medicine at MICHIGAN

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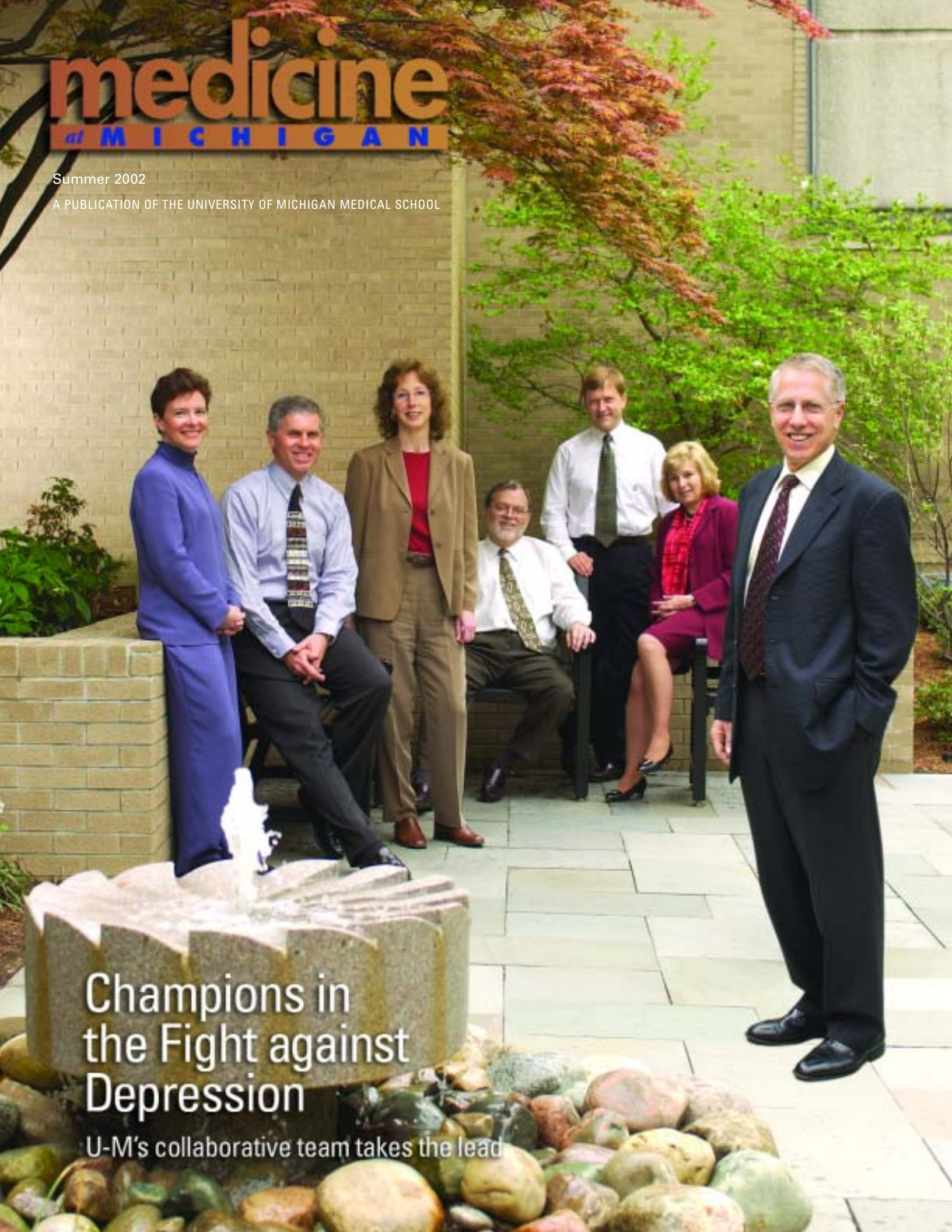


Champions in the Fight against Depression

U-M's collaborative team takes the lead

Above the Huron

The Self-Healing Brain?

Photo: Marcia Ledford

"There is some cue in common that activates neural development and growth." —Jack Parent

University of Michigan neurologist Jack M. Parent, M.D., is fascinated by how primitive neural cells called neuroblasts respond to acute brain injuries. In a series of experiments with laboratory rats, Parent found that neuroblasts multiply and form neural chains that move across the brain to the injury site in an attempt to form new neurons. Understanding how this self-repair mechanism works could someday help physicians reduce brain damage from strokes or neurodegenerative diseases.

"There is some cue in common that activates neural development and growth. We don't know what it is, but we are looking for candidate molecules — growth factors or neurotrophic factors — that stimulate the proliferation and migration of precursor cells," says Parent, an assistant professor of neurology in the U-M Medical School.

Until recently, scientists believed the mammalian adult central nervous system — the brain and spinal cord — was incapable of generating new neurons from adult stem cells, a process known as neurogenesis. But now scientists know that precursor cells in a part of the brain called the subventricular zone or SVZ continue to produce new neurons throughout life for the brain's olfactory bulb, which processes scent. Another area of the brain called the dentate gyrus also generates neuroblasts, which form neurons in the hippocampus — the section of the brain involved in learning, memory and regulating emotions. "Many other sites in the brain's cortex contain neural progenitor cells, but they never develop into neurons," Parent adds.

Parent cautions that, while his results are intriguing, many years of research at the molecular level and in animals will be necessary before human clinical trials could even be considered. "It's not enough to stimulate the development of neuroblasts in human brains and hope they do what you want them to do," Parent says. "There can be harmful consequences."

Parent's research is supported by the National Institute for Neurological Disorders and Stroke of the National Institutes of Health and the Parents Against Childhood Epilepsy Foundation. His research collaborators include Daniel Lowenstein, M.D., from Harvard Medical School and Donna Ferriero, M.D., and Zinaida Vexler, Ph.D., of the University of California-San Francisco Medical School.

—SFP

Read the complete story at:
www.med.umich.edu/opm/newspage/2002/neuralstem.htm

See Parent's home page at:
www.med.umich.edu/neuro/parent.htm

RhoC: Early Warning Sign for Aggressive Breast Cancer?

Photo: Marcia Ledford

Celina Kleer, Sofia Merajver and Kenneth van Golen

RhoC, a protein found in breast tumors, could someday help doctors and patients spot potentially metastatic breast cancer before it begins to spread. A test to detect the protein is still more than a year away from clinical trials. But research at the U-M's Comprehensive Cancer Center shows that RhoC could be a marker for breast tumors that are most likely to spread or metastasize — identifying them when they are less than one centimeter in diameter.

U-M scientists developed the test based on their prior research on the RhoC gene. They evaluated its effectiveness as a cancer marker in 182 tissue samples from 164 patients whose breasts had been biopsied at U-M, as well as information about whether they had cancer or benign breast disease like fibrocystic changes.

> "We hope RhoC will help identify early-stage cancer that could be vulnerable to aggressive treatment." –Celina Kleer

The RhoC test detected invasive cancer with the potential to metastasize with 88 percent specificity, and with 92 percent specificity for tiny tumors that had already metastasized. In contrast, samples of normal breast tissue, benign breast cysts, or non-invasive breast cancer contained little RhoC. U-M scientists presented their results at an April meeting of the American Association for Cancer Research.

"RhoC is a very promising marker for small, but invasive breast cancers, which are hard to identify," says Celina Kleer, M.D. (Residency 1999), an assistant professor of pathology in the U-M Medical School who specializes in breast cancer. "While more research is needed before clinical testing can begin, we hope RhoC will help identify early-stage cancer that could be vulnerable to aggressive treatment."

Kleer and her U-M colleagues — including Sofia Merajver (M.D. 1987, Residency 1993), Ph.D., associate professor of internal medicine, and Kenneth van Golen, Ph.D., assistant professor of internal medicine — designed the study to find out how much RhoC was produced in different kinds of breast cancer cells compared with normal breast cells.

"We found RhoC only in invasive cancers, and almost always correlated with the presence of metastases. Very few non-metastatic cancers contained high levels of RhoC," Kleer says. "The level of RhoC expression also increased as the stage of the breast cancer increased, which is another confirmation that it's a marker of more aggressive cancer. We had enough samples from invasive metastatic cancers of less than one centimeter in size to show that RhoC is highly specific for those tumors, but we'd like to look at more samples to be sure."

Kleer, Merajver, van Golen and their colleagues are preparing to examine more breast tissue samples for the presence of RhoC, to see if their initial results hold up. The team also is planning clinical studies to test the predictive power of RhoC.

The study was funded by the National Institutes of Health, the Department of Defense's breast cancer research program, and a grant from the John and Suzanne Munn Endowment at the U-M Comprehensive Cancer Center. Additional collaborators on the study were Zhi-Fen Wu, M.D., and Yanhong Zhang, Ph.D., U-M research associates; and Mark Rubin, M.D., an associate professor of pathology and urology in the Medical School.

—KG

Read the complete story at:
www.med.umich.edu/opm/newspage/2002/breastcancer.htm

For more information on RhoC:
www.cancer.med.umich.edu/news/genenews.htm

For more information on breast cancer:
www.cancer.med.umich.edu/learn/breastinfo.htm

The Duvernoy Dynasty

At Michigan, medicine is a family affair

When Claire Sibylle Duvernoy (M.D. 1990, Residency 1993) was a little girl, someone made the mistake of giving her a nurse's outfit, while her brother, Christian, received a white coat and toy stethoscope. The future physician was not amused. "My mother says I stamped my foot and said: 'No! I'm going to be a doctor, too!'"

It's not surprising that Claire Duvernoy grew up wanting to be a physician. Her father, Wolf Duvernoy, M.D., was chief of cardiology at Detroit's Providence Hospital with a thriving private practice. Claire often accompanied her father on weekend rounds at the hospital. She learned to read EKGs by practicing on the family dog. And for vacations, the entire family went to cardiology meetings.

Today, Wolf and Claire Duvernoy have more than a close family relationship. They are the only father-daughter physicians in the U-M Medical School. She is an assistant professor of internal medicine-cardiology who specializes in interventional cardiology, conducts research on cardiovascular disease in women, and directs the Cardiac Catheterization Lab at the VA Ann Arbor Healthcare System. He is a clinical professor of medicine who teaches house officers and treats patients at outpatient clinics in the U-M Health System.

"Wolf Duvernoy is the kind of cardiologist I would want were I to be a patient, and the kind of role model I aspire to be as a cardiologist," says Kim A. Eagle, M.D. — the Albion Walter Hewlett Professor of Internal Medicine and chief of clinical cardiology in the U-M Health System — who two years ago recruited Duvernoy to join the faculty — and his daughter, a faculty member since 1998.

If a "doctor gene" exists, scientists will find it in the Duvernoy family genome. The first Dr. Duvernoy on record moved to Germany from

Photo: Martin Vloet

Wolf and Claire Duvernoy

U-M Medical School: No. 8 and Climbing!

University of Michigan Medical School

The University of Michigan Medical School is one of the 10 best research-oriented medical schools in the country, according to the annual "Best Graduate Schools" rankings released April 5 by *U.S. News & World Report.*

The U-M Medical School is now ranked eighth among the nation's 125 accredited medical schools, an increase from last year's ninth-place finish. Only one other medical school affiliated with a public university — the University of California-San Francisco — placed higher.

U.S. News & World Report also ranked the U-M in the top 10 for five medical specialties — drug/alcohol abuse (10), family medicine (10), geriatrics (6), internal medicine (8), and women's health (6). This is the first year the Medical School has placed in the top 10 in the areas of drug/alcohol abuse and women's health.

Among separate rankings of primary care-oriented medical and osteopathic schools, the U-M ranked 14th, up significantly from last year's 26th-place ranking.

"The kudos go to our talented and dedicated faculty. Their commitment to excellence in patient care, research and teaching is driving this upward trend," says Allen S. Lichter,

France in 1698 to serve as personal physician to Duke Friedrich Karl von Wuerttemberg. Continuing the long family tradition, Wolf's father and older brother were physicians in their native Germany.

In 1960, Wolf Duvernoy graduated from the Eberhard-Karls Universität Tübingen Medical School in Tübingen, Germany. He and his wife, Eva, a multi-lingual interpreter, moved to Michigan so Wolf could accept a fellowship in internal medicine and cardiology at Detroit's Henry Ford Hospital.

"Maybe because we were immigrants, we have always been a very close family," says Claire Duvernoy. "Papa worked long hours, but we always waited to have dinner until he came home. My brother and I internalized the values our parents showed us every day — the importance of education, hard work and trying to be the best you can be." Christian Duvernoy went on to become an attorney currently living in Belgium.

Claire Duvernoy's dream of becoming a physician nearly ended in 1985, just six weeks after she enrolled in the U-M Medical School. "I had just finished my first gross anatomy exam and was crossing Fuller Road, when I was hit by a drunk driver," she says. Seriously injured, Claire had to leave medical school for a year to recover. "I got gray hair overnight," adds Wolf Duvernoy.

In 1990, Claire Duvernoy graduated from the U-M Medical School and went on to complete her residency and fellowships in internal medicine and cardiology at U-M. "Cardiology combines the aspects of medicine I like best," she says. "There's the instant gratification of being a surgeon, plus all the cerebral aspects of internal medicine."

"Cardiology is a demanding profession, and especially difficult for a woman with a family," says Wolf Duvernoy. "You are caring for very sick patients and you must be available for them. Traditionally, in this country, women have gravitated to other disciplines, such as pediatrics."

It was during her U-M fellowship that Claire met her future husband, Frank Bogun, M.D., who had come to Ann Arbor from Germany to study the field of cardiac electrophysiology with Fred Morady, M.D., a U-M professor of internal medicine.

"I can always tell if someone's from Germany," says Claire. "We spoke the same dialect and our families were from the same part of the country." When Claire spent a year studying in Germany, the relationship progressed. They married one year later, and Bogun now is completing his cardiology fellowship at Henry Ford Hospital.

"What she won't tell you is that she received Fulbright and Humboldt Scholarships to study in Germany, and that she presented a paper at the World Cardiology Congress in Berlin," adds Wolf, who points out a framed certificate in Claire's office indicating that she is the recipient of a scholars' grant from the Society for Women's Health Research and Pfizer, Inc.

> If a "doctor gene" exists, scientists will find it in the Duvernoy family genome.

To his daughter's somewhat embarrassed surprise, he also pulls from his briefcase a drawing of the transvenous system that was part of Claire's science fair project when she was 10 or 11. "Isn't it amazing that she was able to do this at such a young age?" he asks.

Claire Duvernoy works a four-day week now, so she can spend time at home with two-year-old Maximillian, who naturally has his own little doctor's kit and a "Future Cardiologist" T-shirt. "I was always working, so I never diapered my own children," says Grandpapa Duvernoy. "But now I'm learning from Max."

Visibly proud of her accomplishments, Wolf Duvernoy likes to tell people he's following in his daughter's footsteps. "When one of my patients needs a catheterization or arteriogram, I call Claire and ask: 'Can you take just one more for Dad?'"

"He gives me all the hard cases," Claire responds.

"Claire has the right approach; she's very attached to her patients," Wolf says. "Our family tradition is that the patient always comes first."

—SFP

M.D., dean of the U-M Medical School. "The move from No. 12 two years ago, to ninth last year, to this year's No. 8 ranking shows that our peers realize that great things are happening at the U-M Medical School."

For the first time, *U.S. News & World Report* also ranked Ph.D. programs in the biological sciences. The U-M placed 14th overall. In the specialty of microbiology, the U-M was ranked seventh. This represents a campus-wide achievement, as the Medical School and the College of Literature, Science and the Arts were surveyed as one. At the U-M, about half of the doctorates in the biological sciences are awarded through the Medical School.

In determining its overall national rankings, *U.S. News & World Report* considers several quality indicators, including reputation among medical school deans and senior faculty, levels of research funding, student selectivity, and faculty/student ratios. To determine rankings in the biological sciences, department heads and deans or directors of graduate studies at each program in each discipline were surveyed.

In 2001, the U-M Medical School selected 170 first-year medical students from 4,688 applications. The School's current total enrollment is 666 medical students and 347 graduate students.

—MBR

See this year's complete rankings at:
www.usnews.com

Anthrax Spores Use Failsafe Germination System

Photo: Bill Wood

John Ireland and Philip Hanna

Protected by a tough outer coat that is impervious to cold, heat, drought and harsh chemicals, anthrax spores can remain dormant in the soil for decades. Once inside a living host, however, they can shed that coat, germinate and begin infecting cells in as little as 10 minutes.

Scientists know very little about what triggers an anthrax spore to break dormancy. Identifying the biochemical signals that start the process is an important first step in preventing anthrax infection.

A study by Medical School scientists John A.W. Ireland, Ph.D., and Philip C. Hanna, Ph.D., shows that germination requires the coordinated activity of several genes, receptor proteins and amino acids in at least two simultaneous signaling pathways. The U-M study, published in the March 2002 issue of the *Journal of Bacteriology*, is the first to match anthrax genes with specific amino acids and signaling pathways that trigger germination.

"Anthrax doesn't rely on a single signal," says Hanna, an assistant professor of microbiology and immunology. "Spores have a redundant germination mechanism. It's the bug's way of ensuring that it won't lose its protective armor until conditions are right for germination."

Hanna and Ireland discovered that amino acids, the fundamental building blocks of all proteins in the body, in combination with purine ribonucleosides, the building blocks of DNA and RNA, are triggers for anthrax spore germination. The process appears to begin when receptor proteins on the spore's membrane bind to ring-shaped or aromatic structures found on certain amino acids and ribonucleosides.

"The receptor protein is the lock and ring structures are the keys," says Ireland, a U-M post-doctoral research fellow.

"The only place we know where all the required elements for germination are present is inside our cells, especially our phagocytes — the scavenger cells of the immune system," Ireland explains. "But even in the macrophage, where conditions are perfect for germination, the spore stays intact until at least two separate signaling pathways are activated."

The process appears to begin when receptor proteins on the spore's membrane bind to ring-shaped or aromatic structures found on certain amino acids and ribonucleosides.

Because it can be handled safely outside a high-level bio-containment laboratory, Hanna and Ireland used Sterne-based strains of anthrax in their research. The Sterne strain has been altered, so it cannot infect people.

In future research, Hanna will test the amino acids and ribonucleosides to see if they trigger anthrax spore germination in tissue cultures. Eventually, he hopes to expand the study to animal models. His research is supported by the National Institutes of Health and the Office of Naval Research.

—SFP

Full text of the published article is available on the American Society of Microbiology Web site:
http://jb.asm.org/cgi/content/abstract/184/5/1296

To learn more about Hanna's research, go to:
www.med.umich.edu/microbio/faculty/hanna.html

To learn more about anthrax, see the U.S. Center for Disease Control Web site:
www.bt.cdc.gov

Photo: Gregory Fox

Neali Hendrix

Graduate Student Council Winter Banquet

The second Annual Graduate Student Council Winter Banquet last February brought together students from all graduate disciplines in the biomedical sciences to honor those graduating this year and to present faculty and students of Detroit Community High School with funds toward new science equipment for the School. Each year the Council helps raise funds for local community service projects; last year the group helped build a Habitat for Humanity home in Ann Arbor. Allison Miller, a third-year student in pathology, served as Graduate Student Council president during the 2001-02 academic year.

Conventional Approaches to Gastritis May Not Be the Best

If you need to soothe the burning pain of gastritis, reducing the amount of acid in your stomach may seem like a good idea. But scientists at the U-M Medical School have learned it could be the worst thing you can do.

In a series of recent experiments with laboratory mice, U-M scientists found that antibiotics were actually the best way to treat an inflamed stomach and kill the bacteria that cause gastritis. Mice treated instead with prescription drugs called proton pump inhibitors or PPIs, which block acid production and often are used to treat gastritis in humans, had more bacteria and developed more inflammatory changes in their stomach linings than untreated mice.

"The inflammatory response, which triggers overproduction of hydrochloric acid, is the stomach's primary response to bacterial colonization," says Juanita L. Merchant, M.D., Ph.D., a Howard Hughes Medical Institute assistant investigator and associate professor of internal medicine and physiology. No matter what type of bacteria causes the problem, gastritis is a serious medical condition which, if untreated, can lead to peptic ulcers and stomach cancer.

"Inflammation of the stomach lining coincides with production of peptides called cytokines, which stimulate production of a hormone called gastrin. Gastrin triggers parietal cells in the stomach lining to produce more hydrochloric acid, which kills off most invading microbes. If you inhibit gastric acid production, you interfere with the stomach's natural defense mechanism against invading bacteria."

Since Merchant wanted to study the relationship between other bacteria and gastric acid, *Helicobacter pylori*, bacteria that 75 percent of people with gastritis test positive for, were excluded from the study. *H. pylori* is the only bacterial organism in the stomach that cannot be killed by hydrochloric acid.

Without controlled clinical trials, Merchant says she can't say whether the results would be exactly the same in humans. But since reduced gastric acidity does appear to make the mammalian stomach more vulnerable to bacterial invasion and gastritis, Merchant suggests physicians may want to re-evaluate the long-term use of proton-pump-inhibiting drugs in their patients.

"The bottom-line message is that a two-week course of antibiotics to treat the inflammation is essential for a successful cure," Merchant adds. "Once you get rid of the inflammation, the gastric acid levels should return to normal."

In addition to the Howard Hughes Medical Institute, the research was supported by the National Institutes of Health. Linda C. Samuelson, Ph.D., associate professor of physiology in the Medical School, developed the strain of transgenic mice used in the experiments. Former U-M post-doctoral fellows Gabriele Rieder, Ph.D., and Amy Ferguson, Ph.D., collaborated in the study.

Results of the research were published in the January 2002 issue of *Gastroenterology.*

—SFP

"If you inhibit gastric acid production, you interfere with the stomach's natural defense mechanism against invading bacteria." —Juanita Merchant

Photo: Marcia Ledford

Juanita Merchant

Read the complete story at:
www.med.umich.edu/opm/newspage/stomachacid.htm

A press release from the Howard Hughes Medical Institute is available at:
http://www.hhmi.org/news/merchant.html

Medical School Moves to Number Nine in FY 2001 NIH Funding Rankings

'Indicator of faculty commitment'

Researchers in the University of Michigan Medical School received a record $203 million in funding from the National Institutes of Health in federal fiscal year 2001, making the school ninth in the nation and third among public universities in total NIH grants. In fiscal year 2000, the Medical School was ranked 10th. The Medical School has more than doubled its NIH funding over the past decade.

According to data released in March 2002 by the NIH and revised in April 2002, U-M Medical School grants increased 14.5 percent since fiscal year 2000, with 561 awards totaling $203 million. Of these grant allocations, 489 were for individual research awards, the seventh-largest such total in the nation for two consecutive years. Training grants, fellowships, research and development contracts and other awards also are included in the total funding figure.

"We first entered the NIH top-10 tier in 1988, with $71 million in total support. Growth since then, including this year's move to the number nine spot, is an indicator of our faculty's commitment to seeking visionary advances in scientific research," says Allen Lichter (M.D. 1972), dean of the U-M Medical School. "We're also proud to be the third-highest ranked in training grants because of our continuing commitment to professional education."

Not only do the NIH awards make up a majority of the Medical School's external funding, but they also comprise a significant percentage of NIH and total research funds awarded to the entire University. Medical School NIH awards account for more than 67 percent of the total $302.3 million in NIH funding to the U-M, helping to again make the University sixth in the nation in NIH awards to higher education institutions.

The National Institutes of Health are the nation's largest funding agency for biomedical research, and the amount of funding that a medical school receives is a major indicator of research activity.

—MBR

The list of research awards is available on the NIH Website at:
*http://*grants1.nih.gov/grants/award/rank/medttl.htm

Kids Who Snore Act up More

Photo: Martin Vloet

Ronald Chervin

Children who snore frequently are nearly twice as likely as other children to have attention and hyperactivity problems, according to a study published in the March 2002 issue of the journal *Pediatrics*. Conducted by researchers at the University of Michigan, the University of Pittsburgh and Stanford University, the results of the study provide solid evidence of a link between sleep problems and behavior in children.

The link is strongest in boys under eight years of age; habitual snorers in this group were over three times more likely than non-snorers to be hyperactive. Based on a survey of the parents of 866 children treated in U-M Health System pediatric clinics, the study is among the largest to explore the connection between sleep and hyperactivity.

While the study does not provide any clues as to whether and how sleep problems might contribute to behavior issues, or vice versa, the evidence of a link between the two is strong enough to warrant further and thorough investigation — says lead author Ronald Chervin, M.D., director of the U-M's Michael S. Aldrich Sleep Disorders Laboratory and associate professor of neurology in the U-M Medical School.

> "It's conceivable that by better identifying and treating children's snoring and other nighttime breathing problems, we could help address some of the most common and challenging childhood behavioral issues." –Ronald Chervin

"If there is indeed a cause-and-effect link, sleep problems in children could represent a major public health issue," says Chervin. "It's conceivable that by better identifying and treating children's snoring and other nighttime breathing problems, we could help address some of the most common and challenging childhood behavioral issues. But more research will be necessary to show whether this is the case."

Besides Chervin, the study's authors included former U-M nurse Kristen Hedger Archbold, Ph.D., now at the University of Washington; U-M child psychiatrist James Dillon, M.D; U-M pediatricians Parvis Panahi, M.D., and Kenneth Pituch (M.D. 1981, Residency 1985); and sleep specialists Ronald Dahl, M.D., of the University of Pittsburgh and Christian Guillemenault, M.D., of Stanford University. The study was funded by the National Institutes of Health and the U-M Health System.

—KG

Read the complete press release at:
www.med.umich.edu/opm/newspage/2002/sleepproblems.htm

To learn more about the Michael S. Aldrich Sleep Disorders Laboratory, see:
www.med.umich.edu/neuro/sleep.htm

"The fish does naturally what medicine would like to do therapeutically."

–Peter Hitchcock

Nature's Way of Healing Eye Injuries

When a teleost, or bony, fish experiences an injury to its retina, it is able to do something that humans cannot. It regenerates retinal neurons, repairs the damage, and restores vision. Fish are among two classes of vertebrates — amphibians being the other — that make new retinal neurons throughout their lifetimes.

Kellogg Eye Center scientist Peter F. Hitchcock, Ph.D., is studying this biological phenomenon because it could provide insights into therapies for human retinal injuries and other neural disorders. Among the more dramatic possibilities is that of transplanting stem cells capable of generating new tissue to heal injuries to the retina or central nervous system. Hitchcock, associate professor of cell and developmental biology and associate professor of ophthalmology in the U-M Medical School, says, "We know that stem cells reside in the retinas of fish. The fish does naturally what medicine would like to do therapeutically."

Hitchcock's study of neurogenesis in fish is important because the process is similar to that in the human nervous system. Vertebrates — including humans and fish — share a similar retinal anatomy and physiology.

Currently, Hitchcock and his colleagues are trying to identify the genes that regulate the production of new retinal neurons under normal conditions and during regeneration following an injury. Says Hitchcock, "Identifying the gene is just the beginning, because that allows you to move on to the really interesting biological questions — how these genes function, which cells express them, and what roles they play in retinal repair."

Hitchcock's research is funded in part by the National Eye Institute.

—*BN*

Read the complete article at:
www.kellogg.umich.edu/patient/advances.html

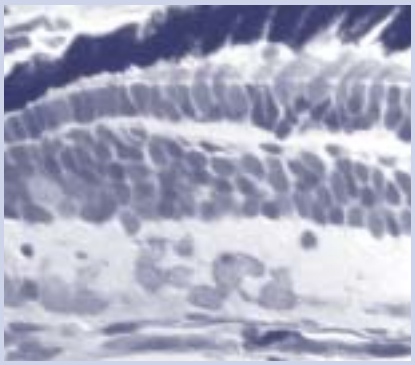
For more information on Peter Hitchcock's research:
www.kellogg.umich.edu/bios/peter_hitchcock.html

See the Department of Ophthalmology and Visual Sciences Web site at:
www.kellogg.umich.edu

Photo: Lin Goings

(Above) **Peter Hitchcock, who studies the fish's remarkable ability to make new neurons that repair the retina and restore sight after an injury.**

(Below) **The cellular structure of this cross-section of the retina of a teleost fish is essentially identical to that of the human retina.**



When Transplant Rejects Host

Cytokines key to common bone marrow complication

U-M scientists have discovered how graft-versus-host disease, a common and deadly complication of bone marrow transplants, attacks and often kills its victims. The discovery could help prevent the deaths of at least 500 Americans each year, and reduce the risk of hospitalization and debilitating side-effects for more than 5,000 others who receive donor bone marrow transplants annually, primarily to treat leukemia and other cancers.

Results from the study, published in the June 2002 issue of *Nature Medicine*, show how skin, liver and gastrointestinal cells in mice with the disease are destroyed from a distance by a firestorm of immune system proteins called inflammatory cytokines.

"Cytokines turn healthy immune cells in donated bone marrow — something given to cure patients — into lethal weapons capable of killing them," says James L.M. Ferrara, M.D., director of the U-M Blood and Marrow Transplantation Program and a professor of internal medicine and pediatrics in the U-M Medical School.

Ferrara says the study calls into question a widely accepted assumption that T cells — immune cells which attach to and kill just one target cell at a time — are the major cell-killing agents of graft-versus-host disease. "It's the difference between a direct attack by ground troops and a general air strike," Ferrara explains.

The study's findings will help scientists focus graft-versus-host disease prevention strategies on its primary killing agents. "Now that we know cytokines are the major cause of graft-versus-host disease-induced cell damage, we can look for ways to neutralize them or block their production," Ferrara says.

Instead of the patient's body rejecting a donated organ, as occurs in an organ transplant, the donated bone marrow, called the graft, rejects cells in the host or patient. Damaged by heavy doses of radiation and chemotherapy used to destroy the patient's cancerous bone marrow before the transplant, these cells secrete substances that activate antigen-presenting cells in the patient's immune system.

James Ferrara

Instead of the patient's body rejecting a donated organ, as occurs in an organ transplant, the donated bone marrow, called the graft, rejects cells in the host or patient.

Previously, researchers assumed that pre-transplant radiation killed all the host's antigen-presenting cells, so scientists discounted the importance of these cells in graft-versus-host disease But the U-M study found that a few antigen-presenting cells remain deep inside tissue. If even one percent survives, it is enough to trigger the graft-versus-host reaction.

When immune cells from the donor's bone marrow meet antigen-presenting cells carrying substances from host cells, some of the donor cells are sensitized to see the patient's cells as the "enemy." These cells respond by firing salvos of inflammatory cytokines. The cytokine barrage transforms "good" immune cells in the patient's new bone marrow into an army of destructive effector cells all primed to attack and kill the host.

In clinical trials under way at the U-M Cancer Center, Ferrara and colleagues are investigating new drugs to determine if they can prevent cell damage in patients with graft-versus-host disease and lung disease after a bone marrow transplant. In a future study, Ferrara hopes to determine whether other drugs can block the original interaction between host antigen-presenting cells and donor immune cells, preventing the initial activation phase of acute graft-versus-host disease.

The study was supported by the National Institutes of Health. Additional U-M collaborators were Takanori Teshima, M.D., Ph.D., now at Japan's Okayama University; Kenneth R. Cooke, M.D., assistant professor of pediatrics and communicable diseases; Rainer Ordemann, M.D., research fellow; Pavan Reddy, M.D., lecturer in internal medicine; and Svetlana Gagin, M.D., research assistant.

—SFP

Read the complete story at:
www.med.umich.edu/opm/newspage/2002/gvhd.htm

To learn more about the U-M Blood and Marrow Transplantation Program, go to:
www.cancer.med.umich.edu/clinic/bmtclinic.htm

For information on clinical trials, call U-M's Cancer Answer Line at 1-800-865-1125.

Photo: Marcia Ledford

Timothy M. Johnson and Christopher Bichakjian

The Web sites identified in the U-M study that were accessible with standard search engines and contained the most complete and accurate melanoma information were:

www.med.usyd.edu.au/medicine/melanoma/index.htm

www.melanoma.net/index.cfm

www.melanoma.com

http://ontumor.com/melanoma/wynk/index.htm

Melanoma Information on the Internet:
USER BEWARE

Popular Internet sites on melanoma may seem trustworthy, but the information they provide is often only skin-deep, according to physicians at the U-M Medical School. The study suggests that people should be skeptical when using the Web to learn about melanoma, and that physicians should guide patients to sites that give complete and accurate information.

"No one expects every Web site to include every bit of information available, but the lack of even basic preventive, diagnostic, treatment and risk factor data on so many sites amazed us," says Christopher Bichakjian, M.D., a lecturer in dermatology. "The fact that melanoma so often strikes young adults — who are more likely to turn to the Internet for medical information — makes melanoma Web site quality even more important."

Bichakjian and his colleagues found Web sites for their study by searching for "melanoma" on six of the most popular commercial search engines, as well as two well-known medical search engines. After discarding dead links, duplicates and pages with no facts, they found 74 Web sites to assess against a "gold standard" checklist of 35 factors developed by the National Comprehensive Cancer Center Network.

Fourteen percent of these sites had erroneous information. Most inaccuracies were relatively minor, but some were dangerous. "Some sites recommended unnecessary tests and more invasive, unnecessary surgery," says Timothy M. Johnson, M.D., director of the U-M melanoma clinic and the William B. Taylor Professor of Dermatology.

Other Medical School collaborators in the study included Sybil Biermann, M.D., assistant professor of surgery; Timothy Wang, M.D. (Residency 1997), clinical assistant professor of dermatology; Jennifer L. Schwartz, M.D., lecturer in dermatology; and Janette Hall, M.S., senior research associate in orthopedic surgery.

—KG

Medstart:
A Decade of Influencing Children's Health and Development

Photo: Gregory Fox

John Barks

John Barks, M.D. (Residency 1987), associate professor of pediatrics and communicable diseases in the U-M Medical School, leads a workshop during the 2002 annual Medstart community conference, "Surroundings and Society: Shaping our Children," held on March 9 on the U-M campus. Barks discussed the effects of maternal chemical dependency on fetal and child development.

Medstart is a coalition of students from the University of Michigan Medical School and the Schools of Public Health, Nursing, Social Work, Public Policy, Education and Law. Now in its 10th year, Medstart, founded by Kevin N. Hibbert (M.D. 1996) and others, promotes a multidisciplinary approach to child advocacy and exposes current and future professionals to children's issues early in their careers through its programs and activities, which include volunteer opportunities at U-M Mott Children's Hospital, health fairs, prenatal support for expectant mothers, and Child Watch, a program developed by the Children's Defense Fund. Michelle Berg (M.D. 2002) served as Medstart's president for the 2001-02 academic year; next year's leadership will be shared by Brian Bednarski (Class of 2003) and Alison Gehle (Class of 2004). Many Medical School students are involved in Medstart's programs and contribute to its success and longevity.

www.umich.edu/~medstart

Photo: J. Adrian Wylie

in Medicine at Michigan

Eric Jackson, from West Bloomfield, is a member of the Medical School's Class of 2002. He entered a seven-year neurosurgery residency program at the University of Pennsylvania this June.

"Going into our residency is anxiety-provoking, but at the same time it's exciting. We've definitely learned the basics of what we need to do — the thought process and the way to approach different situations. I think the biggest question is whether we feel comfortable assuming the role of the decision-maker, and that question is what I think provokes the most anxiety.

"The adjustment to a new level of responsibility is going to be one of the more difficult aspects of residency. I expect that this difficulty will become apparent when I show up in June and take my first call — when everyone else leaves the hospital, and I'm the one there to make the decisions. It's easier when you're a student and your decisions are not final.

"I think the most important aspect of medical school training I've experienced here is not necessarily in learning any specific material, but rather in learning a way of thinking and approaching what I will encounter. Throughout my career, medicine will continue to change — facts I learned in medical school will prove to be incorrect as research reveals new insights. Part of medical education is coming to the realization that you don't — and can't possibly — know everything. Still, if you can at least generate the questions, then you can find the right place to look for the best solutions." —*RS*

Part of medical education is coming to the realization that you don't — and can't possibly — know everything.

Photo Courtesy Daniel Eitzman

Normal mice (left) and obese mice without the gene for leptin (right) were essential to the U-M discovery of leptin's link to blood clotting.

Eitzman and his research team also are studying the relationship between leptin and insulin sensitivity to try to discover why diabetics have a higher-than-normal risk of blood clots.

Leptin Linked to Blood Clots and Obesity

A new risk factor for cardiovascular disease?

High levels of leptin, a hormone produced by fat cells in the body, could explain why obese people develop dangerous blood clots — which can cause heart attacks and strokes — more often than people who are not overweight.

The association between obesity and blood clots is well known; but the cause has remained a mystery. Now, new research with mice conducted by scientists at the University of Michigan Medical School and published in the April 3 issue of the *Journal of the American Medical Association* indicates that leptin may be responsible.

"Our results suggest that clot formation begins with some type of interaction between leptin and the leptin receptor on platelets — blood cells which stick together to make clots," says Daniel T. Eitzman, M.D. (Residency 1991, 1996), a cardiologist at the U-M Cardiovascular Center and an assistant professor of internal medicine in the Medical School.

Knowing how to block this leptin-receptor interaction could help prevent heart attacks and strokes in people who are either obese or overweight, which is half the adult population of the United States.

According to Eitzman, leptin released by fat cells regulates body weight in part by suppressing appetite. When leptin levels in blood go up, the brain signals us to stop eating. But the system breaks down for those who are significantly overweight. Since they have more and larger leptin-producing fat cells than thinner people, their leptin levels increase substantially with every pound of additional weight gain. When leptin reaches very high levels in the blood, Eitzman explains, obese people become resistant to leptin's signal, making them increasingly vulnerable to leptin-induced blood clotting.

While it certainly plays a major role, Eitzman emphasizes that leptin may not be the only factor involved. "The link between obesity and cardiovascular disease is very complex, and there is much we don't know about how other blood clotting factors are regulated in obesity," he says.

Eitzman's discovery of the relationship between leptin and clotting was a lucky accident. Originally, he had no intention of focusing on leptin at all. He just wanted to examine how obesity affects blood clot formation. So he decided to use the fattest laboratory mice he could find – a strain of mutant mice that just happened to be missing the gene required to produce leptin.

Recent research by other scientists finds evidence for leptin's role in human blood clotting. Results from the West of Scotland Coronary Prevention Study, published in the December 2001 issue of *Circulation*, showed that high levels of leptin were an independent risk factor for cardiovascular thrombotic events, such as heart attacks and strokes, in 1,160 men enrolled in the prospective study.

Photo: Martin Vloet

Daniel Eitzman

"We suspect that the more leptin in blood plasma, the higher the risk of forming blood clots, but we haven't quantified the relationship yet," Eitzman says. "We know that losing weight lowers the amount of leptin in your bloodstream, however. So for now diet and exercise remain the best ways to prevent blood clots and the strokes and heart attacks they cause."

This study was funded by the National Institutes of Health. Other U-M Medical School researchers involved in the study included Peter F. Bodary, Ph.D., the paper's lead author, who is now at the University of Toledo; Randal J. Westrick, graduate student; Kevin J. Wickenheiser, undergraduate; and Yuechen Shen, M.D., research associate.

—SFP

To learn more about the U-M Cardiovascular Center and cardiovascular disease, go to: www.med.umich.edu/cvc