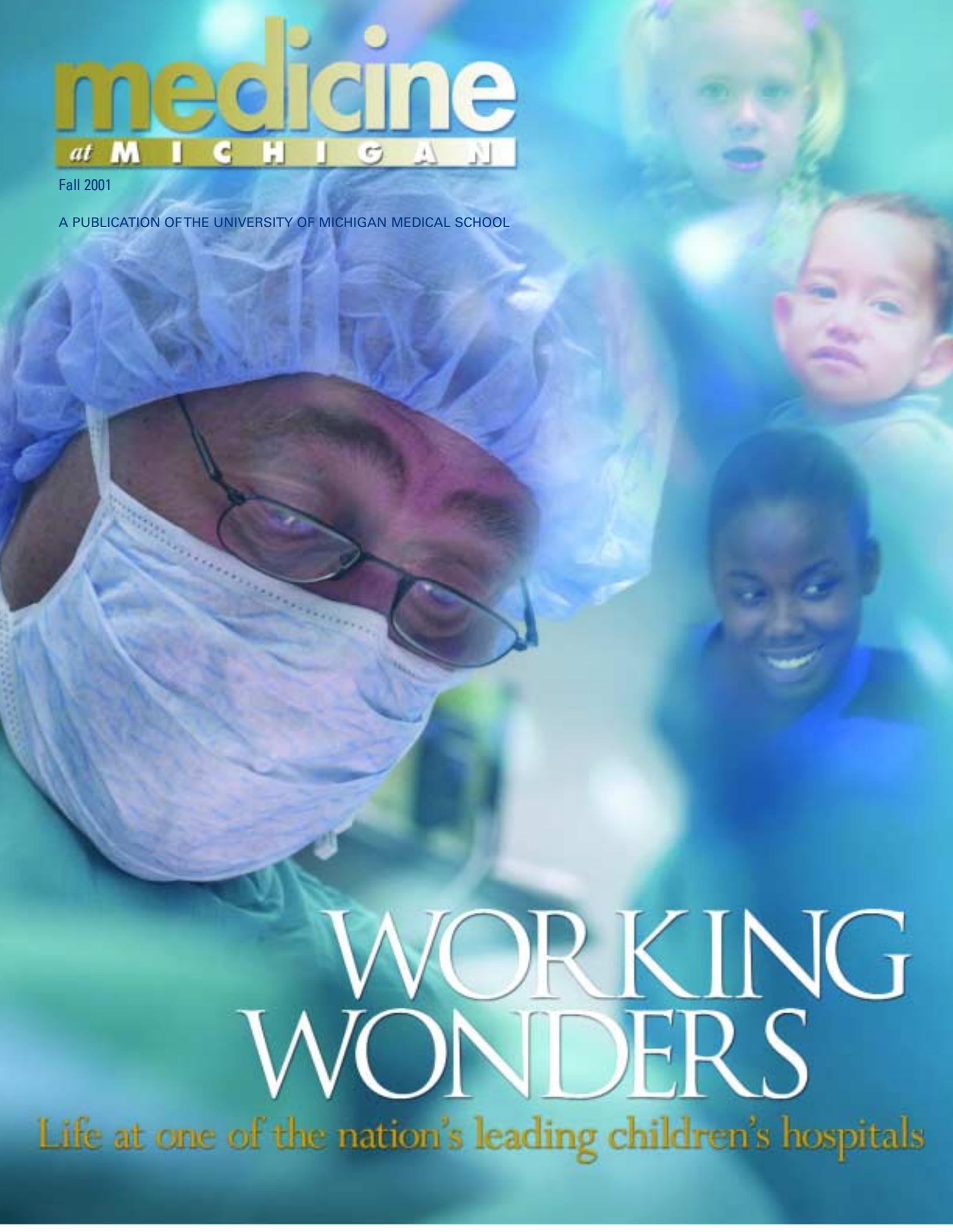


medicine

at M I C H I G A N

Fall 2001

A PUBLICATION OF THE UNIVERSITY OF MICHIGAN MEDICAL SCHOOL



WORKING WONDERS

Life at one of the nation's leading children's hospitals



Above the Huron

MAMA-2B Helps Pregnant Women Buckle Up Safely

A high-tech, pregnant crash-test dummy called MAMA-2B — for Maternal Anthropomorphic Measurement Apparatus, version 2B — is helping U-M physicians and scientists learn more about how to protect a pregnant woman and her unborn fetus during an automobile crash.

Designed by engineers at the U-M Transportation Research Institute (UMTRI), First Technology Safety Systems and Mark Pearlman, M.D., the S. Jan Behrman Professor of Reproductive Medicine in the U-M Medical School, MAMA-2B represents a 30-week pregnant woman and contains sophisticated instrumentation to relate its response in crashes at different speeds and under varying conditions to the likelihood of adverse fetal outcome.

MAMA-2B is part of a multi-phase long-term research study of automotive safety during pregnancy. Results show that good fetal outcomes are more likely to occur when the mother uses correctly positioned lap and shoulder seat belts.

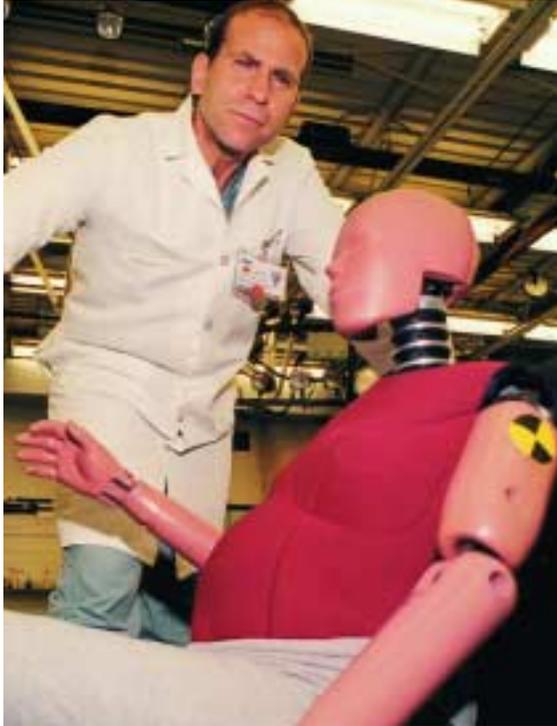
“Creating this dummy was particularly interesting because of the unique anthropometry of a pregnant woman,” says Pearlman, who also is vice chair of obstetrics and gynecology and an associate professor of surgery. “The limited amount of biomechanical data available on injury in pregnant women also presented a challenge.” Pressure measures in the fluid-filled abdomen component, he says, are related to the risk of adverse fetal outcome.

“We estimate that between one and two percent of motor-vehicle crashes during pregnancy may result in an adverse fetal outcome, including fetal death,” says Pearlman. The most common cause of fetal death in a motor-vehicle crash is from *abruptio placentae*. This occurs when the placenta, which supplies nutrients and oxygen to the fetus, prematurely separates from the uterine wall.

Associated projects that supported development of the MAMA-2B included investigations of 43 actual vehicle crashes involving pregnant women. “Examining real-world crashes lets us review how restraints are working to prevent injuries in the field,” according to Pearlman. Another project examined how belt fit and seated anthropometry change over the course of pregnancy.

Pearlman recommends that expectant mothers sit in an automobile seat equipped with both a lap belt and a shoulder belt. “If there is no other available restraint system, a lap belt is better than no belt at all,” he says. Don’t disconnect the air bag, adds Pearlman, but tilt the steering wheel up toward the face and chest, so the bag is not pointed directly at the abdomen.

Photo: Martin Vloet



Mark Pearlman with pregnant crash-test dummy MAMA-2B

To properly protect themselves while driving, expectant mothers should wear the lap belt positioned underneath the bulge of pregnancy, so it can load through the pelvis and not the fetus, says Pearlman. The shoulder belt should ride along the side of the uterus, between the breasts and over the mid-portion of the collarbone. This will leave the pregnancy bulge with as little lap belt or shoulder belt over it as possible and restrain the mother and fetus — preventing the mother from crashing into the steering wheel, dashboard and windshield or being thrown from the car.

Pearlman emphasizes that if a pregnant woman is involved in a motor-vehicle crash, even a minor one, she should contact her obstetrician or nurse-midwife as soon as possible, especially if the trauma occurs in the second or third trimester of pregnancy.

Members of the research team include Lawrence Schneider, Ph.D., a senior research scientist at UMTRI; Jonathan Rupp and Kathleen Klinich, research engineers at UMTRI; and James Ashton-Miller, Ph.D., senior research scientist in the College of Engineering.

—Krista Hopson

Read a related story online at:

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

For more information on Mark Pearlman and his research, go to:

www.med.umich.edu/obgyn/fachompg/pearlman.html

To learn more about health and safety during pregnancy, visit:

www.smartmoms.org/health-safety/index.html

Building Bones to Fight Osteoporosis

The first clinical trial of a new therapy, which uses the patient's own bone marrow to grow new cells and strengthen bones, is underway in the U-M Medical School. If the trial's results show promise, the treatment one day could help millions suffering from osteoporosis — a degenerative disorder in which bones slowly become thinner and weaker.



Robert Lash

“Current treatments try to stop osteoporosis from getting worse and prevent additional bone loss,” says Robert W. Lash, M.D., a clinical associate professor of internal medicine in the Medical School. “One of our goals is to develop new therapies that can help people build new bone.”

Technology developed by Ann Arbor biotechnology firm Aastrom Biosciences, Inc., is an integral part of the new treatment. “We take a small amount of the patient's bone marrow and put it into a special device called the AastromReplicell™

System,” says Lash. “The system grows these cells in very, very large numbers, which we then return to the patient.” When these bone-forming or bone progenitor cells are injected back into the patient they hone in on places in the body with bone — in effect, going where they are needed to strengthen existing bone.

“We hope to give patients enough of these active, bone-forming cells to turn on the bone-producing process to a much greater degree than would occur naturally,” says Lash. Currently, the therapy is being tested on women with significant osteoporosis and is not designed for patients with minimal bone loss or for those who are concerned about bone loss in the future. Lash emphasizes that preventive measures are still vitally important in warding off osteoporosis. “Our goal is always to prevent osteoporosis, and we certainly encourage women to take calcium and vitamin D from their teenage years through their adult years,” Lash says. “We urge people to maintain healthy lifestyles, to exercise, not to smoke, and not to drink excessive amounts of caffeine or alcohol.”



Bone progenitor cells produced in the AastromReplicell™ System for possible treatment of severe osteoporosis. Courtesy of: Aastrom Biosciences, Inc.

—Valerie Gliem

Read the complete story on the Web at:

www.med.umich.edu/1libr/1cellreg.htm

For more information on Robert Lash, visit:

www.med.umich.edu/intmed/endocrinology/Lash.html

For general information on osteoporosis, please see:

www.med.umich.edu/1libr/womens/gyn07.htm

Copper Counts

Copper transport gene vital for healthy embryos?

Copper could be more important to the health of your unborn baby than folic acid, giving up smoking or abstaining from alcohol — according to a new study at the University of Michigan Medical School.

In the June 5 issue of the *Proceedings of the National Academy of Sciences*, U-M scientists report that copper and a protein called Ctr1, which helps copper get inside cells, are essential for normal embryonic development in mice. Although scientists knew that Ctr1 was involved in copper transport in yeast microorganisms, no one knew exactly how the gene worked in mammals until now.

“Since the genetic structure and function of Ctr1 is nearly identical in mice and humans, it is very likely that Ctr1 is essential for human embryonic development, as well,” says Dennis J. Thiele, Ph.D., a professor of biological chemistry in the U-M Medical School, who directed the study.

“Without copper,” Thiele says, “cells can’t produce energy, metabolize iron or detoxify free radicals. Without copper, we can’t grow blood vessels, synthesize neuropeptides that control muscle contractions, or make the collagen that gives our skin its elasticity.”

Thiele’s research team created a new strain of mice by using genetic engineering technology to remove one of two alleles — or copies of the Ctr1 gene — found in normal mice. Although these heterozygous mice appeared and acted normal, U-M researchers found that their brains and spleens contained about half as much copper as was found in normal littermates.

Photo: Martin Voelt



Dennis Thiele

The big surprise came when researchers bred male and female heterozygous mice to see what would happen to mice without either copy of the Ctr1 gene. When Thiele examined mouse embryos from these crosses, he discovered that embryos without the Ctr1 gene all died 10 to 12 days after fertilization. In addition, all these embryos were much smaller than normal and had major abnormalities in organ and cell development.

“I anticipated the importance of copper in development, but I didn’t expect it to be so critical that all the mouse embryos without Ctr1 would die,” Thiele said. “Based on these results, it wouldn’t surprise me to find that human embryos lacking both copies of Ctr1 are aborted spontaneously during pregnancy.”

To test whether copper supplements would help, U-M researchers added it to the drinking water of female

experimental mice three weeks before and during their pregnancies. Although they received 50 to 100 times more copper than control mice, the effect on their embryos was unchanged.

“These data suggest there is no alternate system for copper uptake into cells that can compensate for loss of the plasma membrane Ctr1 transporter, and that the presence of at least one functional copy of the Ctr1 copper transporter gene is essential for normal embryonic development,” Thiele says.



Laboratory mouse on a piece of copper ore.

Photo: Dennis Thiele, U-M Medical School

This research was supported by grants from the National Institutes of Health, the International Copper Association and the American Heart Association.

Jaekwon Lee, Ph.D., U-M post-doctoral research fellow, and Joseph R. Prohaska, Ph.D., of the University of Minnesota-Duluth, were co-authors of the study.

—Sally Pobojewski

Read the complete story online at:

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

Information on Dennis Thiele’s research:

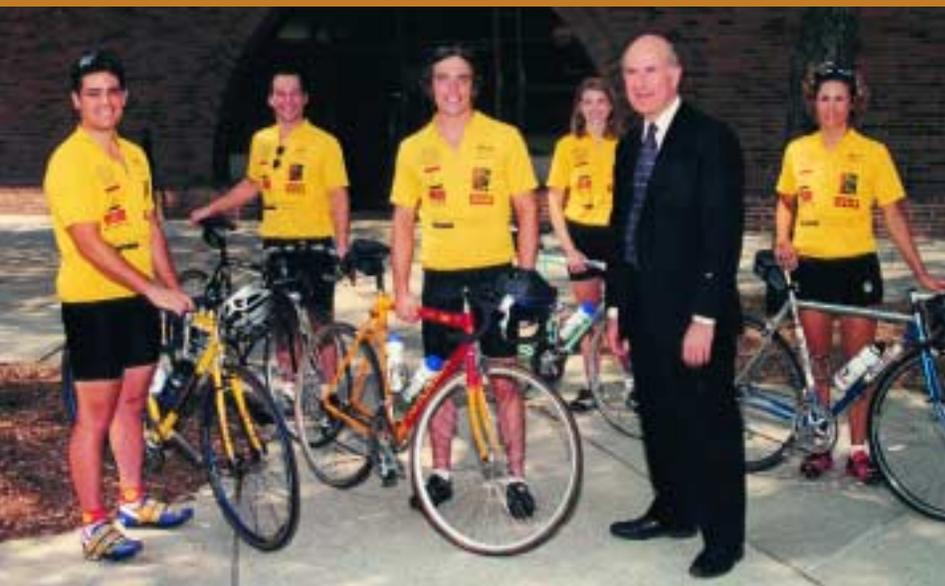
www.med.umich.edu/biochem/all.faculty/thiele.html

For information on copper and health from the International Copper Association, visit:

www.copperinfo.com/health/health_fr.htm

“Based on these results, it wouldn’t surprise me to find that human embryos lacking both copies of Ctr1 are aborted spontaneously during pregnancy.”

—Dennis Thiele



Team DAX members were introduced to U-M Regents at their July 20 meeting by U-M Executive Vice President for Medical Affairs and Health System CEO Gil Omenn and were recognized for their efforts to increase awareness about diabetes. Pictured in front of the Fleming Building, left to right, are second-year medical students Andrew Heyman and Aaron Daniel; Kevin Lochner; second-year medical student Cara Kettler; Gil Omenn; and Barbara Behling.

U.S. News & World Report Ranks U-M in Top 10 “Best Hospitals”

The University of Michigan Health System has once again taken its place among America’s top 10 hospitals, according to an annual ranking released recently by *U.S. News and World Report*. It is the only health care system in Michigan to make the list.

UMHS ranked seventh this year, up from 12th in 2000. Only 15 hospitals make the prestigious *U.S. News and World Report* honor roll.

Three specialties were in the top 10 — ear, nose & throat, geriatrics, and hormonal disorders — including endocrinology and diabetes.

“This honor reflects the commitment of every U-M Health System employee to bring our patients the best care and the latest medical technologies available,” says Gilbert S. Omenn, M.D., Ph.D., U-M executive vice president for medical affairs and chief executive officer of the U-M Health System. “We are all proud of this No. 7 ranking which highlights the national recognition of our clinical care programs that are strengthened by our outstanding research and educational mission.”

The top three hospitals identified by *U.S. News & World Report* were: Johns Hopkins Hospital in Baltimore, Maryland, Mayo Clinic in Rochester, Minnesota, and Massachusetts General Hospital in Boston.



—Valerie Gliem

Biking for A Cure

U-M students ride cross-country for diabetes

A team of students from the University of Michigan took the biggest ride of their lives this summer — a 3,500-mile bicycle trip through 13 states from San Francisco to New York City.

The goal: to increase awareness for diabetes — a condition that affects 16 million Americans and is the seventh leading cause of death in the United States — and raise funds for diabetes research and education projects along the way.

The journey began June 11, 2001, and took about eight weeks. The team traveled between 50 and 70 miles per day along the historic Lincoln Highway, which meanders through mountain passes and deserts, across the Great Plains, and near major metropolitan areas.

“To us, this was kind of an emotional journey, maybe even more so than a physical one,” says Andrew Heyman, a second-year student at the U-M Medical School, and one of the founders of Team DAX — for Diabetes Awareness Cross-country. “I think, in some way, this trip was symbolic of what people with diabetes have to go through every single day. Each of us brought our own special reasons for doing this which, combined, were a source of strength for all of us to reach our goal.”

During their journey, the students stopped at diabetes treatment and education centers recognized by the American Diabetes Association. Team members kept a daily diary of their adventures and posted photos on their Web site.

For information on how to support Team DAX, email TeamDax@umich.edu or visit their Web site at www.med.umich.edu/teamdax.

— Valerie Gliem



Denise Tate and Hope Haefner

For Hope Haefner (M.D. 1985), her year as a fellow in the Hedwig van Ameringen Executive Leadership in Academic Medicine (ELAM) Program for Women was an opportunity to network and discuss topics from mentoring

spring session concludes with a two-day forum, attended by deans of the fellows' institutions.

"We are heavily committed to seeing women advance into leadership in academic medicine," says Allen Lichter (M.D. 1972), dean of the U-M Medical School, "and we recognize that this needs to happen not merely by accident, but by design. ELAM is one of the strongest programs in the country for introducing women to the issues of academic medicine and helping them build the skills needed to advance their careers."

ELAM is sponsored by the Institute for Women's Health at MCP Hahnemann University in Philadelphia, with support from the U-M Medical School, the School of Dentistry and the Office of the Provost. In addition to Haefner and Tate, two other U-M medical and dental faculty women have participated in the ELAM program. They are Lisa Tedesco, Ph.D., vice president and secretary of the

Women in Medicine

ELAM strengthens leadership skills

to financial management. Denise Tate, Ph.D., appreciated the chance to sharpen her negotiating skills, polish her public speaking and prepare to serve as a role model for junior faculty.

"The ELAM program was very valuable to me," says Tate, associate professor and director of research in the department of Physical Medicine and Rehabilitation and director of the U-M's Model Spinal Cord Injury Care System. "It gave me the leadership skills I needed to occupy positions of greater responsibility — administrative skills, financial skills, preparation in personnel management."

"It's an amazing program," adds Haefner, associate professor of obstetrics and gynecology and director of the U-M Center for Vulvar Diseases. "It really reinforced my institutional commitment. Hearing people talk about their departments and institutions made me realize how strong we are, but how we can still improve."

The competitive fellowship program, which selects about 40 participants each year, helps mid-career women faculty at academic medical centers prepare for leadership roles. While U.S. medical and dental schools are attracting increasing numbers of female students, women are still rare in senior academic administrative positions. Of the nation's 125 medical schools, only seven have women as deans; three women (one of whom is an ELAM alumna) serve as deans at the 55 U.S. dental schools.

The effects of this imbalance spill out into society, ELAM administrators believe. Fewer women heading academic medical centers mean less emphasis on women's health issues, they assert. ELAM aims to rectify the imbalance by offering training in the skills, perspectives and knowledge that managers need and by focusing on issues of special concern to women leaders.

The program includes two one-week sessions of intensive study in the Philadelphia area, attendance at the Association of American Medical Colleges annual meeting, independent assignments and an institutional project. The

While U.S. medical and dental schools are attracting increasing numbers of female students, women are still rare in senior academic administrative positions.

U-M, interim provost and a professor in the School of Dentistry; and Eva Feldman, M.D., Ph.D., professor of neurology in the Medical School.

—Nancy Ross-Flanigan

Used with permission of University Record.

Genetic Mutation Increases Risk of Crohn's Disease

Nod2 Gene is Key

Researchers from the University of Michigan Medical School have identified a genetic mutation that increases the risk of Crohn's disease. The discovery provides the first insight into the complex causes and mechanisms of this chronic condition.

U-M scientist Gabriel Nuñez, M.D., with researchers from four other institutions, found that mutations in Nod2, a gene involved in the immune system's initial response to bacterial infection, significantly increased susceptibility to Crohn's disease. Having one copy of the mutated gene doubled the risk of Crohn's disease. Having two copies increased the risk 15- to 20-fold.

Crohn's is a chronic inflammatory disease of the gastrointestinal tract, usually the small intestine. It affects about 500,000 people in the United States and tends to cluster in families. Symptoms include abdominal pain, diarrhea, fever and weight loss. The cause is unknown, but most scientists think the immune system over-reacts to viruses or bacteria in the intestine triggering an ongoing, uncontrolled inflammation.

"There is an important link between bacteria in the gut and genetic factors related to Crohn's disease," said Nuñez, an associate professor of pathology in the U-M Medical School and a scientist at the U-M's Comprehensive Cancer Center whose laboratory originally identified Nod2. "Nod2 could explain this missing-link connection between genes and bacteria."

The Nod2 gene is expressed predominantly in monocytes — primitive defensive cells that can detect and engulf invaders. Nod2 encodes a protein that helps the innate immune system recognize and respond to the presence of a molecule found in the outer membrane of certain types of bacteria.

Working with co-author Judy Cho, M.D., of the University of Chicago, Nuñez found that mutated forms of Nod2 lacked about three percent of the protein found with normal versions of the gene. The mutated gene was less effective at recognizing bacteria and triggering an immune response. So how does a less effective immune response by the gene trigger an over-active immune response in the gut? At this point, Nuñez, Cho and their collaborators say they have more questions than answers. More research will be needed to solve the puzzle.

U-M members of the research team included Yasunori Ogura, Ph.D., Naohiro Inohara, Ph.D. and Felicia Chen. The research was funded by the National Institutes of Health, the Crohn's and Colitis Foundation of America, the Scaife Family Foundation, the Meyerhoff IBD Center, the Logan Foundation and the Gastrointestinal Research Foundation.

— Sally Pobjewski

Read the complete story on the Web at:

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

See Gabriel Nunez's Web page at:

www.pathology.med.umich.edu/faculty/Nunez/biosketch.htm

For patient information on Crohn's disease, visit:

www.niddk.nih.gov/health/digest/pubs/crohns/crohns.htm

Photo: Mark Demming



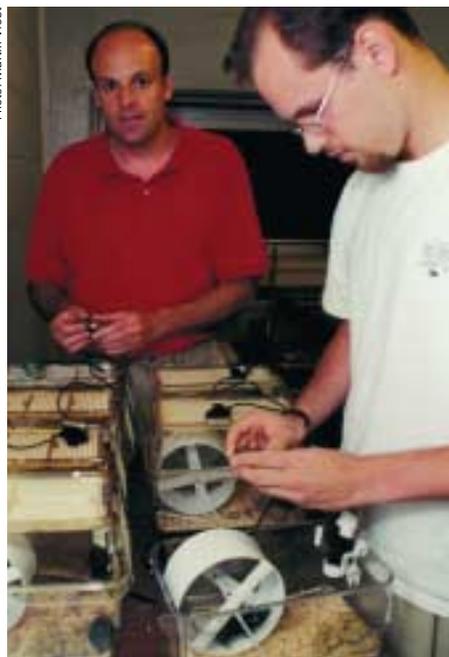
(l to r) Yasunori Ogura, Felicia Chen, Naohiro Inohara and Gabriel Nuñez

Photo courtesy Robin's Pathologic Basis of Disease, 6th Edition, W.B. Saunders



The colonic mucosa and muscularis. The mucosa shows chronic inflammatory cells and granulomas — classic features of Crohn's disease. Inflammation throughout the gut wall, including the muscular layer, is demonstrated by the lymphocytes streaming in between the muscle fibers. A fistula tract, or fissure, is also prominent, developing from the lumen and extending through the muscular wall.

Photo: Martin Voet



While most laboratory mice in the Medical School live under stress-free conditions, mice in the Center for Integrative Genomics have a more spartan lifestyle. This one is helping U-M graduate student Nathan LaCross (right) learn how exercise affects mice with genetic mutations involving obesity and cardiovascular performance. The Center provides expertise and equipment for those studying the complex interactions among genes, organisms and the environment. Joseph M. Metzger, Ph.D. (left), an associate professor of physiology and of internal medicine, directs the new Center.

Cooling the burn

Procedure provides long-term relief from acid reflux

As part of a multi-center clinical trial, U-M Medical School physicians are evaluating a simple, outpatient procedure that could provide long-term relief to the 14 million Americans who suffer from severe, chronic heartburn. Called the Stretta procedure, it was approved by the U.S. Food and Drug Administration in April 2000 to treat gastroesophageal reflux disease.

"In nearly all patients, the procedure gave partial or complete relief from symptoms of gastroesophageal reflux disease," says Timothy T. Nostrant, M.D., professor of internal medicine in the U-M Medical School. Nostrant is lead researcher for the U-M Health System's part of the study. Stanford University coordinated the multi-center trial.

"Patients reported increased quality of life, decreased medication use and continued improvement in symptoms even 12 months after treatment," Nostrant says.

The disease may develop from a combination of factors, says Nostrant, "but the most important is that the valve, or sphincter, separating the stomach from the esophagus is too weak to keep acid in the stomach."

The Stretta procedure uses an intense pulse of radio waves to tighten muscle control at the point where the esophagus, or food pipe, meets the stomach. This prevents acid from traveling upward. U-M gastrointestinal specialists are now offering it to patients whose heartburn has progressed far beyond the occasional post-dinner upset. The procedure uses equipment made by Curon Medical, which sponsored the clinical trial that led to FDA approval.

"It doesn't strengthen the muscles, but instead produces a little bit of scarring between the esophagus and the stomach, which makes the valve less likely to open," Nostrant says.

Photo: Martin Voet



Timothy Nostrant with the Stretta device

On May 23 at the Digestive Diseases Week meeting in Atlanta, results were presented on 119 patients — 72 men and 47 women — who received the Stretta procedure. Sixteen of them were U-M patients. All patients were between the ages of 22 and 75 and all had chronic heartburn or regurgitation, chronic acid exposure in the esophagus, minor hiatal hernia (a condition where part of the stomach protrudes through the diaphragm from the abdomen into the chest) or esophagitis, an inflammation of the esophagus.

At 12 months, two-thirds of patients no longer needed the anti-reflux medications they were taking before the Stretta procedure. Esophagitis was present in 33 patients at the start of the study and in 25 patients six months after the procedure.

Nostrant added that those with severe hiatal hernias, or patients who only experience heartburn occasionally — as much as half the American population — are not candidates for the treatment.

The next step is to continue monitoring patients who received the Stretta procedure to determine its long-term effectiveness. A double-blind study also is planned to rule out the placebo effect.

—Valerie Gliem

See the complete story online at:

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

For more information on Dr. Nostrant, visit:

www.med.umich.edu/intmed/gastroenterology/

Patient information on GERD is available at:

www.niddk.nih.gov/health/digest/pubs/heartbrn/heartbrn.htm

Survival Flight Gets New Pad

University of Michigan Health System survival flight helicopters have a new \$7-million helipad facility that gives critically ill patients and medical staff faster and more direct access to the emergency department through a tunnel under East Medical Center Drive. The new facility replaces a 15-year-old landing pad located on the roof of the U-M Hospital complex.



Photo: Bill Wood

Ultrafast Laser Brings New Precision to Cornea Surgery

Researchers at the Kellogg Eye Center and the College of Engineering have developed a new, ultrafast laser that makes clean, high-precision surgical cuts in the human cornea. The new laser will be used to cut a flap in the cornea — the first step in the popular LASIK vision correction surgery. Because it is more precise than the mechanical blade surgeons now use, it is expected to reduce complications associated with LASIK. Use of the laser for cutting the LASIK flap received Food and Drug Administration approval earlier this year.

“Although useful in treating several eye diseases, current commercial lasers are not able to cut or remove tissue without disrupting the eye’s delicate superficial tissues, which can cause significant inflammation and scarring,” says Ron Kurtz, M.D., an assistant professor of ophthalmology and visual sciences in the U-M Medical School.

Light pulses produced by the laser are so short and intense they are measured in femtoseconds or millionths of a billionth of a second. This enables eye surgeons to make extremely precise cuts with far less damage to adjacent tissue than is possible with current LASIK surgery technology.

Kurtz and Tibor Juhasz, Ph.D., an associate professor of biomedical engineering, co-founded IntraLase™ Corporation to commercialize the new laser with support from the National Science Foundation, the NIH National Eye Institute, and the Department of Defense.

Femtosecond laser technology for ophthalmic applications was developed at the

U-M Center for Ultrafast Optical Science, a National Science Foundation Science and Technology Center, and the Kellogg Eye Center. The research team is now exploring the possibility of extending this technique to other eye procedures — such as corneal transplants or glaucoma treatment.

Others involved in development of the new, ultrafast laser include Gerard A. Mourou, Ph.D., the A.D. Moore Distinguished University Professor of Electrical Engineering and Computer Sciences, who directs the Center for Ultrafast Optical Sciences in the U-M College of Engineering; and Paul R. Lichter, M.D., the F. Bruce Fralick Professor of Ophthalmology and director of the Kellogg Eye Center.

—Randall Wallach

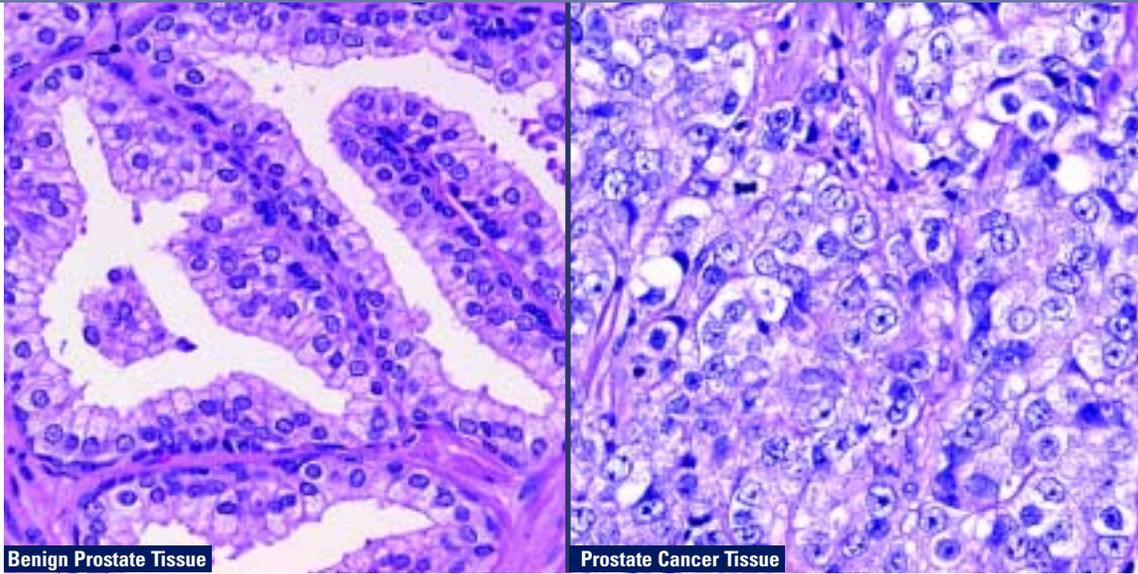
For more information, see the IntraLase Web site at:
www.intralase.com/home.html

See more information from the U-M Kellogg Eye Center on LASIK at:
www.kellogg.umich.edu/LASIK/index.html



Ron Kurtz

Photo courtesy of U-M Department of Ophthalmology and Visual Sciences



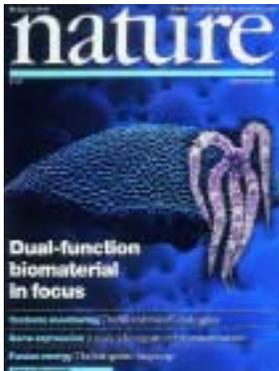
Benign Prostate Tissue Normal prostate tissue (left) has an organized structure with prostate epithelial cells (stained blue) which surround and line prostate glands (white areas). **Prostate Cancer Tissue** Cancerous tissue (right) is completely disorganized. The uncontrolled growth of malignant cells has destroyed the normal glandular structure. Photos: Mark Rubin, U-M Medical School

Cancer's Fingerprint

U-M study links new genes to prostate cancer

Like most killers, prostate cancer leaves fingerprints. Every malignant cell has a unique pattern of active genes and proteins that spells the difference between benign, localized or metastatic tumors. Hidden in this molecular profile are answers to questions doctors hear every day: Is surgery really necessary? Can I afford to wait? Will the cancer come back?

Until now, physicians have been unable to decode these fingerprints, which hold the key to understanding the relationship between gene expression and future prognosis for men with prostate cancer. But a new study from the University of Michigan



Medical School, published in the August 23 issue of *Nature*, offers scientists their first look at the genetic and molecular profile of prostate cancer.

“Our study has important applications in the diagnosis, prognosis and treatment of prostate cancer,” says Mark Rubin, M.D., a co-

author of the *Nature* paper and an associate professor of pathology and urology in the U-M Medical School. “The ultimate goal is to help physicians determine which patients need immediate, aggressive treatment and which can be watched and treated more conservatively.”

Rubin and colleagues at the U-M Comprehensive Cancer Center analyzed prostate tissue samples from 50 men and found nearly 200 genes or gene fragments in which activity profiles varied consistently, depending on whether the tissue was normal or malignant.

They then used DNA “chips” called microarrays to identify which genes were active in four types of tissue. These included normal prostate tissue from men with and without prostate cancer, tissue with benign changes, localized prostate cancer and aggressive, metastatic cancer. Tissue samples were obtained from the U-M Prostate Specialized Program of Research Excellence tumor bank, funded by the National Cancer Institute and directed by study co-author Kenneth Pienta, M.D., a professor of internal medicine and of surgery in the Medical School.

“Microarray technology allows us to look at thousands of genes in prostate cells simultaneously,” says Arul Chinnaiyan, M.D., Ph.D., an assistant professor of pathology in the U-M Medical School, who directed the study. “This is important, because it is most likely that many genes are involved in the development and progression of prostate cancer—each controlling a different step in the process.”

While some of the genes identified in the U-M study are well known to cancer researchers, many others have never before been associated with prostate cancer. Two of these new genes are hepsin and pim-1, which could turn out to be important new clinical biomarkers for prostate cancer, according to Rubin.

“The ultimate goal is to help physicians determine which patients need immediate, aggressive treatment and which can be watched and treated more conservatively.”

—Mark Rubin

Photo: D. C. Goings



Arul Chinnaiyan and Mark Rubin

“This approach could give us many new diagnostic tests for prostate cancer within three to five years,” says Rubin. Eventually, it could lead to a diagnostic kit physicians could use to determine the best treatment and prognosis for their patients with prostate cancer.

The research was supported by the National Cancer Institute’s Specialized Program of Research Excellence in Prostate Cancer. The U-M has applied for a patent on prostate cancer gene expression profiles for future diagnostic and therapeutic use.

Other U-M scientists involved in the study include: Saravana M. Dhanasekaran, Ph.D., research fellow; Terrence R. Barrette, research associate; Debashis Ghosh, Ph.D., assistant professor of biostatistics in the U-M School of Public Health; Rajal Shah, M.D., assistant professor of pathology; Sooryanarayana Varambally, Ph.D., research fellow; and Kotoku Kurachi, Ph.D., professor of human genetics.

—Sally Pobjewski

Read the full story on the Web at:
www.cancer.med.umich.edu/news/relprostate.htm

See Arul Chinnaiyan’s Web page at:
www.pathology.med.umich.edu/faculty/Chinnaiyan/biosketch.htm

See Mark Rubin’s Web page at:
www.pathology.med.umich.edu/faculty/Rubin/biosketch.htm

For patient information on prostate cancer:
www.cancer.med.umich.edu/prostcan/prostcan.html

Photo: J. Adrian Wylie



**MOMENTS IN
 Medicine at Michigan**

Christopher Kim is in his second year of a four-year program combining pediatrics and internal medicine. Born in Seoul, South Korea, he has lived in this country since he was eight.

“I think of myself as American, but the idea of being Korean American will always be with me. Sometimes this cultural heritage helps me relate to a patient.”

“I was working with an adolescent girl with a terminal illness. Her mother was Korean and a lot of people had a hard time dealing with the mother. She was a devoutly religious individual and would oftentimes be very resistant to procedures or certain individuals or treatment methods. Sometimes people thought, ‘Why is this mother behaving this way?’ There were times I thought it through from my American-hospital-physician point of view and I thought her behavior was irrational. At the same time, if I thought it through with my Korean-American background, then I could see where she was coming from. To understand what it is like to be a parent faced with losing a child is impossible, I think, no matter who that parent is. But the fact that this mother was Korean gave me a little extra insight.”

“It’s for that reason that I especially like working with the very young and the very old. In pediatrics, you’re dealing with hearts that are so pure, no ulterior motives. They have a willing spirit and a good spirit and you just want to help them get well, grow up and have fun. What I like about internal medicine is the ability to interact with people who have had multiple life experiences. As you delve into their medical history, you find out how they actualized their illness, what they’ve gone through. And older folks tend to be at a point in their lives where they’re not as bitter about what’s going on. They’ve come to a point of acceptance. They have a certain sweetness about them.”