The family of William R. Orthwein Jr. and the William R. Orthwein Jr. and Laura Rand Orthwein Foundation, a St. Louis, Mo.-based philanthropic organization, have made a combined $2.5 million gift to the School of Medicine to endow a new Yale Scholar in Ophthalmology and Visual Sciences. The Yale Scholars program, a recent initiative of Dean Robert J. Alpern, M.D., provides four years of research funding to the most promising new faculty members recruited at the medical school.

Orthwein, a 1938 graduate of Yale College, did a brief stint after graduation as a salesman for the General American Life Insurance Company, but soon moved to McDonnell Aircraft Corporation (later to become McDonnell Douglas, now part of the Boeing Company), where he would enjoy a 45-year career. According to his daughter, Nettie O. Dodge, of Wheatland, Wyo., Orthwein began in a personnel division of the company and eventually headed that unit. He later became the first president and chairman of McDonnell Douglas Automation Company, or McAuto, which pioneered systems integration in the aircraft industry, particularly in the realm of computer-aided design and manufacturing.

Although Orthwein is dealing with complications of a stroke he suffered in 2003, he gathered in February with family and friends to celebrate his 90th birthday. Stephen Jones, J.D., a 1970 graduate of Yale College and trustee of the Orthwein Foundation who attended the celebration, considered the best is yet to come, p. 3

Betty and John Anlyan have made a lasting mark on the School of Medicine.

"Yale gave me my start," he says. "It gave all three of us our start."

In gratitude for the aid Yale provided to John and his brothers, a difficult time in their lives, John and Betty Anlyan made arrangements in 1990 to leave their estate to the School of Medicine, setting in motion the largest-ever alumnus gift to the medical school. Once fully realized, the Anlyans’ pledge could yield more than $50 million. Thanks to their desire to see their philanthropy in action at Yale, they have transferred millions of dollars to the school already. In addition, at Betty Anlyan’s request, their estate will endow a professorship in the humanities at Yale.

John Anlyan would have finished medical school a year earlier had he not contracted tuberculosis at the start of his first year. The disease started, "he says. "It gave each of us a mark on the School of Medicine, setting in motion the largest-ever alumnus gift to the medical school."

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Gene defect plays role in early-onset heart disease
Yale scientists led by cardiologist Arzy Mani, M.D., have identified a rare defect in a single gene associated with early heart disease and metabolic syndrome, a cluster of risk factors that includes high levels of harmful low-density lipoprotein cholesterol and triglycerides, low high-density lipoprotein cholesterol, or “good,” cholesterol, hypertension, and diabetes.

"The belief is that coronary artery disease and most other diseases are caused by mutations in several genes. Each gene, in combination with environmental factors, exerts a small effect, so it is very difficult to identify them in the general population," says Mani, assistant professor of medicine.

“But if we find families in which some members have an extreme form of the disease, such as very early onset, while other family members are unaffected, they are optimal for genetic research.”

As reported in the March 2 issue of the journal Science, on a research trip to his native Iran, Mani discovered one such extreme case: a man with high blood pressure, high cholesterol and diabetes who had suffered a heart attack at age 48. Although the man had been treated with coronary artery bypass surgery, atherosclerotic plaque continued to build up in his grafted heart arteries and in his coronary arteries, and he eventually died of a stroke.

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Making hospitals better

For management expert, the key to good health care is all in the details

As a teenager in New Britain, Conn., Elizabeth H. Bradley, Ph.D., volun-
teered at the local hospital, but she had little interest in being a physician. “The adults I knew were in manufacturing as engineers or management,” says Bradley. “To me, the interesting part of a hospi-
tal was how it was organized and managed—and how much it was not like a regular business.”

Now a professor of public health at the School of Medicine, director of its Health Management Program and co-director of the Robert Wood Johnson Clinical Scholars Program, Bradley is still drawn to the orga-

After receiving her undergradu-
ate degree at Harvard University, Bradley went on to earn an M.B.A. in health administration at the Uni-
versity of Chicago Graduate School of Business. She then completed an administra-
tive fellowship at Massa-
chusetts General Hospital in Boston, where she stayed on as an adminis-
trator for several years. “As a hospital administrator at Mass General, I helped make lots of changes—in staffing levels, work flow, admissions practices,” Bradley says, “but we never had the time to evaluate whether the changes were making a difference.” Physicians conduct randomized trials to assess the safety and effectiveness of drugs and procedures, but Bradley says there was no equivalent scrutiny of organizational changes made by hospital managers. “I was eager to step back from what I was doing and apply the same rigorous meth-
odology to evaluate management practices as those used to evaluate medical care,” she says.

After obtaining her Ph.D. in public health from Yale in 1996, Bradley embarked on just the kind of management systems research she felt was lacking. She has since published many research articles on the organizational and other factors involved in translating our best health care knowledge into the best possible systems of care for real-world patients. Bradley has worked in the areas of hospital care, long-term care, and hospice care; since 1996 she has col-
laborated with the John D. Thompson Hospice Institute for Education, Training, and Research, Inc., in Branford, Conn.

Recently, Bradley was part of a team led by Harlan M. Krumholz, M.D., the Harold H. Hines Jr. Pro-essor of Medicine, that enlisted researchers from the School of Medicine, the School of Nursing, Yale-New Haven Hospital and several other institutions to devise ways to shorten “door-to-balloon time,” the critical period between a heart attack patient’s arrival at a hospital and the completion of an angioplasty procedure in a cardiac catheterization lab. The group identified six best practice strategies, published in the New England Journal of Medicine in 2006, which have formed the basis for a national alliance of more than 800 hospitals devoted to improving outcomes for heart attack patients.

There are large differences among hospitals in severity-adjusted mortality rates after heart attack, and the two researchers now plan to determine which organizational strategies are linked to reduced mortality.

Bradley is also using her man-
gagement skills in Ethiopia, where government officials requested help in improving hospital care. With a team of 23 Yale-Clinton Foundation Fellows in International Healthcare Management, she has developed a strategy to implement fundamental elements of good hospital manage-
ment, including triage systems, inventory management, and practices to reduce hospital-acquired infections, and quality improvement methods. Although her work in Eth-
pia might seem far removed from streamlining heart attack patients’ trips to the catheterization lab, Bradley says the goal in both cases is encouraging hospitals to adopt best practices.

Both projects also include an evaluation component, ensuring that these practices are supported by objective evidence.

“We want to learn what dis-
tinguishes the hospitals that get the best results,” Bradley says, but she won’t settle for assumptions or anecdotes. “We need the evidence to back it up.”

Student-run auction for New Haven charities has a banner year

The annual student-run Hunger and Homelessness Auction, held last November, raised more than $36,000 for seven community agencies in New Haven, the most ever raised by the auction and an increase of $5,000 over the previous year.

This year’s auctioneer was Wade Brubacher, father of first-year medical student Jake Brubacher. State Attor-
ey General Richard Blumenthal, J.D., made a guest appearance to auct-
tion his own donation—lunch and a personal tour of the State Capitol.

Recipients of this year’s funds are the Community Health Care Van; HAVEN Free Clinic; Community Soup Kitchen; Domestic Violence Services of Greater New Haven; Im-
mmanuel Baptist Shelter; Leeway Inc.; Loaves and Fishes; and the St. Thomas More Catholic Chapel and Center at Yale University.

As in past years, the fundraising began with a silent auction from November 13 to 16, followed by a live auction in the Harkness Ballroom on November 16.

From Ethiopia to your local emergency department, Elizabeth Bradley’s hard-
nosed research is promoting improved hospital care and management.
A bold experiment in mental health care reaches a new milestone

When Yale psychiatrist Frederick C. "Fritz" Redlich, M.D., met with newly elected Governor Abraham A. Ribicoff in 1955 to discuss how services for Connecticut's mentally ill might be improved, he came prepared, according to Benjamin S. Bunney, M.D., the Charles B.G. Murphy Professor of Psychiatry. Redlich, who served as psychiatry chair from 1950 to 1967, had given a great deal of thought to public policy issues surrounding mental health, much of which he later crystallized in Social Class and Mental Illness, a classic 1968 book he wrote with Yale sociologist August B. Holingshead, Ph.D.

When Redlich appealed to Ribicoff for more services for Connecticut citizens with psychiatric disorders, particularly the poor, Ribicoff shot back, "Well, Fritz, what is Yale going to do about mental health?" In reply, Redlich described the innovative department he had built in his first five years as Yale's psychiatry chair, based on a graduate-school model, the basic and clinical research done by its faculty members formed the foundation for all of its teaching and patient care. Redlich argued that a mental health center adhering to the same philosophy would provide the best, most scientifically sound psychiatric treatment to Connecticut's citizens.

Over the next four years the Department of Psychiatry and the state of Connecticut hammered out a joint partnership that proposed a wholly new approach to mental health care: a community-based center in which psychiatric treatment, training and research would be brought together under one roof.

In the summer of 1966, with the opening of the Connecticut Mental Health Center (CMHC), Redlich's vision became a reality. The 65,000-square-foot facility featured space for day patient and outpatient services, 22 beds for inpatients, an additional 22 beds for clinical research, an emergency unit, a 40-seat auditorium, classrooms and a library. Redlich served as the CMHC's first director; the research facilities were later named in honor of Governor Ribicoff.

Today, the CMHC still stands as a model for research-based mental health training and patient care.

Under the direction of Professor of Psychiatry Selby C. Jacobs, M.D., the center complements its scientific and educational roles with inpatient and outpatient psychiatric services for over 7,000 New Haven-area residents each year. As part of the Yale "Tomorrow" capital campaign, the medical school has launched a special fundraising drive to expand and improve upon CMHC's facilities.

"The ideas that research would define care and training, and that all parties—psychotherapists, psychologists, social psychologists and biological psychiatrists—would be brought together within one building were really revolutionary,” Bunney says. "The CMHC has an entire floor where one side is basic laboratories and the other is an inpatient research ward for biological psychiatry. This brought the basic science and clinical investigators together long before the term ‘translational research’ was ever invented. At the CMHC, basic researchers learned about clinical problems and clinical researchers learned the vocabulary of the basic scientists, which made communication possible between these two groups. This in turn spawned all kinds of collaborations, including hypothesis-driven clinical research."

Beginning in the early 1970s, CMHC scientists led by George K. Aghajanian, M.D., made the first electrophysiological recordings in the brain regions that make use of the neurotransmitters noradrenaline and serotonin. By studying the functioning of these neurotransmitters, these scientists laid the groundwork for drug treatments for opiate dependence, depression, anxiety disorders and attention deficit disorder. Meanwhile, basic scientist Bunney made similar recordings in brain regions that use the neurotransmitter dopamine; Robert H. Roth Jr., Ph.D., studied the biochemistry of dopaminergic systems; and clinical researcher Malcolm B. Bowers Jr., M.D., studied the dopamine system in patients with schizophrenia. This work lent support to the emerging concept that some of the brain's dopamine systems are hyperactive in schizophrenia. This research ultimately led to a new generation of antipsychotic medications with greater efficacy and fewer side effects.

Another important early research accomplishment at the CMHC, the discovery of clozapine as the first non-antiparkinsonian drug for the treatment of opiate dependence, vividly illustrated the power of Redlich's integrated model of psychiatry.

In work with animals, Aghajanian and D. Eugene Redmond, M.D., now professor of psychiatry and neurosurgery, found that inhibiting the noradrenaline system with clonidine decreased the symptoms of opiate withdrawal, an important early step toward relatively painless withdrawal possible for addicted individuals.

Building on this research, Mark S. Gold, M.D., now Distinguished Professor of Psychiatry at the University of Florida, Professor of Psychiatry Thomas R. Kosten, M.D., and Herbert D. Kleber, M.D., now professor of psychiatry at Columbia University, found that patients being treated at CMHC, page 4

For better health, can the soft drinks

The annual U.S. production of soft drinks exceeds 600 billion servings per person. These bubbly beverages have become a fixture of our culture and are the subject of a host of studies correlating soft drink consumption with a wide array of health problems. Kelly D. Brownell, Ph.D., professor of psychology and epidemiology and director of Yale's Rudd Center for Food Policy and Obesity, recently led a thorough analysis of 88 previous reports on the health effects of drinking soda. In the March issue of the American Journal of Public Health, Brownell's group reports that soda increases caloric intake and body weight, decreases intake of calcium and other nutrients and raises the risk of type 2 diabetes. Moreover, the additional calories associated with soft drink consumption add up to more than those in the drinks themselves, suggesting that even healthy soda may increase hunger or decrease a sense of fullness.

When cancer is a family affair

In life's genetic lottery, we often inherit unfavorable characteristics. Some, like mom's wiry hair, are innocuous, but certain defective genes can slowly wreak biologic damage over time. In two such genes, BRCA1 and BRCA2, mutations predispose their carriers to develop breast cancers, especially breast and ovarian cancers.

To determine how prevalent and risky BRCA2 mutations are, Harvey A. Rosch, M.D., Ph.D., professor of epidemiology, and colleagues in Ontario, Canada, asked ovarian cancer patients to report the incidence of cancers among their first-degree relatives. The patients were tested for BRCA1 or BRCA2 mutations, which were correlated with the family histories.

In the December 6 issue of the Journal of the National Cancer Institute, the team estimates that BRCA1/2 mutations lurk in 1 of every 99 individuals (1.01 percent) in the general population—a much higher frequency than previously thought—and that carriers are 4.5 to 102 times more likely than noncarriers to develop ovarian, testicular, pancreatic and female and male breast cancers.

"Families with appreciable histories of any cancers, not just breast and ovary and not just cancers in kids, should think about mutation screening because methods of prevention are becoming available,” Risch says.
the CMHC for opiate abuse recovered even more rapidly if given an opiate blocker along with clonidine.

John H. Krystal, M.D., who was a student at the School of Medicine at the time, was greatly impressed by the CMHC’s pioneering research on clonidine.

This research was a landmark in the understanding of mood disorders, one of the most significant advances in the theory of antidepressant drug action, according to one of the leading proponents of the neurogenic hypothesis of addiction, Eric J. Nestler, M.D., Ph.D., now the Louis and Ellen McGinley Distinguished Chair in Psychiatric Research at UT-Southwestern Medical Center in Dallas, led groundbreaking studies on the neurobiological basis of drug addiction.

The unusual productivity of the CMHC’s translational approach continued into the 1990s, as Eric J. Nestler, M.D., Ph.D., now the Lou and Ellen McGinley Distinguished Chair in Psychiatric Research at UT-Southwestern Medical Center in Dallas, led groundbreaking studies on the neurobiological basis of drug addiction. Today, Ronald S. Durman, Ph.D., the Elizabeth House and Jameson Mears Professor of Psychiatry, is one of the leading proponents of the neurogenic theory of antidepressant drug action, one of the most significant advances in the understanding of mood disorders in decades (see related story, p. 5).

This record of achievement is all the more remarkable given the organizational and cultural differences between a university and a government agency, says the psychiatry department’s state partners at the Connecticut Department of Mental Health and Addiction Services (DMHAS).

According to Thomas A. Kirk Jr., Ph.D., DMHAS commissioner, “The fact that this partnership has been sustained so long is really a statement about the shared commitment to clinical services, research and teaching. The National Alliance on Mental Illness recently reviewed the mental health systems of each of the states and assigned grades. Connecticut was one of the top two states in the nation, and I think our relationship with CMHC was clearly a contributor to our high grade.” DMHAS Deputy Commissioner Wayne Dailey, Ph.D., agrees. “A lot of the policy questions that we deal with are pretty complicated, and they affect thousands of people’s lives. In a university setting, tenured faculty have a rather long view of things, but the median term of office of a commissioner of mental health in the United States is about 21 months,” Dailey says. “There’s a lot of pressure on commissioners to act quickly, and often the evidence and data available to a commissioner in making a key policy decision are not very good because of that pressure. But when you have a university partner that is bringing research that’s been used in developing evidence-based practices into the policymaking process, you have a much stronger basis for making those decisions.”
Over the past two decades, researchers in the School of Medicine’s immunobiology group have led the way in unlocking the secrets of the immune system. Richard A. Flavell, Ph.D., chair of the newly designated Department of Immunobiology pioneered the use of genetically engineered mice to study the fundamental principles of organization and regulation of immune responses. Using mice to mimic human diseases, researchers found evidence of immune system involvement in many maladies, including cancer and heart disease.

But there are enough differences between the immune systems of mice and humans that Flavell and his colleagues have hit a wall when it came time to test their therapies in people with diseases. Frustrated by the barriers to moving laboratory findings into the clinic, Flavell devised a plan to bridge the chasm between mouse and man. His solution, embedding clinical researchers in the Department of Immunobiology, resulted in the medical school’s newly launched program in Human and Translational Immunology (HTI), which will eventually include six new faculty members whose research spans both basic research and clinical experimentation. The program will also reach out to clinical researchers in a variety of medical departments with an interest in immunology.

The new program will be headed by Jordan S. Pober, M.D., Ph.D., the founder and former director of Yale’s highly successful interdepartmental translational research program in Vascular Biology and Transplantation. Pober, whose own research has elucidated the role of the immune system in vascular disease and organ transplantation, became the vice-chair of the Department of Immunobiology for the Section of HTI in January.

“To make translation work, you need a way to connect physicians and basic scientists, and that is best done by people with both interests who are willing to work in the middle,” says Pober. “That’s what HTI is going to provide.”

The work of the program’s first recruit, Kevan Herold, M.D., is a model of translational research. While at Columbia University, Herold, now professor of immunobiology and medicine at the School of Medicine, advanced the most promising new treatment for type 1 diabetes in children. The disease starts when the immune system mistakenly attacks insulin-producing islet cells in the pancreas. As the cells die, insulin production declines, and儿童s become dependent on multiple daily injections of insulin.

First in mice, and then in human clinical trials, Herold and Jeffrey A. Bluestone, Ph.D., of the University of California, San Francisco, and their research teams have shown that administering antibodies designed to inhibit a particular immune response in children with early symptoms of type 1 diabetes delays, and may even prevent, the full-blown development of the disease. The antibody formulation, further refined by MacroGenics of Rockville, Md., under the name MGJ501, is currently in advanced-phase clinical trials for Food and Drug Administration (FDA) approval. The FDA recently named MGJ501 an “orphan drug,” a designation that provides special incentives to companies developing compounds to treat rare diseases.

Herold and his work represent “the best kind of bridge,” says Carolyn W. Slayman, Ph.D., Sterling Professor of Genetics and deputy dean for academic and scientific affairs at the School of Medicine. “He brings together a track record for excellent basic research with a new treatment for an important human disease.”

Slayman adds that Herold’s work links immunobiology with another strong Yale academic unit, the interventional medicine/endocrinology group led by diabetes researcher Robert S. Sherwin, M.D., the C.N.H. Long Professor of Medicine.

The HTI initiative comes at an opportune time for translational research at Yale. In October, the newly formed Yale Center for Clinical Investigation received a five-year, $57 million Clinical and Translational Science Award from the National Institutes of Health, funding that will help provide the infrastructure HTI investigators need to conduct research and to train a new generation of clinical immunologists.

By removing roadblocks to clinical research, Flavell, Pober and their HTI colleagues hope to see Yale discoveries turned into treatments for a wide range of diseases, from diabetes and cancer to heart disease and stroke.

“For 18 years, immunobiology has been focused on studying the basic mechanisms of immunology and applying that to disease, but almost all our focus has been on mice,” Flavell explains. “So the new program is the same thing, really, just now in humans.”

Two Yale RNA experts receive Ellison awards

The Ellison Medical Foundation (EMF) has named two Yale scientists Senior Scholars in Aging, an award that recognizes creative and productive research into processes that affect lifespan and age-related diseases and disabilities.

Frank J. Slack, Ph.D., associate professor of molecular, cellular and developmental biology, and Sandra L. Wolin, M.D., Ph.D., professor of cell biology and of molecular biology and biochemistry, will each receive $500,000 per year for four years to support their research.

Slack studies a pool of micro-RNAs, or miRNAs, short strands of genetic material that act as “switches,” orchestrating development and aging by activating or shutting down patterns of genetic expression at once. In research on the microscopic roundworm C. elegans, Slack and his colleagues have elucidated how two miRNAs known as lin-4 and let-7 ensure that organs emerge at their proper time during the worm’s development. Slack has also shown that the miRNA let-7, which he discovered as a postdoctoral associate at Harvard Medical School, is poorly expressed in human lung cancers, a finding that has led him to propose that many cancers may be caused by dysfunctions in miRNA regulation over the lifespan.

Slack joined the Yale faculty in 2000 after doctoral work in molecular biology at Tufts University School of Medicine and postdoctoral training at Stanford University School of Medicine and at Harvard. He is a member of Yale Cancer Center.

Wolin studies how RNA molecules fold into intricate shapes inside the cell and how a protein known as Ro binds RNA molecules that have been misfolded. She and her research team have shown that RNA binding by Ro helps cells survive damage from ultraviolet radiation.

They also found that mice lacking Ro develop serious immunological disease that resembles lupus, indicating that the normal function of Ro could be important for preventing autoimmunity.

Damaged small RNAs have been detected in the brains of animals and patients with neurodegenerative diseases such as Alzheimer’s and Parkinson’s. With the help of the Senior Scholar in Aging award, Wolin hopes to identify genes involved in detecting and degrading damaged RNAs and to determine how they may contribute to aging and neurodegeneration.

Wolin joined the medical school faculty in 1991. She received her B.A. and her Ph.D. degree in molecular biophysics and biochemistry from Yale, and completed her postdoctoral training at the University of California, San Francisco, in other laboratories. She is also a member of the Yale Cancer Center.

The Bethesda, Md.-based EMF was created by Lawrence J. Ellison, founder and chief executive officer of software giant Oracle Corporation, and Joshua Lederberg, Ph.D., who received his doctoral degree at Yale and went on to share the 1958 Nobel Prize in Physiology or Medicine for his studies of genetic recombination.

Growing out of depression

For decades, people suffering from mood disorders have found relief with antidepressants, but the biological basis for the action of these highly prescribed medications remains unclear. One theory, based on landmark studies by Ronald S. Duman, M.D., Ph.D., the Elizabeth House and Jameson Mears Professor of Psychiatry, proposes that these drugs exert their effects by stimulating neuronal growth factors; these proteins generate new nerve cells in certain brain areas that lead to changes in mood and behavior.

With Jennifer Warner-Schmidt, Ph.D., a former graduate student now at Rockefeller University, Duman has identified a vascular endothelial growth factor, or VEGF, as one such protein.

In the March 13 issue of the Proceedings of the National Academy of Sciences, the team reports that VEGF is produced in the brain’s hippocampal region following administration of various antidepressants. Higher VEGF levels led to increased cell division and positive behavioral responses in well-established models of depression. Conversely, blocking VEGF action inhibited these effects. These findings point to the VEGF pathway as a possible target in the development of new and better antidepressant drugs.

A closer look at bacterial insurgents

American troops in Iraq are bat- tling on yet another front, one as ancient as war itself, yet as modern as the post-penicillin era. Over 240 wounded soldiers are afflicted with bloodstream infec- tions of the antibiotic-resistant bacterium Acinetobacter ba umannii. Left unchecked, this bacte- rium causes urinary tract infec- tions, pneumonia, meningitis, sepsis and even death.

Inquiries of drug technology from 454 Life Sciences, a Branford, Conn., biotech company, Michael Snyder, Ph.D., the Lewis B. Cullman Professor of Molecular, Cellular and Developmental Biology, and colleagues analyzed the bacterium’s entire genome. In the March issue of Genome and Development, Snyder’s group revealed that a surprising 17 percent of A. baumannii’s genetic material originates in other microorganisms. Over half of these “alien islands” contain genes that are critical to the bacterium’s abili- ty to harm humans.

The study shows that the organism has gained a tactical ad- vantage by incorporating foreign DNA. Understanding these evolu- tionary adaptations will bolster the antibiotic armamentarium.

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Wolin joined the medical school faculty in 1991. She received her B.A. and her Ph.D. degree in molecular biophysics and biochemistry from Yale, and completed her postdoctoral training at the University of California, San Francisco, in other laboratories. She is also a member of the Yale Cancer Center.

The Bethesda, Md.-based EMF was created by Lawrence J. Ellison, founder and chief executive officer of software giant Oracle Corporation, and Joshua Lederberg, Ph.D., who received his doctoral degree at Yale and went on to share the 1958 Nobel Prize in Physiology or Medicine for his studies of genetic recombination.
stranded him in a sanatorium near New Haven—playing poker, as he recalls, with his fellow patients and waiting to be liberated from his confinement. His recollection of medical school in the early 1920s is a parade of larger-than-life professors whose personalities, one gets the sense, were matched at times by that of their student. He recalls Harry Zimmerman, M.D., the eminent neuropathologist and friend of Albert Einstein, as a lively teacher who would go on to become the first dean of the Einstein School of Medicine.

Anlyan and his classmates were also impressed by Milten C. Winterritz, M.D., another professor of pathology who had transformed the medical school during his deanship from 1920 to 1935.

Anlyan remembers him as “a little short guy who was just like dynamite. He made the medical school.” Students called him “Winter” when he wasn’t listening, and a high-spirited Anlyan used the same moniker one morning when passing Winterritz in the hall. “I said, ‘Good morning, Winter,’” he recalls, his companions falling silent. “There was a moment’s pause, and then he put his arm around me and said, ‘Call me Milt. It’s more informal.’” The tension dissolved in a burst of laughter.

Richard Breck, M.D., a retired geriatrician in Wallingford, Conn., and a close friend of Anlyan remembers Anlyan as a popular student and life of the party. “He was well known for his ability to tell stories and jokes,” Breck recalls.

When Mani looked at the medical records of 58 of this man’s blood samples from affected family members had in a gene on chromosome 12 known as lrp6. One change in an amino acid in the lrp6 gene altered the activity of the protein it encodes, which acts in certain malignant tumors. The family studied by Mani exhibits an extreme case of heart disease and associated metabolic risk factors, and the mutation he identified is quite rare. However, genes with similar functions to lrp6 and the Wnt pathway itself have been highly conserved over evolutionary time in species as diverse as frogs and humans. This suggests that the pathway has basic physiological importance, and Mani believes that further study of Wnt-related genes will reveal that defects in the pathway are involved in more common forms of cardiovascular disease.

“The main finding is the role of Wnt signaling in the development of metabolic syndrome and CAD,” Mani says. “That is where science has to focus now to understand the basic molecular mechanism of the disease.” Lifton agrees. “We expect that studies of the Wnt signaling pathway in patients with early CAD and metabolic syndrome will provide new insight into the basic biology of disease causation and allow new approaches to disease prevention,” he says.
Grants and contracts awarded to Yale School of Medicine September/October 2006

Federal

Maria Teresa Baquero, Department of the Army, Mineral-Associated Protein Expression and Predicting Tissue Response, 3 years, $11,640; Clifford Johnson, NIB, 1 year, $6,000; Homebase Gene Essential for Liver Development, 2 years, $451,000; Lloyd Cauley, NTH, Stem Cells in Organ Regeneration: A New Paradigm-Based Training for Cognitive Behavioral Therapy, 3 years, $110,000; Junjie Chen, NTH, Promoting and Social Resilience in Young Children, 2 years, $12,288; Michael Krahnthaller, NTH, Test Mining as a Translational Tool in Biomarkomics, 3 years, $413,672; Dennis Lee, NTH, Cerebral Mechanisms of Sleep Learning, 7 months, $353,729; Chiang-Shan Li, NTH, Imaging Inhibitory Circuits in Cacoxenous Papio, 2 years, $28,080; Haifan Lin, NTH, Regulation of Germine Stem Cell Division in Drosophila, 1 year, $48,875; Benchao Li, NTH, Molecular Mechanisms of Glioma: Targeting RTK Inhibitors, 3.5 years, $163,302; Xiaomi Ma, NTH, Myelophylic Syndromes: Paroxysms, Surveys, and Quality of Life, 5 years, $64,800; Robert Malison, NTH, Genetics of Optic Dependence in a Homing (that) Mouse, 1 year, $55,520; Myron Monll, NTH, Molecular Strategies to Define Carcinoids and Rationale Surgical Intervention, 3 years, $12,583,520; Laura Niklison, NTH, Biological Vascular Grafts, 4 years, $1,265,587; Rui Yu, NTH, Flow Cytometry of T Cells in Physiological and Pathological States and Consumer Selection of Health Plans for Health Care Research and Quality, 2 years, $43,474; Mallory Ruediger, NTH, Risk and Prediction of Pulmonary Hypertension, 3 years, $12,341,967; Michael DiGiorgio, Breast Cancer Research Foundation, Activated 

ers Orthwein a "surrogate father" and then. And what would Bill Orthwein do?" "It's a role that he always has played, and will always play in my life."
Honoring fifty years of far-reaching scientific influence

Physiologist caps an illustrious career with nephrology award

In recognition of his 50 years of research, teaching and leadership in the field of nephrology, Gerhard H. Giebisch, M.D., Sterling Professor Emeritus of Cellular and Molecular Physiology, was awarded the 2006 John P. Peters Award from the American Society of Nephrology (ASN). Giebisch is the first Yale faculty member to receive the Peters Award, named in honor of a well-known physiologist and served as chief of the Metabolic Section of Yale’s Department of Medicine from 1922 to 1955.

Born in Vienna, Austria, Giebisch moved from Cornell University Medical School to Yale in 1968 to chair the Department of Medicine from 1922 to 1955. In recognition of his 50 years of research, teaching and leadership in the field of nephrology, Gerhard Giebisch, M.D., Sterling Professor Emeritus of Cellular and Molecular Physiology, was awarded the 2006 John P. Peters Award from the American Society of Nephrology (ASN). Giebisch is the first Yale faculty member to receive the Peters Award, named in honor of a well-known physiologist and served as chief of the Metabolic Section of Yale’s Department of Medicine from 1922 to 1955.

Although Arthur L. Horwich, M.D., prefers to spend as much of his time as possible in the lab, he made a happy exception on April 6, when he returned to The Rockefeller University in New York City to accept the Wiley Prize in Biomedical Sciences. The prize is given by the Wiley foundation, which was established in 2001 by the late John Wiley & Sons, a 200-year-old publisher of scientific, technical and medical books and online services.

Horwich, the Eugene Higgins Professor of Genetics and Pediatrics and a Howard Hughes Medical Institute investigator, was honored along with Franz-Ulrich Hartl, M.D., Ph.D., of the Max Planck Institute for Biochemistry in Germany for their significant contributions to understanding how proteins fold. Scientists have long wondered how proteins make the transformation from chains of amino acids to three-dimensional structures with specific functions that determine their function. Over the last 20 years, Horwich and Hartl’s labs have helped unravel this mystery.

“arachnophors are double-winged molecules that assist in protein folding by binding unfolded proteins in an open ring and then encapsulating them under a cooperating ‘lid’ structure (GroES) where they can fold without sticking to each other. This prevention of aggregation is an important function because such aggregates can harm the cell as in a number of neurodegenerative diseases. The two rings of a chaperonin turn take binding and folding proteins so that as one ring finishes a folding reaction, the other takes over with a new ‘substrate’ polypeptide.

Frequency a protein does not fold properly with one passage into the machine and will be released from it without having reached folded form; the machine will then make another attempt, binding the non-folded chain and attempting once again to correctly fold it. This process of cycling consumes energy, which is supplied in the form of adenosine triphosphate, or ATP, which binds to the machine to enable the encapsulation step and then hydrolyzes thereafter, allowing release of polypeptide.

“Athor’s work has beautifully demonstrated that the notion that all proteins can fold unassisted is simply wrong. In fact, emerging experimental evidence in his laboratory indicates that when a protein misfolds, it can cause the cell and the organism to die,” Horwich said.

“Athor is a natural choice for the Peters Award, which honors broad contributions to the field over and above a successful research career. ‘He’s trained many, many people who have gone on to open laboratories all over the world. He’s been a leader in many societies, organized many conferences and he’s edited what has become the major textbook in renal physiology,’” says Aronson. “For the last thirty years, Dr. Giebisch has been probably the most prominent ‘international statesman’ of nephrology.’”

Dean and Ensign Professor of Medicine Robert J. Alpern, M.D., himself a nephrologist and researcher, concurs.

“While Gerhard has been honored throughout his career for his research, the Peters Award recognizes his contributions to the broader nephrology community,” Alpern says. “He has directly mentored researchers all over the world, but in addition Gerhard has been an advisor and supporter for a multitude of researchers in nephrology. He is internationally recognized for his intellect and generosity.”