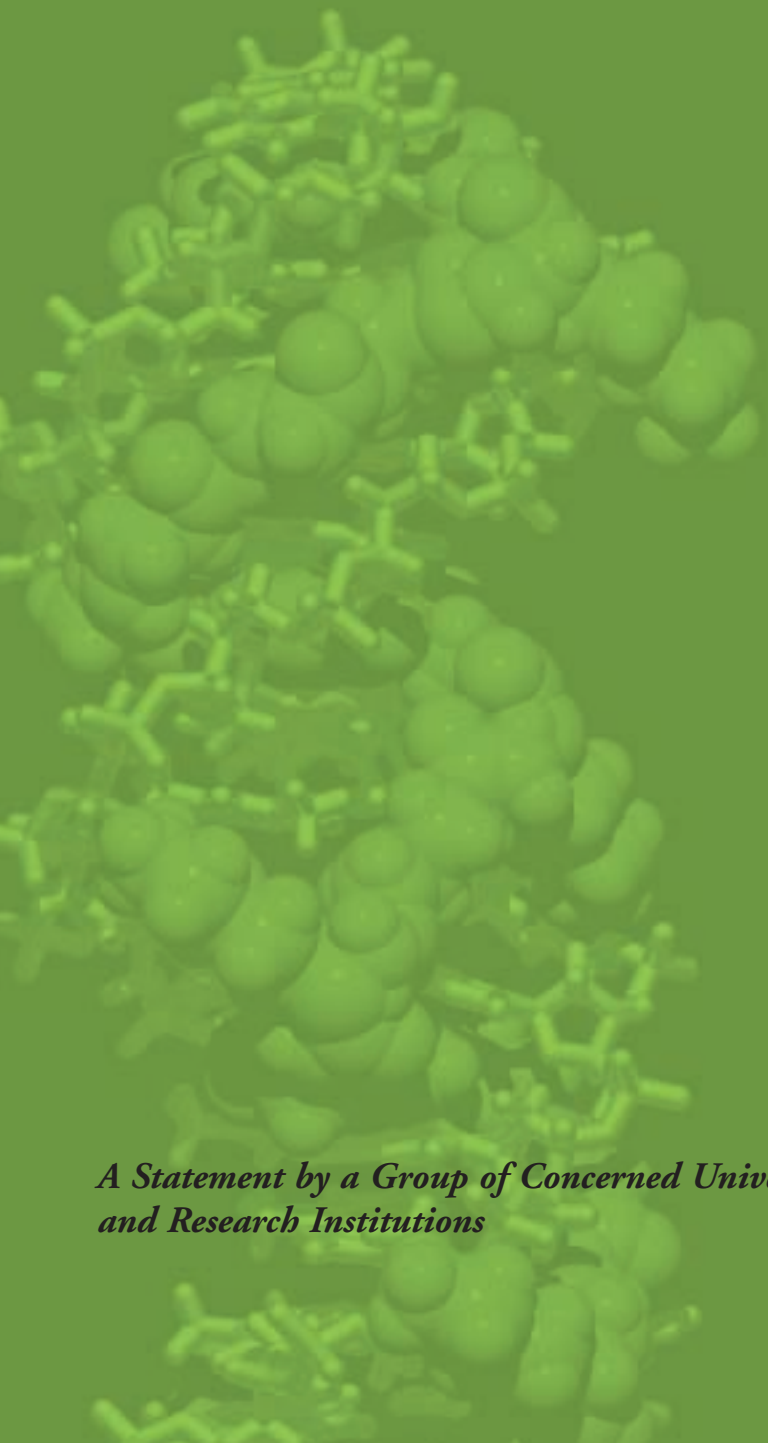
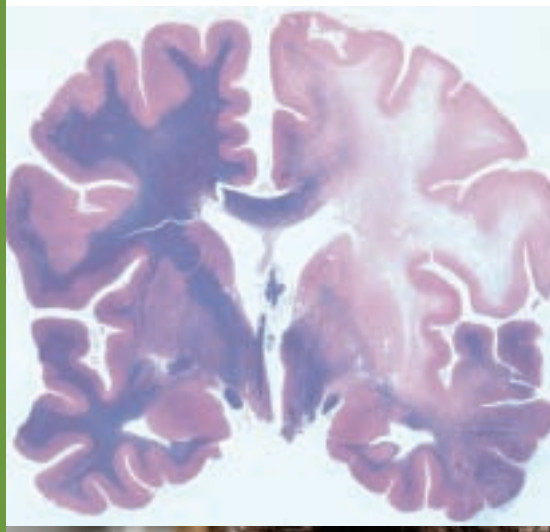
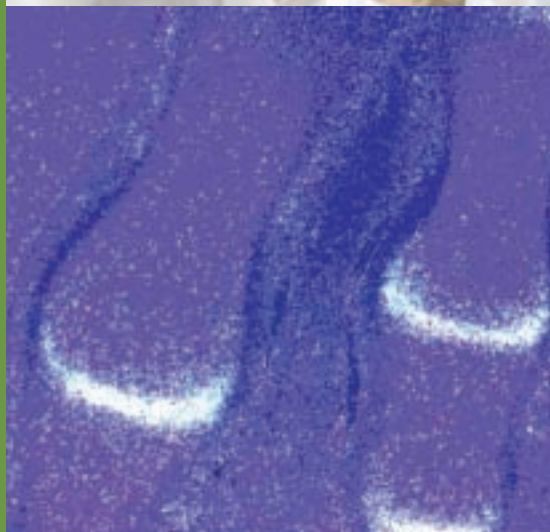
Within Our Grasp—Or Slipping Away?

Assuring a New Era of Scientific and Medical Progress







A Statement by a Group of Concerned Universities and Research Institutions

"Before the human genome was sequenced, researchers would take a single protein and study it intensely. It was like studying a single screw from an airplane to figure out how the airplane flies. With the genome sequence and new tools, we now have the complete parts list and can begin to understand the collective behavior of the components. There's no way we could've done that previously."

Vamsi Mootha, M.D.
Massachusetts General Hospital and Harvard Medical School

What Will it Take to:

- Prevent the ravages of Alzheimer's disease?
- Effectively target cancer?
- Stop the twin epidemics of obesity and diabetes?
- Heal a severed spinal cord?
- Fight emerging infectious diseases?
- Maintain the United States' global leadership in biomedical science?

The singular answer to these questions is a strong and vibrant program of basic research. This research underpins all past, and potential future, medical breakthroughs. The cumulative results have created an explosion of knowledge and technology that promises to further transform medicine and health.

The federal government's National Institutes of Health (NIH) funds this research, conducted in university and other laboratories nationwide. The results are rigorously peer-reviewed and freely available. Private entities cannot replace this public investment, given their understandable focus on applied research.

But today, flat funding of the NIH, combined with inflation, is eroding research budgets. Scientists are being forced to downsize their laboratories and abandon some of their most innovative and promising work. These conditions may also be putting at risk a generation of young researchers.

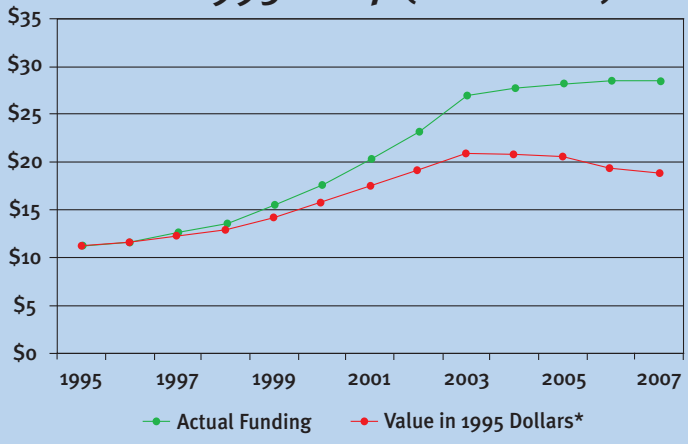
This funding slowdown comes at a time of escalating threats to human health. New diseases, such as severe acute respiratory syndrome (SARS), arise unexpectedly. Pandemic influenza is a real possibility, and HIV continues to spread worldwide. Obesity is a problem of national and global proportions, and bioterrorism is more than a theoretical threat.

The implications are far-reaching for science, medicine, the economy, and U.S. leadership in biomedical science. This looming crisis of diminished resources and research can be averted, however, and the time is now.

"The biomedical research effort in the United States has far exceeded that in any other country—largely due to the steady funding of the NIH research grant program. But we are beginning to lose our competitive edge because of the funding crisis at the NIH. Once the impetus is lost, I fear it will be difficult to reverse."

M. Daniel Lane, Ph.D.
The Johns Hopkins University School of Medicine

NIH Funding History
FYs 1995-2007 (in billions)



Source: National Institutes of Health
*Reflects inflation based on the Biomedical Research and Development Price Index

Medical Breakthroughs We Live By

Drugs that prevent certain breast cancers by blocking estrogen receptors, treat depression by regulating brain chemicals, and control HIV—all began from seemingly esoteric discoveries of basic research. Such discoveries have made the difference between life and death for many. And the average American is living six years longer than in the 1970s. Here are some recent medical breakthroughs we live by:

HIV is no longer an automatic death sentence. Since identifying HIV in 1983, scientists have deduced the entire life cycle of the virus and probed its structure. As a result, today there are more than 20 licensed drugs and a diagnostic blood test, most of these developed in the past decade. Many who would have succumbed to the disease now lead productive lives.

Heart disease deaths are down 63%, and deaths from stroke are down 70% from the 1970s. Ground-breaking laboratory research has made a huge difference in reducing mortality. It has led to the development of cholesterol-lowering therapies; the issuance of evidence-based guidelines for management of blood pressure; and a new understanding of diabetes as a vascular disease.

Stopping childhood killers. Rotavirus, a diarrheal disease that kills 600,000 children a year worldwide, is now being stopped with two safe and effective vaccines, one of which was approved in 2006 in the United States. A vaccine for *Pneumococcus* became available in 2000. That bacterium causes pneumonia, meningitis, and acute ear infections and kills up to 1 million children worldwide every year.

Predicting risk for type 1 diabetes. Researchers have learned volumes about the biology underlying autoimmune, or type 1, diabetes, and they can now predict who is at high risk. This knowledge allows diagnosis and treatment of diabetes before life-threatening complications can develop. Very recently, researchers found a region of the human genome that accounts for half the increased risk for the disease.

Preventing cervical cancer. In 2006, women gained a potent weapon against cervical cancer: a vaccine that can stop the human papillomavirus (HPV), the major cause of this deadly cancer that claimed more than 200,000 lives worldwide last year.

Public-private partnerships. Between 1998 and 2005, U.S. research institutions brought 3,114 new technologies to market, often in partnership with private industry.

"Physicists, chemists, mathematicians, and biologists are integrating their expertise, devising totally unique approaches and technologies. We're going to be able to probe diseases in ways that were unfathomable to us."

Joan Brugge, Ph.D.
Harvard Medical School

"I do science because I believe I can better the lives of patients.... Have you seen the bellies of patients who inject themselves with insulin? Or the skin of women with multiple sclerosis? They have so much scar tissue that each new injection is terribly painful. We owe it to our patients to come up with solutions."

Nicholas Peppas, Sc.D.
The University of Texas at Austin

"The doubling brought in a cohort of research 'baby boomers.' These new investigators suddenly have to compete heavily against each other and against senior investigators for grants. Many of them are leaving. This is a crisis for the research community. What is going to happen to the future of health research in the U.S?"

Lee Riley, M.D.
University of California, Berkeley

Revolution in Science and Medicine

From statins that lower cholesterol and reduce heart attacks, to targeted treatments for cancers, the knowledge and technology generated by NIH-funded research gives rise to the vast majority of new medicines. This vibrant government-university partnership received a crucial boost between 1998 and 2003, when Congress doubled the NIH budget and set a course for far-reaching advances in health.

The new fields of genomics and proteomics blossomed, enabling scientists to probe biological phenomena beyond reach just 10 years ago. Scientists have now identified nearly all of the 25,000 human genes. This genetic code reveals the instructions that create and maintain human life, and errors that can lead to disease. Scientists have discovered more than 1,800 disease-causing genes.

Using high-throughput technologies and powerful imaging techniques, scientists are also identifying the hundreds of thousands of human proteins that do the work of the body. Together, these advances are uncovering core causes of disease and leading to better modes of prevention and treatment.

One discovery that has accelerated research is RNA interference (RNAi), a cellular mechanism that can shut off any gene. Its finding in 1998 launched a new field of research, and it may soon be used to treat conditions such as a form of age-related blindness and infection with hepatitis C virus. Its discovery through NIH-supported laboratories won the 2006 Nobel Prize for Physiology or Medicine—a mere eight years after the power of RNAi was uncovered.

Universities' own financial commitments have contributed to the fast pace of discovery. Medical schools invested $8.6 billion in laboratories between 1990 and 2002, and planned to spend an additional $9.5 billion between 2003 and 2007. The NIH's highly visible commitment to research helped universities raise funds from private donors. Together, the NIH and research institutions have created a remarkably productive research enterprise.

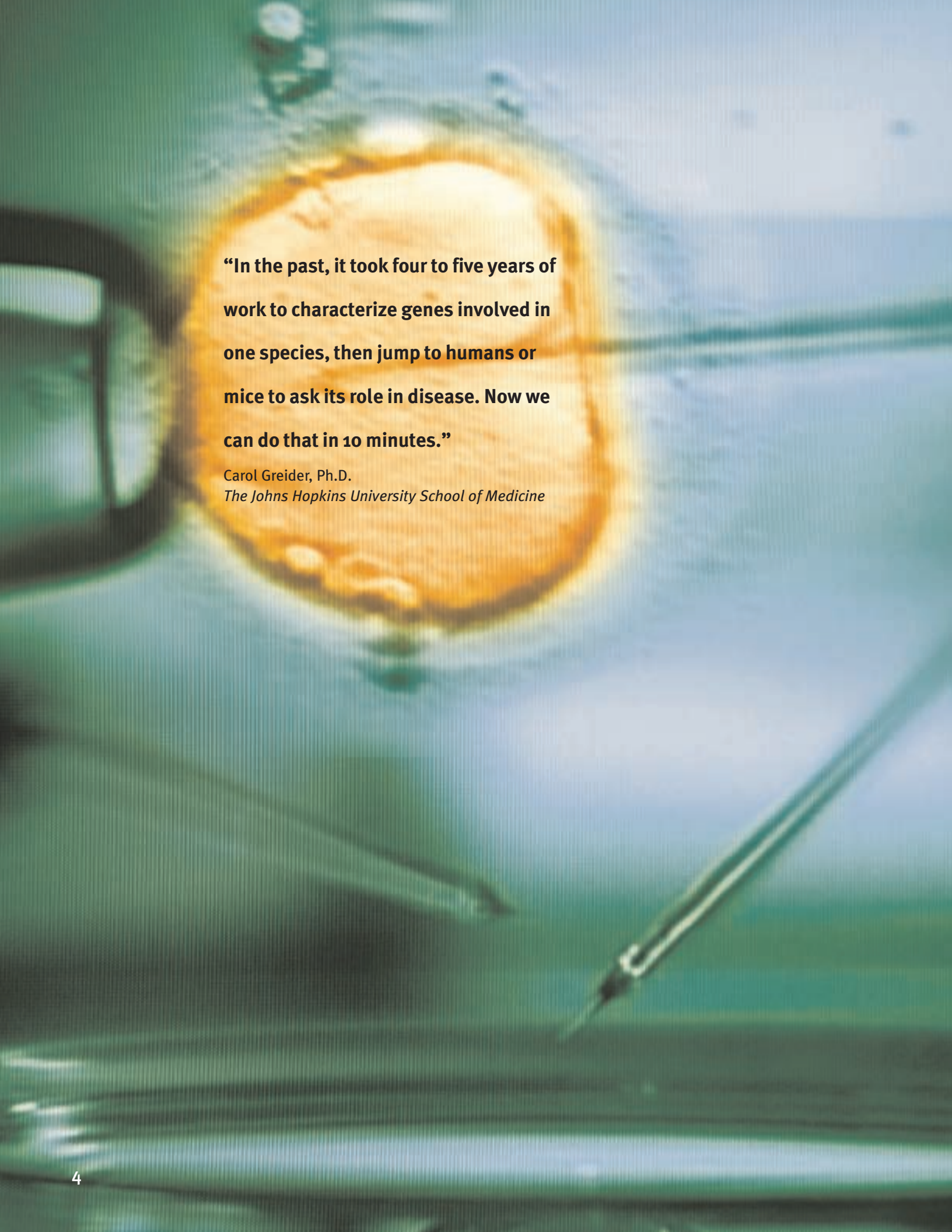
These advances can sometimes enable scientists to move more directly from basic research to addressing medical problems. One telling example is West Nile Virus, a potentially deadly infection. It appeared in New York in 1999 and by 2004 had reached California. Today, researchers are testing several vaccines, and scientists at Washington University in St. Louis have identified a powerful drug that is about to enter clinical trials. Working with genetically modified mice, they discovered an antibody that can clear the viral infection even after it reaches the brain, and then adapted the antibody to work in humans.

As a nation, we have banked much on basic research and reaped previously unimaginable rewards. The United States has a cadre of talented researchers who have the tools, knowledge, passion and drive to continue to unravel the persistent mysteries of life and thus improve human health.

But the full benefits of these national investments cannot be realized as long as funding for basic biomedical research remains stalled. Flat funding will delay promising research and discourage students from pursuing research careers. Consistent and robust funding of the NIH—that at the very least does better than inflation—is a must.

"The inherent risk taking—the driving engine for research—that's the heavier toll of flat funding. People don't take as many risks. You can't afford to swing the bat and miss too many times."

Jerry Chi-Ping Yin, Ph.D.
University of Wisconsin-Madison



“In the past, it took four to five years of work to characterize genes involved in one species, then jump to humans or mice to ask its role in disease. Now we can do that in 10 minutes.”

Carol Greider, Ph.D.
The Johns Hopkins University School of Medicine

Advances to Watch

Every research discovery has its own path. While the research that leads to discovery typically takes five to eight years, it can span decades. Still more time elapses between patenting a new pharmaceutical and making it available as a treatment.

But it is impossible to predict when a finding in basic research will revolutionize our ability to treat human disease. Such was the case with the discovery of the "restriction enzymes" that bacteria use to recognize and cut foreign DNA. "The discovery of these enzymes was the basis for the entire biotechnology industry," says molecular geneticist Jerry Chi-Ping Yin at the University of Wisconsin-Madison. "And no one could have foreseen it."

Today, scientists are using new research tools—such as high-throughput DNA sequencing and meticulous imaging techniques—to accelerate research. Researchers are probing the ingenious ways pathogens cause disease, how the immune system fights back, and ways genes and the environment interact in myriad other diseases. Progress is being made across the spectrum of biomedical science. Here are six areas—among many—to watch.

- Saving and Improving Memory
- Targeted Therapies for Cancer
- Outwitting the Agents of Infectious Disease
- Tackling Twin Epidemics of Obesity and Diabetes
- New Tools for Bioterrorism Preparedness
- Repairing Spinal Cord Damage

Richard Davidson

Brain Wave Patterns Lead to New Autism Treatment

Functional magnetic resonance imaging (fMRI), a technology that came to fruition in the last 10 years, has enabled Richard Davidson, at the University of Wisconsin-Madison, to detect distinct patterns of blood circulation in the brain associated with difficulty in regulating negative emotion. The pattern involves decreased activation in the brain's prefrontal cortex, and hyper activation of an area critical to fear, the amygdala.

Davidson recently found similar patterns in autistic children when they are exposed to innocuous stimuli, such as neutral faces. "We believe this leads to 'gaze aversion,' a key aspect of social withdrawal in autistic children," Davidson says. This finding has enabled Davidson's team to develop experimental "neurally inspired" behavioral treatments for children with autism.



Photos (left to right): Leon Thal, Jerry Chi-Ping Yin and Eric Kandel

New knowledge and technologies paving the way to better health:

Saving and Improving Memory

Alzheimer's disease has emerged as one of the most important diseases of aging in the 21st century, afflicting 4.5 million people in the United States alone, at a total cost of over $100 billion a year. A host of other diseases—from Huntington's disease to schizophrenia—also cause memory disorganization and loss. Scientists are discovering the molecular pathways of memory and using these findings to disrupt the disease process.

The True Culprit in Alzheimer's Disease

Aided by the genomic revolution, scientists have discovered several genes associated with Alzheimer's and are honing in on others. They have found that four overproduce amyloid, a small protein that accumulates in the brains of Alzheimer's patients.

"The NIH doubling allowed investigators to understand how amyloid is made and processed in the brain," says Leon Thal* at the University of California, San Diego. As a result, new drugs to block it are in clinical trials. Thal notes, however, that more than amyloid may be at the root of the disease, and, if that is true, "it would mean going back to the drawing board. It would be nice to have the funds to adequately explore alternate hypotheses."

Secrets of Memory Found in the Fruit Fly

CREB, a gene central to long-term memory formation, was identified in the fruit fly and later found in humans. Jerry Chi-Ping Yin, at the University of Wisconsin-Madison, tested its role in memory formation. Working with genetically modified fruit flies, Yin and his colleagues showed that disrupting CREB blocks the formation of long-term memories, and that boosting it speeds memory formation. Several biotechnology companies are now developing drugs to enhance memory. Yin notes that CREB-based drugs could also be used to treat mental illnesses through enhancing relearning and breaking the old associations at the heart of phobias and anxieties.

Relieving the Memory Disorganization of Schizophrenia

Schizophrenia affects 3 million people in the United States, usually strikes during adolescence, and remains a lifelong disability. There have been no major improvements in treatment of the disease for more than 30 years. This may soon change, however. Using a transgenic mouse, Eric Kandel and his colleagues at Columbia University discovered why existing drugs fail to improve the extreme memory disorganization of schizophrenia: they fail to reach secondary changes caused by the overexpression of a particular neural dopamine receptor during development. And it is those secondary molecular changes that Kandel's research is now targeting, holding out real hope for new, effective medicines.

"Microchip technology allows us to scan for SNPs—single changes in the human genome. Originally, one chip could scan DNA for several hundred SNPs. The next generation chip will cover 1 million SNPs. We are using this technology to scan DNA from 1,000 families with Alzheimer's, looking for common genetic patterns and the genes involved in late-onset Alzheimer's disease."

Leon Thal*, M.D.
University of California, San Diego

**Dr. Leon Thal, one of the world's leading researchers in Alzheimer's disease, passed away unexpectedly as this publication went to press.*

“We’d like to get to the point when an oncologist can go beyond X-rays, to use genetic analyses to determine the patient’s subtype of cancer and show which drugs will work. Then we can dial in the most appropriate treatment for that patient. This should be possible for almost every form of cancer.”

Richard K. Wilson, Ph.D.
Washington University in St. Louis

Photos (left to right): Richard K. Wilson, Joan Brugge, Ira Mellman and Carol Greider

New knowledge and technologies paving the way to better health:

Targeted Therapies for Cancer

Most current cancer drugs are toxic to all cells, and the outcome of therapy depends on which cells succumb more quickly—the cancer cells or healthy cells. But new "targeted" cancer therapies are beginning to replace such broad-brush approaches. Progress in understanding both the genetic causes of cancer and how cells regulate proliferation, survival, and metabolism are enabling interventions that target individual cancers without destroying healthy cells. Advances are coming on other fronts as well: from efforts to disrupt the molecular controls that allow a cancer cell's immortality, to blocking a tumor's nutrient and oxygen supply, or boosting the body's immune response to cancer.

Individualizing Therapy

By comparing the genomes of tumor cells and normal cells taken from the same person, Richard K. Wilson at Washington University in St. Louis is identifying the precise genetic malfunctions involved in individual cancers. He has already found genetic indicators that show which lung cancer patients will respond to certain therapies. Wilson's work is part of the NIH-supported Cancer Genome Atlas, which initially aims to identify all the genetic abnormalities in tumors of the ovary, lung, and brain (glioblastoma)—which collectively account for more than 245,000 U.S. cases of cancer each year.

Predictive Models for Blocking Cancer

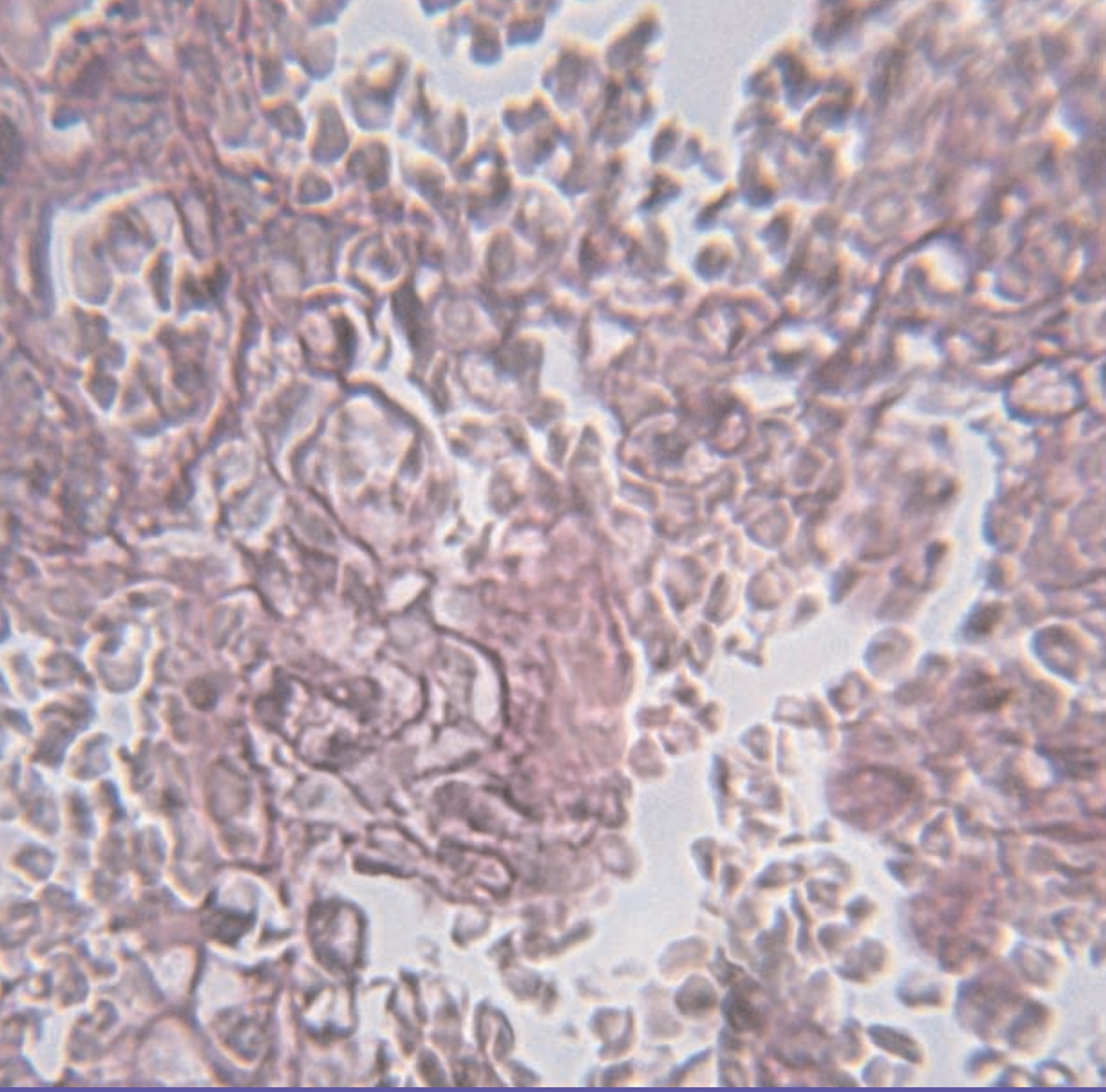
Joan Brugge, at Harvard Medical School, has developed a three-dimensional model of breast cells that organize into structures resembling breast glands. Using the model, which is much truer to life than work with a simple cell culture, Brugge is identifying pathways that tumor cells use to escape cell death and spread to adjoining tissue. She has found key cellular signals that set the stage for breast cancer. Her team is now using its model to test drugs that can block breast cancer from progressing beyond an early stage.

Overcoming a Failure of the Immune System

Ira Mellman, at Yale University School of Medicine, aims to boost the body's immune defense against cancer. His focus is dendritic cells, which are uniquely responsible for initiating basic immune responses. "How can we convince these purveyors of immunity, these dendritic cells, to take cancer cells more seriously?" asks Mellman. To do so, he is working on ways to trick the immune system into thinking of cancer cells as invading microbes. It's a different way to think about a vaccine, and is already being tested against some cancers.

Stripping Cancer of Its Fountain of Youth

Telomerase, an enzyme that helps maintain the ends of chromosomes, is elevated in more than 85% of all human cancers. It enables cancerous cells to divide indefinitely, making them virtually immortal. The discovery of telomerase was fortuitous. While seeking to understand how chromosomes stay intact, Carol Greider at The Johns Hopkins University School of Medicine and Elizabeth Blackburn at the University of California at San Francisco discovered telomerase in a single-cell pond organism. Greider has since engineered a "knockout" mouse that shows dramatic reductions in cancer when telomerase is absent. Now, several biotech companies are devising anti-cancer drugs to block telomerase.



“Whatever you do to understand how a bacteria causes a disease, helps to understand how to prevent it.”

Jorge Galán, D.V.M., Ph.D.
Yale University School of Medicine

Photos (left to right): Robert Siliciano, Lee Riley, Jon Clardy and Jorge Galán

New knowledge and technologies paving the way to better health:

Outwitting the Agents of Infectious Disease

Infectious diseases caused more than one-quarter of the 57 million deaths worldwide in 2002, and no country is safe from new or re-emerging diseases. In addition, growing resistance of pathogens to drugs that treat everything from HIV to childhood ear infections highlights the need for basic research into infectious diseases.

Flushing HIV Out of Hiding

HIV hides from the body's immune system. Robert Siliciano at The Johns Hopkins University School of Medicine discovered how: while in a latent state, HIV hides in resting CD4 cells of the immune system. There, it avoids the drugs being used to combat AIDS, making a complete cure impossible. These viral reservoirs harbor drug-resistant forms of the virus that can re-emerge at any time. Siliciano is now devising ways to "see" the genes of the hidden virus and, thus, determine its profile of drug resistance. This will enable personalized medical treatments to overcome resistant viruses.

Preventing Tuberculosis

Tuberculosis (TB) infects one-third of the global population, but only 10% ever develop active, contagious infection. With the help of recent advances in mass spectrometry and animal models, Lee Riley at the University of California, Berkeley, has discovered 13 bacterial genes involved in latency, and found that expression of their key proteins precedes active disease. He suggests that a simple, protein-based test could predict the onset of active disease, and thus allow pre-emptive treatment to prevent the activation of disease. "If people who are latently infected never develop disease, TB could be eliminated from the planet," Riley says.

Blocking Communication

Communication is as important to bacteria as it is to humans, and much of it is performed by the small molecules bacteria produce. Jon Clardy of Harvard Medical School wants to discover these molecules in order to understand how to block bacterial infections. To this end, he works with a huge "library" of small molecules, many of them produced by soil microbes. Using high-throughput screening—devices not seen in academic labs a decade ago—Clardy's lab has already found a number of intriguing small molecules. Some disrupt bacterial signals, others are novel antibiotics, and a related study found anti-malarial compounds.

Nanomachines Point to New Medicines

Salmonella enterica, a major cause of food poisoning and of typhoid fever, uses a microscopic "nanomachine" on its outer coat to inject proteins into human cells. Jorge Galán at Yale University School of Medicine discovered this nanomachine and used molecular imaging techniques to describe its structure and function. Scientists now know that many other pathogens—including those that cause plague and complications of cystic fibrosis—possess the same mechanism. Blocking or shutting it down could lead to new types of drugs able to avert the problem of antibiotic resistance. Several are now being tested.

Photos (left to right): M. Daniel Lane, Nicholas Peppas, Vamsi Mootha and Amparo Villablanca

New knowledge and technologies paving the way to better health:

Tackling Twin Epidemics of Obesity and Diabetes

Obesity and type 2 diabetes—two disorders that go hand-in-hand—are increasing at a startling rate. Fewer than half of U.S. adults are at a healthy weight and every age group is getting heavier. One result: diabetes is a growing childhood threat. Both obesity and diabetes profoundly affect Americans' risk for heart disease—the leading killer in the U.S. The fields of genomics, computational biology, and bioengineering are yielding new treatment approaches.

Enlisting the Brain to Control Overeating

M. Daniel Lane at The Johns Hopkins University School of Medicine is revealing the genetic underpinnings of overeating. His work affirms the central role of the brain in managing hunger and offers new targets for drugs that manipulate a gene that he found is central to satiety. Lane is studying the interaction among several proteins that work in the brain's hypothalamus to control food intake. Using genetically engineered knockout mice and the newer gene-trap technology, he is also learning how stem cells "decide" to become fat cells. His goal is to tackle obesity from two sides: teach the brain to know when it's full, and stop fat cell formation.

A Better Way to Deliver Insulin

People with type 1 diabetes dream of a day when they can stop their daily insulin injections or throw away their insulin pumps. Nicholas Peppas at The University of Texas at Austin is engineering a new insulin formulation that can be taken as a pill. Peppas has devised a biomaterial that will carry the insulin through the acidic environment of the stomach, then swell and release the insulin slowly through the wall of the upper intestine into the bloodstream. His team is devising similar drug delivery systems for growth hormones to treat dwarfism, interferon alpha to treat cancer, and interferon beta for patients with multiple sclerosis.

Manipulating Mitochondria to Treat Diabetes

Vamsi Mootha, a Harvard Medical School researcher at Massachusetts General Hospital, has been fascinated with mitochondria, the so-called powerhouse of the cell, since medical school. And for good reason. When his lab developed computational genomics tools to find the root causes of type 2 diabetes, it found that people with, or at risk for, diabetes have fewer and less active mitochondria. Mootha is working with partners to manipulate mitochondria to improve the prognosis for people with diabetes.

Gender Matters

Both obesity and diabetes are harmful to the heart and blood vessels—how much so is just now becoming clear. The impact is different for men and women because the blood vessels and the cardiovascular disease process differ between the sexes. Now, in work with genetically engineered mice, Amparo Villablanca at the University of California, Davis, School of Medicine has found the differences revolve around receptors for the hormone estrogen within the cells that line blood vessels. She hopes to devise approaches that target the early stages of disease by changing the hormone environment—by either altering the receptors or changing the action of the hormones.

"We have learned so much about how diabetes and obesity damage blood vessels. All of the consequences of diabetes—kidney failure, blindness, loss of limbs, heart disease, and stroke—are vascular issues. And, in obesity, fat cells are factories of inflammatory substances that harm the blood vessel walls. All this knowledge comes from basic research."

Amparo Villablanca, M.D.
University of California, Davis

Photos (left to right): Brent Iverson and Samuel Stanley (with student)

New knowledge and technologies paving the way to better health:

New Tools for Bioterrorism Preparedness

"After 9-11, it became clear that we lacked a fundamental understanding of how many pathogens—like anthrax, plague, and pox viruses—actually cause disease," says Samuel Stanley of Washington University in St. Louis. "That basic science gap makes us vulnerable." Using an array of tools and approaches, he and others are taking important steps to reduce that vulnerability.

Preventing and Treating Anthrax Infection

In 2001, a bioterrorism anthrax attack in Washington, D.C., and the East Coast sickened 22 people and killed five. There was no medicine strong enough to save them. Today, one is in advanced stages of testing. Scientists identified a human antibody capable of fighting anthrax—and then improved its performance 200-fold. Its development was made possible by NIH funding for basic research in the laboratory of Brent Iverson at The University of Texas at Austin. The genius of the candidate drug is that it is a human antibody, only better. Enhanced by science, it can remove anthrax and anthrax toxins from the body—a feat no unaltered human protein had ever performed.

Patterned Defense

In the 1990s, scientists discovered toll receptors in cells of the fruit fly, and later found similar receptors in human cells. These receptors trigger the body's immune response to a number of dangerous bacteria and viruses, including plague and *E. coli.* They do so by detecting patterns found within the invaders' cell walls, rather than by recognizing the exact identity of the microbe. Researchers are working on ways to better stimulate this immune response, says Samuel Stanley of Washington University in St. Louis. A strengthened response could provide the best defense against an unidentified microbe, or buy time to develop a vaccine or more targeted drugs.

Virus Hunting with a Virochip

A new Virochip can be used to rapidly identify the type of virus causing infection. The small chip contains more than 20,000 distinct DNA sequences that represent every known virus—some 2,000 in all. These sequences exist as tiny spots on a small glass chip. Researchers expose DNA from an infected tissue sample to the chip. Any viral DNA present in the tissue will adhere to like-DNA on the chip, allowing researchers to identify the virus. The chip was first used to classify SARS in 2003. Stanley notes that it could prove indispensable in responding to a bioterrorism attack with a mystery pathogen.

"Our product is not just our technology or medical breakthroughs. Our College of Natural Sciences alone puts 1,000 undergrads in research situations in labs, and most with NIH funding. That is a catalyst for creating innovative new scientists."

Brent Iverson, Ph.D.
The University of Texas at Austin

Photos (left to right): Stephen Strittmatter and Thomas Jessell

New knowledge and technologies paving the way to better health:

Repair of Spinal Cord Damage

At least 250,000 people in the United States live with paralysis or other disabilities caused by spinal cord injuries. These commonly result from motor vehicle accidents, combat injuries, and other violence. Whereas nerves in the arms and legs often heal, severed nerve cells in the spinal cord—as well as in the brain—cannot grow back. Scientists are using new biomedical tools to discover the molecules and genes that prevent self-repair, and are working to overcome this limitation.

Repair for Paralysis?

First, researchers found NOGO, a molecule that blocks regeneration of nerves in the spinal cord. In particular, NOGO prevents the regrowth of cut axons, the long nerve fibers that conduct electrical signals telling muscles to move. Stephen Strittmatter at Yale University School of Medicine co-discovered the molecule and found its receptor, situated on the axon. He is now investigating whether preventing NOGO from binding to its receptor will enable spinal cord nerve cells and neurons in the brain to self-repair. An experimental drug has already worked in rodents and should soon enter clinical trials in patients, Strittmatter says.

A surprising finding: blocking NOGO improves brain function in genetically engineered mice with an Alzheimer's-like condition and in others with induced stroke. This suggests a connection between axon function and cell loss in neurodegenerative diseases—opening up new avenues of inquiry for treating such conditions.

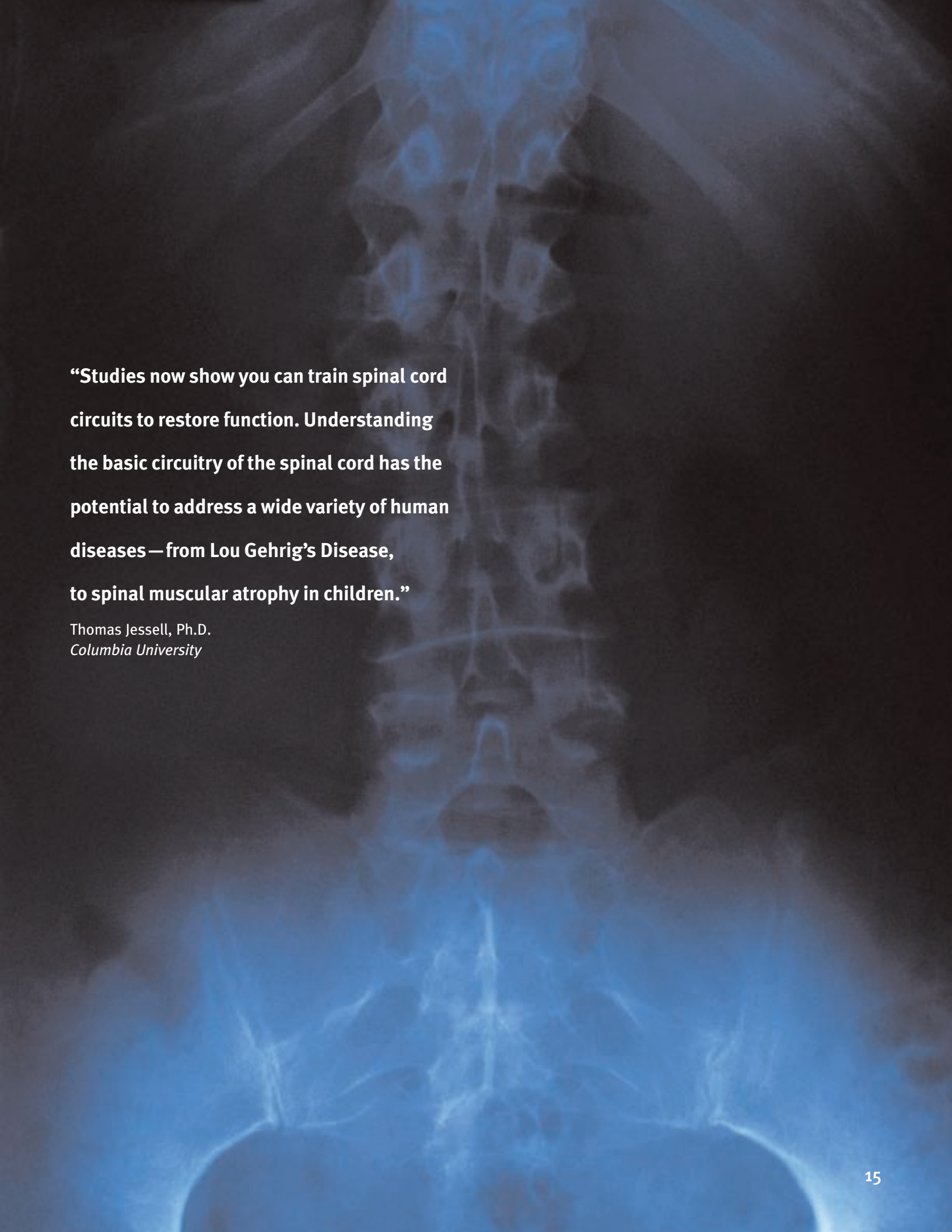
How Nerves Wire Up

To regenerate spinal cord nerves, Thomas Jessell at Columbia University is learning how motor neurons in a developing embryo manage to reach out to the correct muscle target and wire up. Over the last decade, scientists have found that normal embryonic development involves both molecules that promote nerve connections and those that inhibit connections in order to preserve the precision of the correct wiring. A key finding: The same inhibitory molecules that are so necessary to development in embryos prevent regeneration of axons and neurons in adults.

"By knowing those classes of molecules, you can test which ones are putting the brakes on regeneration. Then, you can start designing drugs to overcome their influence," Jessell says. Biotechnology companies are doing just that, screening for compounds that will reverse the lesions in spinal muscular atrophy, treat amyotrophic lateral sclerosis (ALS), and even repair neurons in the brain's cortex.

"Ten years ago, the search for treatment for spinal cord injury was a daunting and hopeless task. Then molecules like NOGO were discovered. Now there is hope. The neurological sciences are on the launching pad of a revolution."

Stephen Strittmatter, M.D., Ph.D.
Yale University School of Medicine



“Studies now show you can train spinal cord circuits to restore function. Understanding the basic circuitry of the spinal cord has the potential to address a wide variety of human diseases—from Lou Gehrig’s Disease, to spinal muscular atrophy in children.”

Thomas Jessell, Ph.D.
Columbia University

"Until recently, young minority investigators have been making unprecedented gains in the laboratory and in access to career-making grants. Their work is addressing everything from the biology of cardiovascular disease to cancer, and their research is generating knowledge and applying it in ways that will help eliminate health care disparities between minority groups and the larger population.

A flattening of the NIH budget—in real terms, a decrease in funding—is already having a serious impact on the ability of these young investigators to realize sustained federal support. Without reasonable growth in NIH funding of basic science, our nation will be at risk of losing the remarkable perspective this generation of researchers brings to science."

David Nichols, M.D.
Vice Dean for Education
The Johns Hopkins University School of Medicine

Cracks in the Foundation

The Impact of Flat Funding

The promise of basic research is great. Yet, even as substantial advances appear within our grasp, they are at risk of slipping away.

The reason is simple. Doubling the NIH budget between 1998 and 2003 enabled researchers to achieve historic progress. But after this great push forward, the budget stagnated. Some work has been frozen midstream, and eight out of 10 grant applications now go unfunded, according to NIH figures.

The effects of the flat budget have been exacerbated by inflation, and together account for an 8% loss in purchasing power for the NIH (based on the Biomedical Research and Development Price Index). As a result, the NIH is able to buy less and less with its research dollars—constraining progress in real ways.

The effects are being felt by both principal investigators and young researchers trying to enter the field. Investigators are forced to spend excessive time writing multiple grants—time that could be better spent doing the hard work of laboratory discovery. They report having to abandon some of their most productive collaborations and innovative work, as projects seen as risky are less likely to be funded. Certain NIH institutes, such as the National Cancer Institute, report they can only fund 11% of research project grant applications, and must, therefore, reject many grants of exceptional quality.

For young investigators, the low funding rate is contributing to another problem: they have to wait ever-longer to obtain their first grant. In 1970, the average age of first grant was 34.2 years; today it is 41.7. Senior investigators report that many of the brightest young minds no longer see the promise of a career in science, choosing law, business and other alternatives. Mid-career investigators also see a bleak future, with few opportunities to build on previous momentum and discoveries.

The funding problem is of such magnitude that the NIH's 2007 "Fiscal Policy for Grant Awards" urges decision makers to consider "the goal of not losing outstanding laboratories," as they allocate limited funds.

Meanwhile, countries from Singapore to Switzerland are making investment in biomedical sciences high national priorities. Singapore, for example, announced a doubling of its R&D budget over the next five years and is actively recruiting star U.S. scientists. Universities throughout the European Union are wooing back investigators who had come to the U.S. to study. The availability of state-of-the-art infrastructure and adequate research dollars is attractive to investigators at a time when NIH purchasing power is dropping.

Many question whether the United States will be able to maintain its global leadership in biomedical research if flat funding continues.

"Young people are not going to pursue a career in science because the funding situation is so bleak. That will have a generational impact that will take 15 years to fix."

Richard Davidson, Ph.D.
University of Wisconsin-Madison

"We have led the world in biomedical sciences—primarily due to NIH support. We've created an infrastructure that draws the best people in the world. We've spawned a biotech industry second to none and a pipeline of products. The fuel has been NIH funding. Choking that off is shortsighted and will have economic impacts."

Samuel Stanley, M.D.
Washington University in St. Louis

"Very, very productive scientists are doing no research. They are spending all of their time trying to get their labs funded again."

Robert Siliciano, M.D., Ph.D.
The Johns Hopkins University School of Medicine

NIH 101

How the System Works

The National Institutes of Health (NIH) is responsible for funding most U.S. biomedical research. Its budget is established through congressional appropriations. Some 85% of the NIH budget is used to support research carried out by thousands of scientists at 3,000 universities and research centers around the country.

These pioneers of science perform critical research and train the next generation of young investigators. The majority of NIH extramural funding goes to investigator-initiated (R01) research grants for which scientists compete through a world-class peer review process. A national pool of scientific experts helps the NIH select the applications to be funded.

Funding decisions are meant to be based on scientific and technical merit and the likelihood of advancing the NIH mission—the pursuit of knowledge to extend healthy life and reduce the burdens of illness and disability.

This publicly funded basic research lays the foundation for nearly every new treatment, prevention and diagnostic tool. NIH-funded "translational" research and clinical trials often take basic research the next step toward clinical application. NIH discoveries fuel the biotechnology and pharmaceutical industries' pipeline of new health products.

If the source of this innovation in health and medicine constricts, our ability to improve human health will weaken. The American people will ultimately pay the price for inadequate funding of biomedical research.

Conclusion: The Time Is Now

The United States and the world are approaching a fundamental transformation of medicine, informed by new knowledge generated by genomics and proteomics, new technologies that allow imaging of previously unseen molecular worlds, and the tools of molecular biology developed in just the last couple of decades.

To conquer current and future challenges and deliver the next medical breakthroughs, there is nothing more important than continuing a strong and vibrant basic research enterprise. Basic research has given birth to new industries and provides the foundation for every advance in health. And America's biomedical research enterprise, funded as collaborations between the U.S. government, through the National Institutes of Health, and America's universities, has led the world.

Consistent and robust funding for the NIH—that substantively overcomes inflation—is in the national interest: advancing the health of all people, strengthening the U.S. economy, and enhancing U.S. competitiveness and global scientific leadership.

"The last 10 years saw a tremendous build up in scientific capacity. The country needs this. The scientific community drives the economy. In biology, it drives the pharmaceutical industry, and will help people live longer in a productive way. Now, the rug has been pulled out. We'll lose manpower to European countries, India, China, and Japan."

Eric Kandel, M.D.
Nobel Laureate, Columbia University

"The impact of flat funding has been felt all over. Certainly, senior investigators are not immune. It is causing us to reduce the size of our labs. People are working on conservative topics. And there will be less international collaboration in the future, because people are feeling less inclined to split resources."

Jon Clardy, Ph.D.
Harvard Medical School

"The doubling built the momentum. Then the momentum comes crashing to a halt. That threatens the foundation in a very insidious fashion."

Ira Mellman, Ph.D.
Yale University School of Medicine

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**Dr. Leon Thal, one of the world's leading researchers in Alzheimer's disease, passed away unexpectedly as this publication went to press.*

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