Above the Huron

Medicine Made to Match your Genetic Profile

You say the antibiotic that cured your best friend's bladder infection made you break out in a full-body rash? And the hormone therapy they used to shrink your father's prostate cancer made it grow instead? And the only drug that ever helped your irritable bowel syndrome was just taken off the market, because five people died from its side effects?

Don't blame the drug, says Wendell Weber, M.D., Ph.D., a medical geneticist at the University of Michigan Medical School. The real problem is likely to be your genes.

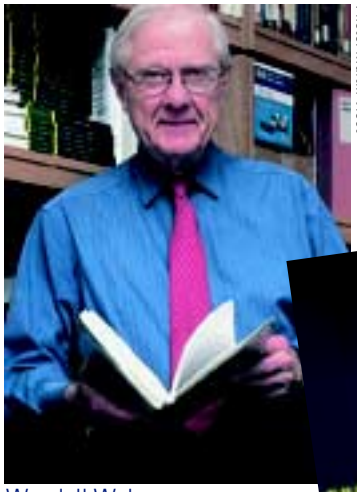

Photo: Martin Vloet

Wendell Weber

"Physicians and patients understand that genes influence health and disease, but most don't realize the harmful effects pharmaceutical drugs can have on genetically susceptible people," explains Weber, a U-M professor emeritus of pharmacology. "Genetic diversity is a major contributor to variations in human drug response."

A pioneer in the field of pharmacogenetics and author of a definitive book by the same name, Weber has devoted his career to studying how small genetic mutations called polymorphisms can lead to big differences in how people respond to drugs or environmental chemicals. The same drug that helps one individual may have no effect on, or even harm, someone else.

The polymorphisms Weber studies can be as small as a one-for-one substitution of amino acids in a gene made up of thousands of amino acids. Like other genetic mutations, they are inherited and can involve single or multiple genes. Polymorphisms are associated with type one diabetes, a serious heart condition called long QT syndrome, susceptibility to asthma, a bleeding disorder called thrombophilia, and an inability to metabolize common drugs like codeine, beta-blockers and antidepressants, which can result in dangerous overdoses.

As the Human Genome Project nears completion, pharmacogenetics is getting a lot of attention, because it could make it possible for physicians to prescribe safer and more effective drugs and therapies tailored to each patient's unique genetic code.

—Sally Pobojewski

For more information on Weber and his work, visit www.med.umich.edu/pharm/weber.html

Kellogg Eye Center Faculty Member Heads National Eye Institute

Leading U-M ophthalmologist Paul A. Sieving, M.D., Ph.D., was named director of the National Eye Institute, the arm of the National Institutes of Health that funds and oversees much of the nation's eye research and education. Sieving, the Paul R. Lichter Professor of Ophthalmic Genetics and director of the Center for Retinal and Macular Degeneration in the Department of Ophthalmology and Visual Sciences at U-M, joined NEI in the spring.


Paul A. Sieving

As the NEI's second director, Sieving will oversee a budget of $510.6 million, a staff of 300 scientists and administrators, and approximately 1,600 research grants and training awards made to scientists at more than 250 institutions across the country and around the world.

"Dr. Sieving joins a distinguished list of U-M faculty in leadership roles in the NIH," says Allen S. Lichter, M.D., dean of the U-M Medical School. "We are proud that our faculty are serving the nation and the world in these important posts."

U-M Medical School Ranks 9th in Nation

Three U-M Medical Specialties also Get Top 10 Status

The University of Michigan Medical School is one of the 10 best research-oriented medical schools in the country, according to the annual "Best Graduate Schools" rankings announced in the April 9, 2001, issue of *U.S. News & World Report*.

U-M tied with Stanford University for the #9 ranking among the nation's 125 accredited medical schools, an increase from last year's 12th place finish. It is one of only two medical schools affiliated with public universities to place in the Top 10. U-M also ranked in the Top 10 for three medical specialties – geriatrics (7), internal medicine (7) and family medicine (8).

"It's gratifying to be recognized by our peers as one of the finest medical schools in the U.S.," says U-M Medical School Dean Allen S. Lichter, M.D. "We have a 151-year tradition of providing our students with the highest-quality medical education in all areas, and we're particularly proud of the talented, dedicated research and teaching faculty who make our success possible."

— Sally Pobojewski

For additional information about the U-M Medical School, visit: www.med.umich.edu/medschool/aboutms.html

Treating the Whole Person:

UMHS, Washtenaw County launch nation's first program linking mental and physical health for Medicaid, indigent patients

In a pioneering effort to bridge the gap between mental and physical health care for Medicaid recipients and indigent patients, the University of Michigan Health System and the Washtenaw County Board of Commissioners have launched a new program that may become a model for the state and the nation.

The $50-million program, called the Washtenaw Community Health Organization, aims to streamline care for thousands of local residents through improved coordination. It brings together the Health System's medical and psychiatric services, and the mental health and substance abuse services provided by Washtenaw Community Mental Health.

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"The program will make it easier to find the best ways to improve care while containing costs," says Tom Carli, (M.D. 1972, Residency 1973), the new program's medical director and a U-M clinical associate professor of psychiatry. "We'll be able to look at how well certain therapies work, examine connections between mental and physical conditions, and determine which diseases and disorders have the highest treatment costs and opportunities for better management."


Tom Carli

"This initiative addresses an immediate, dire need for better and more seamless care for those who often fall between the cracks in the public health care system," says Gilbert S. Omenn, M.D., Ph.D., U-M executive vice president for medical affairs and CEO of the Health System.

The new program is designed to overcome the "disconnect" between mental and physical health care providers. It will make it easier and more cost-effective for persons with a mental illness, an addiction or a developmental disability to receive primary and specialty care for their medical problems at U-M facilities.

— *Kara Gavin*

For the complete text of this article, go to www.med.umich.edu/opm/newspage/WCHO.htm

Photo : Martin Vloet

(Left) **Carly Knazze is a U-M sophomore and member of the women's track team. Record-breaking runners like Knazze have a secret weapon — high levels of a protein called parvalbumin in their skeletal muscle.**

The Heart Promise of Parvalbumin

The same protein that helped Maurice Greene become the "world's fastest man" at the 2000 Summer Olympic Games could one day help millions of Americans who suffer from a common type of progressive heart failure, according to scientists at the University of Michigan Medical School.

The protein, parvalbumin, helps skeletal muscle fibers in the arms and legs contract and relax rapidly and efficiently. Olympic sprinters have high levels of parvalbumin in their skeletal muscle, which helps explain why they can run faster than the rest of us, according to Joseph M. Metzger, Ph.D., associate professor of physiology and of internal medicine. Parvalbumin works like a sponge helping skeletal muscle cells relax faster by soaking up calcium ions.

Photo : D.C. Goings

Joseph M. Metzger

In a study published in the January 15, 2001, issue of the *Journal of Clinical Investigation*, Metzger and a team of U-M researchers show for the first time that parvalbumin also can improve heart function in laboratory rats — restoring normal relaxation rates in hearts with a condition that mimics the abnormally slow cardiac relaxation common in human heart failure. "Our findings raise the intriguing possibility of one day using parvalbumin therapy to treat progressive heart failure in humans," says Metzger.

"In a healthy heart all cells work together like an orchestra with one conductor," Metzger says. "In a heart with diastolic dysfunction, the cells relax too slowly, so the heart pumps inefficiently and body tissues are starved for oxygen."

The gene for parvalbumin is found in every cell in the body, but it is not naturally activated or expressed in heart muscle cells. To test the protein's ability to relax cardiac muscle, U-M researchers used a common adenovirus to deliver human parvalbumin genetic material into heart cells of laboratory rats used in the study.

"This was a proof-of-principle, short-term study," Metzger says. "Since adenoviral vectors elicit an immune response after about six days in animals, they aren't suitable for this application in humans where parvalbumin must be expressed for long periods of time. There are many new adenoviral-related vectors in development, however, which could be just as effective without provoking an immune response."

The U-M study was funded with grants from the American Heart Association, the National Institutes of Health, the Culpepper Foundation and the U-M Center for Integrative Genomics. The U-M has applied for a patent on the technology.

Michael Szatkowski, M.D., a senior research fellow in the U-M Medical School and a neonatology fellow at Thomas Jefferson University in Philadelphia, is first author on the paper. Other U-M collaborators include Margaret V. Westfall, assistant professor of physiology and surgery; Carly A. Gomez, M.D., clinical assistant professor of pediatrics and communicable diseases; Philip A. Wahr, Ph.D., assistant research scientist; research fellow Daniel E. Michele (Ph.D. 2000); graduate student Christiana DelloRusso; and research associates Immanuel I. Turner, Katie E. Hong and Faris P. Albayya.

— Sally Pobojewski

Read the full text of this article at www.med.umich.edu/opm/newspage/parva.htm

U-M Celebrates Start of New Life

The countdown has begun for completion in 2003 of the University of Michigan's Life Sciences Institute. Hundreds of U-M faculty, students, staff and guests attended an official kickoff ceremony on April 11 for construction of the $96-million new research and education facility. The Institute is part of the U-M's Life Sciences Initiative, launched in 1999 as an effort to coordinate and expand teaching and research in the life sciences across campus.

"The Life Sciences Institute will be an intellectual and physical bridge between the medical complex and main campus," says Jack E. Dixon, co-director of the Institute and the Minor J. Coon Professor of Biological Chemistry in the U-M Medical School. "It is an opportunity to bring together scientists from different disciplines, give under-

Cell Biologist and Insulin Expert Joins U-M Life Sciences Institute

There are about 14 million adults living with Type 2 diabetes in the U.S. today who have a vested interest in research at the University of Michigan's new Life Sciences Institute. These are people at risk for kidney failure, blindness, heart disease, amputations and death — all caused by their inability to produce enough insulin or use it properly.

Photo : D.C. Goings

Alan R. Saltiel

"Insulin is the most important hormone in the human body," says Alan R. Saltiel, Ph.D., a cell biologist and the first faculty member appointed to the U-M Life Sciences Institute. "Scientists have been studying insulin for almost 80 years, but we still don't completely understand how it works. Increased understanding is the first step to more effective treatments for diabetes."

Saltiel specializes in the field of signal transduction – the study of how hormones relay their messages within cells. Working with a team of research associates, he recently discovered a series of critical insulin signaling events that take place inside specialized compartments called caveolae in cell membranes.

"Almost every step in insulin's signaling pathway appears to take place in a separate compartment," says Saltiel. "Right now, we are studying a group of unique scaffolding proteins involved in this process. Some serve as transport vehicles carrying proteins and enzymes to different caveolae; some grab two proteins and bring them together."

"Alan is a world class scientist who has made major contributions to our understanding of the molecular pathogenesis of diabetes," says Jack Dixon, Ph.D., co-director of the Life Sciences Institute and the Medical School's Minor J. Coon Professor of Biological Chemistry.

In addition to his Institute appointment, which was approved by the U-M Board of Regents on March 15, Saltiel also was named a professor of internal medicine in the medical genetics division and a professor of physiology in the U-M Medical School.

"Alan's reputation as a research scientist will enhance the strong reputation of our medical genetics division," says David Ginsburg, M.D., the Warner-Lambert/Parke-Davis Professor of Medicine, who is a Howard Hughes Medical Institute investigator and a professor of internal medicine and of human genetics in the Medical School. "Alan's work is integrated with many other U-M researchers, so he will serve as a bridge connecting us to other disciplines. It's a win-win situation for everyone."

> **"Alan's work is integrated with many other U-M researchers, so he will serve as a bridge connecting us to other disciplines. It's a win-win situation for everyone."**
>
> **–David Ginsberg, M.D.**

Scheduled for completion in 2003, the Life Sciences Institute is a new research complex that will serve as a hub for cross-disciplinary research and teaching in the life sciences. Part of the U-M's Life Sciences Initiative, the Institute was established with an endowment of $130 million and will include up to 30 new faculty members.

Joining the U-M Life Sciences Institute is a "unique and special opportunity," says Saltiel. "I look forward to a high standard of scientific excellence in the Institute and to exciting collaborations with U-M faculty in other disciplines."

Previously, Saltiel was distinguished research fellow and senior director of the Department of Cell Biology at the Parke-Davis Pharmaceutical Research Division of Warner-Lambert Company – now part of Pfizer Global R&D. Before moving to Ann Arbor to join Parke-Davis in 1990, he was an assistant professor at Rockefeller University. He also worked as a postdoctoral research scientist at Wellcome Research Laboratories and taught at Cornell University's School of Medicine. Saltiel graduated from Duke University in 1975 and received his Ph.D. in biochemistry from the University of North Carolina in 1980.

—Sally Pobojewski

Sciences Institute

Scott Emr and Jack Dixon

graduate students their first research experience, and provide graduate students with the skills they need for productive careers."

Research at the Institute will focus on cell signaling in biology and human disease, according to Scott D. Emr, professor of cellular and molecular medicine in the Medical School of the University of California-San Diego, who will become co-director with Dixon in July 2002. Many diseases, including cancer and diabetes, are related to defects in cell signaling.

— Sally Pobojewski

For the full article, go to www.lifesciences.umich.edu/news/featurestory.html#home

One of the panels of life sciences artwork displayed along the perimeter of the Life Sciences Institute construction site, created by students at Ypsilanti High School as part of the Health Occupations Partners in Education (HOPE) program. Photos by Bill Wood.

Kellogg Microarray Accelerates Genetic Research at U-M

If all our cells contain the same genetic material, how does each group of cells know what its job is and how to carry it out successfully? The answer lies in differential expression. Studying this aspect of DNA recently got a big boost when the Kellogg Eye Center became one of the first departments in the country to be granted funding from the National Eye Institute to create a Gene Microarray Facility.

Gene microarray, also known as DNA chip technology, allows researchers to study thousands of DNA segments at once, looking for changes in the usual genetic sequence.

The Gene Microarray Facility will ultimately assist researchers who study not only vision, but also hearing, taste and smell. U-M scientists plan to use the microarray on a variety of projects, including macular degeneration, cataract formation, eye development, retinal regeneration, glaucoma, inner ear development and deafness.

The microarray research project team includes Anand Swaroop, Ph.D., project director; Julia Richards, Ph.D., associate director; Mohammad Othman, Ph.D., project manager; and research staff Rafal Farjo, Shigeo Yoshida, M.D., Ph.D.; Jindan Yu and Yuhong Zhang.

—Randall Wallach

Anand Swaroop

Photo : D.C. Goings

Thomas Chenevert, Alnawaz Rehemtullah and Brian Ross

Technology for Tomorrow's Medicine:

TRACKING TUMOR RESPONSE WITH DIFFUSION MRI

Scientists at the U-M Comprehensive Cancer Center are testing the ability of diffusion magnetic resonance imaging to detect the earliest signs of a cancerous tumor's response to treatment. Although the technology is commonly used to diagnose strokes, U-M researchers are the first to report its successful use in cancer treatment.

By analyzing diffusion MRI images, physicians may be able to assess the effectiveness of therapy without having to wait weeks or months until changes in tumor size become visible — according to Brian Ross, M.D., associate professor of radiological sciences and biological chemistry and co-director of the Health System's Center for Molecular Imaging.

By analyzing diffusion MRI images, physicians may be able to assess the effectiveness of therapy without having to wait weeks or months until changes in tumor size become visible.

"One of the biggest problems in dealing with many solid cancers is measuring their response to treatment in a timely way," says Ross. "Even though chemotherapy and radiation kill tumor cells immediately, it can be weeks before the body absorbs enough dead cells to produce a change in tumor size that is visible on a conventional MRI scan."

Diffusion MRI uses a strong magnetic field to align in the same direction molecules of water in the body — like a magnet aligns iron filings on a plate. A computer tracks the direction and speed of these water molecules as they move through and between cells, and then assembles the data into images reflecting differences in water diffusion through body tissues. Healthy cells have unbroken outer membranes that slow water's movement, but membranes around dying or dead cells break down, allowing water to diffuse freely and quickly.

Ross and U-M colleagues Thomas Chenevert, Ph.D., and Alnawaz Rehemtullah, Ph.D., published preliminary findings of studies with animals and two human patients in the December 20, 2000, issue of the *Journal of the National Cancer Institute*. They presented additional data at the American Association for Cancer Research meeting in March 2000. Planning is underway for a multi-center clinical trial to begin late in 2001.

The research was sponsored in part by the Charles A. Dana Foundation, the National Cancer Institute and the U-M Clinical Research Partnership Fund.

—Kara Gavin

For the full text of this story, go to www.med.umich.edu/opm/newspage/diffmri.htm

Medical School Establishes Three New Departments

Neurosurgery, Orthopaedic Surgery and Urology Gain New Status July 1

The University of Michigan regents recently approved the establishment of three new departments — Neurosurgery, Orthopaedic Surgery and Urology — at the University of Michigan Medical School. The departments, all currently sections in the Department of Surgery, will become independent on July 1. All three clinical programs are ranked among the top 25 in the nation by *U.S. News & World Report* magazine.

"These three disciplines have matured into unique areas of clinical, academic and scientific activity, and, like many medical schools around the nation, we have decided to recognize them as such," says Dean Allen Lichter, M.D. "Their new status will enable both staff and students to grow further in their academic careers, and will help the University attract the best faculty and trainees from around the country."

On a national level, all three disciplines have been recognized as distinct from other areas of surgery and medicine by the American Board of Medical Specialties and the Accreditation Council on Graduate Medical Education.

Established as a section in 1920, **Neurosurgery** provides a broad range of adult and pediatric neurosurgical care, and helps advance the field through research and education. The section's 14 faculty offer specialized expertise in brain tumors, cerebrovascular diseases and disorders such as aneurysms, degenerative disc disease, epilepsy, head and spinal cord injury, movement disorders, peripheral nerve disorders, pituitary disorders and spinal disease.

Fourteen physicians are currently training in the seven-year neurosurgery residency program, which dates to 1926 and is recognized as one of the best in the nation. Julian Hoff, M.D., Richard C. Schneider Professor of Neurosurgery and current section head, will chair the Department of Neurosurgery.

Orthopaedic Surgery, founded in 1930, has seen tremendous growth in the past two decades, tripling its faculty to 20 surgeons and three research faculty. Together, the section's staff saw 48,000 outpatients last year and performed more than 4,000 operations on adults and children. More than 40 percent of U-M's serious trauma patients require orthopaedic care.

Clinical care includes advanced approaches to bone and soft tissue cancers,congenital anomalies, fractures, joint implantation, metabolic disorders, reconstructive problems, spine disorders, sports medicine and trauma.


Hoff


Hensinger


Montie

Thirty orthopaedic surgery residents are currently training at the U-M and affiliated sites, in a five-year program founded in the 1930s. Robert Hensinger, (M.D. 1964, Residency 1974), is the current section head and future chair of the Department of Orthopaedic Surgery.

Urology's history at U-M dates to the arrival of its first faculty member in 1920. It became a section of Surgery in 1930. Eighteen urologists, scientists and other physicians form the faculty today, offering specialized care in bladder function and incontinence, prosthetic devices, male impotence and infertility, prostate hyperplasia, urinary stones, and cancers of the prostate, bladder, kidneys and testes.

The section has special expertise in microsurgery and houses the Center for Minimally Invasive Surgery, specializing in laparoscopic and endoscopic procedures, and also provides specialized pediatric urology care to young patients from a wide region.

Fifteen residents are currently training for careers in urology through the section's six-year program, which gives trainees experience in patient care and research at several hospitals. Current Section Head James Montie (M.D. 1971), Vallasis Professor of Urologic Oncology, is the future Department of Urology chair.

—Kara Gavin

> "These three disciplines have matured into unique areas of clinical, academic and scientific activity..."
>
> –Dean Allen S. Lichter

For further information on these departments, visit the following Web sites:

www.med.umich.edu/surg/ortho/
www.med.umich.edu/surg/neuro/
www.urology.med.umich.edu/

Dynamic Leader, Oncologist and Research Pioneer:
Internal Medicine's New Department Chair

Marc E. Lippman, M.D., former director of the Lombardi Cancer Research Center in Washington, D.C., is the new chair of the Medical School's Department of Internal Medicine and the John G. Searle Professor of Medicine.

While directing the Lombardi Cancer Research Center, Lippman also chaired the Department of Oncology at the Georgetown University Medical Center and was a professor of medicine and chief of the Hematology-Oncology Division at Georgetown Medical School.

"Marc is a dynamic leader and a wonderful collaborator," says Allen S. Lichter, M.D., dean of the U-M Medical School. "He is a clear and concise thinker who can envision where research directions are heading. He creates an environment that makes you want to achieve."

Lippman has close, longstanding ties with faculty and administrators at the Medical School. Before moving to Georgetown Medical School, he directed the Medical Breast Cancer Section at the National Cancer Institute — one of the National Institutes of Health — where he collaborated on breast cancer clinical trials with Lichter and taught Max Wicha, M.D., the director of U-M's Comprehensive Cancer Center.

"He was my attending physician when I was an oncology fellow at NIH," says Wicha. "Now the two of us will be seeing patients in clinic one morning each week. It's ironic how we started our careers at NIH together, and now here we are together again at Michigan."

Lippman's groundbreaking research established the critical role of growth factors in the biochemical pathways that regulate tissue and blood vessel growth in breast tumors. In addition to his administrative and clinical duties, Lippman plans to continue his research at U-M.

Lippman graduated from Cornell University in 1964, earned his medical degree from Yale University in 1968 and completed his residency at Johns Hopkins Hospital in 1970.

A gourmet chef, scuba diver, underwater photographer and life-long resident of New York City and Washington D.C., Lippman, in a recent interview, discussed with Sally Pobojewski, science editor for *Medicine at Michigan,* his plans for the Internal Medicine Department and new developments in cancer research.

What attracted you to the U-M Medical School?

This school has an extraordinary scientific infrastructure – not just in the basic sciences, but also in public health, epidemiology and health sciences research. In my previous job running a cancer center, I spent much time dealing with scientists in other fields. What I found — which was inspirational and very exciting to me — is that the technologies used to investigate disease and conduct research on issues related to cell death, cell motility and angiogenesis are essentially the same. I was struck by what fun it is to link across disciplines. Working at a place like Michigan, with its broad expertise and established infrastructure in chemistry, structural biology, proteomics and other disciplines, will enhance my own personal areas of interest.

What is your top priority as department chair?

This is a wonderful department with extraordinary talent whose people need to be reinvested with a sense of mission. My first task is to provide leadership and help the Department of Internal Medicine rediscover itself as an exciting venture in basic and clinical research.

Do you plan to emphasize clinical trials at the Medical School?

I have expertise in translational research – rapidly moving discoveries from laboratory bench to clinic, so I'd like to play a role in that here. There has been less of an emphasis here on formal clinical trials, but that is not true just at

Photos: Martin Vloet

Michigan. The NIH has been slow to fund this area, and since much of the funding has come from for-profit groups or drug companies, it has not been quite as prestigious. But there's a critical need for clinical trials to verify the science and make it useful for human beings.

How do you feel about technology transfer – moving academic research into the private commercial sector?

I'm very enthusiastic about enhancing that activity here. It's certainly true that, with a few exceptions, academic institutions have not received maximum value from their intellectual property. One of the things I'd like to contribute to here is how to deal with our intellectual property in a thoughtful fashion that is beneficial to the institution and to individual investigators' research initiatives.

Not everyone wants to start a company, and that's fine. But if you are an investigator in my department, I have an important responsibility to be sure the investment we made in your research is protected. The idea is not to turn scientists into little businessmen or commercializers, but to provide the right kind of contacts, business sense and commercial guidance, so the institution benefits.

What do you see in the future for academic medical centers?

It is very difficult for an academic medical center to compete solely on an economic basis with a community hospital, because of several distinct missions we need to fulfill that they don't: Number one, we treat the poor. Number two, we train physicians, and that is intrinsically less efficient. Number three, we regard it as our mission to do research.

Our primary goal is not to be a clinical care facility. There is no reason for the U-M to maintain this multi-million-dollar enterprise if our sole goal is to care for the sick. We are an academic center and our goal is to train the next generation of physicians, scientists and health care workers.

There are many more economic pressures on academic medical centers than there used to be, and many medical centers and hospitals have gone under. I use the metaphor of sliding down a roof. Some of us started higher up, and for some, the slope is less steep, but we are all in the wrong position. Financially, we walk a razor edge that requires extreme dexterity, graceful stewardship and some degree of outside assistance from philanthropy or business contacts.

What is the most exciting development in cancer research in the past five years?

The single most important development in cancer research has been a series of clinical trials using agents that directly target the oncogenic causes of cancer and seeing those therapies work. I could name eight to 10 clinical activities — recently approved or about to be approved — which are changing the face of cancer treatment.

Many people think of cancer as a label applied to a cell of origin, like breast cancer or prostate cancer. What we increasingly appreciate is that, whatever the tissue of origin, there are a limited number of molecular pathways involved in cancer's development that have no relationship to the cell of origin.

Cancer is not a single disease and it has a multiplicity of causes. Understanding the causes of disease almost inevitably results in improved treatment. We are seeing that in cancer at astounding rates today.

Fifteen years ago, testicular cancer was 98 percent lethal. Now it is 96 percent curable. Mortality rates for breast cancer are plummeting. When I entered the field 31 years ago, one of every two women diagnosed with breast cancer died of the disease. Now the mortality rate is 19 percent. That's unbelievably gratifying.

—Sally Pobojewski

Internal Medicine is the Medical School's largest department. The Department's 368 faculty members brought in $73 million in research funding last year – in addition to teaching medical students, directing house officers and providing clinical care for patients in the U-M Health System.

U-M Neurosurgeon Urges Women to Protect their Children by Taking Folic Acid

Fast Facts about Folic Acid

Folic acid is a common B vitamin found naturally in grains, fruits, leafy green vegetables and beans. It is also available in synthetic form in vitamin tablets and in fortified foods.

Neural tube defects are birth defects that occur in about 2,500 babies and numerous stillborn and miscarried fetuses each year in the U.S. The defects occur when development of the brain or spine during pregnancy does not progress normally.

Evidence suggests that more than half of all neural tube defects could be prevented if women got enough folic acid during pregnancy.

Since more than half of all pregnancies are unplanned, it's important for all women of childbearing age to get enough folic acid all the time, in case they become pregnant. Many neural tube defects occur before a woman even knows she's pregnant.

Folic acid may help prevent heart disease, stroke and other birth defects.

The recommended daily dose of folic acid for all adults is 400 micrograms per day. Many multivitamins contain this much, and breads and cereals are fortified with extra folic acid.

To learn more about folic acid, check these Web sites:

March of Dimes at http://www.modimes.org/Programs2/FolicAcid/

Centers for Disease Control and Prevention at http://www.cdc.gov/nceh/cddh/folic/folicfaqs.htm

Photo: Lin Goings

Karin Muraszko

In her career as a pediatric neurosurgeon, Karin Muraszko, M.D., has helped hundreds of children born with debilitating spinal birth defects — while coping with the effects of her own, a mild form of spina bifida.

If all women of childbearing age took vitamin supplements and changed their diets to include more foods rich in folic acid, Muraszko explains, the result could be fewer babies born with neural tube defects — abnormalities in the developing brain or spinal cord.

Evidence suggests that more than half of all neural tube defects could be prevented if women got enough folic acid during pregnancy.

"Folic acid appears to be extremely important in the development of the fetus," Muraszko says. "It's vital for women in their childbearing years, because it affects the fetus at a crucial time in development when the brain and spinal cord are forming. Since this occurs within the first four to six weeks, generally before a woman even knows she's pregnant, it's extremely important that women take folic acid before they become pregnant."

The same advice holds true for women in their child-bearing years who aren't even planning to have a baby, Muraszko adds, since more than half of pregnancies aren't planned. That's why many experts suggest that all women of childbearing age take a daily multivitamin that contains the recommended 400 micrograms of folic acid.

Muraszko hopes her messages can help reduce the number of children coming to her for help. "As chief of pediatric neurosurgery, I spend much of my time caring for children with complex neural tube defects, and I see the effect it has on their lives," she explains. "And as someone with a mild form of spina bifida, I know what it's like to live life with a disability."

How can such a simple nutrient stop such a complex problem? The exact mechanism is unclear, but Muraszko explains that it has to do with the intricate process of fetal development, in which different tissues and organs form during pregnancy. The neural tube is the structure within the fetus that develops into the brain and spinal cord. In most cases, the process goes smoothly. But in some pregnancies, something goes wrong during neural tube development.

If the brain develops abnormally, the child can be born with a condition called an encephalocele, in which the brain is not entirely contained within the skull. Or they can fail to develop a full brain, a fatal condition called anencephaly that usually results in miscarriage or death soon after birth. A birth defect caused by a problem in spinal cord and spine development is called spina bifida, and can range from a small defect in the spine to a serious condition called a myelomeningocele.

"In these children, the spinal cord doesn't form properly. It is simply an open flat area in which there isn't any covering on the spinal cord," Muraskzo says. "This happens within the first month of pregnancy, and these children are affected for the rest of their lives. They often have other anomalies, which make it difficult for them to walk and control their bladder and bowel. They often have difficulties with brain development, as well."

The fact that there's an easy way to prevent such dramatic and life-altering conditions should be enough to convince women to get more folic acid, Muraszko says. Scientific studies have shown that a significant number of neural tube birth defects could have been prevented, if only the mothers had gotten enough folic acid before and during pregnancy.

—Kara Gavin

Find the full text at www.med.umich.edu/opm/newspage/folica.htm

Can a Vitamin a Day Help Keep Heart Disease Away?

Photo : Martin Vloet

Mark Fendrick

Americans could live longer, healthier lives if more of us got the Food and Drug Administration's recommended daily amount of folic acid and vitamin B12, according to U-M researchers. The benefit would be most cost-effective if people with elevated blood levels of homocysteine, a harmful amino acid, took daily multivitamin supplements. Although the reasons are unclear, scientists believe homocysteine is associated with an increased risk of heart attacks and strokes.

The finding, published in the December 11, 2000, *Archives of Internal Medicine*, backs up recent calls for middle-aged Americans to get more of both nutrients. The study was based on a computer model that analyzed costs and benefits of folic acid/B12 supplements in light of what's known about homocysteine's harmful effects and folic acid's ability to lower levels of homocysteine in the blood.

Gilbert S. Omenn, M.D., Ph.D., U-M executive vice president for medical affairs and CEO of the U-M Health System, was a co-author of the study. "It will be years before current clinical trials will show definitively how much we can reduce heart disease risk by reducing elevated homocysteine levels. This analysis suggests we should go ahead now and encourage blood testing and increased intake of folic acid and B12 through diet or supplements," says Omenn, who co-authored a major study on homocysteine which was published in the *Journal of the American Medical Association* in 1995.

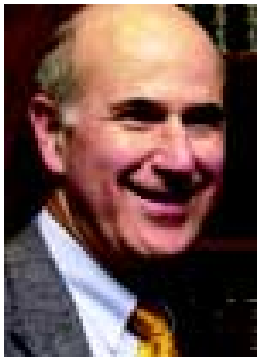

Photo : D.C. Goings

Gil Omenn

The research model used in the current U-M study is called a decision analysis. It's especially helpful in situations when physicians have a lot of information about a substance's potential risk or benefit, but no conclusive proof, says co-author Mark Fendrick, M.D., of the U-M's Consortium for Health Outcomes, Innovation and Cost-Effectiveness Studies, or CHOICES.

"Homocysteine is a notable case of a known medical risk where we strongly suspect a possible benefit from an inexpensive intervention. This conservatively designed study suggests that the benefit doesn't need to be very large to make the intervention worthwhile," Fendrick says.

Homocysteine and related compounds are found everywhere in the body. Laboratory studies show these compounds can damage the lining of blood vessels, encourage more smooth muscle cells to grow in vessel walls, and create an environment in which blood clots more easily — all risk factors for clogged arteries and heart disease.

Some — but not all — studies have found that people whose homocysteine levels are even mildly high are more likely to have heart disease, and that risk rises with levels above 11 micromoles per liter. An estimated 40 percent of men over 40 years of age and 32 percent of women over 50 years of age fall into this group.

Fortunately, scientists have found that folic acid can lower homocysteine levels by helping in its breakdown. They've determined that the most effective dose for this effect is 400 micrograms (mcg) a day; higher doses don't seem to lower homocysteine levels much further. It takes about six weeks for folic acid to bring levels down. Vitamins B12 and B6 can help, also. 400 mcg is also the Food and Drug Administration's recommended daily allowance for folic acid, based on its proven ability to prevent neural tube defects in babies if their mothers get enough of the nutrient.

Because there's evidence that high folic acid can mask a vitamin B12 deficiency, the U-M group and others recommend that B12 be taken with folic acid supplements. Most multivitamins contain both nutrients, as do whole grains, oranges and green vegetables.

The U-M study was funded in part by the Agency for Healthcare Research and Quality. The paper's authors also include Brahmajee Nallamothu, M.D., Sanjay Saint, M.D., MPH, Melvyn Rubenfire, M.D., and Rajesh Bandekar, Ph.D.

—Kara Gavin

For more information, read the complete story on-line at:

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

Disabled, Elderly Women Who Live Alone Are Less Likely to Get Help

Who is caring for elderly, disabled Americans who live at home, but need assistance with daily activities like bathing, eating, managing money or taking medications? Two recent studies by U-M Medical School researchers suggest that those who most need help may be less likely to get it.

According to a study published in the February 2001 issue of *Medical Care,* unmarried people age 70 and older who lived with their adult children received about 40 hours a week of Medicare-paid home care, compared with just 26 hours received by unmarried elders who were equally disabled and lived alone.

"Having an adult child on hand to navigate the Medicare system seems to have a major impact on the amount of home care the elderly receive," says Kenneth M. Langa, M.D., Ph.D., assistant professor of internal medicine.

Another study, published in the December 2000 issue of *The Journal of the American Medical Association,* found that disabled, older women – whether married or single – received about one-third fewer hours of informal home care from family members than disabled men.

"Providers can't assume that disabled female patients are getting the care they need, even if they live with a spouse," says Steven J. Katz, M.D., associate professor of internal medicine in the Medical School and associate professor of health management and public policy in the School of Public Health.

> "Having an adult child on hand to navigate the Medicare system seems to have a major impact on the amount of home care the elderly receive."
>
> —Kenneth Langa

Photo: Martin Vloet

Kenneth M. Langa

Photo : Lin Goings

Steven J. Katz

"In the next 50 years, more and more disabled elderly people will need help, but the number of grown children available to help care for them will continue to decrease," says Katz. "This leaves health care providers and health policymakers with the responsibility of finding the best ways to meet their needs."

The studies are based on 1993 and 1995 data from the national Health & Retirement Study, a survey of more than 3,000 Americans aged 70 and over who live in the community, rather than a nursing home or assisted living facility. Funded by the National Institute on Aging, the Health & Retirement Study is conducted at the U-M Institute for Social Research.

—Diane Swanbrow and Valerie Gliem

For more information, read the complete articles on-line at:

http://www.med.umich.edu/opm/newspage/homecare.htm

http://www.umich.edu/~newsinfo/Releases/2001/Feb01/r020701.html