Mapping the Human Proteome

MICHIGAN PIONEERS GIL OMENN, PHIL ANDREWS AND SAM HANASH EXPLORE THE CHALLENGING WORLD OF HUMAN PROTEINS

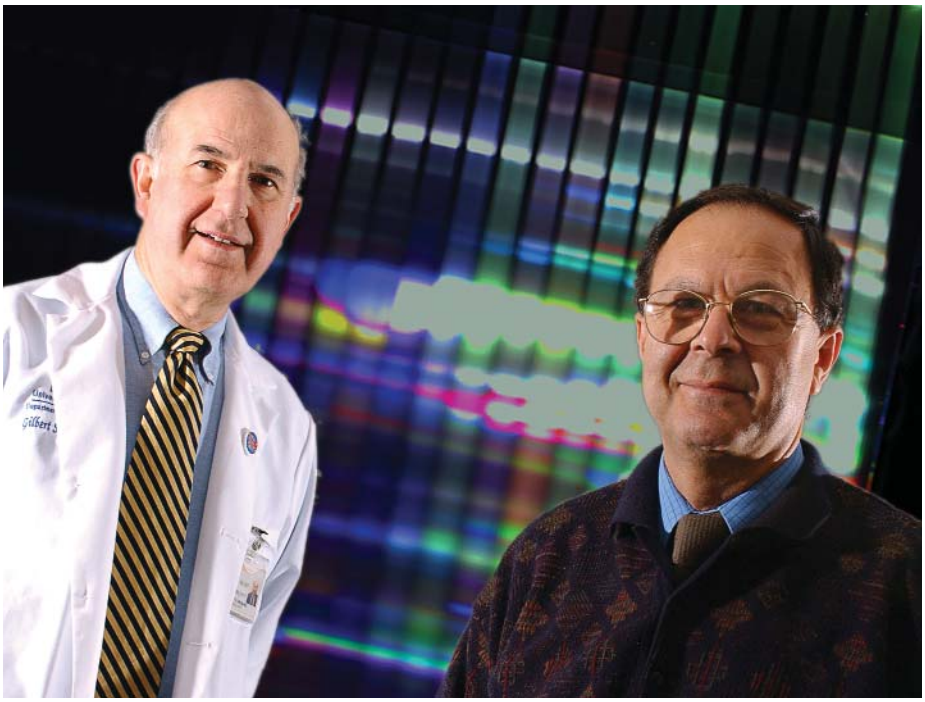
June 26, 2000, was a big day for DNA. At a press conference in Washington, D.C., scientists announced the long-awaited first draft of the genetic code for all 30,000-plus genes in the human body. As reporters struggled to explain the inner workings of DNA to the general public, champagne corks started popping in genetics laboratories around the world. But even as geneticists celebrated the culmination of years of hard work, three scientists in the U-M Medical School were already thinking ahead to the next step: how to map the human proteome. They knew one thing for sure: it wouldn't be easy.

U-M scientists Gil Omenn, M.D., Ph.D., Phil Andrews, Ph.D., and Sam Hanash, M.D. (Ph.D. 1976), are pioneers in proteomics – an important emerging field in the life sciences. While geneticists study the genes in a cell or organism, proteomics researchers concentrate on proteins – complex molecules that do the work of living cells. To understand the function of a gene, scientists must identify the proteins produced when that gene is active and figure out what those proteins do in the cell. When scientists say a gene is active, they mean that a copy of its DNA is being transferred from the cell's nucleus to the ribosome, the cell's protein production plant.

But the path from gene to protein is seldom direct. Unlike genes, which are stored permanently on DNA in the cell's nucleus, proteins are ephemeral. They come and they go, responding to genetic instructions or biochemical signals from other cells or proteins. To make it even more complicated, most genes can produce several variants of the same protein. And interactions with other proteins and signaling molecules can radically change a protein's structure and function.

"We're tracking a moving target," says Omenn, a professor of internal medicine and human genetics in the U-M Medical School and of public health in the U-M School of Public Health. Omenn directs the Human Plasma Proteome Project – one of several initiatives organized by an international collaboration of scientists that make up the Human Proteome Organization (HUPO). "The human proteome contains hundreds of thousands of constantly changing proteins. The proteome's complexity goes to the heart of why proteins are so important, because they are responsive to and mediate changes associated with health and disease."

Photo: Martin Vloet



Gil Omenn and Sam Hanash

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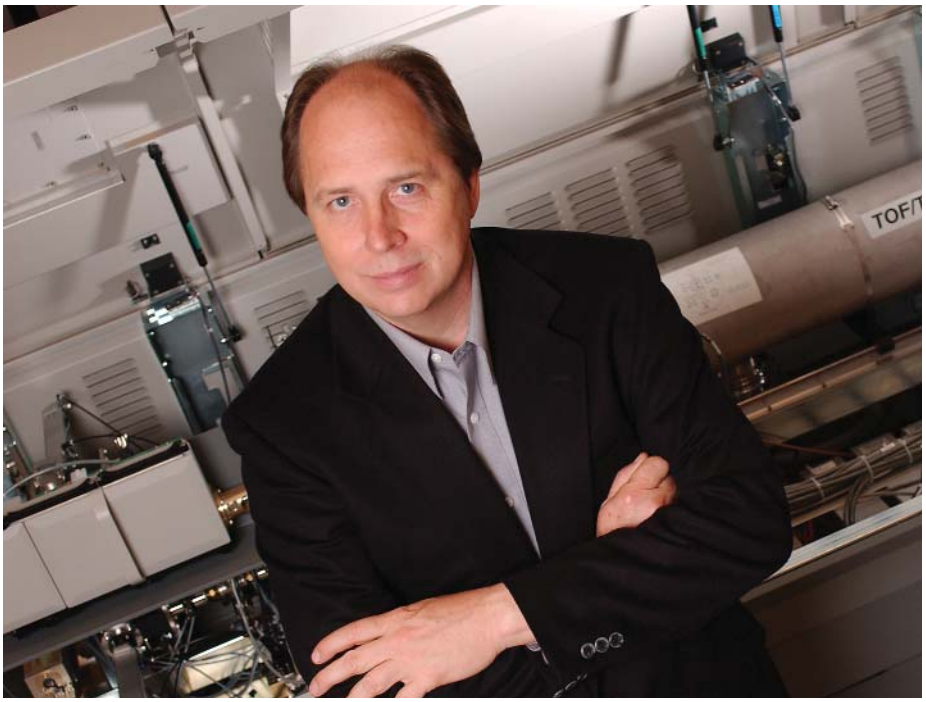
> —*Gil Omenn*

HUPO began in April 2001, when Omenn and Hanash, a U-M professor of pediatrics, met with 30 scientists and policy-makers from several countries to work out a strategy for tackling the challenge of the human proteome. That meeting led to the formation of HUPO, with Hanash agreeing to serve as its first president, and, shortly afterward, a group decision to focus on proteins in three types of human tissue – blood plasma, liver and the brain.

The Plasma Proteome Project was chosen as the first HUPO initiative, because blood is the most accessible human tissue. It's easy to obtain blood samples with informed consent from volunteers or use stored samples from blood banks. "Since blood bathes all cells and organs in the body, it contains proteins which could be biomarkers of changes associated with specific diseases," Omenn says.

The second major initiative focuses on proteins in the human liver. "The liver plays a role in many different diseases," Hanash says. "There are major public health problems related to liver disease, especially in China where hepatitis is widespread and primary cancers of the liver are a leading cause of death. Chinese scientists are taking the lead on this initiative with funding from the Chinese government." Scientists in Germany are leading the third HUPO initiative, which concentrates on proteins in the human brain.

Photo: Martin Vloet



Phil Andrews

Back in 1998, when the field of proteomics was in its infancy, Andrews, a U-M professor of biological chemistry, received a $750,000 pilot grant from the medical school to create the first U-M proteomics center. Andrews used this initial investment to build the basic infrastructure required to receive a $13.7-million grant in 2001 from the Michigan Life Sciences Corridor to provide proteomics technology and expertise to industry and academic investigators throughout the state.

"Proteomics is important to researchers in many specialties, but especially in biomedical research," Andrews says. "Genetic differences between people are reflected in the different mix of proteins in their cells. Proteins show how cells respond to pathogens or chemicals, and how cells change as they age. Proteins also serve as traffic cops directing complex biochemical signaling pathways in the body."

Detecting trace amounts of a protein — which may exist in cells only for fractions of a second — requires extremely sensitive and expensive equipment to rapidly separate, analyze and identify all protein components in a cell sample, according to Andrews. This generates massive amounts of data, which must be processed and stored in powerful, high-speed computers. And, just to keep things interesting, the technology is moving so fast, it is usually outdated within two to three years.

In 2003, Andrews received an $11.9-million grant from the National Center for Research Resources, a branch of the National Institutes of Health, making U-M a national leader for research and development on advanced proteomics technologies.

"This additional funding made it possible to expand our program in emerging proteomics technologies," Andrews says. "For proteomics to reach its full potential, we need to develop more sensitive techniques for use with smaller tissue specimens, new mapping technologies, and improved software and computational tools."

While researchers in the U-M Proteomics Consortium focus on new technologies, HUPO's scientists are concentrating on their immediate goal — developing scientifically valid methods for the preparation and analysis of proteins in tissue specimens. Currently, scientists have many different ways to separate and identify individual proteins in a mixed sample, but no one knows which way is most accurate, reliable and cost-effective.

U-M scientists emphasize that much basic research remains to be done before proteomics can live up to its potential in medicine. But that potential could make all the hard work worthwhile.

"Right now, if you want to diagnose breast cancer, you use mammography," Hanash says. "If your doctor suspects lung cancer, you get a CT scan. For colon cancer, you need a colonoscopy. We're talking about a blood test with screening panels for all the common types of cancer."

"When I was in medical school 40 years ago, only 15 percent of lung cancer patients were still alive five years after they were diagnosed," Omenn says. "Here we are in 2004 and the survival rate is exactly the same. It's even worse for patients with pancreatic cancer. If we had biomarkers for these cancers, we would have a chance to diagnose them at a stage where a surgeon could remove them or they could be targeted with new drugs. That would be a wonderful legacy."

—SFP

Medical School Advances to 7th in Nation

The University of Michigan Medical School now ranks No. 7 among the nation's 125 accredited medical schools, according to the annual "Best Graduate Schools" rankings released in April 2004 by *U.S. News & World Report.*

The school's seventh-place finish continues a steady advance in rankings from 12th in 2000, to 10th in 2001 and 8th the last two years. Only one other medical school affiliated with a public university placed higher than U-M.

U.S. News & World Report also placed the medical school in the Top 10 for four medical specialties: family medicine (5), geriatrics (5), internal medicine (8) and women's health (5).

See complete medical school rankings information at: www.usnews.com

—SFP

Scans Find Urological Problems Other Tests Often Miss

A new procedure requiring one 15-minute scan with a modern computed tomography (CT) machine may be all it takes to find tiny cancers, stones and other problems in the kidneys, bladders and urinary tracts of high-risk patients — saving them from additional tests and the risks of delayed detection and treatment.

Called multi-detector CT urography, or MDCTU, the procedure uses modern CT machines found in many large hospitals. MDCTU can spot problems in the tiny vessels of the body's urine collection system, as well as detect bladder cancer, kidney and bladder stones, and kidney cysts and cancers.

Radiologists in the U-M Health System say that MDCTU is a better option for high-risk patients than the traditional intravenous pyelogram (IVP) or urography (IVU). Often performed on patients with symptoms such as blood in their urine or problems with urination, X-ray exams using IVP or IVU are far less accurate and have high rates of false-positive or false-negative results.

"Our experiences with MDCTU in patients with prior bladder and urinary tract cancers have convinced us that it is as good as IVP — and probably far better — for detecting all abnormalities of the urinary system," says Richard H. Cohan, M.D., a professor of radiology in the U-M Medical School.

"We're able to see tumors as small as two- to three-millimeters, in areas where other exams can't go, and we've been able to save patients the delay and aggravation of coming back for repeated diagnostic scans and procedures," adds Elaine Caoili (M.D. 1993), a clinical assistant professor of radiology.

Working closely with physicians in the Michigan Urology Center, U-M radiologists have spent four years perfecting MDCTU technology. With more than 1,000 patients scanned, they are one of the most experienced MDCTU teams in the nation. Through presentations at medical meetings, U-M radiologists are sharing their methods and encouraging colleagues to adopt the new technique, which they say is extremely sensitive, very accurate and relatively easy to learn.

Photo: Martin Vloet

Richard Cohan and Elaine Caoili

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>
> *—Elaine Caoili*

MDCTU scans use super-fast helical CT scanners, which pass X-rays through the patient's body from many angles and collect them on the other side using multiple detectors surrounding the patient. During the scan, the path of the X-rays is slightly altered by a contrast dye given intravenously to the patient. The dye works its way through the bloodstream into the kidneys and urinary tract, allowing the CT scanner to make detailed images of the patient's entire urinary system in "slices" less than one millimeter thick. Computers combine them to make cross sections and three-dimensional images, which can be viewed in different ways to spot problems.

Says Caoili, "We hope that MDCTU will become the first and only imaging test used for evaluating high-risk patients with urinary system symptoms, and that it will soon allow patients everywhere to get accurate early diagnoses that might improve their clinical outcomes."

—KG

Read an expanded version of the story:
www.med.umich.edu/opm/newspage/2003/ctscans.htm

More information on cancers of the kidney, bladder and urinary tract:
www.cancer.med.umich.edu/learn/leadis.htm

Causes of Yeast Infection Challenged by Study

Women may be able to blame their husbands or boyfriends for headaches, tears and stress, but contrary to popular belief, they can't blame them for common, recurrent yeast infections. According to a new U-M study, certain sexual activities are the real culprits.

"Many physicians, and many women, believe that women get recurrent yeast infections because their partner passes the yeast back to them during intercourse," says Barbara Reed, M.D., a professor of family medicine in the U-M Medical School. "Our study refutes that belief."

The study, which was published in the December 2003 issue of *Journal of Women's Health*, involved 148 women with confirmed *Candida vulvovaginitis* and 78 of their male sexual partners. U-M researchers found many factors were unrelated to recurrent infection. These included the presence of *Candida* bacteria in either the man or woman, number of sexual partners, frequency of intercourse and the woman's age at first intercourse. Receiving oral sex was the most common factor associated with recurrent infection. Research suggests that *Candida* exists in some women in balance with other organisms and immune components in the vaginal area, and that saliva may disrupt the balance, leading to symptoms of yeast infection.

Photo: Gregory Fox

Barbara Reed

The study was funded by the National Institute of Allergy and Infectious Diseases. Other U-M researchers included Philip Zazove, M.D., clinical professor of family medicine; Daniel W. Gorenflo, Ph.D., research investigator in family medicine; and Carl L. Pierson (Ph.D. 1972), assistant professor of microbiology in pathology.

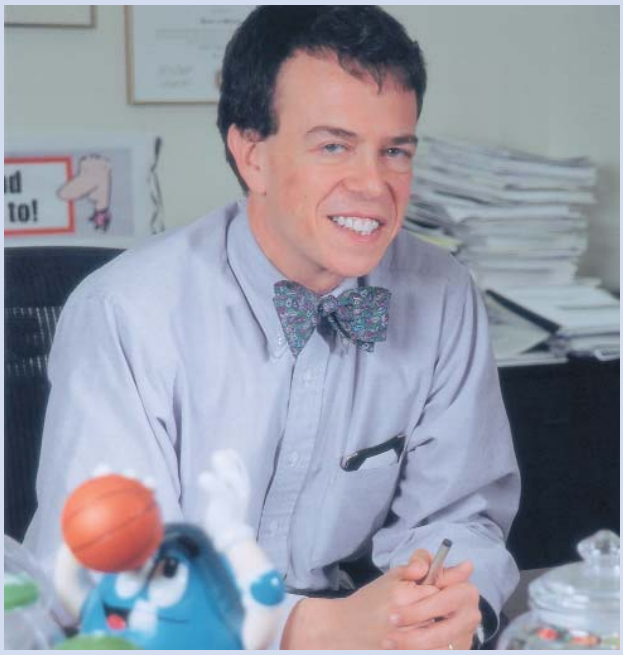
—NF

Read the expanded version of the story:
www.med.umich.edu/opm/newspage/2003/yeastinfections.htm

For patient information on yeast infections:
www.med.umich.edu/1libr/aha/aha_candidia_crs.htm

Physicians Report More Parents Questioning Vaccines

Photo: Marcia Ledford



Gary Freed

Pediatricians and family physicians on the "front lines" of the nation's childhood vaccine delivery system are being asked more questions by parents about the safety and effectiveness of routine childhood vaccinations.

According to a recent national survey, 69 percent of 743 physicians reported a substantial increase in the number of parents' questions or concerns about childhood vaccines. Ninety-three percent of pediatricians and 60 percent of family physicians responding to the survey reported that a parent had refused a vaccination for his or her child.

Many of the concerns reported in the survey involved known short-term effects from vaccines, such as pain and fever. But other concerns were about unproven, or disproved, allegations that childhood vaccines can cause everything from autism to diabetes.

The study was directed by Gary Freed, M.D., M.P.H., the Percy and Mary Murphy Professor of Pediatrics and Child Health Delivery in the U-M Medical School, and his colleagues in the U-M Health System's Child Health Evaluation and Research Unit.

"It's important for physicians to respond with sensitivity to parents' concerns about vaccine safety and be prepared to provide up-to-date, accurate information about side effects and complications, as well as the benefits of vaccination," says Freed.

—KG

For an expanded version of this story:
www.med.umich.edu/opm/newspage/2003/vaccineconcerns.htm

U-M Health System's vaccine safety resource page for parents:
www.med.umich.edu/opm/newspage/2003/vaccinefacts.htm

The Force Surely Was with Him

Yoda, the world's oldest mouse, celebrated his fourth birthday on April 10 in a quiet, pathogen-free rest home for geriatric mice belonging to Richard A. Miller, M.D., Ph.D., a professor of pathology in the Geriatrics Center of the University of Michigan Medical School. At 1,460 days old, Yoda's longevity equates to about 136 human years. The lifespan of the average laboratory mouse is slightly over two years. Sadly, 12 days beyond his remarkable milestone, Yoda, a dwarf mouse, died peacefully with his cage mate, Princess Leia, at his side.

Miller is an expert on the genetics and cell biology of aging. His geriatric mice are providing important clues about how genes and hormones affect the rate of human aging and risks of disease late in life. His current work focuses on identifying defects in T cells from aged mice that interfere with a normal immune response, and finding ways to reverse those defects.

—SFP

Photo: Richard A. Miller, U-M Medical School

Yoda contemplates a model of a fruit fly, the other major genetic model used in research on aging.

Mott Family Network: Computer connections for every child

Photo: Martin Vloet

Patient Adrian Leach plays a flight simulation game on a Mott Family Network computer while recovering from a recent procedure just days before his 17th birthday. Adrian, who lives in Maine, has been a Mott patient most of his life, flying in for care when necessary, and uses the bedside computers to keep up with his homework as well as keep in touch with friends and family back home.

C.S. Mott Children's Hospital is the first children's hospital in the Midwest to provide a computer network connection and computers at every bedside. Patients and their families can access the Mott Family Network at no charge using either a donated Mott computer or the patient's personal computer.

Patients can use the network to access the Internet, e-mail, DVD movies and games. Online educational programs and software are available to help patients keep up with their schoolwork. The network is user-name and password protected to ensure secure and controlled access to online materials.

The project was made possible with funding from the annual C.S. Mott Golf Classic. In addition, several computer corporations donated maintenance support, software and hardware. Nearly 70 U-M employees volunteered hundreds of off-shift hours to design, wire, build and install the computers.

—KH

Read an expanded version of this story:
www.med.umich.edu/mott/newsletter/spring04/p14.html

Inflammation Linked to Deep Vein Thromboses

Photo: Martin Vloet

Daniel Myers and Thomas Wakefield

Thomas Wakefield is trying to figure out exactly what happens inside veins when a blood clot develops. In a recent research study with genetically engineered mice, he and colleague Daniel Myers discovered that inflammatory molecules and immune system cells play a major role in the process.

Deep vein thromboses, or DVTs, are a serious health problem, especially in the elderly. When blood clots form in deep leg veins, they can permanently damage the venous system or even be fatal, if a clot travels to the lungs.

Until recently, deep vein thromboses were thought to be solely a blood or vascular disorder. Now, U-M Medical School scientists have discovered intriguing new evidence to support the idea that the development of blood clots in veins — just like blocked arteries in atherosclerosis — is an inflammatory process.

"When a blood clot develops in superficial veins of the leg — a condition called phlebitis — the redness and swelling associated with inflammation are visible," says Thomas W. Wakefield, M.D., a professor of surgery in the medical school and a vascular surgeon in the U-M Cardiovascular Center. "When a clot forms deep inside the leg, these signs are hidden, so physicians have rarely associated DVTs with inflammation."

Working with Daniel D. Myers, D.V.M., an assistant professor of vascular surgery and animal medicine in the medical school, Wakefield is trying to figure out exactly what happens inside veins when a blood clot develops. In a recent research study with genetically engineered mice, he and Myers discovered that inflammatory molecules and immune system cells play a major role in the process.

One strain of mice used in the study had a genetic mutation, which caused them to have abnormally high levels of a pro-inflammatory molecule called P-selectin circulating in their blood plasma. A second group of mice lacked the gene required to produce P-selectin. The mice were surgically treated to induce thrombosis in the major vein carrying blood from the lower body back to the heart.

Myers and Wakefield found that mice with the highest levels of P-selectin in their blood developed the largest venous blood clots and had more inflammatory cells in their vein walls. Blood from mice with high levels of P-selectin also contained microparticles — small fragments of cell membrane from degraded cells, which accelerate the clot-forming process.

Wakefield says the ultimate goal of his research is finding new ways to inhibit clot formation in his patients by using an anti-inflammatory approach, instead of relying on anticoagulants to treat DVT after it develops. "All current blood-thinning medications can cause serious bleeding problems in patients, so there's a need for new treatment options," he says. "The more we understand about the mechanism of DVT formation, the better our chances of finding safer ways to treat it."

The study was funded by the National Institutes of Health and Wyeth Research of Cambridge, Massachusetts.

—SFP

Read an expanded version of this story:
www.med.umich.edu/opm/newspage/2003/venous.htm

For more information on deep vein thromboses:
www.med.umich.edu/1libr/aha/aha_dvthromb_sha.htm

Zapping Faulty Heartbeats

TECHNIQUE BRINGS HOPE – AND DRAMATIC RESULTS – TO PATIENTS WITH ATRIAL FIBRILLATION

An innovative procedure, tested and perfected at the U-M Cardiovascular Center, completely cures the overwhelming majority of patients with atrial fibrillation — the most common form of irregular heartbeat. Called radiofrequency catheter ablation, it delivers tiny bursts of intense energy that destroy areas of disorganized electrical activity in heart muscle and connecting veins, while sparing nearby tissue.

In recent presentations at the American Heart Association's Scientific Sessions 2003 meeting and an article published in *Circulation*, U-M cardiologists reported that more than 85 percent of U-M Health System patients with intermittent atrial fibrillation were cured after a single session of catheter ablation. After the procedure, these patients no longer needed medications to stabilize their heartbeat and cut their risk of clotting and strokes. Complication rates were extremely low.

"We have treated more than 500 patients in the last three years and have achieved very favorable results," says cardiologist Hakan Oral, M.D., an assistant professor of internal medicine in the U-M Medical School. "It's still a technically challenging procedure, but we hope to continue to simplify and improve it, and train others to perform it."

More than 2.2 million Americans have atrial fibrillation. In addition to causing heart palpitations, fatigue and pain that can be debilitating, the condition greatly increases the risk of stroke and can cause heart enlargement.

The U-M Health System is one of only a handful in the world where catheter ablation is performed. In addition to treating patients with paroxysmal atrial fibrillation, U-M cardiologists treat patients with a much more debilitating and harder-to-treat form of the disorder called persistent AF.

Oral and Fred Morady, M.D., a professor of internal medicine in the U-M Medical School, hope to make more cardiologists and patients aware of radiofrequency catheter ablation's importance in the treatment of atrial fibrillation. Recent developments, including new ablation strategies and the ability to make three-dimensional digital maps of the heart and its electrical signals, have enhanced the procedure, according to Oral. Morady points to increased success at ablating areas in the left atrium wall, rather than just the juncture between the pulmonary veins and the left atrium.

The U-M team's research is funded by the Ellen and Robert Thompson Atrial Fibrillation Research Fund. Other members of the U-M Cardiovascular Center's atrial fibrillation research team include Christoph Scharf, M.D., Aman Chugh, M.D., Burr Hall, M.D., Peter Cheung, M.D., Eric Good, D.O., Mehmet Ozaydin, M.D., Srikar Veerareddy, M.D., and Frank Pelosi Jr., M.D. (Residency 1999).

—KG

Read an expanded version:
www.med.umich.edu/opm/newspage/2003/atrialfibrillation.htm

For patient information on atrial fibrillation:
www.med.umich.edu/1libr/aha/aha_atfibril_car.htm

Photo: Martin Vloet

Fred Morady and Hakan Oral

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