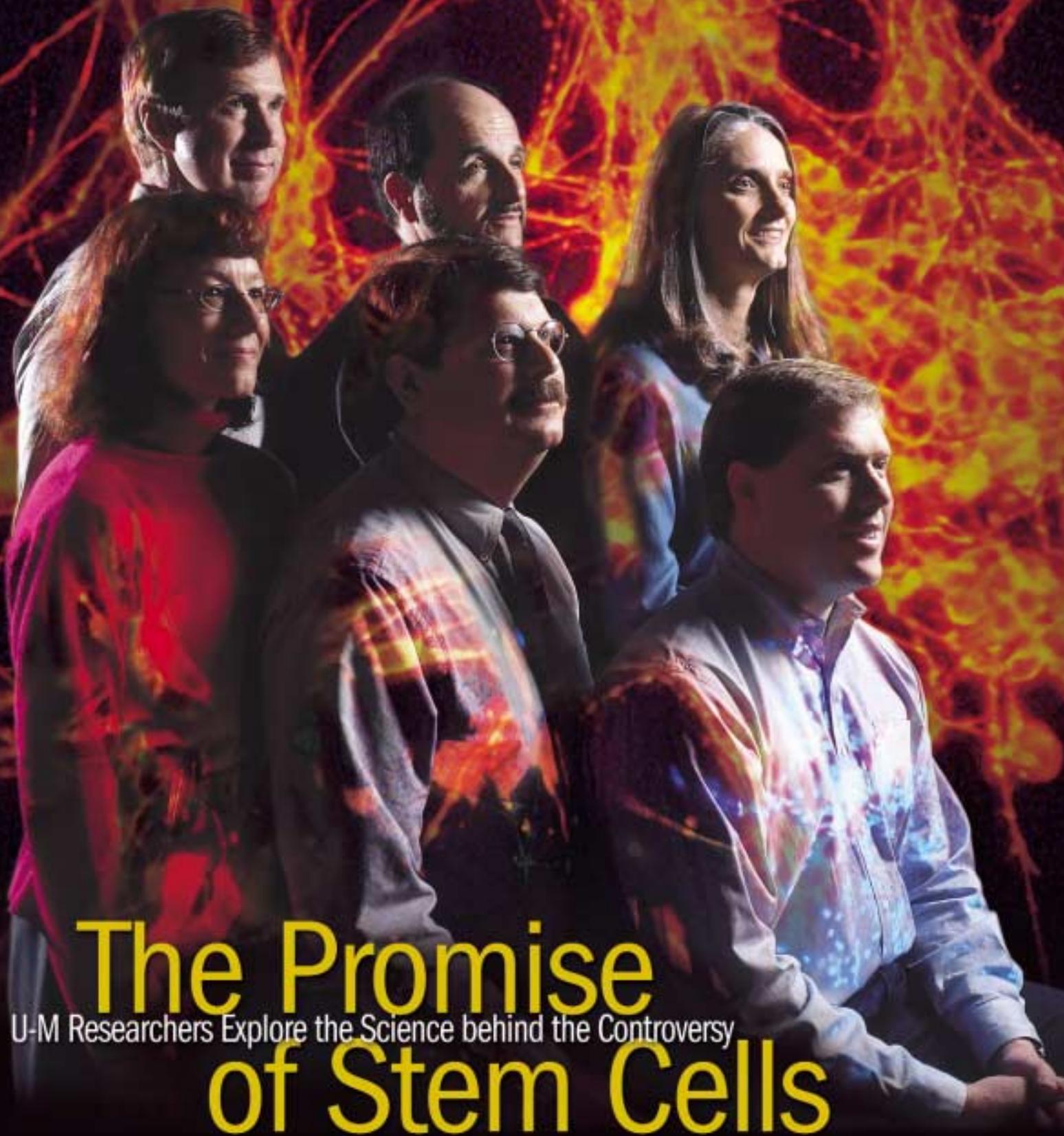


medicine

at M I C H I G A N

Winter 2002

A PUBLICATION OF THE UNIVERSITY OF MICHIGAN MEDICAL SCHOOL



The Promise

U-M Researchers Explore the Science behind the Controversy

of Stem Cells



Above the Huron

Surgery Gets New Chair

The U-M Medical School has appointed surgeon Michael Mulholland, M.D., Ph.D., to chair its Department of Surgery; his appointment, effective February 1, fills the vacancy left by the retirement of Lazar Greenfield, M.D. The Department includes the sections of General Surgery, Plastic and Reconstructive Surgery, Thoracic Surgery, Pediatric Surgery, Vascular Surgery and Oral Surgery.

“With expertise and ongoing accomplishments in education, research, and clinical care, Michael Mulholland is a true ‘triple threat,’” says Allen Lichter, M.D., dean of the Medical School. “He is well prepared to take his place in the line of great surgeons who have led the Department in the past.”

Mulholland has been a member of the Department of Surgery since 1988. He was associate chairman for research from 1993-97. Since 1997 he has been the section head for General Surgery and director of the General

Surgery Residency Program. He was also associate chairman for education from 1997-2000. “Mike is a splendid surgeon, an excellent, well-funded researcher, and an outstanding departmental and institutional leader,” says Gilbert S. Omenn, M.D., Ph.D., U-M executive vice president for medical affairs and CEO of the U-M Health System.

Prior to joining the U-M, Mulholland was an assistant professor in the Department of Surgery at the University of Washington in Seattle. He is a graduate of Northwestern University and Northwestern University Medical School. He completed post-graduate training in general surgery at the University of Minnesota in Minneapolis, where he also received his Ph.D. in surgery.

Mulholland's clinical interests focus on gastrointestinal surgery, including laparoscopic surgery and surgical endoscopy. Special interests include pancreaticobiliary disease, inflammatory bowel disease, gastric diseases and advanced laparoscopic surgery. Mulholland's research interests include neurocrine control of digestive activity.

“I believe the Department can become recognized as the premier surgery department in the U.S., and I’m looking forward to being a part of this initiative.”

—Michael Mulholland

Photo: Kurt Parfitt



Michael Mulholland

"The Surgery Department has a tradition of service to the Michigan community and its patients through its technical brilliance and innovation. I believe the Department can become recognized as the premier surgery department in the U.S., and I'm looking forward to being a part of this initiative," Mulholland says.

Mulholland is the author of more than 100 articles, 50 chapters, and seven textbooks, and he is a co-editor of the textbook *Surgery: Scientific Principles and Practice* which has become the leading text in the field. He will become the senior editor for the next edition. Mulholland currently has four active clinical trials, all funded by NIH. He holds board certifications in surgery and critical care and as a medical examiner.

—Mary Beth Reilly

U-M Depression Center is the First of Its Kind in the U.S.

The nation's first comprehensive center devoted to depression treatment, research and education, has been established at the University of Michigan Health System.

The new Depression Center will expand and unite the U-M's extensive clinical and laboratory research programs; patient, family and community education programs; and training programs for health care professionals and students with the wide range of coordinated patient care services available at the U-M Health System. Its broad scope will allow the U-M to advance the field of depression on all fronts.

"The time is right to focus all our resources on understanding and defeating this illness, and the social stigma it carries, so we can help the 18 million Americans who suffer from depression every year," says John Greden, M.D., the Center's executive director. Greden is chair of the Department of Psychiatry and the Rachel Upjohn Professor of Psychiatry and Clinical Neurosciences at the U-M Medical School.

According to Greden, the new Center will address depression in people of all ages, as well as the postpartum, bipolar and treatment-resistant forms. A network of more than 100 physicians, scientists, psychologists, social workers, nurses and staff will care for patients, conduct research and provide education.

"We hope to lead the way in accelerating the pace of neuroscience research in depression, bringing the products of that research to patients, and reaching out to those who are coping with depression, those who care for them and those who make decisions about their care," says Greden.

—Kara Gavin

Read more about the Depression Center, at:

www.med.umich.edu/depression

www.med.umich.edu/opm/newspage/depctr.htm

See John Greden's Web page at:

www.med.umich.edu/psych/faculty/greden/greden.htm

For patient information on depression, visit:

www.med.umich.edu/1libr/mental/depres03.htm



Photo: Marcia Leadford

John Greden

"The time is right to focus all our resources on understanding and defeating this illness so we can help the 18 million Americans who suffer from depression every year."

—John Greden

Photo: Martin Vloet



Steve Weiss

Since 1924,
The Journal of
Clinical Investigation
has published
research on the basic
science behind
clinical advances.

Photo: Bill Wood



David Ginsburg

Photo: Martin Vloet



John B. Lowe

High Impact

Scientific Reputation of Journal Increases Under U-M Editorial Guidance

It's not as though Steve Weiss didn't have enough to do. An expert on tissue-damaging enzymes involved in inflammatory disease and metastatic cancer, Weiss juggles the demands of managing an active research laboratory with the teaching and administrative responsibilities required of a U-M professor of internal medicine.

But the opportunity to serve as editor of one of the world's premier biomedical research journals, *The Journal of Clinical Investigation*, was simply too good to pass up. "We knew it would be a real feather in Michigan's cap if we were able to move the *Journal* here," says Weiss, M.D., the E. Gifford and Love Barnett Upjohn Professor of Internal Medicine and Oncology. "We felt it was an opportunity to serve the Department and the Medical School. And since the *Journal* focuses on science and biomedical research — topics near and dear to the heart of all active investigators — we thought it might actually be fun."

The *Journal of Clinical Investigation* is the official publication of the American Society of Clinical Investigation (ASCI), a prestigious organization with about 2,600 physician-scientist members working in academic medicine. Since 1924, the *Journal* has published research

on the basic science behind clinical advances. Every five years, ASCI members choose a new editor to manage the *Journal*, and the editor appoints a new editorial board from faculty at his or her medical school.

Weiss became *JCI's* editor in March of 1997. To assist with day-to-day management, he appointed two deputy editors — David Ginsburg, M.D., a Warner-Lambert/Parke-Davis Professor of Medicine, professor of internal medicine and of human genetics in the U-M Medical School; and John B. Lowe, M.D., a Warner-Lambert/Parke-Davis Professor of Medicine and professor of pathology in the Medical School. Ginsburg and Lowe also are investigators in the Howard Hughes Medical Institute.

Weiss convinced 10 other U-M faculty members to volunteer as associate editors who read and make initial

evaluations of thousands of submitted manuscripts. Only 14 or 15 papers are accepted for each of the *Journal's* 24 issues every year.

"Steve has a reputation as a no-nonsense, rigorous scientist who never compromises his standards," says Lowe. "During his five years as editor, his focus on publishing the best possible science has made it much more difficult to have a paper accepted for publication and has roughly halved the size of *JCI*. I can't say he's made a lot of friends, but the quality of the publication has definitely improved."

In their spare time, Weiss, Ginsburg, Lowe and the U-M editorial board also modernized *JCI's* entire administrative infrastructure, converted to a computerized manuscript tracking and management system, and actually made money in the process. They stress that none of it would have been possible without the superb administrative staff that manages the *JCI* office.

"We are most proud of our success in advancing the scientific reputation of the *Journal*," says Weiss. "Scientific journals are ranked by something called an impact factor, which



“Steve [Weiss] has a reputation as a no-nonsense, rigorous scientist who never compromises his standards.” —John Lowe

For more information on The Journal of Clinical Investigation: www.jci.org

For information on the American Society of Clinical Investigation, go to: www.asci-jci.org

The Journal of Clinical Investigation Editorial Board:

Stephen J. Weiss, M.D., *Editor*
David Ginsburg, M.D., *Deputy Editor*
John B. Lowe, M.D., *Deputy Editor*

Associate Editors:

Laurence A. Boxer, M.D., *professor of pediatrics and communicable diseases*
Eric R. Fearon, M.D., Ph.D., *Emanuel N. Maisel Professor of Oncology; associate professor of internal medicine, pathology and human genetics*
David A. Fox, M.D., *professor of internal medicine*
Ronald J. Koenig, M.D., Ph.D., *professor of internal medicine*
Steven L. Kunkel, Ph.D., *professor of pathology*
Benjamin L. Margolis, M.D., *professor of internal medicine and biological chemistry; associate investigator, Howard Hughes Medical Institute*
Gary J. Nabel, M.D., Ph.D., *director, Vaccine Research Center, National Institutes of Health and U-M professor of internal medicine and biological chemistry (on leave)*
Elizabeth G. Nabel, M.D., *director, Clinical Research Program, Division of Intramural Research, National Heart, Lung, & Blood Institute, National Institutes of Health*
Alan R. Saltiel, Ph.D., *U-M Life Sciences Institute; professor of internal medicine and physiology*
James A. Shayman, M.D., *professor of pharmacology and internal medicine*

takes into account the frequency with which published articles are cited by other scientists. In the last two years, our rankings have significantly exceeded those of our former competitors.”

On March 1 the U-M Medical School's responsibility as host institution for *JCI's* editorship ended and a new editor, Andrew Marks, M.D., from Columbia University, took charge. The U-M editorial board is looking forward to a break from what Lowe describes as the “relentless stream” of incoming manuscripts.

“If I could do it over, I sure would like to come up with a better way of spending less time at

this,” admits Weiss. “By asking all the editors to read carefully each of the papers they handle and to meet weekly to discuss thousands of submitted papers, we ended up making commitments to the process that far exceeded anyone's expectations. But without a consistent effort to improve the product in a competitive world, the *Journal* would have suffered. I think our greatest service has been serving as the authors' advocates to help them improve the impact of their work for the general readership, as well as the scientific community at large.”

—Sally Pobjewski

Omenn to Step Down as U-M Executive Vice President for Medical Affairs

Photo: D.C. Goings



Gilbert S. Omenn

Former U-M President Lee Bollinger announced in December 2001 that Gilbert S. Omenn, M.D., Ph.D., will step down upon completion of his term as the U-M's first executive vice president for medical affairs, effective July 31.

Bollinger said that Omenn “has devoted himself entirely to the University and to the Health System” and achieved many of the objectives for which the position was created in 1997, including creating a vision of an integrated health system and achieving synergy across the Medical School, hospitals and health centers, and M-CARE; strengthening the faculty and faculty research support in the Medical School; and progressively enhancing the national standing of the hospitals, Medical School and M-CARE, all of which have significantly improved their national rankings.

“Always striving for excellence and always looking to make improvements, he [Omenn] set a very high standard and helped take this Medical School to a higher level of achievement,” said Allen S. Lichter, M.D., dean of the Medical School.

Omenn, who also holds the title of professor of internal medicine, human genetics and public health, came to the U-M from the University of Washington where he served as dean of the School of Public Health. He was associate director of the White House Office of Science and Technology Policy and the Office of Management and Budget during the Carter administration. After a year's leave Omenn intends to take up a faculty role at the U-M.

“Always striving for excellence and always looking to make improvements, he set a very high standard and helped take this Medical School to a higher level of achievement.”

—Dean Allen S. Lichter

—Kara Gavin

U-M Biomedical Research to Gain New Facility

The U-M Board of Regents has approved a striking architectural design emphasizing light and curves for the Medical School's new \$220-million Biomedical Science Research Building. The south wall of the building is a curved, glass ribbon of office space, which is separated from the terra cotta- and metal-clad laboratory areas by a sky-lit atrium.

Comprised of more than 470,000 square feet, the BSRB will be the largest research facility on campus, covering an entire city block. Faculty working on similar projects will find it easier to work together in the building's 240 laboratory modules, because workspace will be flexible, organized around scientific themes rather than the traditional department-based model.



"The Medical School recognizes that scientific collaboration and innovation are essential to making significant advances in biomedical research," says Allen Lichter, M.D., dean of the U-M Medical School. "The building's unique design will foster multidisciplinary collaborations and create conditions for accelerated visionary research and training, which we hope will profoundly impact science and clinical care."

According to Lichter, programmatic research themes likely to be located in the new BSRB will include:

- **Geriatrics and biogerontology** — cellular and molecular biology of aging and late life
- **Immunology** — basic, translational and clinical investigations of how the immune system defends against viruses, bacteria and other pathogens
- **Cardiovascular science** — genetics, developmental biology and design of treatment strategies for the heart and its blood vessels

- **Cellular and molecular therapeutics** — integration of the disciplines of genetics, biochemistry, microbiology, immunology and cell biology at the cellular and molecular levels for a better understanding of health and disease
- **Organogenesis** — unraveling the basic mechanisms by which organs and tissues are formed and maintained in order to correct acquired and genetic human diseases
- **Neuroscience** — understanding the fundamental biology of brain cells, functions of the brain, and the impact of genetic variations for improved treatment of brain disorders

Its focus on collaborative, multidisciplinary research and its location on the medical campus will make the BSRB an important hub in the development of the U-M Life Sciences Initiative. The Initiative is a campus-wide effort to coordinate and expand research and teaching in all areas of study that are influenced by the life sciences.

In the six-level building, approximately 263,000 square feet will be designed for wet research laboratories, laboratory support space, offices, interaction space and a 300-seat, below-ground-level auditorium.

The BSRB, scheduled for occupancy in 2005, will be located across Huron Street from the U-M's Palmer Drive Development, which includes the new U-M Life Sciences Institute.

—Mary Beth Reilly

For additional construction details about the BSRB, visit:

www.plantext.bf.umich.edu

To take a virtual tour through the new building, go to:

www.med.umich.edu/medschool/video/index.html

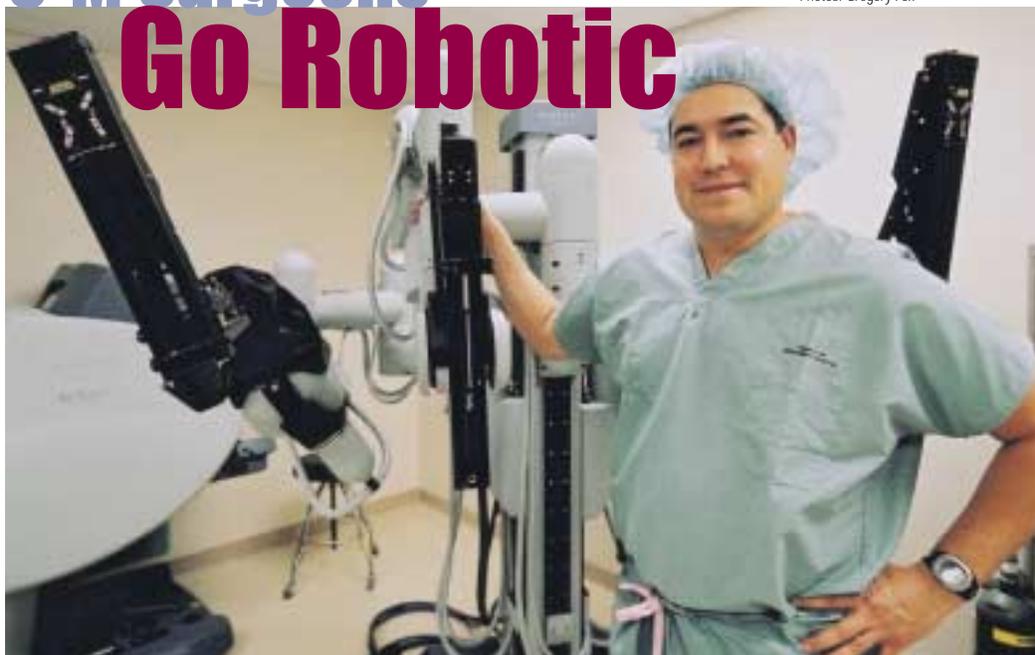
U-M Surgeons Go Robotic

Photos: Gregory Fox

Surgeons in the U-M Health System have a new high-tech assistant — a \$1-million, seven-foot-tall robot, which has proven its worth already in several surgical procedures.

U-M is one of the first hospitals in the U.S. to perform robot-assisted surgery since the FDA approved its use for laparoscopic surgery in July 2000.

On October 15, 2001, Juan Arenas, M.D., an assistant professor of surgery in the U-M Medical School, used the robotic device for a laparoscopic living kidney donation. The surgery was a success and the patient made a full recovery. The robot also has been used for prostate removal, hysterectomies, and several surgeries to remove organs for transplant.



Juan Arenas



Juan Arenas operates from a console a few feet away from the patient using the arms of the robot.

controlling remotely the surgical instruments. Although a second surgeon and medical assistants are next to the patient, Arenas performs the entire procedure using the arms of the robot.

Laparoscopic surgery is minimally invasive, because it is performed through a small incision rather than a large opening. Surgeons slide a tiny video camera inside the patient's body and operate with small instruments. In robot-assisted surgery, the robot actually has three arms — one holds the camera, and two perform the operation.

"The primary advantage of robotic surgery is that it provides a full range of motion similar to a human's wrist. Traditional laparoscopic surgery doesn't allow that," Arenas says. "But the robot goes beyond just wrist movement. It can actually rotate 360 degrees, something humans could never do. This gives surgeons more precise and accurate movements."

Instead of performing surgery by the patient's side, Arenas operates from a console a few feet away, viewing a three-dimensional image of the incision and

The robot was created by Intuitive Surgical Incorporated. Before using it, surgeons must undergo extensive laparoscopic training, in addition to training from the company on how to operate the machine.

Arenas emphasizes that the robot isn't intended to replace the surgeon. "The robot literally gives us an extra set of hands at the operating table," he notes. "It's the next major step in surgery for the 21st century."

—Carrie Hagen



To learn more about the U-M's new robotic surgical assistant, go to: www.intuitivesurgical.com

Medical School Appoints Director for New Bioinformatics Program

David J. States, M.D., Ph.D., was selected to lead the U-M Medical School's new bioinformatics program for graduate education and research. Bioinformatics applies sophisticated computational methods to biomedical and scientific research, especially in molecular biology and genomics. States, who began his U-M duties July 1, 2001, was also appointed professor of human genetics.

"David possesses a rare combination of administrative experience, research expertise and a solid background in the biological sciences and computer science," says Medical School Dean Allen S. Lichter. "Private corporations and research universities are all competing for individuals with backgrounds in these areas. The fact that he chose to come here is a testament to the quality of the U-M's reputation in biomedical research."

States comes from Washington University School of Medicine in St. Louis where he was director of the Institute for Biomedical Computing and an associate professor of genetics. His research focuses on minor genetic variations and how they affect gene regulation and people's response to infection or immune-related medical conditions.

"Bioinformatics is inherently multidisciplinary," says States, "and the University of Michigan is strong in all the relevant areas — especially human genetics, cell biology, engineering and medicine. I was attracted by the opportunity to build a new bioinformatics program at a large research university. My five-year goal is to make it one of the top-ranked bioinformatics programs in the country."

States received his M.D. and Ph.D. degrees from Harvard in 1983. He completed his residency in internal medicine at the University of California-San Diego in 1986. Before joining Washington University, States was a clinical associate for the National Institutes of Health and a senior staff fellow at the NIH National Center for Biotechnology Information in Washington, D.C.

Photo: Bill Wood



David States

"Our students are in excellent hands."

—Michael Savageau

"We are delighted that David States is heading the bioinformatics program at Michigan and joining the Department," says Thomas D. Gelehrter, M.D., professor and chair of Human Genetics in the U-M Medical School. "His breadth of interests and expertise will greatly strengthen our efforts in genomics and the genetics of common complex diseases."

As director of the program, States will recruit and hire four new junior faculty members and technical support staff for a new Bioinformatics Core Facility to assist U-M research faculty and graduate students. States also directs the U-M's new graduate program in bioinformatics, which began last fall.

"Eight students have been accepted; six are pursuing Ph.D. degrees and two are working toward Master's degrees," says Michael A. Savageau, Ph.D., professor and chair of Microbiology and Immunology in the U-M Medical School. Savageau served as interim director for the bioinformatics program and chaired the committee that developed the curriculum and initial courses for the new graduate program. "David already has taken an active role in shaping the program," says Savageau. "Our students are in excellent hands."

—Sally Pobjewski

Found:

An international research team led by University of Michigan Medical School scientists Marci Lesperance, M.D., and Margit Burmeister, Ph.D., has identified a gene responsible for an unusual type of hearing loss called low frequency sensorineural hearing loss.

U-M researchers discovered that children who inherit one copy of the mutated gene called WFS1 gradually lose their ability to hear low-frequency sounds. The hearing loss becomes more severe over time, and eventually hearing aids are required. Patients with different types of mutations affecting both copies of the gene develop Wolfram Syndrome 1 — a rare, devastating condition involving juvenile diabetes, optic atrophy, and often deafness and psychiatric illness.

Photo: Marcia Ledford



Margit Burmeister

Photo: Marcia Ledford



Marci Lesperance

New Gene for Lost Hearing

The wider significance of this discovery is that mutations in this gene may be a common cause of low-frequency hearing loss in the general population, even in those who may be unaware that their hearing loss could be inherited.

Results of the study appeared in the October 22, 2001, issue of *Human Molecular Genetics*, published online November 20 at <http://hmg.oupjournals.org>.

"Discovering a new gene and its related protein gives scientists another piece of information to increase their understanding of inner ear development and function," says Lesperance, an assistant professor of otolaryngology in the U-M Medical School. "These proteins are produced in tiny amounts in the inner ear or cochlea — an area that is inaccessible for tissue sampling and difficult to study."

Lesperance's research team worked closely with Burmeister and Irina Besselova, Ph.D., of U-M's Mental Health Research Institute, as well as with collaborators at the University of Antwerp and Rockefeller University, to identify mutations in six families from the U.S. and The Netherlands with a history of low frequency hearing loss.

"Affected individuals in each family had one of five minor variations called missense mutations in their WFS1 gene," says Burmeister, an associate professor of psychiatry and of

human genetics in the Medical School and senior associate research scientist in the Mental Health Research Institute. "Even though these mutations changed just one amino acid in the string of 890 amino acids that make up the protein, it was enough to produce progressive hearing loss."

Lesperance believes there may be a connection between mutations in WFS1 and the more common form of progressive sensorineural hearing loss involving high-frequency sounds like human speech.

we think. Many people in these families did not know about their hearing loss until they went to a rock concert and temporarily lost hearing in the high frequencies, as well."

Lesperance believes there may be a connection between mutations in WFS1 and the more common form of progressive sensorineural hearing loss involving high-frequency sounds like human speech. While family members with WFS1 mutations had low-frequency hearing loss as children, they often lost the ability to hear high-frequency sound as they got older. "High-frequency hearing loss is caused by aging, noise exposure or drug toxicity, but mutations in WFS1 might make people more susceptible," she says.

One of the most challenging parts of the study was locating families with this type of hearing loss. "People who can't hear low-frequency sounds may not be aware of it, because their ability to understand speech isn't affected," adds Lesperance. "So it's possible that this type of hearing loss is more common than

Lesperance also wants to explore possible involvement of the WFS1 gene in Meniere's Disease — a common, disabling condition that combines periodic attacks of low-frequency hearing loss with severe vertigo and tinnitus, or ringing in the ears.

The study was funded by the National Institutes of Health, the U-M Biomedical Research Council, the University of Antwerp and the Flemish FWO, the Starr Center for Human Genetics and the American Hearing Research Foundation.

Collaborators from the University of Michigan included Irina N. Besselova, Ph.D., former research investigator, now an assistant professor of psychiatry at Mount Sinai School of Medicine; David J. Brown, M.D., house officer in otolaryngology; Ayse E. Erson, a graduate student in human genetics; Purnima Kurnool, former research associate; and Theru A. Sivakumaran, Ph.D., research fellow in otolaryngology.

—Sally Pobojewski

For more information on inherited hearing loss and Lesperance's research, visit:

www.med.umich.edu/childhearinginfo
<http://otosclerosis.khri.med.umich.edu>
www.khri.med.umich.edu/research/lesperance_lab/index.htm

To Tell the Truth...or Not

The Influences Behind Medical Decisions

Photo: Marcia Ledford



Peter A. Ubel

Let's say your patient is a 55-year-old woman with stable severe angina caused by coronary artery disease. Even though she takes the maximum amount of medication, she still has chest pain with low levels of physical activity. Her insurance company won't pay for bypass surgery unless her symptoms get worse. What would you do?

In a recent random survey of 890 physicians using similar scenarios, 11 percent of doctors said they would misrepresent the patient's condition to obtain HMO approval for surgery or additional procedures. Seventy-seven percent said they would appeal the decision, and only 12 percent said they would accept it. The survey was conducted by Peter A. Ubel, M.D., an associate professor of internal medicine in the U-M Medical School and a research investigator at the Ann Arbor Veterans Administration Medical Center.

Ubel directs the Program for Improving Health Care Decisions, a new research program funded jointly by the U-M and Ann Arbor's Veterans Administration Medical Center. "Our goal is to conduct interdisciplinary research on how patients, clinicians and policymakers make health care decisions," says Ubel.

"In medical school, we learn about the Krebs cycle and Latin names for every point where muscle attaches to bone — information we rarely use again," he says. "But we learn almost nothing about how humans make decisions, especially when they are overwhelmed with information."

As an example, Ubel cites a woman who must decide between several treatments for breast cancer. "As her physician, should I tell her what to do or suggest a second opinion? What is the best way to explain her treatment options? Should I use numbers or graphs? How do I know she understands what I'm saying?"

When psychologists study decision-making, Ubel says the research subjects are usually undergraduates or consumers deciding which product to purchase. "We want to focus on how people make medical decisions, such as what motivates a physician to appeal a managed care decision?"

In his survey, Ubel discovered that the severity of the patient's condition and the "hassle factor" — the amount of time required by the appeals process and the likelihood of a successful appeal — were all directly related to a physician's willingness to deceive the insurance company. The sicker the patient and the greater the hassle factor, the more likely the physician was to lie.

"It's important to not see this as an us-versus-them issue," says Ubel. "We ought to see it as how to find the best way to give people appropriate care, while restraining the use of expensive tests that bring small benefits. The more it is seen as us-versus-them, the more doctors will begin playing by their own rules. If that happens, it is everyone's problem."

Angela Fagerlin, Ph.D., a research investigator in the U-M Medical School, is a co-author on the study, along with Rachel M. Werner, M.D., now a research fellow at the University of Pennsylvania, and G. Caleb Alexander, M.D., now a research fellow at the University of Chicago.

—Sally Pobjewski

For more information on the Program for Improving Health Care Decisions or to participate in their "Decision of the Month," go to: www.med.umich.edu/pihcd

The severity of the patient's condition and the "hassle factor" — the amount of time required by the appeals process and the likelihood of a successful appeal — were all directly related to a physician's willingness to deceive the insurance company.



Medical School's 152nd Class Welcomed at Annual White Coat Ceremony

A late-summer downpour did nothing to dampen the spirits of incoming first-year medical students, their families and friends at the University of Michigan's sixth White Coat Ceremony held last August at the Power Center in Ann Arbor. The 170 members of the Class of 2005 donned their first white lab coats to mark the beginning of their medical training. In welcoming the students to Michigan's medical community, Dean Allen S. Lichter (M.D. 1972) told them they are "part of a long legacy and rich tradition," and that part of becoming a physician at the U-M Medical School is taking responsibility for being an alumnus/a of the institution. Dean Lichter acknowledged Detroit-area attorney Karl Schettenhelm, trustee for the Norman Mette Foundation, for the Foundation's ongoing scholarship support, as well as Robert Goldsmith, M.D., representing the Class of 1951 which established a scholarship awarded this year for the first time. The dean also acknowledged the faculty of the Department of Pathology for endowing the Paul W. Gikas Scholarship in honor of the pathology professor and former assistant dean of admissions.

The White Coat Ceremony is sponsored by the Medical School and by the Medical Center Alumni Society, the School's alumni/ae organization.



Visit www.med.umich.edu/magazine to see additional photos from this event.

Kellogg Geneticist Works to Decode Riddle of Macular Degeneration

Macular degeneration is a slow, relentless deterioration of central vision that cannot be corrected with glasses or surgery. Thirteen million people in the U.S. alone now suffer from some form of the disease, a number that will increase to 45 million by 2030. With no cure currently available, scientists are looking to genetic research for answers.

Kellogg Eye Center faculty member Radha Ayyagari, Ph.D., has been studying families in which members of all ages, from teenagers to the elderly, experience vision loss. "Macular degeneration is one of the leading causes of blindness in the world," she says, "and with an aging population, we will see more of this disease in the years ahead."

Macular degeneration is a complex inherited disease whose many forms have puzzled researchers for decades. Although most people begin to suffer the effects of macular degeneration only after the age of 60, some begin to lose vision much earlier. "One person in a family will get the disease in his or her 20s, while a sibling won't be affected until age 50 or older," Ayyagari says. Macular

degeneration is considered a multi-factorial disease because the environment, diet, or some other external factor may combine with one or even many genetic defects to produce the disease.

Ayyagari hopes to clarify the role of genetics in the disease by studying large four- and five-generation families who suffer from "early-onset" macular degeneration. By selecting patients who begin to lose central vision in their early 40s, as compared to the typical onset at age 60, she can collect more — and more varied — information about the progression of macular degeneration. The ultimate goal of Ayyagari's research is to develop treatments that will delay the onset, slow the progression, or prevent the disease altogether. After identifying the gene or genes that cause macular degeneration, Ayyagari will eventually be able to develop a test to help diagnose individuals at risk for the disease.

She is particularly interested in why members of a single family are affected at varying ages — or not at all — and uses a multi-genera-



Radha Ayyagari

tional chart or "pedigree" to give her a picture. "A genetic defect obviously exists," she explains, "but something is protecting certain family members from the disease. If you can identify what stimulates the good gene, you can protect other family members." By studying the disease across generations, Ayyagari hopes to get at the cause — and some day the cure — for macular degeneration.

—Randall Wallach

Discovery of Blood-Clotting Disorder Suggests New Treatment

Researchers led by David Ginsburg, M.D.— a Warner-Lambert/Parke-Davis Professor of Medicine, professor of internal medicine and of human genetics, and a Howard Hughes Medical Institute investigator in the U-M Medical School — have discovered the cause of an inherited blood-clotting disorder, thrombotic thrombocytopenic purpura or TTP, which can lead to deadly kidney failure or stroke.

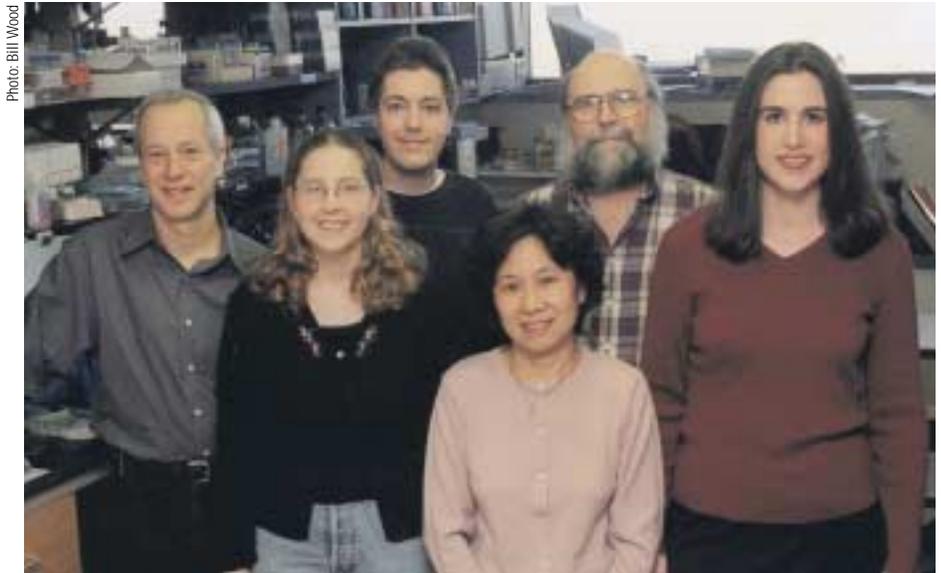
In a paper published in the October 4, 2001, issue of *Nature*, the research team reported that TTP is caused by mutations in a gene that makes an important enzyme ineffective. Now that the cause is known, it might be possible to treat people with TTP by giving them an active form of the enzyme, in the same way that people with hemophilia receive clotting factor.

“The cause of the disease was a mystery,” says Ginsburg. “Patients suddenly became very ill and the only treatment was replacing their blood plasma.”

Earlier studies had implicated a clotting-related protein known as von Willebrand factor (VWF) in the disorder. These studies found that the blood of TTP patients showed an abnormally large form of the VWF protein. The protein had not been cut into two smaller sizes, as is normally the case. According to Ginsburg, this led scientists to believe that a defect in a protein-clipping enzyme called a protease might be responsible for TTP.

An assay developed at the Montefiore Medical Center and Albert Einstein College of Medicine was used to test blood samples from four families with an inherited form of TTP. The assay showed that family members with TTP had low VWF protease activity, while carriers of the disease showed medium levels of activity and unaffected individuals had normal levels.

“The findings seemed too good to be true,” says Ginsburg. “They clearly showed the presence of a recessive gene in which all the carriers, who had one good copy and one bad copy of the gene, had about half the level of protease activity.”



(left to right): David Ginsburg, Beth McGee, David Motto, Angela Yang, David Siemieniak and Gallia Levy

Gallia G. Levy, a graduate student in the U-M Medical School and lead author on the paper, then narrowed the area containing the disease gene to one region of chromosome 9. When Levy studied TTP patients for mutations in this target region, she found the mutations in a gene for a protease called ADAMTS. According to Ginsburg, Levy's findings open the way to understanding how and why this enzyme cleaves VWF and how the failure to cleave the protein causes disease.

“Our current hypothesis is that the large form of VWF is too sticky. Unless the protease cuts it into two smaller forms, it spontaneously sticks to blood platelets and clogs vessels,” says Ginsburg.

“It doesn't appear to take much of this protease to treat the disease and it lasts for awhile in the blood,” Ginsburg adds. “So it might be possible to give people with TTP a periodic injection of the enzyme to maintain their protease activity. Such treatment would work better and be safer than plasma exchange, because of the risk of complications from infusions.”

The research was supported by the National Institutes of Health and the Howard Hughes Medical Institute. Kenneth R. Start, M.D., Ph.D., a U-M house officer in internal medicine collaborated in the study, along with Howard Hughes Medical Institute research specialists Angela Y. Yang and David R. Siemieniak and Beth M. McGee, research technician.

—Adapted by Sally Pobjewski from information provided by Howard Hughes Medical Institute

See the complete story at:
www.hhmi.org/news/ginsburg.html

Learn more about Dr. Ginsburg's research at:
www.hhmi.org/research/investigators/ginsburg.html

Spotlight on Student Research

The 47th Annual Biomedical Student Research Forum last November showcased poster presentations of original scientific research by 60 medical students who participated in summer research opportunities offered by the Student Biomedical Research Program, directed by Brian Zink, M.D., assistant dean for medical student career development. Sixty students from the Undergraduate Research Opportunity Program in the College of Literature, Science and the Arts also presented, in the grand venue of the Michigan League Ballroom, the results of their research studies.

Student investigators worked with U-M faculty who volunteered to serve as research mentors. Below, second-year medical student Joshua Bess presents to Joline Brandenburg, also a second-year medical student, his findings in comparing the effectiveness of an updated version of the computer-based gross anatomy learning aid "Dissector Answers" with its previous 2000 edition. Bess conducted his research under the guidance of Thomas Gest, Ph.D., of the Department of Medical Education's Division of Anatomical Sciences.



Photo: Bill Wood

Ezra Lowe with West Middle School Students Rabia Haji-Hassan, Indrea Joplin and Ryan Gore.



Photo: J. Adrian Wylie

MOMENTS IN

Medicine at Michigan

Ezra Lowe, from Brooklyn, New York, is in his fifth year of working on a Ph.D. in pharmacology

"Pharmacology rocks! It incorporates so many fields — chemistry, molecular biology, physiology. What do drugs do to the body? What does the body do to drugs? Those are the questions that drive the work. You start with a simple idea and then it jumps from a cell to an animal to a human being. Right now I'm working on an enzyme, nitric oxide synthase, seeing how tobacco inhibits it.

I love the reality of laboratory discoveries, the doing, the seeing with your own eyes.

"We have a program, Science Unlimited, where we go into the Ypsilanti Public Schools. We go to middle schools with predominantly minority kids and explain simple science concepts, like how bacteria grow. We'll let the kids run rampant and swab different areas of the school — the floors, the bathrooms, even their mouths. Then we put the swabs on culture plates and come back a week later. When they see the bacteria growing on the plates, there's actually joy on their faces! There was a question and now there's an answer. It's that reality thing. The doing, the seeing with your own eyes. Even kids who've never really experienced science before get it."

"Pharmacology Rocks!"