Of moths and mice: jumping genes make big leap to mammals

Cut-and-paste DNA is a powerful research tool, may advance gene therapy

The Human Genome Project succeeded at the monumental task of assembling a complete parts list for the human body by decoding the DNA sequence of each and every human gene. But an even harder job remains: determining the function of DNA.

DNA sequence of each and every gene in health and disease.

A new tool for genome research, developed by Tian Xu, Ph.D., professor and vice chair of genetics and Howard Hughes Medical Institute investigator, with colleagues at Fudan University in Shanghai, China, promises to greatly accelerate the work of assigning purpose to thousands of unexplored human genes. The tool is a jumping gene, a small piece of DNA called a transposon that moves around the genome with a preference for settling in other genes and suppressing their activity, which allows scientists to discern their function.

Transposons are active players in many plant and insect genomes, and they helped to make the fruit fly Drosophila the darling of geneticists, as these mobile DNA fragments were used to decipher the role of nearly every gene in that model organism. But for decades scientists could not find an equivalent transposon for mammals.

As reported in the August 12 issue of the journal Cell, Xu and researchers in Shanghai, at Duke University and at the University of Colorado tweeked a transposon.

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A major boost for recruiting top doctors

Greenwich philanthropist calls $10 million gift a "strategic investment"

James M. Allwin, president of Aetos Capital, LLC, an investment management firm based in New York, has donated $10 million to the School of Medicine to attract more of the world's best clinicians and clinical researchers to Yale.

Allwin, a resident of Greenwich, Conn., who serves on the board of the Yale New Haven Health System and on the advisory board of the Howard Hughes Medical Institute, says that his gift mirrors the philosophy he employs in his business: "It's my hope that by investing in world-class practitioners, both the medical school and hospital can achieve their strategic objectives.

The development of the school's clinical mission—the patient care provided by medical school faculty—has been a top priority for Dean and Ensign Professor of Medicine Robert J. Alpern, M.D., since he began his work at the School of Medicine in 2004. "The faculty at Yale are excellent doctors," Alpern says, "but in many cases we don't have a sufficient number of them to provide the best service to our local and more national constituency. There are also a number of areas in which we would like to expand our clinical expertise."

Alpern believes that the medical school and its primary teaching affiliate, Yale-New Haven Hospital, both stand to gain by the new gift. "It will allow us to bring outstanding clinicians and clinical researchers to the faculty who will advance the clinical practice at Yale School of Medicine while also advancing the hospital."

For David J. Leffell, M.D., deputy dean for clinical affairs, the Allwin gift is a godsend for building Yale's medical services. "At a time when all academic health care centers are under enormous financial pressure," he says, "James Allwin's generosity, specifically designated for clinical excellence, will allow us to continue to build our practice in breadth, depth and quality."

As an old hand at investing, Allwin has a well-honed appreciation of the power of compounding, and he hopes that over the coming years the benefits of his gift for both the hospital and medical school will grow exponentially.

"World-class practitioners attract colleagues and counterparts, and could have an impact on both institutions," he says. "The strategic leverage that comes from a gift like this is many times the value of the gift itself."

Program aims to close the gender gap in medical research

Until the National Institutes of Health (NIH), America's largest funder of biomedical research, required scientists to include women in their studies in 1993, it was generally assumed that data gained from clinical research on men would apply to women.

Women's Health Research at Yale (WHER), a multidisciplinary program directed by Carolyn M. Mazure, Ph.D., is proving that assumption false. The program, which aims to close the gender gap in biomedical research, got its start in 1998 with a $6.5 million, five-year grant from the Patrick and Catherine Weldon Donaghue Medical Research Foundation (see related story, p. 3). The initial grant and subsequent funding provide a source for competitive support of pilot studies focusing on health issues unique to or more common in women, and on sex differences in health and disease.

Women's health is often equated with reproductive health. But Mazure, professor of psychiatry and associate dean for faculty affairs, says that while reproductive health is an important focus of women's health, any illness Women, page 3

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New emergency chief aims to shorten patients’ stays—and stop visits altogether

When Gail D’Onofrio, M.D., recently makes it home after a 10-hour shift, her three children always ask the same question: “Did you save anyone’s life today?”

The deep satisfaction of helping patients through medical crises— and sometimes saving lives—first drew her to emergency medicine, says D’Onofrio, who was recently appointed as both chief of adult emergency services for Yale-New Haven Hospital and chief of the section of emergency medicine at the School of Medicine.

Her two jobs carry a long list of duties. In addition to managing the Emergency Department (ED) at YNHH and at the Yale-New Haven Shoreline Medical Center in Guilford, Conn., D’Onofrio is an associate professor in the medical school’s Department of Surgery, conducting research, teaching medical students and training emergency physicians in residence. But D’Onofrio says she would gain the deepest satisfaction if more people were able to avoid visits to the ED altogether, to the end, her efforts are devoted as much to changing lives as saving them.

As medical director of New Haven’s Woman’s Heart Advantage program, D’Onofrio teaches patients and clinicians about the risks of cardiovascular disease in women. Because half of the major trauma injuries seen by ED physicians are related to drugs or alcohol, she also heads Project ASSERT, a program in which peer counselors conduct brief interviews of emergency patients to determine whether they abuse alcohol or drugs and to suggest options for treatment if necessary. While similar programs elsewhere target injured patients, such as those involved in car crashes or falls, Yale screens all patients well enough to be interviewed, even those with minor illnesses such as sore throats.

Like any other unmanaged chronic illness, addiction will likely land patients in the ED again and again. But thanks to partnerships that ASSERT has formed with community agencies, D’Onofrio can point to former repeat patients who no longer show up in the ED because they are succeeding in substance-abuse treatment.

According to the American College of Emergency Physicians, 70 percent of Americans believe emergency departments are approaching a crisis because of overcrowding. And D’Onofrio does not disagree. She thinks of her department as “a canary in a coal mine” that lays bare every deficiency of the larger health-care system, particularly unequal access to care, which places particular stress on her EDs. But she believes that emergency physicians can take positive steps to improve their own departments.

“We need better ways to be efficient,” D’Onofrio says, citing as an example a new center within her department where patients who have chest pain can get stress tests and blood work done very rapidly— evaluating such patients may now take from nine to 20 hours, as opposed to several days if they were admitted to the hospital. She believes that using similar evidence-based protocols for other common ED complaints will reduce unnecessary admissions and move patients through her department more quickly.

Increasingly, D’Onofrio is putting her energy into planning and adjusting systems to ease the overcrowding that plagues ED patients and clinicians alike nationally. But she remains passionate about the fast-paced environment that first attracted her to emergency medicine, a realm where bringing all one’s clinical knowledge and skill to bear in an instant can—as her children remind her— save a life.

Diabetes expert is named dean of nursing

Margaret Grey, Dr.P.H., R.N., the Annie Goodrich Professor of Nursing and associate dean for scholarly affairs at the Yale School of Nursing (YSN), has been named dean of the 82-year-old institution, one of Yale’s 10 professional schools.

A pediatric nurse, Grey is author of over 160 publications and is internationally known for her research on how children adapt to chronic illness, especially diabetes mellitus. As principal investigator for grants totaling over $15 million, Grey has developed ways to manage diabetes and improve the quality of life for young diabetes patients and their parents and to prevent type 2 diabetes in high-risk youth.

Grey has received numerous awards, and she is also a distinguished fellow of the National Association of Pediatric Nurse Associates and Nurse Practitioners. She is a member of the board of directors of the American Diabetes Association, where she has been instrumental in developing standards of care for youth with diabetes.

As dean, Grey will address the school’s most pressing needs—fund-raising and expanding professorships and programs, said Yale President Richard C. Levin, who announced her appointment.

“Margaret Grey has been a leader in strengthening the nursing school over the last 12 years,” Levin said. “She has had an outstanding record of attracting research grants and acting as a mentor for young faculty. With her history here, and as a graduate of the school, she had all the important qualities we were looking for.”

Yale is ranked sixth among nursing schools receiving funding from the National Institutes of Health.

Students come north and aid flows south as Yale lends a hand in wake of Katrina

Faculty and staff from all three arms of the School of Medicine—clinical, educational and scientific—quickly mobilized to lend a helping hand to victims of Hurricane Katrina, the worst natural disaster in U.S. history.

The medical school joined an effort led by the Association of American Medical Colleges (AAMC), the American Hospital Association and numerous other organizations to coordinate the care of storm victims, who were transported by the U.S. Department of Defense from the Gulf region to the NIH Clinical Center in Bethesda and medical centers around the country.

With the aid of the AAMC, two displaced students from Tulane University School of Medicine completed third- and fourth-year clinical rotations at Yale, and three others were accepted at the Yale School of Public Health.

Several researchers and postdoctoral fellows from affected institutions have relocated their labs at Yale as visiting fellows.

The faculty and staff of the School of Medicine responded energetically to a matching-gift payroll deduction program established by the officers and deans of the Yale Corporation, who collectively pledged to match all relief contributions up to $1,000 made by Yale faculty, staff and students. At press time, university-wide donations for assistance to the Gulf States, including matching gifts from the Corporation, totaled $183,676.

Margaret Grey, Dr.P.H., R.N.
**Yale and Donaghue partnership treats research advances as a practical matter**

When the trustees and staff of the West Hartford, Conn.-based Patrick and Catherine Weldon Donaghue Medical Research Foundation meet to make final decisions on the grant proposals they receive, they use a variety of criteria, but one—known as Donaghue as the “but for” test—best captures the foundation’s unique philanthropic vision.

“But for the availability of Donaghue Foundation support,” the foundation’s guidelines read, “what will become of the proposal?”

For the more than 140 faculty members and fellows at the School of Medicine who have received over $50 million in grants and fellowships from the foundation since its founding in 1991—often for unconventional but promising clinical research not well supported by other funding sources—the answer is obvious: But for the Donaghue Foundation’s long-standing and generous relationship with Yale, entire lines of groundbreaking research with real-world impact on the delivery of health care would have never been undertaken.

Ethel Donaghue, one of Connecticut’s first female lawyers, chose her language carefully, stating in her will that the foundation’s mission would be to support research “of practical benefit to the preservation, maintenance and improvement of human life.” The trust she bequeathed to endow the foundation, more than $50 million, was intended not only to advance knowledge for its own sake, but to prevent the kind of suffering she had witnessed in her own parents, the organization’s namesakes.

The wishes of “Miss Donaghue” are invoked frequently and often respectfully and affectionately by Andrews, but Donaghue’s aims have been realized at Yale over the years in ways that she perhaps could not have imagined. For example, the foundation has funded studies of delirium in the elderly as well as predictors of metastatic breast cancer, and it provided the seed money for the Donaghue Women’s Health Investigator Program at Yale (see related story, page 1).

Yale has also been the recipient of several major grants under the foundation’s aptly named Practical Benefit Initiative (PBI). The PBI projects are “the ones with the most risk,” says Executive Director Lynne Garner, Ph.D., as they tend to be large-scale initiatives that venture into new research realms. As with all proposals, she says, if a project could be easily funded elsewhere it will probably be turned down, but an inspired, outside-the-box request might gain support from the foundation.

Such projects can be harder to evaluate than conventional bench science, but the foundation’s impact on day-to-day health care is magnified by its support, says Sheilah B. Rostow, the representative of the foundation’s institutional trustee, Bank of America, who points with pride to a newly launched $1 million PBI patient safety initiative as an example.

The School of Medicine also has received grants under the foundation’s Research in Clinical and Community Health Issues and Donaghue Investigator programs. The latter is unique in that academic medical centers like Yale are critical to the foundation’s own mission. To thanks to the foundation’s support, he says with a smile, “they are talking about ‘practical benefit’ at Yale today.”

Miss Donaghue would be pleased.
Benefit bike ride raises $250,000 for Yale survivors’ clinic

Champion bicyclist Lance Armstrong, whose yellow bracelet has become a cultural icon, may be Earth’s most famous cancer survivor. Along with millions of others, Jeff Keith, survivor of a childhood bout with the disease that claimed much of his right leg, credits Armstrong with “elevating survivorship” and raising public awareness of survivors’ special needs.

So it seems fitting that Keith, of Fairfield, Conn., and 200 others climbed onto the saddles of their bikes on a Sunday morning in August to start the first Connecticut Challenge (see Out & About, right), an annual event Keith has launched with friend John Ragland Jr. to raise funds for a cancer survivorship clinic at the Yale Cancer Center (YCC).

With chemotherapy, radiotherapy and surgery, more people beat cancer than ever before, but long-term physical and psychological consequences of the disease, such as heart problems, decreased fertility and cancer recurrence, are often overlooked.

“Survivorship is almost a ‘black box,’” Keith says. “Not enough attention has been focused on it, but it’s as important as basic care and research because there are 10 million survivors walking around in the United States.”

Survivorship is a “silent need,” agrees Nina Kadan-Lottick, M.D., medical director of Yale’s HERO’s Clinic, a program for childhood cancer survivors funded by the Tommy Fund for Childhood Cancer. “The vast majority of survivors do not even recognize that they have unique health needs or psychosocial needs, because when their therapy was ended it was at a time when we didn’t plan for the future,” Kadan-Lottick says. “They were told, ‘You’re done.’”

The YCC has taken a major step toward an adult cancer survivorship program to parallel Kadan-Lottick’s with the recent recruitment of Kenneth D. Miller, M.D., an oncologist with special interest and expertise in this broad subject.

With Keith and Ragland’s help, Kadan-Lottick and Miller hope to combine forces to create the first center in Connecticut for survivors of all cancers, including adult cancers, a model of care that would be one of the first of its kind in the nation. Richard L. Edelson, M.D., director of the YCC, rode 50 miles in the Challenge, which netted $250,000 for the proposed clinic. The ride was a “tremendously invigorating and inspiring experience, for an extraordi-

narily important purpose,” he says. “The Yale Cancer Center is privileged to join in with the Connecticut Challenge in our joint development of a cancer survivorship program that provides the very best possible care for survivors.”

July 25: A celebration at the medical school’s Child Study Center marked the christening of the Edward Zigler Center in Child Development and Social Policy, formerly the Bush Center, in honor of Edward F. Zigler, Ph.D., the center’s founder and Sterling Professor Emeritus of Psychology at Yale. Zigler, a leading researcher of programs and policies for children and families, was instrumental in the planning and implementation of the Head Start program, the Family and Medical Leave Act, and the Schools of the 21st Century initiative. Timothy P. Shriver, Ph.D., chair of Special Olympics (left), meets Edmund W. Gordon, Ed.D., John M. Musser Professor Emeritus of Psychology at Yale. 2. From left: U.S. Sen. Christopher J. Dodd (D-CT), U.S. Rep. Rosa L. DeLauro (D-CT), former Bush Center Senior Fellow and U.S. Rep. John B. Larson (D-CT), 3. John DeStefano Jr., mayor of New Haven, 4. Zigler (left) and Walter S. Gilliam, Ph.D., assistant professor in the Child Study Center and director of the newly named center.

Out & About

May 8: Members of the Mashantucket Pequot Tribal Nation gathered at the Yale Child Health Research Center (YCHRC) for the unveiling of a plaque marking the establishment of the Timber Scears Endowment Fund in memory of a tribal member who died from a primary immune deficiency in 2001 at age 3. The fund supports both basic and clinical research by the Section of Pediatric Immunology. 1. From left: Danielle Bachinski, Honey Carter, Roxanne Young-Perry, Keri Spears, mother of Timber Spears, and Lake Spears Jr., brother of Timber Spears. 2. Tribal Council Chairman Michael Thomas (left) with Ensign Professor of Medicine and Dean Robert J. Alpern, M.D., after the unveiling. 3. Keri Spears tours the research area. 4. From left: Professor of Pediatrics and YCHRC Director Scott A. Rivkees, M.D., speaks with Joey Carter and Crystal Whipple.

July 9: A kickoff party for the Bike Across America (BAA) Connecticut Challenge, a bicycle ride to raise funds to build Connecticut’s first comprehensive cancer survivorship clinic at the Yale Cancer Center (www.ctchallenge.org), was held at the Fairfield, Conn., home of BAA co-founder Jeff Keith and his wife, Karin (see related story, left). The party and items auctioned that evening raised over $40,000. 1. From left: Steve and Meg Stanton with Mitch McManus, owner of BMW Bridgport and event sponsor. 2. From left: Drs. Michael and Elizabeth Brennan with Suzie Manegia. 3. John Ragland Jr. and John Ragland Sr. 4. From left: Dr. Mel and Linda Coolidge, Richard L. Edelson, M.D., director of the Yale Cancer Center, and Karin Keith. August 30: Medical school alumni, spouses and guests gathered in Sterling Hall of Medicine’s Beaumont Room for the White Coat Dinner, which followed the annual ritual in which newly admitted medical students receive a physician’s coat from leaders of the School of Medicine. 1. From left: David J. Leffell, M.D., professor of dermatology and surgery and deputy dean for clinical affairs, speaks with Maureen and Harold D. Bornstein Jr., M.D., ’53. 2. From left: Samuel D. Kushlan, M.D. ’35, Ethel Kushlan, and Paula Del Guercio. 3. Marie-Louise T. Johnson, Ph.D., ’54, M.D., ’56. 4. Maria Kayne and Martin Gordon, M.D., ’46.
Liver transplantation program formed with an international team of experts

The School of Medicine has launched an ambitious new liver transplant program with a team of doctors recruited from across the United States and Europe.

David C. Cronin, M.D., P.H.D., one of the world’s most experienced pediatric and adult liver transplant surgeons, joined the Department of Surgery in December 2001 as chief of the Liver Transplantation Program. An associate professor of surgery, Cronin came from the University of Chicago, where he performed or participated in more than 600 adult and pediatric liver transplants.

Cronin spent a year working to assemble a team of surgeons, anesthesiologists, nurses, social workers, dieticians, pharmacists and transplant coordinators. In addition, Mario Strazzabosco, M.D., P.H.D., medical director of the adult liver transplantation program at the Ospedali Riuniti di Bergamo in Italy, joined the Yale faculty in September as chief of transplant hepatology and professor of medicine.

Strazzabosco, who trained as a fellow at Yale from 1987 to 1990 under James L. Boyer, M.D., Ensign Professor of Medicine and director of the Yale Liver Center, helped create Italy’s third-largest liver transplant program six years ago in Bergamo. Last year, the Bergamo program performed 90 liver transplants.

Cronin had previously recruited transplant surgeons Sanjay Kulkarni, M.D., from Chicago and anesthesiologist Stephen Luczycki, M.D., from the University of Rochester, one of the world’s busiest live-donor programs.

Between 1987 and 1998, there were 123 liver transplants performed at Yale, but the program was curtailed for re-evaluation after a series of poor outcomes. The revamped transplant service, the result of joint investment by the medical school and Yale-New Haven Hospital through the New Clinical Program Development Fund, listed its first patient in April and performed its first two liver transplants in July and a third in September.

Cronin estimates that 10 liver patients will receive transplants by the end of December and another 20 by 2006, given the service’s current capacity.

As underscored by recent concerns about an outbreak of bird flu in humans, the question is not hypothetical. In 1999, a veterinarian at the Bronx Zoo reported to public health authorities that crows were dying in unusually high numbers, but it took some time before it was recognized that the birds’ illness was the first sign of the emergence of the West Nile virus in this hemisphere.

In order to overcome gaps between experts in animal health and those in human health, the Canary Database, funded by the National Library of Medicine, makes animal-sentinel studies from a variety of biomedical databases easily accessible.

A collaboration of the Yale Occupational and Environmental Medicine program, the Yale Center for Medical Informatics and the U.S. Geological Survey Wildlife Health Center, the database uses an automated and complex research protocol to cull from the veterinary literature papers on animal disease that might have relevance to humans. Five curators, including veterinarians and physicians around the country, review and curate the papers, adding information about epidemiological methods and linkages to human health outcomes.

The information could be used to detect impending disease outbreaks or terror attacks involving chemical or biological weapons. “We want to be a continuing resource,” Rabinowitz says, adding that the database could lead to cross-training between veterinary and medical schools. “We feel that both groups have a lot to learn from each other.”
New lens implant for cataracts is a bionic-style bifocal

For most of us, wearing eyeglasses is an inevitable part of getting older. But for some patients, reaching for a pair of spectacles may soon be a thing of the past. A new lens implant for cataracts that corrects both distance and near vision, allowing 80 percent of patients to see clearly after surgery without wearing glasses or bifocals, is now available at the Yale Eye Center.

“It really represents a whole new technology,” says Brian M. DeBroff, M.D., associate professor and vice chair of the Department of Ophthalmology and Visual Science. DeBroff, who has been performing lens implant surgery for more than a decade, says a handful of physicians in Connecticut trained and licensed to use the new lenses.

More than 20 million people age 65 and older have cataracts, and many opt to undergo surgery to remove the cloudy lenses and replace them with permanent lens implants. Cataract patients who receive implants usually see more clearly, but many still need glasses for reading. With the new lens, however, most patients achieve optimal vision that won’t deteriorate, even as the eye muscles around the lens grow weaker with age.

The new implant, known as the AcrySof ReSTOR lens, uses a technology found in microscopes and telescopes in which a series of 12 circular zones ranging in thickness from 1.3 to 0.62 microns (a human hair is 100 microns thick) allows the lens to focus light from both near and distant objects without relying on the muscles of the eye.

“Approved by the FDA in March, the new implant has been used outside the U.S. since 2005,” DeBroff says. Although lens implants are usually used as a treatment for cataracts, in theory the new implant could also help those over 40 with presbyopia—a common condition affecting near vision in which the lenses become less elastic—who do not wish to wear reading glasses. However, DeBroff says he would not recommend the new lens implants for patients with a high degree of astigmatism or those who do a lot of night driving, because they cause some patients to experience halos around lights.

DeBroff performed his first implant surgery with the new lens in September, and he soon hopes to conduct a study on its use in pediatric cataract patients. Through his surgery to implant the new lens is similar to the procedure used for traditional lenses, doctors must undergo special training on taking proper measurements to achieve the best results.

“One of the important aspects of this implant is the necessity to determine very accurately the power of the lens for the individual patient,” DeBroff says. “At the Yale Eye Center we have some special imaging equipment that uses computerization to determine the proper power of the implant to put in place once the cataract is removed.”

If AVMS are found, they can be treated with embolization, a procedure in which doctors guided by ultrasound, X-ray or MRI images thread a catheter through veins to the malformation and shut off its blood supply with platinum coils or a medical-grade “Super Glue.”

In addition to White, members of the Yale HHT team include Douglas A. Ross, M.D., associate professor of surgery (otolaryngology); Guadalupe Garcia-Tsao, M.D., professor of medicine (diseases); Lawrence H. Young, M.D., professor of medicine (cardiology); Deborah D. Proctor, M.D., associate professor of medicine (diseases); Jeffrey S. Pollak, M.D., associate professor of diagnostic radiology; Katherine J. Henderson, M.S., genetic counselor; and Cinda J. D’Addio, senior administrative assistant.

“We work together, and we all gain something from it,” says White, “so it’s the ideal multidisciplinary collaboration.”

LIVER

For most of us, nosebleeds are no more than an occasional nuisance; however, recurrent nosebleeds can be ignored at one’s peril. For many people with HHT, recurrent nosebleeds caused by ruptured nasal telangiectases—which occur in 40 percent of cases—are the only medical consequence of the disorder. But 40 percent of these patients may also have AVMs in the lungs or brain; these malformations usually have no symptoms and can cause stroke or sudden death if they rupture.

According to Robert I. White Jr., M.D., professor of radiologic pathology, there are straightforward and effective therapies for the life-threatening AVMs seen in HHT. But far too often, he says, a widespread lack of knowledge of the disorder, even among physicians, means that recurrent nosebleeds can be ignored or misdiagnosed, needlessly turning easily treatable AVMs into “vascular time bombs.”

“Why isn’t this well-known?” asks White. “Because HHT affects five organs, and each specialist takes care of their own, and doesn’t know anything about the other organs.”

But White is spreading the word. For more than two decades, in conjunction with the Hereditary Hemorrhagic Telangiectasia Foundation International, an organization he helped to found in 1990, White has been a globetrotting evangelist for screening and treatment, and he has guided the creation of 15 HHT Centers of Excellence across the United States and in Europe and Japan. These centers, each based on a successful model for HHT management that White pioneered at Yale, give patients access to multidisciplinary clinical teams—otolaryngologists, dermatologists, neurologists, gastroenterologists, pulmonologists and radiologists—whose overlapping clinical expertise embraces all the organ systems affected by HHT, along with genetic counseling and specialized nursing services.

At Yale, patients who believe they may have HHT are given MRI scans to screen for brain AVMs and contrast echocardiography (commonly known as a “bubble test”) to search for vascular malformations in the lungs.

Because any child of a parent with HHT has a 50 percent chance of inheriting the disorder, patients are urged to refer members of their extended family to screening and treatment centers.

For 2000 people with HHT, we have moderate to severe nosebleeds, so do not.

Of the 100 people with HHT, we have no nosebleeds.

For a group of 200 members of a family with the HHT test, see how many.

Source: Robert I. White, Jr., M.D.

A Hidden Killer

For 40 of the 100 have malformations in the lungs and brain.

With screening and treatment, life-threatening events can be prevented.

These conditions are not mutually exclusive, so patients may have them in any combination:

nosebleeds with lung malformations, no nosebleeds with both lung and brain malformations, etc.
Genes continued from page 1 called piggyBac, originally identified in the cabbage looper moth by Malcolm J. Fraser, Ph.D., of the University of Notre Dame, so that it can be easily cut and pasted into the genomes of higher organisms, such as mice. "With this transposon, we now have the ability to systematically inactivate each and every gene in a model organism like the mouse," Xu says. David Largaespada, Ph.D., an expert on human genetics at the University of Minnesota who developed another transposon that he and his colleagues recently used in mice to identify genes that may be involved in cancer, agrees. "Researchers now have what is essentially a furry fruit fly." Scientists have traditionally relied on mutation genetics, using chemicals to modify mouse genes, but this is painstakingly slow, and it is often difficult to locate the genes that have been mutated. The piggyBac transposon, when injected into fertilized mouse eggs along with an enzyme known as transposase, is remarkably efficient at jumping into somatic and germ cells and into important coding regions of the genome, and, as its name implies, it can carry genetic tags that allow researchers to locate mutations quickly.

"With piggyBac, we can, from a single gene, add a mutation to it and then inactivate it in the genome of mice, so that in addition to carrying tags that can be used to identify the genes, we can determine the function of these genes," Xu says. This new technology will completely change the game of using mutagenesis to understand the function of mouse genes, and by extension their human counterparts.

PiggyBac could also be a promising new vehicle for human gene therapy, according to Xu, who says that, in addition to carrying tags that mark mutated genes, piggyBac can be engineered to carry whole blocks of DNA containing one or more new genes into the genome. "To demonstrate this genetic piggybacking, Xu and his colleagues used piggyBac to insert a gene for a protein that glows red under the right conditions. As seen in the photo at left, a mother mouse with the gene and any offspring that carry it will show a red hue under the light, but pups without the gene do not. However, many more experiments will be required to know whether the transposon, or some variation of it, could reliably and safely transfer therapeutic genes to humans. "Future approval is to use piggyBac to systematically inactivate every gene in the mouse, one by one, a project that would be unthinkable with traditional mutation genetics methods. "For the past two decades, it has routinely taken years to knock out one gene in a mouse, and altogether about 3,000 genes have been knocked out in mice, out of a total of about 20,000 that are in the genome," Xu explains. With the help of piggyBac, we can knock out genes in 3 months, with two students, we have done 70 genes. We plan to produce mutant mice inactivating most of the genes in three years."
Borgstrom named president/CEO of Yale-New Haven System (YNHHS). She succeeds Joseph A. Zaccagnino, M.P.H., who retired in September after a 35-year career.

During more than a quarter-century at the hospital she has watched it grow into the 944-bed flagship of a health system that stretches along Long Island Sound from New Haven to New London.

As the second-in-command at the hospital, Borgstrom helped develop YNHHS, an affiliation of several dozen organizations including YNHHS and two other large hospitals, Bridgeport and Greenwich. She managed the hospital's $860 million budget and served as primary liaison with the School of Medicine, and also oversaw construction of the $136 million Yale-New Haven Children's Hospital, which opened in 1999.

Because of YNHHS's size and scope, Borgstrom sees opportunities to create better health care by coordinating its provider networks with one another and with the medical school. In particular, she looks forward to the construction of a $40 million cancer center that is awaiting zoning approval by New Haven officials.

Many joint programs—in epilepsy, endocrine surgery and maternal-fetal medicine, to name a few—already bring patients to New Haven from across the country, and a new liver transplantation program (see related story, page 4) is expected to draw pediatric patients from the region and beyond. Borgstrom would like to see more out-of-state patients come to the city for care, and to see continued growth in YNHHS's list of nationally recognized programs.

Neuroscientist Horvath will chair Comparative Medicine

Tamas L. Horvath, D.V.M., Ph.D., associate professor of obstetrics, gynecology, and reproductive sciences, and associate professor of neurobiology, has been named chair of the Section of Comparative Medicine. Horvath takes over from Robert O. Jacoby, M.D., Ph.D., who has led the section since 1978.

Comparative Medicine, founded in 1965 and made a free-standing section in 1973, conducts infectious disease research and provides veterinary services for animals used in research. However, during his long tenure, Jacoby oversaw the creation of the Yale Animal Resources Center as an independent administrative entity within the section devoted to animal care, and the section has since been refashioning itself to become a predominantly academic enterprise.

Horvath followed his father and grandfather into veterinary medicine in his native Hungary, but his training sparked a passion for basic research. He is an expert in the hypothalamus, the brain region that regulates such basic functions as reproductive behavior, eating, biological rhythms and the body's hormonal responses to stress.

Horvath says his intellectual history mirrors that of the section he will lead, “I came here as a veterinarian into the medical school, so personally I had to go through the same transition to become a full-blown academic researcher,” he says. “That’s the sort of philosophy that I would like to translate now to Comparative Medicine, to make this section in the next couple of years an even more integral component of the academic life of the medical school.”

At a reception to mark his new appointment, Horvath said, “It really is an honor and a privilege to follow in the footsteps of Bob [Jacoby]. It’s going to be a major challenge for me to fill his shoes.”

Jacoby says that Horvath’s background is well suited to the section’s 21st-century mission. “Ten or 15 years ago it was tilted toward full-blown laboratory animals. You’re going to see much more attention paid to mechanisms of human diseases expressed in animal models,” Jacoby says, adding that he expects Horvath to strike “the right balance between the section’s regulatory and health care mandates with the need to keep Yale’s research at the forefront.”

*Tamas Horvath

Since the joined Yale-New Haven Hospital (YNNH) in 1979 as an administrative fellow just out of graduate school, Marna P. Borgstrom, M.P.H., has risen in the ranks to become a vice president, the chief operating officer and, as of October 1, the CEO and president of the hospital and Yale New Haven Health System (YNHHS). She succeeds Joseph A. Zaccagnino, M.P.H., who retired in September after a 35-year career.

During more than a quarter-century at the hospital she has watched it grow into the 944-bed flagship of a health system that stretches along Long Island Sound from New Haven to New London.

As the second-in-command at the hospital, Borgstrom helped develop YNHHS, an affiliation of several dozen organizations including YNHHS and two other large hospitals, Bridgeport and Greenwich. She managed the hospital’s $860 million budget and served as primary liaison with the School of Medicine, and also oversaw construction of the $136 million Yale-New Haven Children’s Hospital, which opened in 1999.

Because of YNHHS’s size and scope, Borgstrom sees opportunities to create better health care by coordinating its provider networks with one another and with the medical school. In particular, she looks forward to the construction of a $40 million cancer center that is awaiting zoning approval by New Haven officials.

Many joint programs—in epilepsy, endocrine surgery and maternal-fetal medicine, to name a few—already bring patients to New Haven from across the country, and a new liver transplantation program (see related story, page 4) is expected to draw pediatric patients from the region and beyond. Borgstrom would like to see more out-of-state patients come to the city for care, and to see continued growth in YNHHS’s list of nationally recognized programs.

**Awards & honors**

Roland E. Baron, D.D.S., Ph.D., professor of orthopedics and rehabilitation medicine and cell biology, has received the D. Harry Kopy Award from the International Bone and Joint Research Foundation.

Stanley J. Dudrick, M.D., professor of surgery, has received the 2005 Jacobson Innovation Award from the American College of Surgeons.

Dudrick was honored for research contributions in nutritional support for surgical patients and infants. In 1967, Dudrick was the first to demonstrate that infants could develop normally when fed intravenously.

Marie Louise Landry, M.D., professor of laboratory medicine and director of the Clinical Virology Laboratory at Yale-New Haven Hospital, is the 2005 recipient of the Diagnostic Virology Laboratory of the Pan American Society for Clinical Virology; recognizes her outstanding contributions to the field in the area of rapid detection of viruses for clinical diagnosis.

Stephen M. Strittmatter, M.D., for his work on the Vincent Coates Professor of Neurology and professor of neurobiology, has received the Senator Jacob Javits Award in the Neuroscience from the National Institute of Neurological Disorders and Stroke. Strittmatter studies the development of the nervous system, and has discovered proteins involved in regeneration and repair after injury.

Michael R. Bracken, M.D., Ph.D., the Susan Dwight Bliss Professor of Epidemiology in the Division of Chronic Disease Epidemiology at the School of Public Health, has been named president-elect of the Society for Epidemiologic Research, the largest epidemiological society in the world. Bracken’s research is focused on the epidemiology of diseases of pregnant women and newborns.

Ronald S. Duman, Ph.D., Elizabeth Mears & House Jameson Professor of Psychiatry and professor of pharmacology, has received an NIMH Director’s Merit Award from the National Institute of Mental Health for his research on depression and stress. Duman studies the effects of stress on the hippocampus, and how antidepressants to stimulate neurotrophic and neurogenic actions in that structure.

Richard P. Lifton, M.D., Ph.D., chair and Sterling Professor of Genetics and professor of medicine and molecular biology, has been named a Distinguished Scientist of the American Heart Association. The honor is “in recognition of seminal research that has importantly advanced our understanding and management of cardiovascular disease and stroke.”

Derek K. Toomre, Ph.D., for his work as a postdoctoral investigator in the Department of Cell Biology, has been named the Bayer Fellow in Medicine and Management for 2005-2006.

Thomas M. Gill, M.D., associate professor of medicine and co-director of the Yale Program in Geriatric Medicine, has been inducted into the American Society for Clinical Investigation, one of the nation’s oldest and most respected medical honor societies. Gill studies strategies to prevent functional decline and disability among the elderly.

Bruce L. McLennan, M.D., professor of diagnostic radiology, has been named president-elect of the American Roentgen Ray Society (ARRS), the oldest radiology society in the United States. McLennan, who specializes in genitourinary radiology, began his term in July. The ARRS, founded shortly after the discovery of the X-ray, is dedicated to the advancement of radiology.

Edward M. Uchio, M.D., for his work as a departmental chief surgeon, has received a 2005 Dennis W. Jahnigen Career Development Scholars Award from the American Geriatrics Society (AGS). The $10,000 award, one of 10 granted nationwide by the AGS to support geriatric research, will support Uchio’s research on the effects of aging on a cancer-suppressing pathway in the kidney.