

rocket science

The University of Toledo
College of Medicine

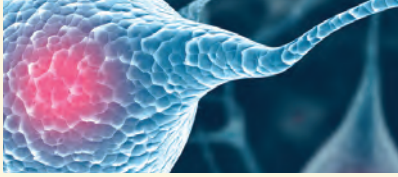
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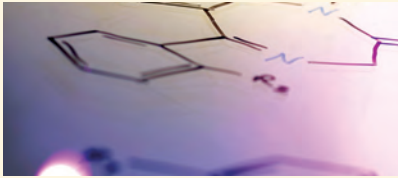
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Exploring the inner workings
of **neurobiology** See page 9



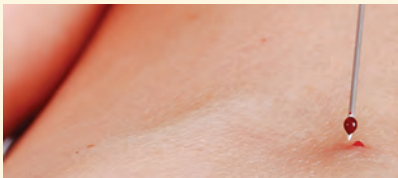
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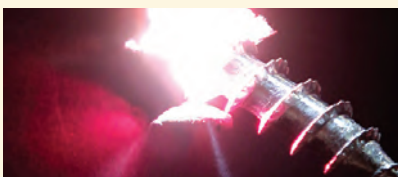
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Joining the Club of 100

Wade into the names of top-flight medical schools and teaching hospitals and you likely will see Ivy League institutions like Harvard and Yale or Berkeley.

These institutions are among about 100 historically elite universities —the leading public and private research universities and academic health care systems — whose faculty members set the educational and clinical standards in most disciplines, whose research wins Nobel prizes and fuels the engines of innovation and inspiration for new industries, and who have earned enviable reputations.

These universities also operate medical schools and clinical enterprises that have earned outstanding reputations and that often appear at the top of surveys and national rankings. Highly regarded nationally and globally in their scope and vision, they offer superb education for talented, motivated health-professions students drawn from every part of the country, conduct leading-edge basic and clinical research that lead to new advances in diagnosing and treating diseases, and operate teaching hospitals that offer high-volume, technologically advanced care by passionately committed staff to patients affected with both physical and social ills. They are institutions that strive to be the best they can and focus on doing the right thing. They have left a deep impress on American medicine, and today are changing its future.

We want The University of Toledo College of Medicine and the UT Medical Center to join this group — what I have called in talks “The Club of 100” — to rank among the top tier of the nation’s academic medical centers, the kind of robust institution that people talk about nationally, an academic health center that aspires to compete with top national performers.

Whether we like it or not, medical schools and teaching hospitals compete for students, faculty members, research scientists, research funding, philanthropic backing, patients and the prestige that comes with being nationally regarded as an elite academic health center. Patients deciding where to get health care as well as prospective medical students and faculty members often are influenced by such rankings as part of their decision-making. They want to be part of top-flight institutions.

This is a worthwhile goal, but to achieve it the medical school and clinical enterprise will have to continue to address and overcome several challenges.

First, too many patients continued to be referred to hospitals in Ann Arbor, Cleveland, Columbus and other cities despite the fact that safe, high-quality and sophisticated treatments are available much closer to home. Losing those patients limits our ability to expose medical and other health-professions students to a wide variety of diseases, to recruit medical students and new faculty members, to participate in clinical research studies of new medications and procedures, and to put the hospital on firm financial footing. Simply put, Toledo needs to become the medical destination for northwest Ohio, regional and national patients.

Our full-time clinical faculty members, who number over 200, are productive, talented and committed, but additional numbers are needed to achieve a more critical mass.

Our basic science and translational research is high quality and of reasonable scope and scale. Our clinical research is high quality, but limited in scope and scale. The research being conducted by our residents and fellows is outstanding, but they are burdened by their clinical duties, leaving inadequate time for research. Bolstering basic and clinical research can help stimulate the high-technology industry and further the regional engagement and economic growth in the state. Academic health science centers not only provide remarkable care, but truly provide regional “tangible wealth” as well through technology transfer and commercialization.

Important tertiary and quaternary fellowships and residencies are absent, and the geographic distribution of clinical education sites for third- and fourth-year medical students has proven to be logistically challenging and variable in quality for selected clinical services.

Our drive to join the nation’s elite medical schools and teaching hospitals comes at a difficult time, a period when:

- Ohio has been hit by an economic “perfect storm.” The traditional economic engines — automotive, tire, steel and appliance manufacturing — have lost jobs, jobs that are never coming back, making Ohio’s transformation to a knowledge- and information-based economy with a more skilled work force more important than ever;
- The health status of northwest Ohio residents is generally poor and the overall cost of care is generally high;
- Ohio’s work force of medical and other health professionals is disproportionately aging and in some areas increasingly inadequate;
- The regional pipeline of health-care faculty and residents is slowly drying up. Over the next 20 years, as the baby-boom generation of physicians retires, there will be an extreme need for physicians;
- The complexity of care needed for both acute and chronic care delivery is growing; and
- An increased need exists for expanded modern venues for medical education for all health care.

Despite these challenges, there are solid reasons for optimism about the future of the UT College of Medicine, the UT Health Science programs and the UT Medical Center.

First, northwest Ohio civic, business, and government leaders increasingly recognize the strong link between UT and region’s economic prosperity and how essential a strong elite research university is at a time when strong international economic forces have transformed a state whose prosperity once rested on automotive, steel, tire and appliance manufacturing. The reputation, the prestige and the visibility a medical school and teaching hospital provides UT has proven to be a major advantage in terms of its general public purpose and benefits to the community. The UT-MUO merger has garnered national recognition, creating an entity increasingly known for excellence and vision.

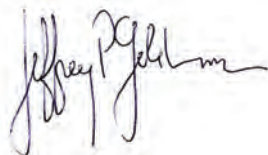
Second, health care continues to be a growth area for northwest Ohio. Toledo wouldn't be where it is without the health-care sector, which generates thousands of high-paying jobs, gives outsiders a reason to want to come here, fuels economic activity on several levels and floods the region with money. Billions in payroll and investment in capital projects are paid out and tens of thousands of jobs are indirectly created through an economic trickle-down effect.

Third, the transformation of the College of Medicine and the clinical enterprise that started in 2003, when Dr. Lloyd A. Jacobs became president of the former Medical College of Ohio, continues. Our fundamental strategy has been to grow, to maximize the physical infrastructure and the assets of the college and medical center, to reallocate funds in order to do new things, and develop high-performance expectations. That has resulted in a sharper focus on first-class teaching and highly focused path-breaking research. We are constantly striving to improve and augment our educational, patient-care and research programs in order to better fulfill our mission to improve the human condition. We continue to attract talented medical and graduate school applicants, and residency program directors continue to find our graduates among the best prepared in the country.

Health education, biomedical research and patient care have the potential to be a means to economic recovery in the short term and a major building block in the state's long-term economic future. The UT College of Medicine and the UT Medical Center can make that happen.

There's always trepidation when you set ambitious goals. But we want to begin thinking of The University of Toledo College of Medicine and UT's clinical enterprise in a new, different way and to shape and forge its reputation, rather than letting others do it for us. UT must strive to be a great public university within Ohio with values, traditions and goals that reflect and support the culture of the state's citizens while participating in a global health care economy. But it also must strive to have academic programs, strategic partnerships and ferment intellectual excellence that characterize great universities like Johns Hopkins, Stanford, Yale and others that have traditionally influenced the nation and the world.

Sincerely,

A handwritten signature in black ink, appearing to read "Jeffrey P. Gold". The signature is fluid and cursive, with the first name "Jeffrey" and last name "Gold" being the most prominent parts.

Jeffrey P. Gold, M.D.
Health Science Campus Provost
Executive Vice President for Health Affairs
College of Medicine Dean

CAMPUS CAPSULES

University names New York scientist as new physiology, pharmacology chairman



Dr. Abraham

Nader G. Abraham, Ph.D., DR.H.C., has assumed duties as the new chairman in the Department of Physiology and Pharmacology in the College of Medicine.

An internationally recognized scientist in the field of molecular biology and gene transfer, he previously served as professor of pharmacology and director of stem cells and gene therapy at New York Medical College in Valhalla, N.Y. He has also been on the faculties at Rockefeller University and the New York University School of Medicine.

He is former chairman of the International Society of Experimental Hematology, and has served as chair of The International Symposium on Treatments of Leukemia and Cancer.

His research has focused on the protein heme oxygenase and its relationship to different diseases such as leukemia, high blood pressure and diabetes. He lectures extensively throughout the world, and has authored or coauthored more than 250 peer-reviewed articles and more than 50 book chapters or reviews. He is editor of seven books and also serves on several National Institutes of Health review committees.

Lab renovation pulls researchers together, modernizes facilities

The University of Toledo College of Medicine has completed a \$3 million laboratory renovation aimed at improving coordination and cooperation between researchers.

Eight professors and about 30 students and staff in the Department of Medical Microbiology and Immunology will ultimately occupy the 15,000-square-foot lab space, which was dedicated at a Jan. 6 event in the Health Education Building on Health Science Campus

Department Chairman Dr. Akira Takashima said the layout of the renovations was just as important as the new equipment and facilities.

"Traditionally, individual professors have pursued research projects independently in their own laboratories," Takashima said. "The new lab space has an 'open lab' concept where multiple professors with overlapping research interests share a large laboratory, as well as many research instruments and equipment."

He explained the design was chosen to promote "accidental collaboration," those casual conversations between researchers that have formed the basis for countless scientific breakthroughs.

"Scientific progress is not something you can plan. You may be wrestling with a challenge for years and suddenly



Dr. Takashima

one conversation with a colleague will enable you to see that challenge in a unique way," Takashima said.

He said such an interaction already has occurred between two professors who

just moved into the space and have joined together to study the role blood components play regarding immune responses to bacteria.

The renovations were paid for in part by a \$1.5 million Third Frontier Grant from the Ohio Department of Development awarded to Takashima. UT matched the grant amount.

Additionally, Chuck Lehnert, vice president for facilities and construction, said the renovations created about 150 construction jobs.

The renovations, which began last May, are the first phase of an effort to modernize and open up laboratories across Health Science Campus to promote researcher collaboration.

UT earns designation as center of excellence

The University of Toledo is among 14 Ohio universities named Feb. 19 as centers of excellence in biomedicine in health care.

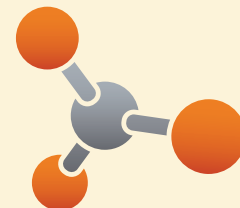
The Biomarker Research and Individualized Medicine Center at UT will focus on figuring out how best to uniquely tailor diagnoses and treatments for individual patients, said Dr. Jeffrey Gold, provost, executive vice president of health affairs, and College of Medicine dean.

Biomarker research is aimed at discovering genes or other molecules in the body that may predict health

problems, that may predict different responses to disease treatments, or that can be used as targets of new drugs.

"It is a highly exciting area, not only because it potentially will dramatically improve the quality of health care, but because of the rapid route to economic development," Dr. Gold said.

The announcement was made by Ohio Governor Ted Strickland and Ohio Board of Regents Chancellor Eric Fingerhut.



'78 Graduate earns Distinguished Alumni Award

Dr. Phil B. Fontanarosa received the College of Medicine Distinguished Alumni Award during events last October. Fontanarosa, who earned a doctor of medicine degree from the former Medical College of Ohio in 1978, is executive deputy editor of *The Journal of the American Medical Association* and vice president of scientific publications and multimedia applications of the American Medical Association. He has been an editor at the journal since 1993.

In addition to his editorial positions, Fontanarosa serves as adjunct professor at Northwestern University's Feinberg School of Medicine and is board-certified in emergency medicine. He earned a master of business administration degree from the University of Notre Dame in 2005. Presented since 2000, the award recognizes graduates who have gained national or international distinction in their profession and whose accomplishments reflect admirably upon UT's College of Medicine.

Faculty member featured in Ohio Magazine

Dr. Vijay Goel, endowed chair and McMaster-Gardner professor of orthopedic bioengineering in the College of Engineering and the College of Medicine, and co-director of the Engineering Center for Orthopedic Research Excellence, is one of four UT faculty members who were profiled in a special section on top educators from some of the state's top colleges and universities in the December 2009 issue of *Ohio Magazine*. The article was titled "Excellence in Education."

"Vijay K. Goel has been instrumental in the development, implementation and assessment of the Department of Bioengineering's subcontract in orthopedic

biomechanics, including teaching and research labs," the article stated.

"He also incorporates findings of basic and applied research in orthopedics into his classroom teaching."



Dr. Goel

CAMPUS CAPSULES

College of Medicine neurologist wins stroke research award

Dr. Gretchen Tietjen, professor and chair of neurology, has received the Stroke Innovation Award by the internationally acclaimed journal *Stroke* for her original investigation published in its September 2009 issue in an article titled "Migraine and Biomarkers of Endothelial Activation in Young Women."

The investigation explored the relationship between migraine and stroke, and was conducted in UT's Department of Neurology. The work was funded by her UT Translational Research Stimulation Award and by a research grant from GlaxoSmithKline.

"'Innovation' is defined broadly; it can be a new approach, a new methodology, new interpretation of existing data or new data with far-reaching implications," wrote Dr. Vladimir Hachinski, editor-in-chief of *Stroke*, in a letter to Tietjen informing her she had won.

"I am very honored and surprised to receive this award, as migraine-related research is often not recognized and valued within the stroke scientific community," Tietjen said. "I am very appreciative of The University of Toledo and GlaxoSmithKline for supporting my research."

This annual award was established by the journal in 2008 and was given during the *Stroke* symposium at the International Stroke Conference of the American Heart Association in San Antonio Feb. 25 according to the Internet.

In 2008, Tietjen's translational work was awarded the Seymour Solomon Research Lecture Award at the 50th annual scientific meeting of the American Headache Society in Boston.

First PhD student in biomedical engineering program graduates



Dr. Bhat

After successfully defending her dissertation, Archana Bhat became the first graduate of UT's joint doctoral program between the colleges of Engineering and Medicine.

Originally discussed by the Medical University of Ohio and UT prior to the 2006 merger, the Biomedical Engineering Program is an example of one of the many positive academic progressions made by the University following the merger of the two institutions.

The doctor of philosophy in biomedical engineering is designed for students with master's degrees in either

engineering or in science fields and centers on several core course requirements in mathematics, engineering and the biomedical sciences. The curriculum also contains an entrepreneurship component. Students take two courses on intellectual property and strategic planning from the College of Business Administration and develop a business plan to commercialize ideas born from their dissertation research.

The curriculum also offers a PhD program for MD students interested in pursuing a dual degree and careers as physician-scientists.

The University's goal for the program is to recruit at least six students per year, a goal that UT is more than likely going to surpass, considering that 18 students have enrolled over the program's three-year history.

For her PhD, Bhat selected the entrepreneurial option, completing two business courses and developing a business plan to commercialize her research on developing artificial bones.



COLLEGE OF MEDICINE GRADUATE RECOUNTS HAITI RELIEF EFFORT EXPERIENCE

By Jim Winkler

A physician who has traveled the world doing medical mission work, Dr. Richard Paat (MED'86) had a pretty good idea what medical care people would be needing when he saw the images of loss and destruction immediately following the massive magnitude 7.0 earthquake that struck Haiti on Tuesday, Jan. 12, killing an estimated 200,000 people.

Within a few days, Dr. Paat, medical director of International Services of Hope, a relief agency based in Waterville, Ohio, outside Toledo, and a 23-member team of physicians, nurses, translators and other health-care professionals gathered nearly \$20,000's worth of supplies, including IV bags, tubing, splints, medications and blankets, and traveled to the devastated country to help.

The team worked around the clock for a week at Double Harvest, a 200-acre farm, school, medical clinic and housing project east of Port-au-Prince, Haiti's capital, bandaging wounds, dealing with fractures and offering a comforting word or embrace.

In sweltering heat, they saw approximately 1,600 patients, many of whom had fractures and crush injuries resulting from toppled concrete buildings. Some had wounds that were severely infected, requiring quick decisions whether to amputate or try to salvage an arm or leg. He estimates the team performed some 100 procedures, the majority being amputations.

The doctors performed procedures in two operating rooms inside the clinic, but most care was given in the school building and under tents outside without sterile equipment. There were fears that aftershocks would collapse the clinic building. Throughout its stay the team had enough supplies, especially after they secured more equipment brought in by the Mexican navy.

With the crushing workload, team members lost track of the days and sometimes even the time of day. At night, they slept on mattresses on the ground, attuned to the sounds of mosquitoes and crying children.

In the early days after the earthquake, Paat and other relief team members were frustrated because medical supplies and drugs sat at the Port-au-Prince airport instead of being delivered to patients.

"Logistically, the supplies weren't getting to where they needed to be," he recalled

He has many stories of hardship and accomplishment.

"We had some good saves," he said. "We delivered a baby, and we treated a lady with a severe neck fracture who we able to get aboard a helicopter that flew her to the U.S. Navy ship Comfort."

Despite the magnitude of the devastation, Paat said the Haitian people never complained, rarely cried and were very appreciative for the help they were getting.

Dr. Michael Hoefflinger (C&S '83, RES '92), a Toledo orthopedic surgeon, and Toledo general surgeon Dr. Timothy Duckett (C&S '84, MED '89 RES '94) were also part of the Toledo relief team, and Dr. Paat's older brother, John, (C&S '80 and MED '84) assistant professor of medicine at Mayo Medical School, was also there.

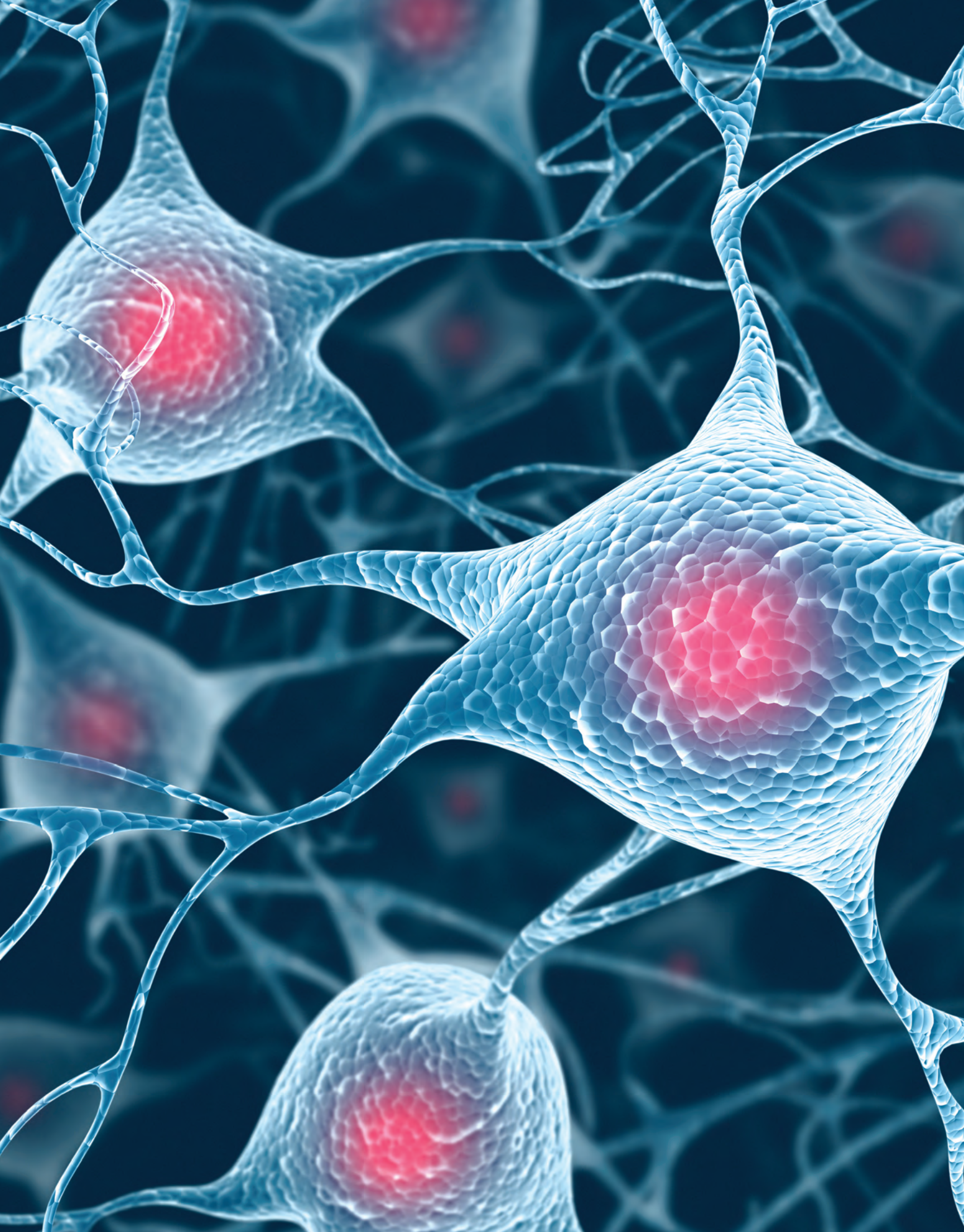
"John and I went into Port-Au-Price and visited some of the tent cities, where people were living in shelters made of nothing more than cardboard, linens and plastic sheets," he said.

Dr. Paat also met Dr. Harlan McCulloch (MED '84), a member of a relief team from a Miami hospital, and Dr. James M. Toth (MED '96), a Sugar Hill, Ga., family physician.

The international response to the crisis was impressive, he said. "It was neat to see all the flags of the different countries that came to help," Dr. Paat said.

For Dr. Paat, the memories of their patients linger, and so too does the concern he has for the country. He says that aid must continue for the country to have a future.

"The country is going to need help for a very, very long time," he said.





EXPLORING GENETIC, ENVIRONMENTAL INFLUENCES ON NICOTINE SIGNALING

By Jim Winkler

Smokers who are trying to kick the habit may sometimes wonder how they got addicted to tobacco in the first place.

The answer may lie partly in their genes, says Dr. Joseph F. Margiotta, professor in the College of Medicine's Department of Neurosciences, who is studying why smoking and tobacco have such a stranglehold on millions of people worldwide.

"Smoking, driven by addiction to nicotine, is the leading cause of preventable death in the developed world," he said. "Quitting the nicotine addiction is a daunting, uphill struggle said to be more difficult in kicking heroin. New studies indicate that point mutations in our genes may predispose some of us to nicotine's allure."

Dr. Margiotta recently completed studies with a \$200,000 Cutting-Edge Basic Research Award (CEBRA) from the National Institutes of Health to learn more about molecular mechanisms involved in nicotine addiction and how underlying circuits of neurons are regulated.

Now the UT faculty member, who has spent more than 20 years studying the cellular, molecular and genetic influences involved in sending electrical signals across nerve connections (synaptic transmission), is expanding his studies in a new direction, intrigued by interesting findings in genome-wide association studies.

"Comprehensive studies that appeared in the literature a few years ago compared the genes of nicotine-dependent smokers, patients with peripheral artery disease and patients with lung cancer with those of normal populations," he explained. "What the studies found in these three groups, compared to the controls, were common point mutations in genes encoding specific classes of nicotinic acetylcholine receptors. The conclusion from these studies is that specific mutations in genes encoding certain nicotinic receptors may be markers for these diseases."

"Quitting the nicotine addiction is a daunting, uphill struggle said to be more difficult in kicking heroin."

Studies have demonstrated that brain circuits change in people who start smoking. Each time a smoker takes a drag, nicotine, which is a toxic, addictive plant alkaloid, travels through the lungs, into the bloodstream and then deep into the brain where it influences specific synapses associated with pleasure and reward. Synapses are junctions where information is communicated between nerve cells by chemical neurotransmitters. Once present at these synapses, nicotine mimics a natural neurotransmitter called acetylcholine and rapidly binds to many of its receptors located on the surface of neurons.

"One hundred percent of the people who use methamphetamine also smoke. Why does that happen?"

"Nicotinic acetylcholine receptors are first responders in the process of nicotine addiction," Dr. Margiotta explained. "After prolonged and repeated nicotine exposure, nicotinic receptors and synapses undergo a series of changes that lead to nicotine sensitization, dependence and ultimately addiction."

There are different nicotinic acetylcholine receptor subtypes. Each is formed from five subunits that assemble to create a pore opened by binding of nicotine or acetylcholine. The subunits include nine different alpha versions and three beta versions. Each version has different physiological and pharmacological properties, which results in many receptor subtypes.

Nicotine receptors with two alpha4 subunits and three beta2 subunits are the prime suspects in causing addiction because they influence release of dopamine, the neurotransmitter that provides the feelings of pleasure and relaxation that smokers say they experience when they light up. Other kinds of subunits are known to assemble with alpha and beta subunits, but their roles in development of nicotine addiction are not well understood.

One subunit that interests Dr. Margiotta is alpha5. The genome-wide association studies show a common point mutation that alters the alpha5 protein in a critical intracellular region. Alpha5 has the ability to assemble with alpha4 and beta2 subunits to form a nicotine receptor subtype. However, it is not unclear how big a role, if any, the alpha5 subunit plays in development of nicotine addiction.

He plans to use a strain of mice in which the genes that direct the development of the alpha5 subunit have been disabled. He then will introduce wild-type or mutant alpha5 in the mice, chronically expose them to nicotine and see if alpha5's signaling functions change, resulting in changes in the mice's behavior.

"The big question is to identify how the alpha5 mutation changes receptor properties and the properties of the cellular environment in which the receptor resides," he said.

Last year, Dr. Margiotta spent six months at McGill University Medical School, learning genetic engineering techniques in the laboratory of Dr. Ellis Cooper, professor of physiology.

Dr. Margiotta and Dr. Bryan Yamamoto, professor and chairman of the Department of Neurosciences, have plans to study possible links between methamphetamine abuse and smoking. A web of comorbidity — the tendency of certain diseases to be accompanied by certain other diseases — appears to exist between methamphetamine use and smoking.

"There is an absolute correlation in these cases," Dr. Margiotta noted. "One hundred percent of the people who use methamphetamine also smoke. Why does that happen? Nicotine may have effects on the blood-brain barrier and that increases the permeability to these addictive substances."

Dr. Margiotta also hopes to learn more about the functions of nicotine receptors on cells that line the inside of blood vessels and in the lungs. The blood-vessel studies hold the promise of coming up with new therapies for patients with peripheral artery disease.

He recently received a \$600,000 grant from the National Science Foundation to study two neurotrophic factors: brain-derived neurotrophic factor, or BDNF, a nerve growth factor that keeps neurons healthy, and the neuropeptide PACAP, which is found throughout the nervous system and is involved in helping signals get from one nerve to another.

"The factors are a subject of intense interest right now because of their ability to stimulate damaged neurons to regrow their connections both in culture and in animal models," he explained. "Thus, they present the possibility for reversing devastating traumatic brain disorders. It turns out that there are other environmental factors that influence how synapses and receptors work, and I have been studying them for years. Both BDNF and PACAP reside in the autonomic ganglion, which make them very convenient for studies of synaptic transmission."

Not only will Dr. Margiotta's grant award allow him to pursue and solve the mysteries of nicotine, it also will be used to blend research with education and allow underrepresented minority students to work in his lab in the summer and learn more about scientific experimentation.



COLLEGE OF MEDICINE SCIENTIST SEEKS NEW INSIGHTS INTO MECHANISMS REGULATING BENZODIAZEPINE WITHDRAWAL

Dr. Elizabeth Tietz is examining the complex and many-faceted neurobiological underpinnings when people hooked on benzodiazepines go through withdrawal

*“Mother needs something today
to calm her down.*

*And though she’s not really ill, there’s
a little yellow pill.*

*She goes running for the shelter of
a mother’s little helper.”*

Lyrics from “Mother’s Little Helper,” The Rolling Stones, 1966

For Dr. Elizabeth Tietz, benzodiazepines, the wonder drugs Mick Jagger sang about in the 1966 Rolling Stones’ hit, “Mothers Little Helper,” have gotten an undeserved bad rap.

“When properly prescribed and sensibly used, benzodiazepines are safe, effective drugs,” she said, stressing their enormous, short-term value in saving lives when people are suffering convulsions caused by epilepsy, in safely sedating surgery patients, in calming nerves and in restoring a good night’s sleep.

Problems develop when people don’t follow instructions or take them with alcohol, she says. Mixed together, sleep aids, anti-anxiety drugs and alcohol can be lethal.

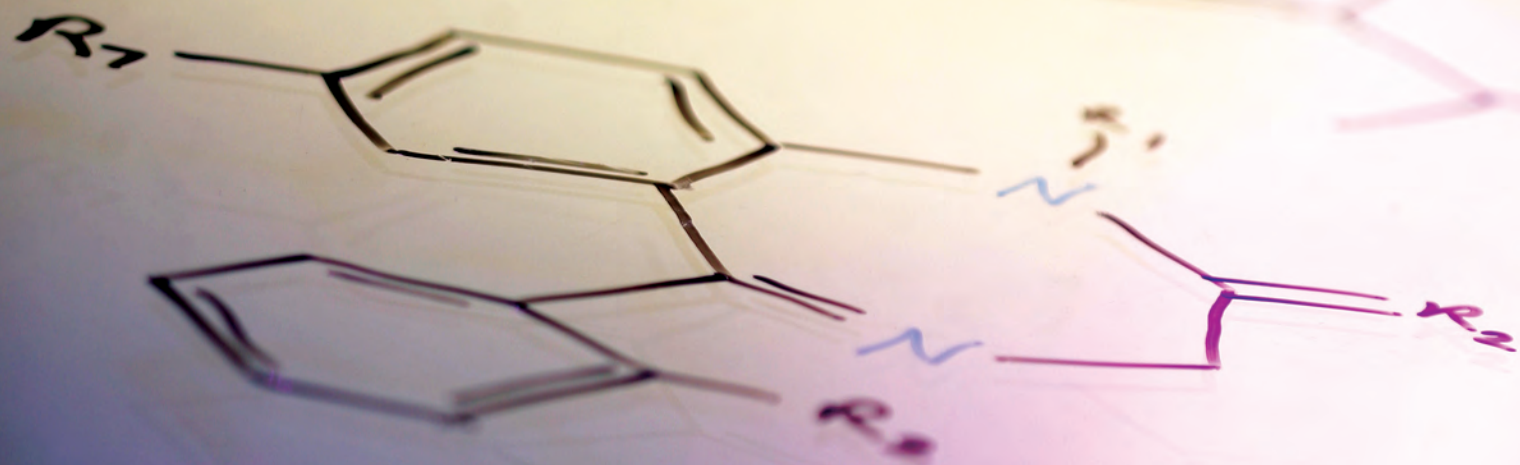
“One reason people abuse benzodiazepines so much is that they are so readily available,” she explained. “People who abuse other drugs also find that benzodiazepines have a nice additive effect. There are social factors involved as well.”

The University of Toledo College of Medicine professor of physiology and pharmacology has studied the neurobiological actions of benzodiazepines like diazepam, also called Valium, which is used to treat mild to moderate anxiety and tension, over the past four decades. In the process, she has earned an outstanding reputation, receiving continuous funding for her studies since 1983, when she wrote a National Research Service Award that was funded by the National Institute of Drug Abuse, an agency that continues to fund her research today.

Today her focus is to learn more about the changes in brain chemistry behind the distress that afflicts people on benzodiazepines during withdrawal. Learning more about the withdrawal-regulating mechanisms holds the promise of new therapies and new ways to treat the problem.

Wildly popular, benzodiazepines are used by millions every year to relieve anxiety, insomnia, panic attacks and other problems. Relieved of the symptoms, people continue to take them and become more tolerant to them — a well-established feature of some drugs — meaning that as time goes on, a greater dose is needed for the same effect.

All benzodiazepines work in a similar way on many brain structures, including two in particular — the hippocampus, a structure crucial for learning and memory, and the amygdala, which modulates fear and is affected by stress. They bind to receptors in those two and other brain regions, boosting levels of a chemical called gamma-aminobutyric acid, or GABA, the brain’s major inhibitory neurotransmitter. GABA helps keep glutamate, the brain’s main excitatory transmitter, in check and tells the brain to slow down. Many drugs of abuse disrupt these pathways.



Wildly popular, benzodiazepines are used by millions every year to relieve anxiety, insomnia, panic attacks and other problems.

GABA receptors come in different varieties depending on the mix of their alpha, beta and gamma subunits. Depending on which types of subunits make up a receptor, different kinds of benzodiazepine bind to it.

Drug tolerance can occur when nerve cells respond by producing fewer receptors for GABA/benzodiazepines. This phenomenon, known as down regulation, means that the number of GABA receptors decreases in response to the enhancement of GABA caused by the drug.

When the drug is stopped, the brain tries to get back to normal by going through withdrawal. Although withdrawal from benzodiazepines can be difficult, it is rarely life-threatening. But it is extraordinarily complex and involves adaptations and long-lasting changes in the brain's learning and memory circuits, according to Dr. Tietz, who oversees a research team that is using cutting-edge analytical tools to examine slices of the hippocampi of rats chronically treated with a benzodiazepine. As is the case for all UT-COM research programs, the development of future scientists and physicians is also an important mission for Tietz's research group. Indeed, many of the insights she has gained about the nerve-cell adaptations were initially conceived by and developed with medical and graduate students in her laboratory.

Because benzodiazepines slow transmission of nerve signals, nerve cells under the influence of these drugs react by sprouting additional types of glutamate receptors called AMPA receptors when benzodiazepine use stops. The brain is suddenly stuck with too many AMPA receptors, making nerve cells hyperactive. That leaves hands jittery, generates intense anxiety and can even provoke seizures as neurons accustomed to the presence of the drug must adjust to its absence.

"When we withdraw benzodiazepines, we see an increase in [neuronal] excitation, and we have been able to show most recently that the increased excitation in the hippocampus shows some similarities and dissimilarities to other models of what we call activity-dependent plasticity," she said. Plasticity refers to how the brain changes, organizes, reorganizes and remembers in response to different experiences.

GABA receptors have "chemical" channels that, when open, allow electrically charged chloride ions to flow into brain cells, a flow that is needed to dampen electrical activity at synapses. During drug withdrawal, members of the Tietz lab have found, these channels may begin to act in reverse — instead of decreasing brain function, they increase it. They theorize that this may spark another type of channel called the voltage-gated calcium channel to gear up. Calcium floods into the cells, setting a script into motion that plays out inside the nerve cell. As a result, the brain also increases its response to glutamate,

which leads to withdrawal symptoms. New drugs could prevent the channel from overworking. "The script is a very conservative response, yet on the other hand it is a plastic response," she said. "In other words, though the brain is making these modifications and it is very labile, it is very conventional in its response."

She added, "We are looking for a therapeutic approach to mitigate these withdrawal symptoms, and whether we can use voltage-gated calcium channel or glutamate antagonists because we have shown that they can reduce anxiety."

Withdrawal also involves another protein found in the hippocampus — NMDA receptors, which also sense glutamate. The receptor, named after the chemical N-methyl D-aspartate, opens and closes to allow calcium ions to flow into each brain cell at the right times.

"In our research, it turns out that the NMDA receptors actually seem to put a brake on anxiety by being removed from the synapse so that the script can no longer play out. We believe that this may be why, unlike alcohol withdrawal, which produces intense, life-threatening signs, benzodiazepine withdrawal can be rather modest and not life-threatening," she said.

Her research shows this script also may play out in other brain areas.

She and faculty colleagues recently submitted a grant proposal to the U.S. Department of Defense to determine if giving benzodiazepines to soldiers coping with traumatic memories of combat could be doing more harm than good. The amygdala will be studied because it modulates fear and its function is affected by stress. Moreover, stress-induced plasticity of the amygdala has been linked to anxiety, a symptom of psychiatric conditions like PTSD.

Dr. Tietz's research underscores the remarkable plasticity of the brain — its ability to form new neurons as well as new connections between those neurons to make it flexible and dynamic — which has encouraged scientists like her to discover new targets to treat benzodiazepine withdrawal.

Dr. Tietz has been invited to present her work at prestigious international conferences such as the "GABA 2000" conference in Australia and the upcoming "GABA 2010" conference later this year in Italy.





UT SCIENTISTS STUDYING METHAMPHETAMINE, ECSTASY TO DECIPHER THEIR DESTRUCTIVE SECRETS

Dr. Bryan Yamamoto is conducting fundamental bench research to learn more about meth addiction and how it operates at the level of individual molecules and nerve cells.

As a new scientist some 25 years ago, Dr. Bryan Yamamoto conducted original, basic-science studies to learn more about Parkinson's disease.

His aim was to identify the cause and develop new medications, but as his studies progressed, he noticed striking similarities between nerve-cell damage in people with Parkinson's and people who regularly got high on methamphetamine and Ecstasy.

"I was studying Parkinson's, which involves the neurotransmitter dopamine," he recalled. "I was using methamphetamine and Ecstasy as tools to experimentally increase dopamine production and found evidence these drugs damaged neurons in the brain. At the time there also was some clinical evidence emerging that the drugs produced brain damage. So it really was not too much of a stretch for me to expand my research focus to the mechanisms of actions underlying the toxicity of these drugs."

Today, thanks to scientific serendipity and determined laboratory work, Dr. Yamamoto, professor and chairman of the College of Medicine's Department of Neurosciences, is a leading member of a fraternity of researchers worldwide working to further elucidate the short- and long-term harmful effects on the brain due to the chronic use of methamphetamine and its chemical cousin, Ecstasy — work that is laying the foundation for better treatments.

With three grants from National Institute of Drug Abuse totaling \$1 million annually, Yamamoto — a native of Gardena, Calif., a Los Angeles suburb — joined the UT faculty in 2008 from Boston University School of Medicine. Yamamoto heads an eight-member research team and collaborators at the University of Cincinnati whose studies are critical as meth abuse ravages the country and becomes a public-health epidemic. He has enjoyed continuous funding from the National Institutes of Health since 1986.

Little is known about meth, a highly addictive synthetic stimulant with many colorful street names, including speed, crystal, love doves, disco biscuits and crank. It comes in pill, crystal or injectable form and offers a quick high — people using meth typically feel euphoric and energetic.

Ecstasy, also known as MDMA, or 3,4 methylene-dioxymethamphetamine, is an old drug, synthesized about 60 years ago for use as a truth serum. The drug was not illegal until 1985, when the U.S. Drug Enforcement Administration placed it on Schedule I, the most stringently controlled of the five categories of drugs. Schedule I drugs are those that have no medical use and have a high potential for abuse. Methamphetamine is in Schedule II, a category for drugs with a medical use but also with a high potential for abuse.

Meth's powerful pull starts at synapses

"Most drug abusers are under a lot of stress — psychological stress, environmental stress," he explained. "It is known that stress can lead to drug abuse and many sufferers of post-traumatic stress syndrome have substance-abuse disorders."

Once considered a regional problem largely confined to the West Coast and the Southwest, methamphetamine and Ecstasy abuse has shown up in rural areas of Midwestern states like Missouri, Indiana and Iowa, ruining the lives of people who become slaves to their habit.

Meth's powerful pull starts at synapses, the junction between two neurons where messages are sent and received by chemicals called neurotransmitters. Meth makes the neurons release dopamine, a chemical involved in transmitting signals in the brain. The euphoric "high" people experience comes from the excess dopamine that is released within the brain.

However, regular, repeated use of meth causes dramatic changes to several brain regions, including the caudate and substantia nigra, which control body movements, the cortex, which is involved in the ability to focus and pay attention, and the limbic system, which includes the hippocampus and the amygdala and which exerts an important influence over learning, emotions and motivation.

The dangers of meth cannot be overstated," Yamamoto stressed. "With regular, repeated use, these brain regions literally change biochemically. They become depleted of dopamine."

Methamphetamine also causes production of free radicals — destructive, short-lived molecules that attack different cell components like DNA, proteins and lipids and kill brain cells, including those that produce dopamine and serotonin.

"Free radicals have been implicated in mediating the damage observed in many neurodegenerative diseases," Dr. Yamamoto explained. "By understanding how those free radicals are being produced by these drugs, maybe we can understand the underlying causes of diseases such as Parkinson's disease. These drugs are valuable tools to produce and then better understand the damage."

Meth addicts may be increasing their risks for Parkinson's disease later in life, Dr. Yamamoto cautions.

Some studies suggest that Ecstasy actually kills cells that produce serotonin.

"We are discovering that the players involved in mediating the toxicity of methamphetamine and Ecstasy appear to utilize the same types of mechanisms that have been linked to the damage produced by Parkinson's and Huntington's disease," he noted. "There are very close parallels to both of those drugs."

Because the long-term effects of meth abuse involve many factors, Dr. Yamamoto has cast a wider research net that has resulted in several unexpected findings with important clinical implications.

In 1992, he demonstrated that at excessive levels, another major neurotransmitter — glutamate — is toxic, causing nerve-cell stress that ends in cell death. In 2002, he was the first to demonstrate that if the animals are exposed to chronic stress prior to being given amphetamines, the drugs' neurotoxicity — the death of brain tissue — dramatically increases. The findings appeared in the journal *Neuroscience*; he is continuing the studies today.

"Most drug abusers are under a lot of stress — psychological stress, environmental stress," he explained. "It is known that stress can lead to drug abuse and many sufferers of post-traumatic stress syndrome have substance-abuse disorders. We think what's happening is that chronic stress elevates the hormone cortisol, which produces changes in the brain that render it more vulnerable. The stress elevates dopamine and

then, when challenged with methamphetamine, augments the concentrations of dopamine and free radicals, which in turn damage the brain.”

In animal studies conducted in 2005, Yamamoto discovered that by damaging the blood-brain barrier, a physical and chemical entity that provides a protective, stable environment for the brain, Ecstasy leaves the brain vulnerable to invasion by viruses and other pathogens. His rat studies showed this vulnerability even 10 weeks after the initial exposure to the drug.

In 2007, he discovered that when haloperidol, a common antipsychotic drug used in emergency rooms to treat methamphetamine overdose, is combined with methamphetamine, this combination damages nerve cells in a brain area regulating movement. He demonstrated that this damage results from exaggerated stimulation by glutamate, which proves toxic to cells that produce GABA. These results were published in the *Journal of Neuroscience*.

Yamamoto also published other articles in the *Journal of Neuroscience* and the *Journal of Neurochemistry* that described how Ecstasy can compromise neurons in the brain by elevating the amino acid tyrosine, damaging their mitochondria — the structures responsible for cellular energy production — and causing these cells to essentially lose power. Also under examination is whether meth causes brain inflammation that is triggered by the production of cytokines, and whether anti-inflammatory drugs like aspirin, ibuprofen or naproxen can mute meth’s effects on the brain.



Ecstasy, a Schedule I stimulant, is often used at "raves" for energy and mood enhancement.

“Although prevention of drug abuse is very important, understanding the consequences and their causes is also important for developing therapeutic intervention strategies.

“Many challenges lie ahead. Through the elucidation of the underlying mechanisms, we may be able to identify potential targets for therapeutics that can prevent or mitigate brain damage. The prevention of brain injury produced by these drugs is not always the most practical or feasible. Therefore, a major goal is to help the brain recover from injury once it has occurred. This is a challenge that is faced by all neuroscientists involved in research on neurodegenerative diseases.”

... a major goal is to help the brain recover from injury once it has occurred.

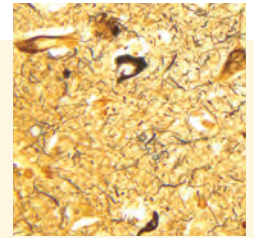




“What I have tried to do is to use neuroinflammation as a guiding principle for identifying proteins or pathways that may contribute to neurodegeneration.”

UT SCIENTIST STUDIES LINKS BETWEEN INFLAMMATION, ALZHEIMER’S, OTHER DEGENERATIVE BRAIN DISEASES

In the fight against Alzheimer’s disease and amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig’s disease, University of Toledo scientist is studying whether inflammation underlies the changes that lead ultimately to the two disabling neurodegenerative disorders.



Inflammation is the body’s way of fighting off disease, but sometimes the process goes awry and the response doesn’t turn off. When that happens, tissues and organs can be damaged, says Dr. Kenneth Hensley, associate professor and director of research in The University of Toledo Medical Center Department of Pathology. Hensley is conducting studies aimed at answering the question of whether inflammatory stress is responsible for the neurodegenerative diseases and whether important intracellular signaling pathways can be interrupted to reduce inflammation.

“What I have tried to do is to use neuroinflammation as a guiding principle for identifying proteins or pathways that may contribute to neurodegeneration. Then, we might be able to block or manipulate those pathways with small-molecule drug candidates,” explained Dr. Hensley, a biochemist by training.

Although many unanswered questions remain, the neuroinflammation hypothesis holds that Alzheimer’s, ALS and other neurodegenerative motor diseases are the result of chronic, low-grade, inflammatory-like responses that happen inside the brain and spinal cord. The faulty responses ultimately cause neurons to function improperly and disrupt regulation of important brain physiological processes.

There is currently no truly effective treatment for Alzheimer’s disease, a disorder that affects about 4.5 million Americans, according to the Alzheimer’s Association. Likewise, there is no effective treatment for ALS, a disorder that attacks motor neurons in both the brain and spinal cord, causing gradual debilitation and death within several years of diagnosis.

Alzheimer’s, a disease that eventually robs people of their memories as well as their ability to reason, communicate and care for themselves, occurs when clumps of a sticky protein called amyloid accumulate in the brain. Dead brain cells and abnormal twisted accumulations of protein called neurofibrillary tangles are also present. Dr. Hensley’s research suggests that the brain’s own innate immune system interprets amyloid deposits as an invasive threat and begins to attack the deposits. Collateral damage then affects surrounding neurons.

The brain’s innate immune system is a set of cells and proteins that the brain uses to fight infections or to kill off early-stage tumors. It is separate from the body’s classical immune system. The neuroimmune

There is currently no truly effective treatment for Alzheimer's disease, a disorder that affects about 4.5 million Americans, according to the Alzheimer's Association.

system relies heavily on microglial cells, which act as sentinels, always on the lookout for trouble, protecting neurons from damage. Another type of glial cell, called astrocytes, nourishes and maintains a healthy environment for neurons. Neurons, microglia and astrocytes use protein messengers called cytokines to communicate among themselves, signaling neurons' needs or triggering defensive actions of the glial cells.

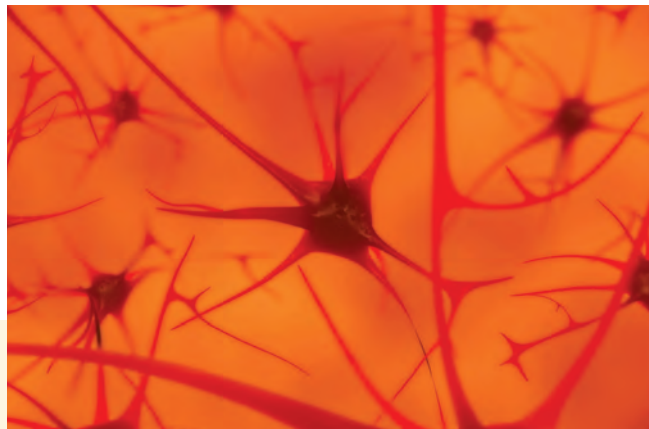
When activated, microglial cells can act as friend or foe to neighboring neurons. As friends, they clear dead brain cells or harmful clumps of proteins and release compounds known as neurotrophic factors that promote healing. But they also can go on the attack, fatally wounding brain cells by oversecreting compounds such as inflammatory cytokines, free radicals and nitric oxide.

“Normally, microglial cells remove dead cells and pre-cancerous cells,” Dr. Hensley said. “But when triggered into a neuroinflammatory state, the microglial cells attack neurons either directly or through ‘collateral damage.’ Activated microglia release a host of toxic agents, especially free radicals such as nitric oxide, which interfere with healthy neuron function.”

The trick, Dr. Hensley suggests, is to find ways to manipulate microglial cells to make sure they don't overreact and lose control — to manipulate them so that instead of persistently (and ineffectively) attacking the plaques and other cellular debris as though they are tumors or pathogens, the cells instead just gobble them up and clear them from the body.

Before joining UT last year, Dr. Hensley conducted research at the Oklahoma Medical Research Foundation (OMRF) in Oklahoma City, studying genetically engineered mice with a heredity form of ALS and characterizing cytokines in the brain's innate immune system.

While in Oklahoma, he discovered a previously unknown compound called lanthionine C-like protein-1 (LanCL1) that binds to glutathione, a small amino acid-derived molecule that is essential for cells to function properly. Glutathione serves important immune functions by changing the sensitivity or “gain” at which cells detect cytokine signals from other cells. Also, glutathione helps protect the body against heavy metals and other environmental toxins. “Glutathione is a very important, multifunctional compound because it acts as a universal detoxicant, a universal antioxidant and an important cell signaling molecule,” said Dr. Hensley.



In studies reported in a 2007 issue of the journal *Biochemistry*, Dr. Hensley found that levels of LanCL1 increased in the spinal cords of genetically engineered mice with ALS.

However, it was not clear whether LanCL1 molecule was a friend or enemy. Dr. Hensley's research has led to the surprising discovery that LanCL1 may trigger glutathione conversion to small molecules called lanthionines that suppress cytokine signaling and directly protect neurons from collateral damage from activated microglial cells.

Data gathered from the lanthionine studies have allowed him to create bioavailable compounds that convert to lanthionines in the brain. One lead compound called LKE appears to improve the condition of genetically engineered mice with ALS. Dr. Hensley is working to patent and develop this technology for ALS as well as Alzheimer's disease.

“We are now working hard to understand how these lanthionine compounds bring about their beneficial effects and we have uncovered a possible pathway where the lanthionine compounds bind to another protein called collapsin response mediator protein-2 (CRMP-2),” Dr. Hensley explained.

CRMP2 appears to be a key molecule in formation of the prime structures in the brains of Alzheimer's patients — neurofibrillary tangles — that kill brain cells under attack from microglia. Dr. Hensley's research suggests that LKE, and possibly some drugs already on the market for treating depression, may bind CRMP2 and prevent or even reverse neuron structural damage.

“This research track has given me a new entry point into Alzheimer’s disease because CRMP2 has emerged in the last 12 months as a fascinating protein,” he said. “This has given me the opportunity to take my LKE compound and test it in mice in the last six months and we have found another compound with a completely different structure that actually increases CRMP2 levels. But we don’t know for certain that is a good thing.”

The compound Dr. Hensley refers to is an atypical antidepressant called tianeptine. Though tianeptine has been used for two decades in Europe and is effective in treating depression, tianeptine does not act through the same mechanisms as classical antidepressants. In fact, the mode of tianeptine action is unknown. Dr. Hensley’s research suggests that tianeptine may be analogous to the LKE molecule by affecting CRMP2. If true, Dr. Hensley’s work could bridge theories relating depression to neurodegenerative diseases like Alzheimer’s.

Dr. Hensley plans to test his ideas and drugs in a recently created, genetically altered mouse model for Alzheimer’s called the 3xTg-AD mouse. This mouse allows researchers for the first time to study the two major lesions of Alzheimer’s disease — plaque and tangle lesion formations — together in one organism.

Dr. Hensley is collaborating with researchers at Case Western Reserve University in the mouse studies and, depending on the results, hopes to move to studies in human patients. They plan to explore the compound’s ability to improve brain function and stop the destruction of neurons, as well as its effects on mouse behavior.

Dr. Hensley says his intellectual journey the past several years is an example of how following interesting scientific observations from one point to the next can reveal system-wide patterns of interactions that aren’t intuitively obvious. “When we began looking at cytokines in ALS spinal cords, we had no idea that we’d stumble upon LanCL1, or that this discovery would lead to lanthionines. We had no clue that lanthionines would lead us to CRMP2 until we did the next experiment. And so on. Now we may be nearing the verge of some breakthroughs in the field of Alzheimer’s disease pharmacology. Sometimes a scientist must follow the white rabbit down its hole, even though you don’t know where you might come out.”

If true, Dr. Hensley’s work could bridge theories relating depression to neurodegenerative diseases like Alzheimer’s.

Dr. Hensley’s interest in neurodegenerative brain diseases like ALS, Alzheimer’s and Huntington diseases dates to his undergraduate days at University of Kentucky in the early 1990s, when he got his first taste of laboratory research. The Ashland, Ky., native earned his undergraduate and Ph.D. degrees from UK in 1992 and 1995, respectively, and joined UT after 14 years at OMRF.

By moving to Toledo, he said it will be easier for him to maintain longstanding collaborations with Dr. Robert Mrazek, professor and chairman of the College of Medicine’s Department of Pathology, who first proposed in the 1990s that Alzheimer’s disease was an inflammatory process, as well as researchers at Case, the University of Michigan, Rush University, the University of Cincinnati, Duke University and UK.





SERENDIPITY CHANGES COURSE OF RESEARCH FOR UT NEUROLOGIST

Epilepsy laboratory studies mechanisms of brain inhibition

Serendipity is the best word to describe the happenstance encounter that created a new research focus for UT neurologist Dr. L. John Greenfield almost a decade ago at a national neuroscience conference.

Strolling through the exhibit booths, The University of Toledo neurologist and epilepsy specialist found the Myoclonus Research Foundation (MRF) and heard that the organization wanted to find out why people who survive after suffering oxygen deprivation or a “sudden death” event when the heart stops beating will sometimes develop involuntary jerking of the arms or legs, known as myoclonus. Due to his longstanding interest in the brain receptors responsible for inhibiting excessive brain activity, an idea occurred to him.

“I proposed that after hypoxia, a loss of oxygen in the brain, the GABA receptors were not working properly, that they changed their composition and how they worked, and that might lead to myoclonus,” recalled Dr. Greenfield, professor of neurology and director of the College of Medicine’s M.D./Ph.D. program. He used a two-page MRF application form to request grant funding to test this novel idea, despite having no preliminary evidence to support it.

Intrigued, the foundation awarded him a \$65,000 research grant, and after early studies confirmed the concept, they provided two additional years of funding. The information gained during these years formed the basis of Dr. Greenfield’s later success in obtaining major grant funding from the National Institutes of Health.

His research focuses on a complex protein, the GABA type A receptor, that lives in the cell membrane of nerve cells in the brain. The GABA-A receptor is turned on by a small neurotransmitter molecule called GABA (gamma-aminobutyric acid) that transmits inhibitory signals in the brain. GABA is released by inhibitory nerve cells and crosses a narrow gap, the synapse, to activate receptors on the opposite “post-synaptic” membrane of the next cell.

The action of GABA on its receptors is like a key being inserted in a lock. When the key is turned, the lock opens and the neurotransmitter activates the receptor. For the GABA-A receptor, turning the key opens a chloride channel that is part of the receptor itself. Negatively charged chloride ions enter the nerve cell, making it less excitable and less likely to fire an action potential that sends a signal on to other neurons. So GABA acts like a brake in the brain, preventing the neurons from getting too excited.

Most nerve cells in the brain have GABA-A receptors that prevent excessive activity. But only a small group of nerve cells secrete GABA. These are called interneurons — neurons that live between the larger principal neurons that spread excitation from one brain region to another. When an interneuron is activated, it can either inhibit the nerve cells that excited it, causing feedback inhibition, or inhibit neurons further down the chain, producing feed-forward inhibition. Both of these actions are important for keeping the right balance between excitation and inhibition. If that balance breaks down, seizures can occur. For years, researchers have suspected that problems with the GABA system have a role in epileptic seizures.

Epilepsy, the tendency to have spontaneous seizures, afflicts almost three million Americans, according to the Epilepsy Foundation of America. In 70 percent of the cases, there is no known cause; head trauma, tumors, strokes, infections or a genetic predisposition are implicated in the others.

Seizures are like electrical storms in the brain. When the finely tuned balance between excitation and inhibition malfunctions, seizures occur as a result of the abnormal electrical discharges. The problem can occur in just one small area of the brain, called a partial seizure, or it can spread through the brain, causing a generalized seizure. In most cases, the seizure comes to an end spontaneously, but if that doesn't happen — in a condition known as status epilepticus — untreated patients can die.

In research he conducted nearly 10 years ago, Dr. Greenfield and his graduate student Lei Gao discovered that when nerve cells are deprived of oxygen, in a condition called hypoxia, the number of GABA receptors decreases. The neurons were exposed to 1 percent oxygen, compared to the 20 percent oxygen in the air. Amazingly, the nerve cells in culture can survive the treatment for several hours without ill effects, even though it would kill an intact animal or person in minutes. Nerve cells have ways of adapting to low oxygen states.

How do they adapt? Low oxygen also stimulates a chemical distress signal called hypoxia-inducible factor, or HIF. Cells use HIF to survive under low oxygen conditions. HIF responds to low oxygen levels by switching on genes that help the cell use sugar to generate energy without oxygen, and by triggering several other processes that allow cells to survive in a low-oxygen environment.

But Dr. Greenfield and his colleagues were not sure whether HIF was really involved in reducing GABA receptors. Maybe it was just a bystander triggered by hypoxia? They reasoned that tinkering with HIF might reveal another switch that turned off GABA receptor production. If HIF was essential for hypoxia to reduce GABA receptors, then alternative methods of stimulating HIF without hypoxia should do the same thing.

So they exposed both NT2-N neuronal cells and rat brain neurons in culture either to low oxygen levels or to chemicals, including cobalt, that stimulate HIF without hypoxia.

What they found was the opposite of what they expected. When HIF was turned on by cobalt rather than by low oxygen, the electrical currents produced by GABA receptors increased.

“What that suggested is that HIF is a compensatory factor,” Dr. Greenfield said. “It helps to make up for the bad things that hypoxia does by instructing the cell to make more GABA receptors.”

Designing new drugs that mimic HIF's effects could be used to increase GABA receptors, which might benefit patients with seizures.

But the question of how hypoxia lowered GABA receptors remained unsolved, at least until recently. Dr. Greenfield and his graduate student Liping Wang found that the decrease occurs because hypoxia causes calcium to enter the neurons, stimulating an enzyme called calcineurin. Calcineurin chemically alters proteins by removing phosphate groups from them, changing their function.

Dr. Greenfield's research relies on a technique called patch-clamp electrophysiology, which allows the detection of electrical currents of a trillionth of an ampere in the membrane, or surface of a cell. It is one of the most widely used tools of cellular physiology.

The technique involves touching a cell membrane with a glass micropipette containing saline solution and creating a seal onto a small patch of the membrane by applying suction. An electronic amplifier is connected to the inside of the pipette. Each pulse of current shows that the ion channel has opened.

This allows him to study how the tunnel-like structures called ion channels control the passage of the positively or negatively charged particles called ions in and out of cells. Every cell has many different types of ion channels that help it communicate and function.

The action of GABA on its receptors is like a key being inserted in a lock. When the key is turned, the lock opens and the neurotransmitter activates the receptor.

Using the technique, Greenfield records how a single channel molecule alters its shape and in that way controls the flow of current within a time frame of a few thousandths of a second.

Many drugs taken by people with epilepsy, including benzodiazepines and barbiturates, act by increasing GABA's ability to inhibit cells, sometimes by increasing the rate of channel opening or how long the channels stay open. When the drug binds to the GABA receptor, more chloride ions can pass into the cell, and the resulting decrease in cell activity calms the electrical firestorms produced by seizures.

However, these drugs are not always completely effective, and they can have nasty side effects. For example, benzodiazepines are not used much for epilepsy because the body becomes tolerant to their antiepileptic effects, and the side effects of increasing GABA activity can include drowsiness, a lack of coordination, impairment of memory and concentration, and confusion.

"One of the problems with the GABA-receptor drugs in general is that they tend to disinhibit you," he noted. "They tend to make your memory worse and make you sleepy. These are all side effects of the GABAergic drugs that limit their use to special situations like status epilepticus, in a way that other medicines are not quite so limited."

Several major questions about epilepsy remain unanswered, according to Dr. Greenfield. One mystery is what exactly happens during the development of epilepsy, a process called "epileptogenesis."

Seizures are like electrical storms in the brain.

"We need to know how seizures develop," he said. "One of the big problems is that after head injuries, particularly after the severe head wounds suffered by soldiers, the incidence of seizures is up to 50 percent. And they don't develop right away. They develop over time — months and years — and we still don't have anything in our armamentarium to prevent that from happening. This is very tragic because these are people who otherwise are recovering very well from their injuries and many of them are going to have this debilitating problem of seizures." Despite the increasing number of available antiseizure medications, there are still no drugs available to treat the disease's root cause.

Much more also needs to be learned about status epilepticus, the life-threatening seizures that don't stop, and why co-morbid conditions like depression are associated with epilepsy.

"It's not just that you are depressed because you have seizures," Dr. Greenfield explained, "It is actually that epilepsy changes the brain to make you depressed. It changes the neurotransmitters like serotonin that are involved in depression. If we could find ways to intervene, the quality of life for people with epilepsy would improve dramatically."





THE NEXT REVOLUTION IN PARKINSON'S THERAPY

New medications, techniques offer promise in treating progressive, disabling disorder

A revolution is under way in the treatment of Parkinson's disease and University of Toledo neurologist Dr. Lawrence Elmer couldn't be more excited.

While there is still no cure for the cruel neurological disorder that erodes the brain's ability to control movements and speech, Dr. Elmer says that Parkinson's patients have reasons to be optimistic. Enormous advances in new medical, surgical and nontraditional approaches to treatment are dramatically improving the quality of life for Parkinson's patients.

"We have seen six or seven new medications come to market in the last 15 years that are both effective and well-tolerated by patients," explained Dr. Elmer. He serves as director of the Center for Neurological Health and the Parkinson's Disease and Movement Disorder Program at The University of Toledo Medical Center and has also emerged as a nationally recognized authority on the subject.

Parkinson's causes slow deterioration of the nerves' ability to control the muscles. It usually starts with small tremors and progresses to a shuffling gait and increased difficulty moving. There is no cure, but medications, exercise and even surgery are aimed at controlling symptoms.

Dr. Elmer started the Parkinson's program in 1998. It has grown to become one of the largest Parkinson's centers in Ohio, Michigan and Indiana, seeing around 250 new patients a year and currently caring for more than 1,000 people with Parkinson's. Approximately 3,000 to 5,000 people in northwest Ohio have Parkinson's; while nationally the number is estimated at 1 million or more. With the aging of baby boomers, these numbers are expected to increase.

The UT Parkinson's program also is a leader in developing new treatments through clinical trials, annually enrolling dozens of patients. At any one time, four to six new drugs are being tested in clinical studies at UTMC. Dr. Elmer is a member of the Parkinson Study Group, a non-profit, cooperative group of Parkinson's experts from U.S. and Canadian medical centers working to improving Parkinson's treatment, allowing him to keep up with the latest advances in the field.

For people with Parkinson's disease, life revolves around taking medicine. Dr. Elmer would love nothing better than to see a drug that can stop Parkinson's in its tracks. Unfortunately, that prospect may be years, even decades, away.

The first of the "breakthrough" drugs providing relief for people with Parkinson's was levodopa, introduced in the 1960s. Levodopa works by increasing dopamine levels in the brain and has remained the principal Parkinson's drug for five decades. Levodopa is usually combined with carbidopa in order to increase its effectiveness and tolerability. The combination of carbidopa/levodopa goes by the trade name Sinemet®, which is available in different sizes and strengths.

In recent years, however, new drugs have improved upon levodopa by reducing long-term side effects such as erratic effectiveness and side effects like involuntary wiggling movements. The new drugs include pramipexole, also known as Mirapex®, and ropinirole, known as Requip®. Both medications are members of a class of drugs that act like dopamine and are called dopamine agonists. Both of these medications have been recently approved in once-daily, "slow release" formulations.

Another advance in the area of dopamine agonists are patches that deliver drugs through the skin. The first patch of this kind contains rotigotine (Neupro®), another chemical that mimics dopamine but is delivered continuously over 24 hours. Patients change the patch once a day. The patch's advantage, according to Dr. Elmer, is that it keeps the amount of medication stable in patients' brains throughout the day. The Neupro® patch was available for patients in the United States from 2006 until 2008, but due to a manufacturing problem, it was pulled from the market temporarily. It is expected to return later in 2010.

"The biggest breakthrough that has happened in the last 10 years is the ability to deliver dopamine to the brain in a more continuous fashion," Dr. Elmer explained. "Avoiding excessive levels of the medication can reduce or eliminate involuntary, uncontrollable movements, called dyskinesias, while maintaining adequate levels of dopamine activity can prevent the weakness and slowness seen in dopamine deficiency."

Dr. Elmer discussed another drug, rasagiline, also known as Azilect®, considering it one of the more significant treatment options for Parkinson's in years. UT participated in national clinical trials that showed the drug to be effective in relieving the symptoms associated with both early and late stages of the disease with very few side effects. However, the studies suggested that Azilect® may also slow the progression of Parkinson's, although that conclusion must be borne out by further studies. The drug inhibits an enzyme known as monoamine oxidase-B, which breaks down dopamine.

"By blocking that enzyme, you actually allow the person's native dopamine to stay around for longer periods of time and once you start Sinemet® or levodopa, that dopamine also stays around for longer periods of time," Dr. Elmer said. "Like the long-acting dopamine agonists, Azilect® smooths and/or modulates the variability in dopamine levels."

Developing innovative, non-dopaminergic therapies for Parkinson's is also under way.

For example, some studies suggest that the caffeine in coffee may help prevent Parkinson's disease. By a fluke of nature, caffeine molecules are similar to a brain chemical called adenosine. "By using chemicals that modify the adenosine receptor, you can smooth out the effectiveness of Sinemet® or other drugs," he said.

No one knows for sure exactly what triggers the disease, but studies have show that environmental factors ultimately may participate in the development of Parkinson's disease. Studies have linked the onset of Parkinson's symptoms with chronic exposure to common pesticides and herbicides, according to the UT neurologist.

... the earliest evidence of the disease process was actually found in the nervous system of the intestines and the olfactory bulb, where the sense of smell is located. Everything that we breathe and everything we eat and drink passes over those two surfaces ...



Gerry Van Wambeke is a volunteer who has participated in a Parkinson's clinical trial at UT Medical Center.

“One of the biggest changes in the way we think about Parkinson’s disease in the last 10 years is our understanding that it seems to be environmentally induced,” he said. “When researchers studied carefully the bodies of people who died with Parkinson’s, they saw that the earliest evidence of the disease process was actually found in the nervous system of the intestines and the olfactory bulb, where the sense of smell is located. Everything that we breathe and everything we eat and drink passes over those two surfaces and thus it appears that something in the environment contributes to the development of Parkinson’s pathology.” Farming communities, he noted, tend to have higher incidences of Parkinson’s disease.

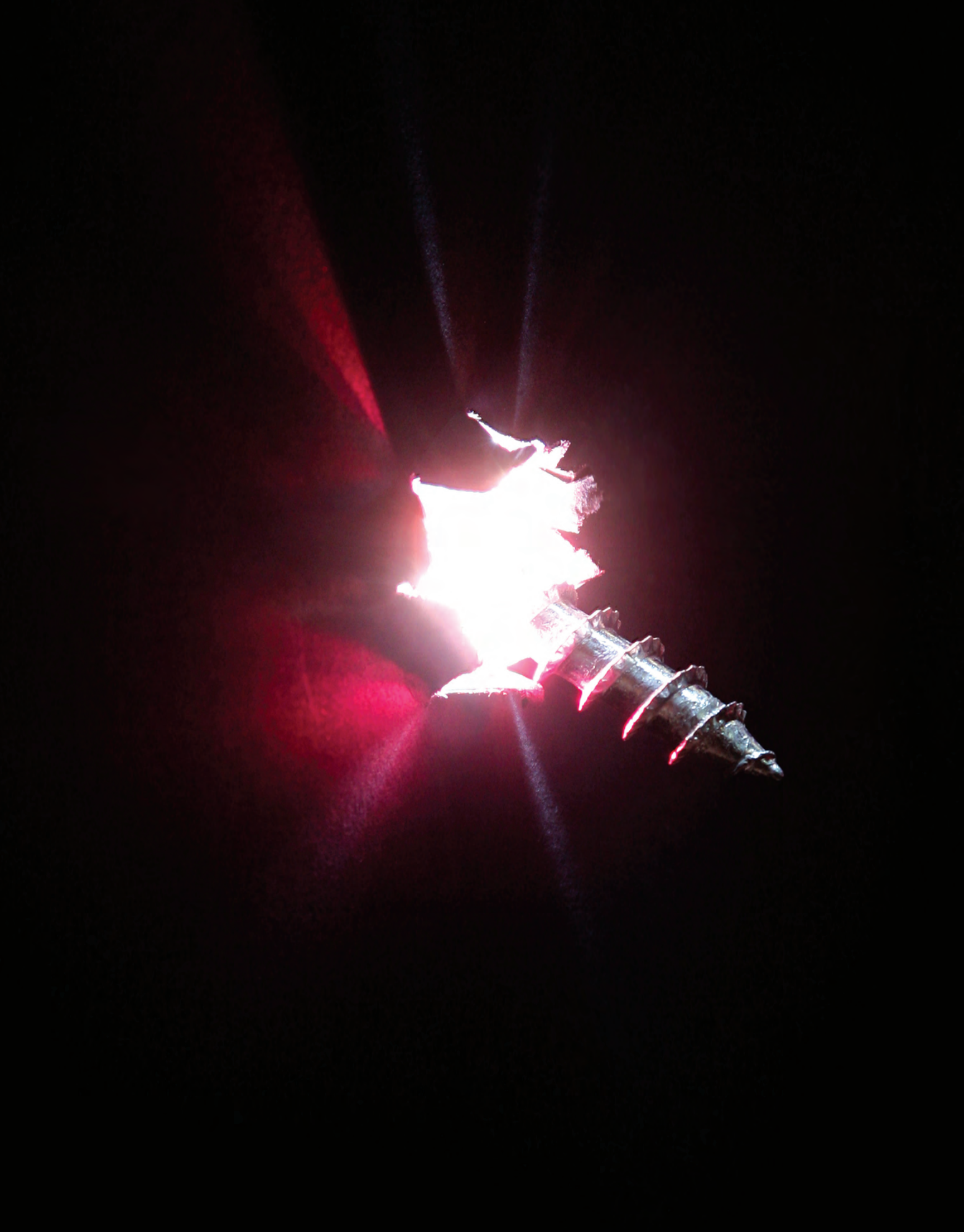
Though medication is usually the major factor in treating Parkinson’s, UTMC’s program also focuses on comprehensive care and a holistic approach. Patients not only meet with neurologists, but benefit from education and care provided by neuropsychologists, nurses, pharmacists, social workers, allied health specialists and others, including patients with Parkinson’s who volunteer in the clinic. There are opportunities to participate in seminars, support groups and exercise classes. Exercise — what Parkinson’s specialists like Dr. Elmer call “big therapy” — has been shown to help the balance, walking and strength of Parkinson’s patients by activating their muscles and sensory system through repetition of specific movements, taking advantage of the brain’s ability to adapt and learn, a concept known as “plasticity.” The UT Medical Center has five physical therapists certified to direct these special exercises.

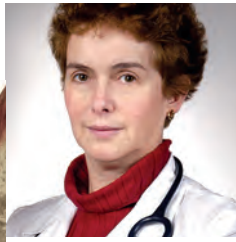
Caring for patients with Parkinson’s disease is challenging, but Dr. Elmer tries to bring a large dose of passion to his work and to the care patients receive.

"In a sense, they have become prisoners — they are being locked inside their bodies and our job is to set them free."

“I see this as a huge opportunity to improve the quality of life in people whose lives, in their mid to late adult years, are literally being robbed by Parkinson’s,” he said. “In a sense, they have become prisoners — they are being locked inside their bodies and our job is to set them free. While we can’t help everyone or treat symptoms perfectly in all cases, we are always grateful when we see improved quality of life for patients and their families receiving our care.”

“What gives me enthusiasm and passion is to see people who have been struggling — maybe Parkinson’s has made it difficult to walk so they have to use a walker or wheelchair or maybe they are unable to do the things they love to do like spending time with family or friends, enjoying outdoor activities, knitting, baking or playing the piano — and we help them recover so they can do the things they want to do,” he explained. “I actually ask my patients to bring us pictures of them with family and friends, when they get back on the golf course, when they go fishing, when they are working in the garden or playing the piano. When they’re baking cookies, I ask them to simply bring some samples of what they’ve baked — our entire clinic enjoys those types of rewards!”





UT NEUROLOGIST PROBES MYSTERIES OF MIGRAINE HEADACHES

Latest study links childhood abuse as risk factor for debilitating condition

Dr. Gretchen Tietjen knows how debilitating, frightening and misunderstood migraine headaches are.

As professor and chairman of the College of Medicine's Department of Neurology and director of The University of Toledo Medical Center Headache Treatment and Research Program, she annually sees more than 1,000 patients who visit her clinic on Health Science Campus looking for relief from the crippling condition.

She also directs a wide-ranging research program and has emerged in the last decade as a national opinion leader in the field and advocate for increased federal funding into migraine research. Her studies have provided new insights into the problem that plagues some 35 million Americans.

Migraines are not normal headaches. They make heads agonizingly throb, are often accompanied by nausea, vomiting, sensitivity to light and sound and blackouts, and can last for hours or days. They are the fourth most common diagnosis made by family physicians, the number one reason patients are referred to neurologists, and a major cause of lost work and school days. Women are up to four times more likely than men to have migraines.

When she began her migraine headache studies a decade ago, few viewed migraines as a systemic disorder. Since then, Dr. Tietjen and other researchers have led a sweeping shift in the theory of migraines, discovering important new links between migraines and stroke, heart disease, depression and other pain syndromes.

Most recently, she made headlines for a study published in *Headache: The Journal of Head and Face Pain* that found that children who were physically or emotionally abused or neglected are more likely to develop chronic migraines and other chronic pain conditions as adults.

No one had previously examined childhood abuse's relationship to migraines in this detail.

Tietjen's group collected data on childhood maltreatment from 1,348 people with migraines who were seen at 11 outpatient headache centers. About 58 percent reported being physically, sexually or emotionally abused or physically or emotionally neglected during childhood. Also, 61 percent reported having at least one painful condition other than migraine.

Dr. Tietjen discovered that in addition to listing migraines, respondents with histories of abuse were more likely to report being treated for other chronic pain conditions such as irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, arthritis and interstitial cystitis.

"Both animal studies and neuroimaging in humans and genetic work have shown that early abuse changes the brain development, and this is known as plasticity," she explained. "It changes what is called the hypothalamus-pituitary-adrenal axis, and this may forever change the way you respond to stress and that probably has some negative effects on health. Some of those changes are not manifested until a person reaches adulthood."

The study, Dr. Tietjen said, adds further credence to a biological concept that neurologists like her call "kindling," which suggests that each headache changes the central nervous system and makes the next headache more likely. Over time, there may be a worsening of the headaches or the development of other pain conditions. Some medical conditions that at first seem to be isolated can be linked to stressful events much earlier in life that smolder for a time, then flare into a fire.

Migraines are not normal headaches. They make heads agonizingly throb, are often accompanied by nausea, vomiting, sensitivity to light and sound and blackouts, and can last for hours or days.

The idea that abuse changes how genes function opens a new window for behavioral and drug therapy, noted Dr. Tietjen, who serves in leadership posts on headache research committees of the American Academy of Neurology, Ohio Headache Association and the American Headache Society.

An emerging field that interests Dr. Tietjen is “epigenetics,” which refers to changes in the chromosome from external events without changes in the DNA sequence. The idea, she says, is that events like trauma, abuse, stress and other behavior and environmental factors can affect how certain genes are “expressed,” that is, how the information in a gene gets translated into proteins.

So what can people do to minimize their risk of migraine that may be part of their genetic or epigenetic predisposition? Dr. Tietjen says lifestyle changes, such as those related to diet, exercise and personal attitude, could actually stave off migraine as they improve overall health.

A test that would identify people at risk of worsening migraine in terms of increasing frequency and severity would be invaluable, she said; that way their treatments might stand a better chance of arresting the progression and the development of other related conditions.

Her studies also have uncovered links between migraines and other conditions.

In a study that appeared in a January 2007 issue of the journal *Neurology*, she found that women who suffer from chronic headaches — more than 15 a month — are four times more prone to major depression than those with episodic headaches, fewer than 15 monthly. Chronic headache sufferers were also three times more likely to report “a high degree” of related symptoms such as fatigue, insomnia, nausea, dizziness, and stomach, back and joint pain.

The study involved 1,032 women who sought care at headache clinics in five states — 593 were episodic headache sufferers and 439 chronic headache patients. About 90 percent of them were diagnosed with migraines.

However, the exact nature of the relationship between migraine and depression remains unclear. Studies following persons over time have shown that migraine patients have an increased risk of developing depression and people who are depressed are at an increased risk of getting migraine attacks.

Dr. Tietjen suspects that the “bidirectional” relationship is actually a result of a common underlying cause for both, such as early life trauma and stress.

In addition, an increasing number of studies show that migraine, particularly attacks with an aura, is a harbinger of stroke and heart attacks.

Eight years ago, she discovered that livedo reticularis, a narrowing of blood vessels in the arms and legs that results in mottled skin discoloring, can be used as a clinical marker to identify migraineurs with an increased risk of stroke.



Dr. Tietjen sees annually more than 1,000 patients looking for relief from migraine.

In a study of 175 people she conducted two years ago, she found that nearly a third of those with migraines with aura had signs of blood vessel damage, almost five times higher than the controls. The finding suggests that people with migraines are at increased risk of strokes, and Dr. Tietjen thinks that in migraineurs, preventing headaches could lower the risk of stroke and heart attack.

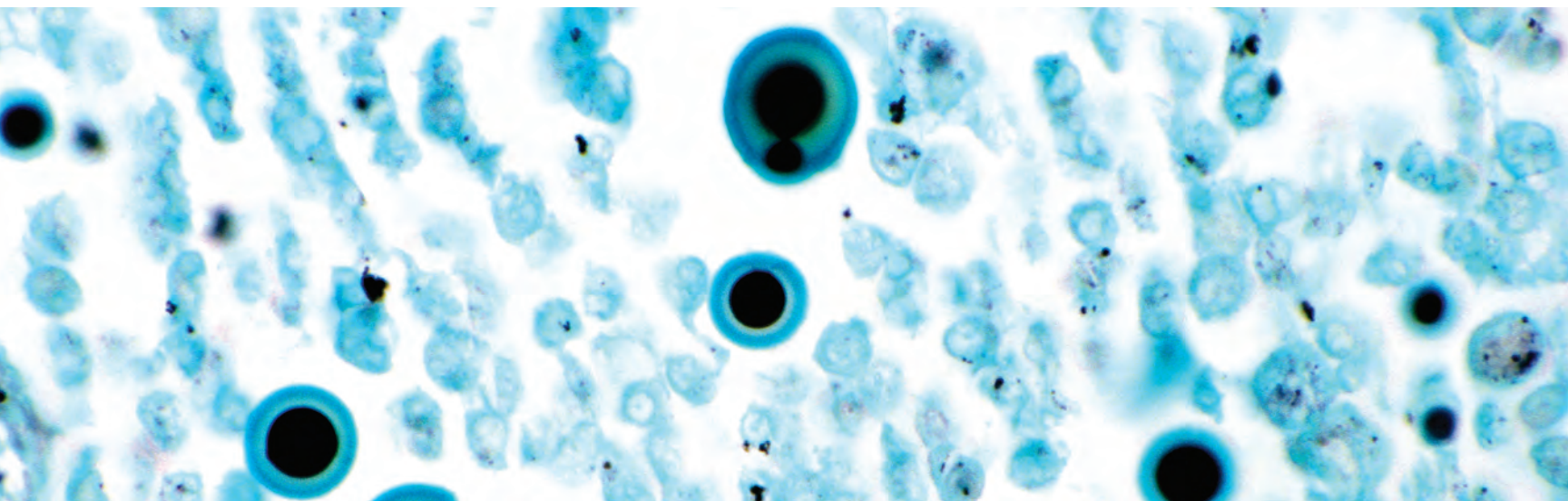
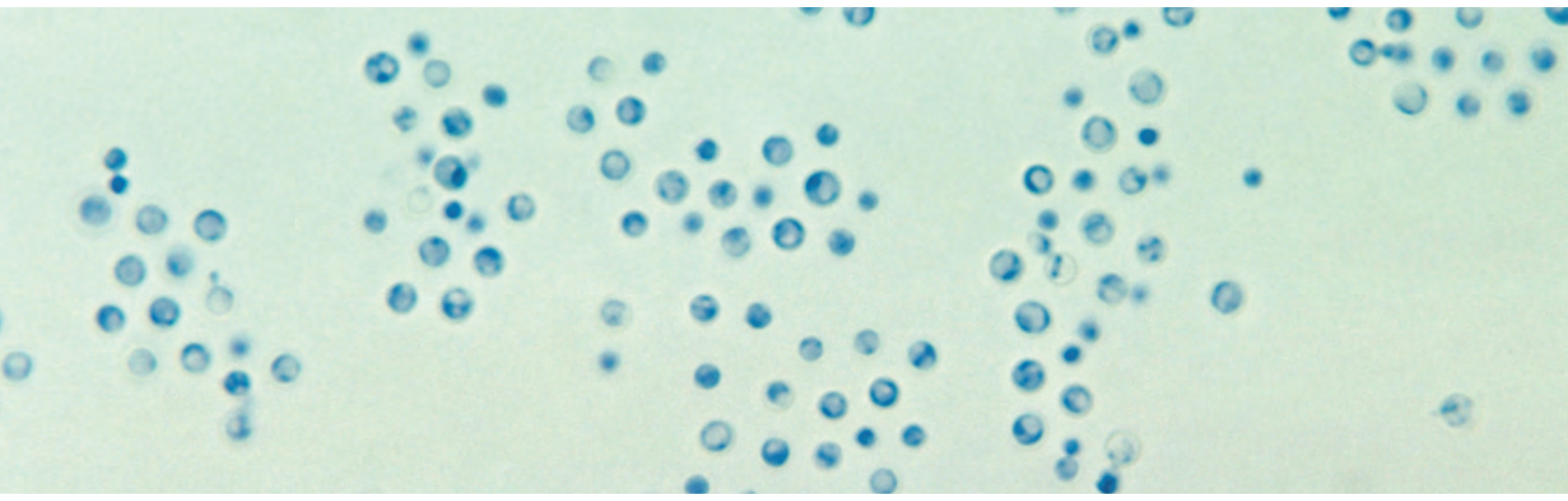
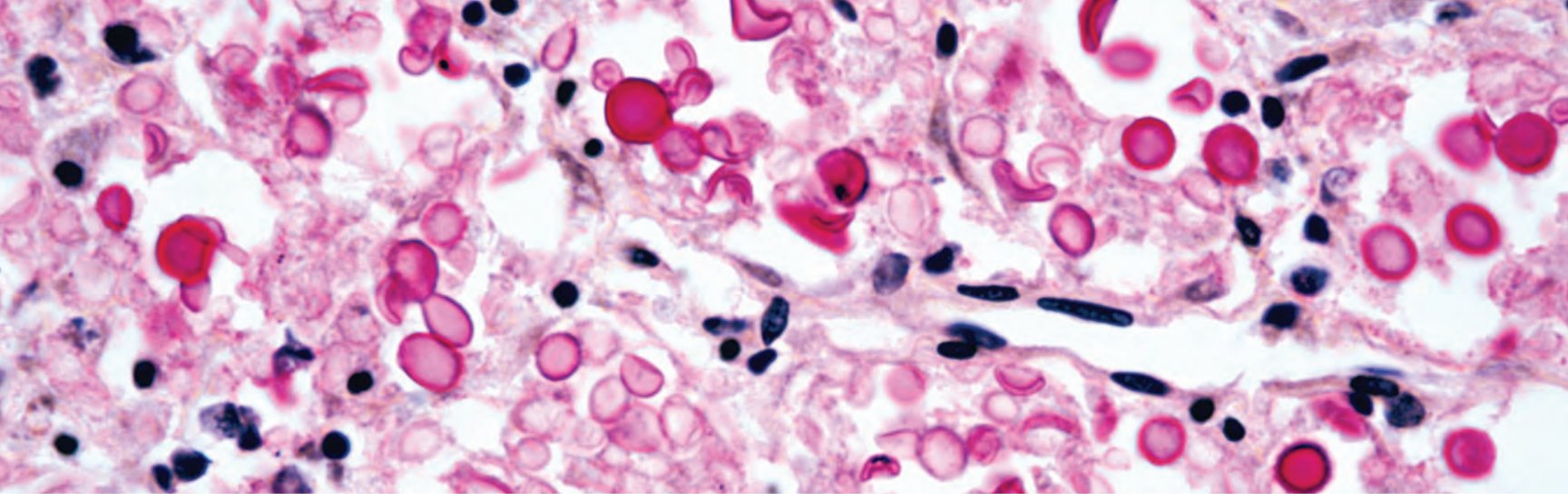
“Now whether migraine causes endothelial dysfunction or endothelial dysfunction causes migraine is a question of some debate,” she said. “Actually, I think both happen.”

To learn more about that relationship, Dr. Tietjen is studying why inflammation of the endothelium, the cells that line the inside of arteries and blood vessels, is more common in women with migraine. Damage to the endothelium harms the smoothness, elasticity and reactivity of blood vessels, which in turn can cause clots, strokes and atherosclerosis.

Last year, she conducted a study examining whether several factors released when the endothelium is damaged — including Von Willebrand factor, IL-6, transforming growth factor beta-1, high-sensitivity C-reactive protein homocysteine, total nitrate/nitrite concentrations — would make reliable biomarkers to assess stroke risk. She did find several markers increased in persons with migraine that are also increased in those with silent strokes on MRI scans.

Those studies are continuing with collaborators at Leiden University Medical Center in The Netherlands.

... stressful events much earlier in life that smolder for a time, then flare into a fire.





MANNING THE FRONT LINES IN THE WAR AGAINST INFECTIOUS, FUNGAL DISEASES

Whether rounding on patient floors at Duke University Medical Center, overseeing studies in his lab at Duke's Medical Mycology Unit, or mentoring Ph.D. or M.D. students, Dr. John R. Perfect (MED '74) has been a key figure in extending the lives of patients with opportunistic infections and fungal diseases, training the next generation of infectious disease specialists and opening up new avenues for research.

There are good reasons for Dr. Perfect's sleuth-like drive to learn more about current species of fungi and track down new ones. Fungi lurk everywhere: in the air, in the water, in the air, on rotting vegetation. They can be beneficial, bizarre, creepy and deadly to humans.

"We live in a fungal world," said the 1974 graduate of the former Medical College of Ohio. "And there are millions yet to be identified, including a few bad actors which cause humans grief and continue to complicate clinicians' management of serious diseases."

Today, Dr. Perfect, 60, tracks elusive, nasty fungi suspected of causing everything from lethal infections in cancer and AIDS patients to persistent illnesses in otherwise healthy people at one of the country's most prestigious academic health centers — North Carolina's Duke University. In the process, he has earned international plaudits in the fields of infectious disease and medical mycology and is one of the medical center's most visible, productive faculty members.

As professor of medicine and chief of the medical school's Infectious Diseases Division — a unit of 100 people, including 34 full-time physicians, 12 infectious disease Fellows and dozens of residents — and director of Duke's nationally recognized medical mycology laboratory, he oversees a thriving infectious-diseases program, one of the country's largest, one that gives him access to an incredible volume of patients with a myriad infectious conditions, who are referred from the Southeast and from Mid-Atlantic states.

A faculty member there since 1977, Dr. Perfect is the prototypical "triple-threat" academic physician. He treats patients; oversees basic science bench research in the laboratory; grills medical students and residents while on rounds examining hospitalized patients; mentors graduate students, responds to email consults from physicians around the world; edits papers; writes grants; participates in clinical-trial meetings; reviews manuscripts and grant applications, and prepares seminars.

He has given talks at virtually every U.S. medical school and at dozens of national and international conferences. He sits on National Institutes of Health grant review and journal editorial boards as well as national panels that develop infectious-disease practice guidelines. He has written five books and authored more than 750 journal articles, letter and abstracts.

“John is one of the most outstanding faculty members at Duke Medical Center,” said colleague Dr. John Hamilton. “He has been the recipient of numerous awards reflecting his contributions to clinical care, teaching and research. These awards, though appropriate, do not begin to tell the whole story. Added to these accomplishments are the personal attributes that make John a beloved mentor, adviser, colleague, friend and family man.”

At a time when medicine is accomplishing headline-grabbing breakthroughs, potent new infectious pathogens have become an increasingly elusive enemy. Opportunistic infectious diseases once held in check by antibiotics have become more difficult to eradicate thanks to jumps in immunosuppressive diseases, notably AIDS, and the use of immunosuppressive drugs and treatments like chemotherapy. Pathogenic fungi also are the fastest-growing cause of hospital-acquired infections.

All this makes Dr. Perfect’s infectious disease and fungal sleuthing critical.

He holds the distinction of taking a single clinical case with the opportunistic, yeastlike fungal pathogen *Cryptococcus* informants that is found in soil and bird droppings and elevating the strain to a model culture for fungal research. It involved a patient with Hodgkin’s disease admitted to Duke Hospital for treatment of cryptococcal meningitis.

He still has the patient chart and case notes in his office and the time and date of the historic discovery — Feb. 14, 1978, at 11 p.m. — etched in his memory. It was when the lumbar puncture was performed that he first saw the encapsulated yeast under a microscope. An infectious disease Fellow at the time, he secured an isolate, cultured it and developed the strain that now goes by the name *Cryptococcus neoformans* H99. Today he donates this fungal strain to researchers worldwide for experiments and has developed an animal model of fungal pathogenesis of *Cryptococcus* that is a screening tool for potential drug targets and for understanding pathogenic mechanisms.

He also was part of a team of Duke and John Hopkins University researchers that documented involvement of the fungus *Cryptococcus gattii* in the deaths of 19 people on Vancouver Island, British Columbia, between 1999 and 2005.

His early years at Duke evolved with the AIDS epidemic. Two decades ago, he wrote the second prescription ever at Duke for AZT, or azidothymidine, in the original trial for the drug. “However, we have seen such a rapid change in this disease and its management that I have not personally written

“Both my training at MCO and my professional life at Duke have been blessings that I sincerely appreciate.”

a prescription for HAART [anti-AIDS drugs] since,” he said. “I have dedicated physicians in the division who specifically specialize in management of this infection. That is progress.

“I like curing acute disease,” he said in explaining his attraction to infectious diseases. “It is incredibly satisfying to care for an infected patient by going back to the lab, discovering the problem and being able to treat it.”

Dr. Perfect considers himself lucky to have an extended tenure at Duke because they have allowed him to do what he wanted.

“It is an extraordinary atmosphere,” he said. “The intellectual energy, the vitality, the excitement, the passion that is exhibited here is addictive, almost like cocaine. To be successful here at Duke you need to focus on excellence in care, education and research. You just have to get out there and produce. Both my training at MCO and my professional life at Duke have been blessings that I sincerely appreciate.”

Not surprisingly, his office walls are lined with academic and professional awards. He was named Duke University Scholar-Teacher of the Year in 1999, a member of the Association of American Physicians in 2001, a fellow of the Infectious Disease Society of America and American Academy of Microbiology in 1991 and 2004, respectively, and a fellow of the American Association for the Advancement of Science in 2007. He received MCO’s 2003 Distinguished Alumni Award and Duke’s 2009 Research Mentoring Award for Translational Research.

A native of Johnstown, Ohio, a village of 4,000 people 20 miles northeast of Columbus, Dr. Perfect wanted to be a doctor since he was 13. On his way to that goal, he graduated from Wittenberg University in 1971, from MCO in 1974, and completed an internal medicine residency training at the University of Michigan. He moved to Duke in 1977 to complete an infectious-disease fellowship.

Looking back on his days in Toledo, Dr. Perfect easily recalls the arduous transition from student to practitioner, deploying basic-science knowledge gained in the classroom while becoming comfortable with the unfamiliar rituals of scribbled physician notes and morning rounds at MCO, Toledo, St. Vincent and Mercy hospitals.

“It was a time when the medical school was already developing itself,” he said, recalling the small size of MCO’s third entering class and the three-year curriculum that quickly exposed students to patient care. “The atmosphere at that time was conducive to learning. We learned and lived together for two years and then were quickly thrown into the mix of patient care at the hospitals. I have great respect for the other 50 students I had in my class. I learned so much from them and frequently think about them.”

Full-time and volunteer faculty members like Drs. Liberato J. A. DiDio, Earl Freimer, Barney Wisinger, Ben Pansky, Robert Tidrick, Peter White and Ken Kropp stoked his intellectual curiosity.

“I was very impressed with Earl Freimer,” said Dr. Perfect, referring to the physician chairman of the Department of Microbiology back then who sparked his interest in infectious disease. “He was very bright. He was kind of a semi-role model who made infectious diseases very attractive to me. I was also impressed with the time and efforts of the community physicians, people like Barney Wisinger. On the surgical side, Ken Kropp was very, very kind to me and he allowed me to do some surgical procedures, and Dr. Tidrick was the grandfather of the place, the soul of the institution in many ways. Finally, Peter White changed my life one night as he looked me up as an intern and graciously spent the time to help me get into a university program for training.”

He credits his wife, Becky, a Marion, Ohio, native and nurse he met in May 1975 during his first-year externship at Riverside Methodist Hospital in Columbus, for much of his professional success.

“I have been very fortunate that my wife has been the ideal partner in all of this,” he said.

The couple has four children: Zack, 30, a Davidson College graduate who works at Duke; Tyler, 28, a Kenyon College graduate who works in real estate in London; Chase, 25, a Duke graduate and teacher in Costa Rica; and Chelsea, 19, a Dartmouth College sophomore.

“It has been a true privilege to be part of the art of teaching, understanding, and healing the human condition,” he said. “I hope patients, students, colleagues and medical science have benefited from the chance that MCO took on training a naïve but committed 21-year-old in 1971.”

"I hope patients, students, colleagues and medical science have benefited from the chance that MCO took on training a naïve but committed 21-year-old in 1971."

COLLEGE OF MEDICINE CLASS NOTES

Gary Schniegenberg MD (MED '78), Bluffton, Ohio, of the Orthopaedic Institute of Ohio, received the Ohio Athletic Trainers Association Team Physician Award 2009. He's team physician for Division VI champs Delphos St. John's and Pandora-Gilboa high schools.

Stephen Brewer MD (MED '79), medical director of Medical Canyon Ranch in Tucson, part of a residence community and resort spa, co-authored a book, *The Everest Principle: How to Reach the Summit of Your Life*, published by Hay House.

Mary Ann Myers MD (A/S '79, Res '91), Glandorf, Ohio, opened a Lima multidisciplinary clinic to treat Parkinson's disease and MS.

Rose (Ohliger) Osowik MD (Pharm '79, MED '87), who has been practicing medicine in the Toledo area for 18 years, joined Toledo Clinic.

Jon Dvorak MD (A/S '80, MED '83), who works with Perrysburg Pediatrics and ProMedica Physicians Group, was named to the America's Top Pediatricians list by the Consumers' Research Council of America, a Washington, D.C.-based independent organization.

Sandra Mendel MD (MED '81) earned her master's degree in biomedical informatics from Oregon Health Sciences University, Portland, in June. She practices internal medicine/pediatrics in Eaton, Ohio.

Darrick E. Antell MD (MED '82), assistant clinical professor of surgery at Columbia University and New York cosmetic surgeon, joined the editorial board of Consumer Guide to Plastic Surgery, an independent resource publication.

E. Edwin Conaway Jr. MD (MED '83) was appointed vice president of medical affairs by Southeastern Med, headquartered in Cambridge, Ohio. He will continue his private practice in family medicine.

Harlan A. McCulloch MD (MED '84), who practices with Southeast Anesthesiology Consultants in Charlotte, N.C., was named to Best Doctors 2009 list in Charlotte Magazine, which polls area physicians on their choices.

Thomas Holloway MD (Res '85) joined the medical staff of MedCentral/Shelby Hospital in north-central Ohio and the practice of Crawford County Anesthesia.

Thomas Steinemann MD (MED '85), professor of ophthalmology at Case Western Reserve University School of Medicine, is a co-investigator in a five-year, \$2.9 million study funded by the National Institutes of Health, working with patients suffering from both Alzheimer's disease and cataracts to document how restored vision improves everyday life.

Ann M. Wolfe MD (Pharm '85, MED '97) joined the West Toledo Internal Medicine Association as a partner. She and her husband, **Todd R. Miller (A/S '89)**, who's a division manager with international containment/filtration company BakerCorp, have two children: twins Tessa and Nicholas.

Don Batisky MD (MED '87) joined Emory University School of Medicine in Atlanta as associate professor of pediatrics and director of the Pediatric Hypertension Program at Children's Healthcare of Atlanta, Emory Children's Center. Previously he was professor and associate dean for admissions and records at the Ohio State University College of Medicine, which honored him with the 2009 Professor of the Year Award. He also ran his first 10K on July 4th in the 40th annual Peachtree Road Race in Atlanta, along with, he says, "about 55,000 others."

David C. Ernst MD (MED '89) was promoted to president of EMPOWERdoc Inc., a software company specializing in medical emergency department documentation systems and electronic medical records. He and his wife, **Christine Barry PhD (MED '85)** live in Vermilion, Ohio.

David J. Ludwick MD (Res '89), medical director and a primary surgeon for Ludwick Eye Center, opened a new office in Waynesboro, Pa., making three in the practice.

Pamela J. Schlembach MD (Univ Coll '89, MED '97) was promoted to associate professor of radiation oncology at the University of Texas' M.D. Anderson Radiation Treatment Center in The Woodlands, where she and her husband,

Chuck (Pharm '78, PharmM '89) make their home.

Elizabeth Raitz Cowboy MD (MED '92, Res '96) joined medical service company Advanced ICU Care in St. Louis as director of virtual ICU. A national presenter in telemedicine technology, she serves on the eICU Research Institute Executive Steering Committee and as a board member for the Society of Critical Care Medicine.

Eric Christoff MD (MED '94) was promoted to assistant professor of clinical medicine at Northwestern University's Feinberg School of Medicine, Chicago.

David Parrett MD (MED '94) is the new medical director of Eagle Creek Nursing Center in West Union, Ohio, where he ran his medical practice for the past two years. He and his wife, Jodi, have two children.

Andrew Krueger MD (MED '95) joined Pisgah Urology on the campus of Transylvania Regional Hospital in Brevard, N.C.

Rebecca C. (Ravas) Doubler MD (A/S '97, MED '00) and her husband, Eric, welcomed the birth of their daughter, Megan Christine, in June 2008. She, brother Kevin and the family live in Avon, Ohio. Rebecca is chief of anesthesiology and medical director at the Premium Surgery Center in Elyria.

Cherilyn M. Schurtz MD (A/S '97, Res '07) married **Jacob N. Maciejewski MD (A/S '01, MED '06, Res '09)**. She's with PediatriCare Associates, he's with Perrysburg Pediatrics.

Mandy Klass MD (A/S '98, MED '01) joined northwest Ohio senior living provider The Meadows of Ottawa-Glandorf as medical director.

William E. Walston MD (Res '00) opened Indian Lake Family Medicine in the village of Russells Point, Ohio.

Charlie Christensen DO (Res '01) joined Mackinac Straits Health System in St. Ignace and Mackinaw City, Mich., as a pediatrician.

Anthony F. Pizon MD (MED '01), professor of health policy and management at Emory University, received the Outstanding Young Alumnus Award from Westminster College in Pennsylvania, where he completed his

undergraduate degree. He's also an ER physician at UPMC Presbyterian Hospital and the Children's Hospital of Pittsburgh.

Alonzo L. Grant III MD (MED '03) joined the medical staff of UPMC Bedford Memorial in Everett, Pa., practicing with Bedford OB/GYN Associates.

Bnan Razoky MD (Res '03) joined the medical staff of St. Mary Mercy Hospital in Livonia, Mich.

Scott Ruhlman MD (MED '04) finished his residency at the University of Washington in Seattle, took his orthopedic boards and is doing a fellowship at Harvard University. He plans to move back to Seattle, where he and his wife grew up, and accepted an offer from a private practice.

Alex Senchenkov MD (Res '04) was appointed to the staff of Canonsburg General Hospital, near Pittsburgh.

Derek Fleming MD (MED '06), who's in his final year of anesthesia residency at the University of North Carolina at Chapel Hill School of Medicine, was selected by peers and medical colleagues as chief resident for the 2009-2010 academic year.

Melinda Fritz MD (MED '06) joined the staff of Henry County Hospital, Napoleon. She and her husband, Kevin, have three children.

Alison T. Chudyk MD (MED '07) married **Justin C. Greiwe MD (MED '09)**. They're both completing residencies in Cleveland, she in radiology, he in pediatrics.

Anas Balaa MD (Res '09) joined Memorial Hospital in Fremont. He's board certified in internal medicine with certification in pulmonary disease, and completed a sleep disorder fellowship at UTMC.

Sonia Ghai MD (Res '09) joined the Geisinger-Lewistown (Pa.) Health System, practicing in women's health.

Obituaries

Carl L. Armstrong MD, Toledo, clinical assistant professor in MCO/MUO Department of Obstetrics and Gynecology from 1971 to 2004, died Feb. 24 at age 81.

Thomas H. Brown Jr. MD, Napoleon, clinical professor of orthopedic surgery who helped originate the Orthopedic Residency Program, died March 17 at age 88. His first volunteer faculty appointment was in 1969 as a clinical associate in orthopedics in the MCO Department of Surgery. He was later promoted to clinical assistant professor, then clinical professor in 1996, also serving as team physician at UT for many years.

Thomas D. Geraciotti MD, Perrysburg, clinical associate professor of medicine, died Oct. 25 at age 76. He began his volunteer affiliation with MCO in 1969.

James A. Hampton MD, Waterville, longtime MCO faculty member, died Dec. 7 at age 61. In 1986, he joined MCO as a researcher in pathophysiology, teaching classes in his specialty in the College of Nursing and Department of Physician Assistant Studies. He became a tenured professor in 2004 and received the College of Nursing's Prism Award for teaching excellence in 2005. Hampton retired in 2007 after being diagnosed with amyotrophic lateral sclerosis and was named professor emeritus in 2009. In 2008, students started the annual "Hampton on the Trail" run and walk to raise funds for the James Hampton Scholarship, which benefits students on Health Science Campus who excel in the pathophysiology course and exemplify Hampton's attributes of character, honesty and integrity.

Harry M. Humeniuk MD (MED '86), died May 11 at age 52.

Warren M. Kleinberg MD, Toledo, died Nov. 20 at age 65. An assistant professor of community medicine and pediatrics at MCO from 1974 to 1982, when he resigned and took a volunteer appointment as clinical assistant professor of pediatrics. He also held the directorship of the Primary Care Clinic, and of Ambulatory Pediatrics. Named pediatric professor of the year in 1980 by the Pediatric Housestaff Association, he was promoted to clinical associate professor in 1986.

Robert Livengood, Traverse City, Mich., on the MCO faculty from 1980 to 1989, died March 30 at age 71. Associate professor and director of the Physical Therapy Program, he

briefly served as acting dean of the College of Allied Health. When he left MCO, he was that college's associate dean for administration. In 1992, a scholarship in his name was established for physical therapy students.

Thomas J. O'Grady MD, Sylvania, clinical assistant professor in MCO/MUO Department of Surgery from 1970 to 2006, died Feb. 28 at age 76.

John "Jack" Tansey MD, Ottawa Hills, att. 1938-1939, clinical assistant professor in MCO Department of Pediatrics from 1970 to 1991, died April 24 at age 89.



Rocket Science

Rocket Science is published annually by University of Toledo College of Medicine for alumni and friends of the college in cooperation with the UT Office of Marketing and Communication and the UT Alumni Association.

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