." H

antiretroviral therapy. They hope to understand how it manages to do so, and thereby design a means to eradicate the virus.

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

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

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

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

From left (row 1): Katherine A. High, Emmanuel J. Mignot, Brendan H. L. Lee, Charles L. Sawyers; (row 2): Robert B. Darnell, Bruce D. Walker, Helen H. Hobbs, Todd R. Golub; (row 3): Robert F. Siliciano, Edwin M. Stone, Christopher A. Walsh, Brian J. Druker.

PAUL FETTERS