KANSAS

MEDICINE+SCIENCE

News from the University of Kansas Medical Center

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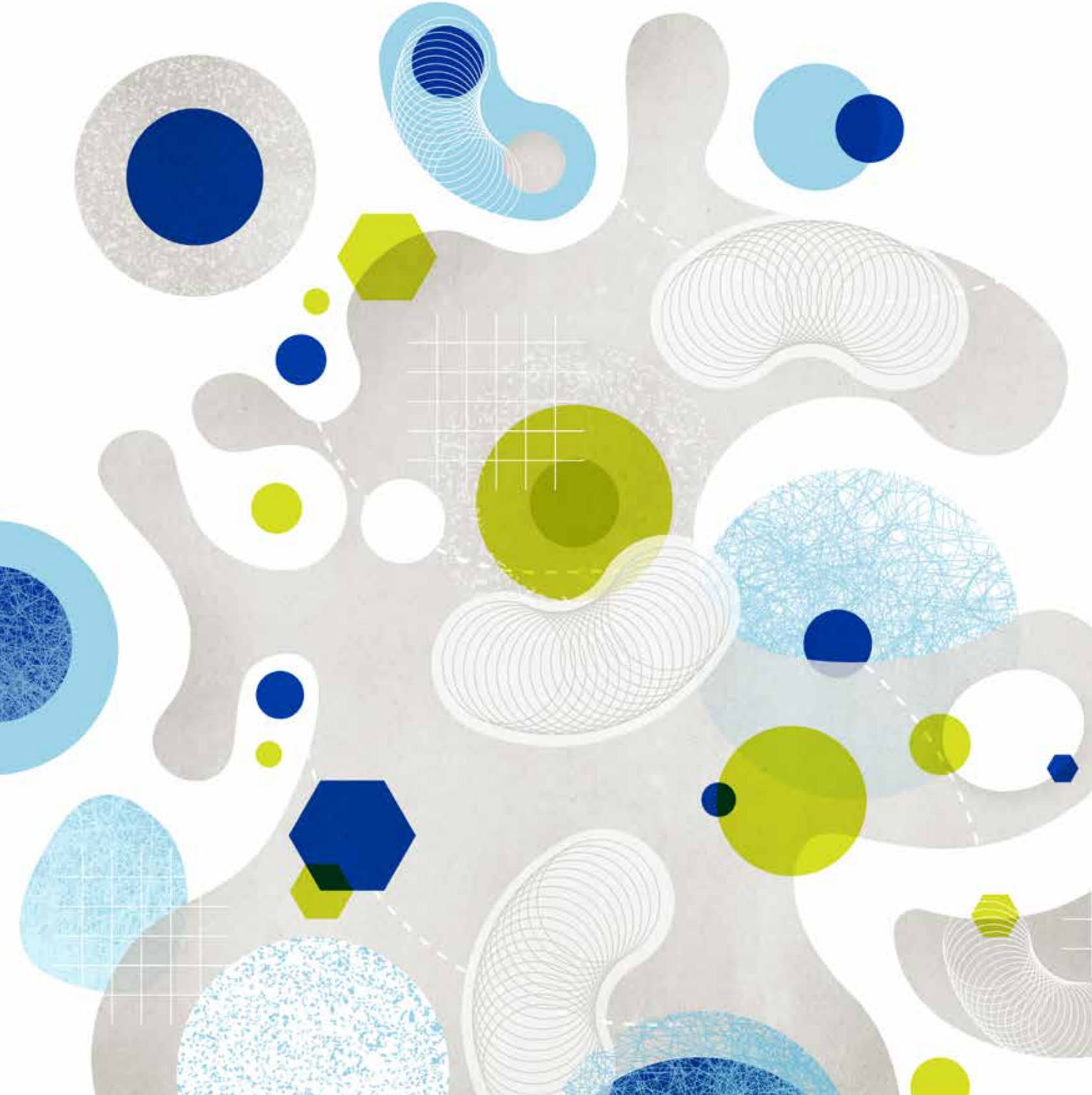

FROM THE EXECUTIVE VICE CHANCELLOR

We have a saying at the University of Kansas Medical Center when we are trying to determine if a story is newsworthy. We ask ourselves "Is it first, is it best or is it only?" Our cover story in this issue of Kansas Medicine + Science explores the role mitochondria most likely plays in disease and the aging process. KU Medical Center's extraordinary researchers — including Danny Welch and Russell Swerdlow — may not be the only scientists who have targeted mitochondria as one of the keys to good health and a long life — but as you will read here, they are certainly among the first and without a doubt among the best.

Elsewhere in this issue, the KU School of Nursing's new associate dean for research, Barbara Polivka, has spent years studying how many common household products contain chemicals that can cause injury and illness. Although her research focuses primarily on how these products can affect adults with asthma, her work could lead to a healthier home environment for all of us.

We also talk with Michael Kennedy, our associate dean for rural health education, who just received the Outstanding Educator of the Year award from the National Rural Health Association. And we follow a group of KU medical, nursing and health professions students as they embark on their international education experience to Santiago de Compostela in Spain this past summer.

We hope you enjoy this issue of Kansas Medicine + Science. We always appreciate your feedback, so please drop us an email at kmands@kumc.edu. We look forward to hearing from you.

Robert D. Simari

Robert D. Simari, M.D.
Executive Vice Chancellor
University of Kansas Medical Center

ON THE COVER
Illustration by Chad Hagen

EXECUTIVE EDITOR
Donna Peck

GRAPHIC DESIGNER
Grace Reap

CONTRIBUTING WRITERS
Kristi Birch
Kay Hawes
Leilana McKindra
Donna Peck
Grace Reap

PHOTOGRAPHERS
Selena Jabara
Elissa Monroe

ILLUSTRATION
Chad Hagen
Jasu Hu
Grace Reap

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NEWS FROM KU MEDICAL CENTER

KU MEDICAL CENTER NAMES AKINLOLU OJO EXECUTIVE DEAN OF THE KU SCHOOL OF MEDICINE

The University of Kansas Medical Center named Akinlolu O. Ojo, M.D., executive dean of the University of Kansas School of Medicine, where he will oversee the Kansas City, Salina and Wichita campuses.

Before coming to KU, Ojo was associate vice president for clinical research and global health initiatives and professor of medicine and health promotion sciences for the University of Arizona in Tucson, Arizona. Board certified in nephrology, he also served as an attending physician at Banner University Medical Center in Tucson and has clinical interests in chronic kidney disease, health disparities and kidney transplantation.

Ojo earned his medical degree from the College of Medicine of the University of Lagos in Lagos, Nigeria. He also earned a doctorate in epidemiology and an MBA from the University of Michigan in Ann Arbor, Michigan, where he rose to the rank of full professor in the Department of Medicine. He also was inaugurated as the Florence E. Bingham Research Professor in Nephrology, becoming the first African American to be granted a named endowed professorship at the University of Michigan Medical School.

After medical school, Ojo served as a postdoctoral fellow in public health at the University of Alabama at Birmingham in Birmingham, Alabama and continued his training at the University of Kentucky Hospitals in Lexington, Kentucky, where he completed an internship and residency and served as chief resident for internal medicine. He served as a clinical fellow and research fellow in nephrology at the University of Michigan Health System in Ann Arbor.

A national leader in research with more than $95 million in current grant funding and more than $200 million in total federal research grant awards during his career, Ojo is a member of the Food and Drug Administration Advisory Panel on Urologic and Gastrointestinal Devices and has been elected into the American Society of Clinical Investigation, the Association of American Physicians and the American Clinical and Climatological Association.

His primary research interests are in the clinical epidemiology and clinical and translational research in chronic kidney disease and kidney transplantation; minority health and health disparities; and global health. He has authored more than 200 peer-reviewed manuscripts.

Ojo replaces Robert Simari, M.D., as the executive dean of the KU School of Medicine. Simari was named executive vice chancellor of KU Medical Center in July 2017 and served as executive dean while a national search took place.

JERRIHLYN MCGEE NAMED VICE CHANCELLOR FOR DIVERSITY, EQUITY & INCLUSION AT KU MEDICAL CENTER

KU Medical Center announced in September that Jerrihlyn McGee, DNP, RN, CNE, is the new vice chancellor for diversity, equity and inclusion. In this newly created role, McGee will serve as the chief diversity officer and will lead and coordinate diversity-related initiatives for all three schools (health professions, medicine and nursing) and on all three campuses of the KU Medical Center (Kansas City, Salina and Wichita). She will develop and oversee programs, services and initiatives designed to enhance the organization's cultural competence and the successful recruitment, professional development and retention of students, faculty and staff from diverse and under-represented population groups. McGee also will chair the Diversity and Inclusion Cabinet. McGee earned a bachelor's degree in biology from Xavier University, and she earned a bachelor's degree in nursing, a master's degree in organizational leadership and a doctor of nursing practice in leadership from the KU School of Nursing.

KU MEDICAL CENTER PART OF CYSTIC FIBROSIS DISCOVERY

KU Medical Center participated in a Phase 3 clinical trial which determined that a three-drug combination improved lung function and reduced symptoms in cystic fibrosis patients who have a single copy of the most common genetic mutation for the disease. In November 2019, the Food and Drug Administration approved the therapy based on the results of the international study, published in the New England Journal of Medicine. A companion investigation appearing simultaneously in The Lancet reported on people with one or two copies of the mutation. Deepika Polineni, M.D., MPH, assistant professor of internal medicine in the Division of Pulmonary, Critical Care and Sleep Medicine at KU Medical Center, and a pulmonologist at the cystic fibrosis clinic for The University of Kansas Health System, is a co-author on the study. Cystic fibrosis is a progressive and frequently fatal disease that affects the respiratory and digestive systems. In the United States, 30,000 people have cystic fibrosis, and there are more than 70,000 people with the disease worldwide.

KU'S DEPARTMENT OF OCCUPATIONAL THERAPY EDUCATION CELEBRATES 75 YEARS

The University of Kansas School of Health Professions Department of Occupational Therapy marked its 75th anniversary in early 2019. The department has developed a national reputation of excellence for educating its students to become therapists who provide essential assessment and support skills that empower their patients with physical or mental disabilities to engage in everyday life activities. Today, KU occupational therapists of all genders can now be found performing clinical rotations in an ever-expanding array of environments worldwide. They also conduct health care-related research that might never have been considered part of an occupational therapist's role 100 years ago.

RESEARCHERS WIN GRANT FROM BLUEKC TO STUDY FOOD INSECURITY

Researchers at KU Medical Center were awarded a $400,000 grant to study how community health workers can help close the food insecurity gap in certain patients. The grant came from a partnership between from BlueKC (Blue Cross and Blue Shield of Kansas City) and Bionexus KC. The project is led by researchers with the Department of Family Medicine and Community Health at the KU School of Medicine. Jennifer Woodward, M.D., MPH, assistant professor of family medicine, and Kristina Bridges, Ph.D., senior research associate, accepted the grant. Other project members include Allen Greiner, M.D., MPH, professor of family medicine research division, and Debra Sullivan, Ph.D., RD, chair of the Department of Dietetics and Nutrition in the KU School of Health Professions. In the study, researchers will seek to enroll patients with type 2 diabetes who tell their primary care physician about food security problems. Participants in the study will be connected with community workers for food and education, and then researchers will measure the participants' outcomes. The Community Health Council of Wyandotte County and Vibrant Health are study partners. Woodward plans to enroll 180 patients from The University of Kansas Health System and 80 more from Vibrant Health.

KU SCHOOL OF MEDICINE PROVIDES RESEARCH IN BREAKTHROUGH TREATMENT OF DEPRESSION

The U.S. Food and Drug Administration in 2019 approved the use of esketamine as a breakthrough treatment for people with major depressive disorders. Sheldon Preskorn, M.D., professor in the Department of Psychiatry and Behavioral Sciences at the KU School of Medicine-Wichita, is one of three physicians with ties to KU School of Medicine in Wichita and Kansas City who played important roles in moving esketamine toward FDA approval. Research that Preskorn completed at the medical school in Wichita recognized that one of three patients with major depressive disorders did not adequately respond to traditional biogenic amine antidepressants. Intransal esketamine is the first non-biogenic amine antidepressant approved in the world. The drug will appear under the brand name Spravato. The nasal spray, which acts within hours, will be administered under medical supervision and can only be used in a certified doctor's office or clinic. Patients will then be monitored for at least two hours after receiving a dose. Matthew Macaluso, D.O., associate professor in the School of Medicine-Wichita's Department of Psychiatry and Behavioral Sciences, said esketamine could be a game changer for the 35%-40% of people with major depression who aren't responsive to biogenic amine antidepressants.

$3.4 MILLION EXPANSION PLANNED FOR SALINA HEALTH EDUCATION CENTER

Plans are now underway for a $3.4 million expansion of the Salina Health Education Center in Salina, Kansas, which serves as the home for the Salina campuses of both the KU School of Medicine and KU School of Nursing. When plans were originally developed to establish a new Salina medical campus for KU in 2016, the project was intended to house only the medical school. In 2017, the KU School of Nursing announced plans to also establish a program in Salina, and both schools were able to share space in the Salina Health Education Center when the building opened in June 2018. Enrollment for the nursing program was planned to increase over time. The first two classes of nurses in the 2017-2018 and 2018-2019 school years were capped at 12 students. This fall, the entering class expanded to 18 students. The entering class will again expand to 24 students for the 2020-2021 school year. Then there will be 48 total third- and fourth year nursing students on campus each year thereafter. The expansion of the Salina Health Education Center will utilize 15,871 square-feet of vacant office space already connected on the south side of the facility with frontage on Phillips Plaza in downtown Salina.

NEW ASSOCIATE DEAN FOR RESEARCH JOINS KU SCHOOL OF NURSING

The University of Kansas School of Nursing has appointed Barbara J. Polivka, Ph.D., RN, FAAN, as its associate dean of research. Polivka came to KU from the University of Louisville School of Nursing, where she had been professor and the Shirley B. Powers Endowed Chair in Nursing Research since 2012. Before that, she had been on the faculty of The Ohio State University College of Nursing since 1999. Polivka was offered the associate dean for research position at the KU School of Nursing after a national search following the retirement of her predecessor, Marjorie Bott, Ph.D., RN., in 2018. Bott, who joined the KU School of Nursing faculty in 1990, became associate dean for research in 2003. After earning her bachelor's degree in nursing from the University of Cincinnati College of Nursing and Health in 1977, Polivka spent the first decade of her career as a practicing nurse. She began her academic career after earning her master of science in nursing degree from the University of Cincinnati in 1983. She earned a doctorate in nursing from The Ohio State University College of Nursing in 1990. Polivka has published widely about environmental health, particularly in the area of how people's health may be affected by hazards in their homes, such as lead paint and chemicals found in many household products.

KU RESEARCHERS STUDY WHETHER HIGH-INTENSITY EXERCISE COULD HELP STROKE PATIENTS

Researchers at the University of Kansas Medical Center have launched a study to determine how much exercise and at what intensity most benefits stroke patients. During a 12-week intervention, participants work with a physical therapist three times a week, receiving mobility and aerobic fitness testing as well as up to 36 walking workouts. Among the options examined will be high-intensity exercise. Sandra Billinger, Ph.D., director of the REACH Laboratory at KU Medical Center, is the study's principal investigator. Billinger said researchers will compare two exercise intensities and different durations to see which regime most improves stroke survivors' walking abilities. Stroke survivors frequently experience problems with speech, swallowing and hemiplegia, or weakness in half of the body, which affects their ability to walk and complete daily activities. The University of Cincinnati and the University of Delaware are also participating in the trial.

KU CANCER CENTER RECEIVES GRANT TO EXPAND CLINICAL TRIALS IN RURAL KANSAS

The University of Kansas Cancer Center and Midwest Cancer Alliance have been awarded a grant to expand the reach of cancer clinical trials to Kansas' rural communities. The six-year grant designates the team as a minority/underserved (MU) community site of the National Cancer Institute's (NCI) Community Oncology Research Program (NCORP). There are 14 such sites in the United States, and the KU Cancer Center-Midwest Cancer Alliance site is the only one that focuses on rural communities. As an NCORP MU community site, KU Cancer Center and Midwest Cancer Alliance will accrue individuals to NCI-approved cancer clinical trials and research studies that encompass cancer prevention, screening, supportive care and symptom management, treatment, quality of life and cancer care delivery. NCORP is a national network of investigators, cancer care providers, academic institutions and other organizations whose goal is to improve patient outcomes and reduce cancer disparities through clinical trials and research studies. NCORP grants are awarded to top institutions that have demonstrated a strong commitment to the communities they serve.

RETIRED NURSE LEAVES $4.2 MILLION GIFT FOR NURSING SCHOLARSHIPS

A retired nurse who grew up in the small town of Whitewater, Kansas, left a $4.2 million gift from her estate to create scholarships for generations of nursing students at KU Medical Center. Margaret Ann Zimmerman, who died in Silver Spring, Maryland, in 2017 at age 94, created a scholarship fund in her name at the KU School of Nursing. The fund will provide support for postdoctoral students and full-time doctoral students. It also will assist in recruiting students in the undergraduate nursing honors program and the Nursing Pathways diversity program. In addition to her career as a nurse, Zimmerman was a devoted volunteer. She helped the American Cancer Society by transporting patients to and from their treatments, among other charity work. Zimmerman was born in Whitewater, in southern Kansas, in 1923 and received a certificate in nursing from the KU School of Nursing in 1947, as well as a public health nursing degree from the University of Minnesota. Sally Maliski, Ph.D., RN, FAAN, dean of the KU School of Nursing, said the generous donation will, among other purposes, assist the school in attracting top talent for its doctoral programs.

KU MEDICAL CENTER EARNS $18.9 MILLION GRANT TO SUPPORT BIOMEDICAL RESEARCH IN KANSAS

KU Medical Center received a five-year, $18.9 million grant from the National Institute of General Medical Sciences of the National Institutes of Health to provide ongoing funding to a program aimed at improving and expanding cell and developmental biology research in Kansas. The Kansas Institutional Development Award Network of Biomedical Research Excellence (K-INBRE) is a multidisciplinary research network of 10 graduate and undergraduate institutions in Kansas and Oklahoma working to enhance biomedical research in Kansas through faculty development, retention and infrastructure, as well as to encourage undergraduate students to pursue careers in biomedical research. One of the largest biomedical research grants received in Kansas, K-INBRE is aimed at positively impacting the biomedical sciences in Kansas through faculty research, student development and educational opportunities. Since it was initially funded in 2001, the research program will have brought more than $82 million into the state through 2023, the end of the current award renewal.

A $1 MILLION GIFT ESTABLISHES COMMUNICATION DISORDERS FUND AT KU MEDICAL CENTER

A gift of more than $1 million from the late speech pathologists Donald L. Robinson and Mary A. Carpenter of Shawnee, Kansas, will benefit people affected by communication disorders. The gift to KU Medical Center will provide assistance for people with limited financial resources. Carpenter, from Marshalltown, Iowa, received a bachelor of arts degree from St. Mary's College in Indiana and went on to earn her master's and doctoral degrees in speech pathology at the University of Iowa. She was a professor in the Department of Hearing and Speech at KU Medical Center for 35 years. Robinson was born in Richmond, California, and received an undergraduate degree from Chico State College and a master's degree in special education at San Francisco State College. Early in his career, he taught for three years in the Department of Hearing and Speech at KU Medical Center and later worked in private practice. Tiffany Johnson, chair and associate professor in the Department of Hearing and Speech, expressed gratitude for the gift, which she said will help provide services to the uninsured and the underinsured while training students to be skilled practitioners in treating communication disorders.

KU HOSTS INAUGURAL SYMPOSIUM ON CONCUSSION MANAGEMENT

Concussions took center stage at a 2019 symposium co-presented by KU Medical Center and The University of Kansas Health System. The inaugural Current Concepts in Concussion Management: Team-Based Interventions Symposium helped expand the knowledge base of practitioners across the region who treat concussion. Featuring KU experts from neurology, neurosurgery, physical medicine and rehabilitation, psychiatry and behavioral sciences, and family medicine, as well as a local optometrist, the day-long event on the KU Medical Center campus drew nearly 250 registered participants, including physicians, athletics trainers, nurses, EMS personnel, therapists and other practitioners. The goal of the symposium was to share evidence-based expertise on treating concussion and to highlight the importance of taking a multidisciplinary, team-based approach to caring for patients with concussion. Symposium topics provided practitioners with a mix of tools and insights useful in diagnosing and managing concussion as well as different potential treatment approaches such as physical, occupational, speech and vestibular therapies.

HOME SICK

A KU School of Nursing researcher has been studying how common products in our homes may be affecting our health

BY KRISTI BIRCH
ILLUSTRATION BY JASU HU

For many people, home is a safe place, a shelter that protects them from the dangers of the outside world. But home environments actually can contain many hazards with the potential to cause both injury and illness. Staircases without handrails can lead to falls, unattended candles can cause fires and mold can trigger allergies and asthma. Other dangers, such as poor air quality and lead in paint, are less visible. Given that the average person spends 65% of their time in their home, understanding all these hazards is important.

They are also the chief interest of Barbara Polivka, Ph.D., RN, FAAN, associate dean for research at the University of Kansas School of Nursing. Polivka, who came to the KU School of Nursing in February 2019 from the University of Louisville School of Nursing, has published widely about environmental health, particularly in the area of how people's well-being may be affected by hazards in their homes. These include chemicals found in numerous household products.

Many products contain volatile organic compounds (VOCs), which are carbon-containing chemicals that become gases at room temperature and are emitted from certain solids or liquids. In addition to being present in many building materials, VOCs are released from a range of everyday consumer goods, including those innocent-seeming products we pull off the shelves at the drugstore or grocery store to make our homes — and ourselves — look and smell nice.

"Many people might be surprised to learn that air fresheners, plug-ins and what makes that new carpet smell — they all contain VOCs," said Polivka. "Dryer sheets also contain chemicals. They coat your clothes in a thin layer of fat, which is why the static cling goes away. All these products can impact our health."

VOCs can potentially cause eye, nose and throat irritations, headaches and nausea, dizziness and damage to the liver, central nervous system and kidneys. Some VOCs are known to be carcinogens, and others are suspected to be. VOCs can also affect the development of children.

And they are ubiquitous. VOCs are found in detergents and cleaning products, paints and varnishes, carpets and floor finishes, glues and adhesives, pesticides, shoe polishes, scented candles, cosmetics, soaps and deodorants, nail polishes and removers, perfumes, printing inks and hobby and craft supplies. They're also released from car exhaust,

cooking and heating fuels and cigarettes. Common VOCs include benzene, formaldehyde, chloroform, acetone and xylene.

Meanwhile, while the government regulates VOC-containing emissions from automobiles, there is far less regulation of chemicals used largely indoors, where levels of VOCs are typically several times higher.

"Chemical companies do not have to prove a lack of harm before a chemical is released [to the market]," said Polivka. "It's kind of scary."

Nonetheless, the health effects vary widely among VOCs. One chemical could be highly toxic while another has little effect. Moreover, the extent to which a VOC is harmful depends largely on the level of exposure, the concentration of the chemical and how long someone breathed it in. About these crucial factors, not much is known. There is also still a lot to learn about which chemicals — and which combinations of them — are connected to certain illnesses.

Polivka is working to help fill in some of that knowledge gap. She is currently completing a five-year study, funded by the National Institute on Aging, on asthma in older adults. Asthma, an inflammatory disorder of the small airways, is the leading cause of chronic illness in children, but more older people are developing the disease. Part of the study is looking at how certain environmental triggers, including VOCs, as well as air particulates, affect older people with asthma.

The study is following 188 adults over the course of a year and a half who are at least 60 years of age and have asthma. In addition to evaluating the study participants' health status through physical exams and questionnaires, Polivka and her co-investigators conduct home environment assessments at the beginning of the study and again at 18 months. (They also conduct an interim health assessment at 9 months.) They look for things like mold, mildew, dust and pests, and assess the moisture level, temperature level and how well ventilated the home is.

In addition, the study monitors participants' homes for 84 different VOCs. Using canisters that capture the air over a 24-hour period, they collect air both inside and outside the home and then analyze the air samples using a mass spectrometer. The next step is to look at any changes in these measurements in relation to the participants' asthma symptoms and lung function.

"We want to see longitudinally if they've had a change and if it's impacted by any of these environmental exposures," said Polivka.

So far, they have found that the concentrations of VOCs indoors are 7.5 times the concentration outdoors. The average number of VOCs detected inside participants' homes is 30. Polivka expects to have all the data collected for all participants by the beginning of 2020. In the meantime, preliminary results show that participants whose homes had concentrations of chloroform above the EPA reference concentration (the concentration above which health effects have been shown) had worse asthma and more trouble controlling it. Chloroform comes from chlorine and is in tap water, bleach, solvents and printers.

Other VOCs that were found at too-high levels in virtually all homes include benzene (which is in car exhaust), gasoline, cigarette smoke, carpet glue, scented candles and furniture. And even though it was banned in 1996, freon, the coolant that was commonly used in air conditioners and refrigerators, is apparently still in the air: it was found at high levels in all homes.

Polivka stresses that the participants are given all the information about their individual health and the healthfulness of their home, and they are advised about what may cause them to have high levels of a certain chemical and how to prevent that. The information about VOCs is important not just for people with asthma, but for anyone who wants to protect his or her health.

So given that there are so many chemicals out there and not enough information about them, how do you make your home safe?

"Limit your exposure and pay attention to what you bring home," Polivka said. "Just because you can buy it doesn't mean it's safe."

Gina Peek, Ph.D., associate professor and cooperative extension housing and consumer specialist in the College of Human Sciences at Oklahoma State University, concurs. Part of Peek's job is helping to educate consumers about how to reduce exposure to environmental contaminants in the home.

"Just because a product is labeled green, that doesn't necessarily mean it's safe," she said. "Look out for 'green-washing.' The word 'green' doesn't necessarily mean anything."

Both Polivka and Peek recommend looking for the Environmental Protection Agency's "Safer Choice" seal, which designates effective home products with relatively safe chemical ingredients. Polivka also recommends the Environmental Working Group site, which lists cleaning supplies certified by Green Seal or EcoLogo.

Katie Davis, a project manager at Helix Architecture + Design in Kansas City who earned a graduate certificate in Green Building and Community Sustainability from the Harvard Extension School, noted that it can be hard to avoid harmful chemicals because often when a chemical is labeled harmful, the chemical company replaces it with something different but just as bad. This is what happened, she said, when the hormone-disrupting bisphenol-A, found in plastics, was replaced with bisphenol-S.

"It's known as chemical whack-a-mole," she said. "They replace a chemical with something similar and it does the same thing."

Davis recommends that consumers wanting to be safe avoid entire classes of chemicals and advises consulting Sixclass.org, a resource produced by the Green Science Policy Institute.

Barbara Polivka said the most effective way for people to protect themselves from home health hazards is to do research and learn what products are safe and which can be potentially dangerous.

The websites below can help provide valuable information:

HEALTHY HOMES PARTNERSHIP
extensionhealthyhomes.org

ENVIRONMENTAL WORKING GROUP: HOME GUIDE
ewg.org/healthyhomeguide

EPA SAFER CHOICE
epa.gov/saferchoice

SIX CLASSES (of chemicals to avoid)
sixclasses.org

Barbara Polivka, Ph.D., R.N., FAAN

Instead of focusing on what products not to use, consumers can also simplify things by narrowing their choices to those known to be safe. The reports given to the asthma study participants after the first home assessments listed some of these safe alternatives, such as plain ammonia and non-chlorine bleach, which have low levels of VOCs. Baking soda works well as a room, rug and refrigerator deodorizer. Club soda is a good spot remover, and white or apple cider vinegar removes mold and mineral deposits. Other relatively safe products include liquid furniture polish and beeswax, and mineral, lemon, olive or linseed oils. A good multipurpose homemade cleaner — and what Polivka uses in her own home — is a mixture of vinegar and water with a few drops of dishwashing detergent.

"It's also cheap and it works," she said. "It's what all the healthy homes folks advocate."

A few common-sense rules can also help. Avoid scented products and spray cleaners, which linger in the air. Use a small amount of products and open the windows to keep the house ventilated. Avoid disinfectants, the overuse of which can lead to antibiotic-resistant bacteria or "superbugs," for routine cleaning. When a disinfectant is needed, such as to remove raw chicken from a cutting board, be sure to leave the product on the surface for as long as the product directions indicate so that it actually kills the germs. Keep the door between your house and your garage closed to keep gas fumes as contained as possible. If you smoke, do it outside.

Learning how to limit environmental hazards is not only good for patients, but also health care professionals.

"A lot of times people don't consider what happens in the home when they are discharging a patient," said Polivka. "But that home has a big impact on health."

KU MEDICAL CENTER STUDENTS SPENT A SUMMER IN HISTORIC SANTIAGO DE COMPOSTELA LEARNING ABOUT SPAIN'S HEALTH CARE SYSTEM

A WHOLE NEW WORLD

BY GRACE REAP
PHOTOS BY ELISSA MONROE

It is an unusually warm afternoon in Santiago de Compostela, Spain, even for July. Five students from the University of Kansas Medical Center find shelter from the afternoon sun in the shadow of an arched colonnade outside the cafeteria on the University of Santiago de Compostela campus where they have just finished lunch. They lean against the stone columns that stay cool in the shade of huge eucalyptus trees as they wait for their ride to arrive to take them to their health care workshop.

The students — Viviana "Vivi" Desmoineaux from the KU School of Health Professions, Michael Arnold and John Perez from the KU School of Medicine, Thien Vu from the KU School of Medicine-Wichita and Avery Kilgore from the KU School of Nursing — switch from English to Spanish and back again as they discuss everything from what happened in the clinical experience that morning, to the medical workshop they had attended in a nearby small town the day before. They reminisce about their recent excursion to Portugal and finalize plans for their upcoming weekend trip to Ons, an island in Spain's Atlantic Islands of Galicia National Park.

The students are nearing the end of their four-week summer experience in Spain, and they are eager to make the most of their remaining time. Their weekdays are full of new learning opportunities — clinical experiences, medical Spanish class, health care workshops and cultural activities. And even in the evenings and on weekends, they are immersed in Spanish culture and experience a different way of life.

Each summer, KU Medical Center's Office of International Programs sends students like these five out into the world to experience health care in other cultures. As Kimberly Connelly, senior international programs officer, is quick to point out, the focus of these trips isn't on "fixing" anything, but on learning and exchanging knowledge.

"We teach the students clinical skills here at KU Medical Center," Connelly pointed out. "We're not looking for somewhere they can get more practice with those skills. We're looking for somewhere they can be exposed to how health care issues are addressed differently in the world."

The Office of International Programs oversees international education experiences for the medical center's students to over 30 countries on five continents around the world. The international experience in Santiago de Compostela that these five students were part of in the summer of 2019 was the brainchild of Maria Alonso Luaces, Ph.D., director of KU School of Medicine's Office of Diversity and Inclusion and an assistant professor of family medicine.

MICHAEL ARNOLD
KU SCHOOL OF MEDICINE

"You get a good overview of what the U.S. has done well, what we have to work on and what we have to learn from each other."

VIVIANA "VIVI" DESMOINEAUX
KU SCHOOL OF HEALTH PROFESSIONS

"I'm glad the experience is made up of a small group. We did everything together in Spain, and we've already talked about having a reunion back in the states."

AVERY KILGORE
KU SCHOOL OF NURSING

"The biggest takeaway for me is understanding what universal health care, preventative medicine and community involvement really mean for an entire nation."

JOHN PEREZ
KU SCHOOL OF MEDICINE

"I want to take the language back with me. I want to be able to talk to patients in Spanish without an interpreter."

THIEN VU
KU SCHOOL OF MEDICINE-WICHITA

"I gravitate towards working with clinics in the U.S. that will take you no matter your ability to pay. But that's every system in Spain. Everyone is treated with equity."

Alonso Luaces was born and raised in Spain, a country with arguably one of the most successful public health systems in the world. In 2017, when she mentioned to Connelly her connections to Spain and the University of Santiago de Compostela (USC), the idea of establishing an international experience between KU Medical Center and USC was born.

"The Office of International Programs is always looking for new opportunities and focusing on the places our students can learn from and bring back, but also leave their own knowledge," Alonso Luaces explained. "Spain is a great place for an international education experience because of the language opportunities, the life expectancy is second in the world, and it has a really effective health care system that is publicly funded. But at the same time, it has holes. So the public health portion of the course looks at, on the one hand, the good health outcomes that Spain has, but also some of the problems and the efforts to address them."

In late June of 2019, Arnold, Desmoineaux, Kilgore, Perez and Vu embarked on the program's second summer trip to Spain.

SANTIAGO DE COMPOSTELA, GALICIA

Santiago de Compostela is in the northwestern Spanish state of Galicia. A temperate region with both mountains and miles of coastline, the wealthy from Spain's major cities often come here for summer vacations. Galicia was once part of the Roman Empire and traces of its Celtic heritage are still visible in Old Town and the local culture. The network of narrow cobblestone streets and alleyways date back to the Middle Ages. They twist and wind around the Cathedral of St. James, which is a destination for hundreds of thousands of pilgrims each year. The pilgrims travel on foot following a footpath system, some beginning as far away as France and Portugal. Old Town is separated from more recent development by Parque da Alameda, a sprawling park with ancient trees that cover its wide pathways and benches in deep shade. At all hours of the day, people come to exercise, sit, talk, walk their dogs or stand looking out over the city from a grand stone terrace built into the hill.

Nested among the eucalyptus trees at the base of the hill is USC's south campus. Consistently ranked as one of the top 10 uni-

The students participate in medical Spanish class.

versities in Spain, USC has a relationship with the city's university hospital, Complejo Hospitalario Universitario de Santiago (CHUS). CHUS hosts many specialists, and patients are referred from all over Spain via the national health system.

"When we started exploring what options were available, we found out that the University of Santiago de Compostela already had programs in place to welcome students into clinical shadowing at the hospital," said Alonso Luaces. "But we wanted to go beyond that. We wanted to have outside involvement that allows the students to not only learn the language and have some of these clinical experiences, but also to learn how to develop public health programs — the structure and benefits."

The curriculum developed is a four-week medical Spanish course, with an emphasis on public health in the context of Spain's national health system. There are four components to the program: clinical internship, medical Spanish class, public health workshops and cultural programs. Each of these pieces are worked into the five students' weekday routine.

CLINICAL INTERNSHIP

Mornings are spent shadowing health care professionals at CHUS where the students gain first-hand experience in another country's health care system. For Avery Kilgore, learning in a hospital environment was a major motivation to join the trip.

"I knew I wanted experience working in a hospital. And public health is such a big part of nursing, so the emphasis on that in Spain was appealing," she said.

The students were given the chance to list the specialties they were interested in shadowing. Thien Vu is attracted to psychiatry and was able to spend the first two weeks of the program in neurosurgery and the next two in psychiatry. John Perez, who wants to be an ER doctor, spent one half the trip in the emergency medicine department and the other in surgery. Kilgore spent time learning from the nurses in recovery, and Michael Arnold followed physicians in internal medicine. Vivi Desmoineaux had the opportunity to work with the speech-language pathologist serving children, much in the same way she is now working in her job with Olathe School District. She appreciated the openness of her Spanish counterparts.

"Professionals in Spain have been very open about sharing what they're doing and how they go about doing it," Desmoineaux said. Having hands-on clinical experience in the Spanish hospital gives the students a front row view of how health care is handled differently outside America.

"I love that the students come to the hospital," Alonso Luaces said. "Seeing that there are other ways besides the American way that work really well is beneficial for the students. I'm excited about that."

Perhaps the most striking difference the students noticed was how Spain's community-centric culture affects health care.

"The interprofessional aspect is more prominent in Spain than in the United States. At home we talk about it a lot, and we're working on it. But it's just not at the level that it is here. I think it's the culture," Vu noted. "American culture is individualistic — you go work on just your stuff. But the culture here is so much more community-based."

Vu pointed out the psych unit, where there are group meetings every morning that include physicians, nurses and health professionals discussing current and new patients before splitting up to attend to their own responsibilities.

For Arnold, whose work at KU Medical Center includes smoking cessation research, the international experience has shown where the U.S. health care system has done well.

"It's opened my eyes to what we've done well in past decades of public health in America, especially comparing what I've learned about the history and progress of smoking cessation in the United States to what I see here," Arnold said. "So many people smoke, even outside the hospital. I see people my age smoking even though they know the consequences. I think this trip has allowed me to see areas like that where we've succeeded."

While clinical experiences give students the opportunity to compare and contrast health care systems, it also help them see universal issues.

"It's important to recognize that even though the health care systems are very different, the vulnerable populations remain the same," Alonso Luaces pointed out. "For example, sex workers tend to be a group that people don't talk about very much in Spain. They are underserved by the public health care system, and it's the same in the United States. Sex trafficking victims, inmates, individuals experiencing mental health challenges or those trying to cope with substance abuse — those are patients, too. These are people that might not be talked about in the students' academic experience, but they will definitely be part of their practice."

MEDICAL SPANISH CLASS

At noon, the students gather at the hospital entrance. They chat about their mornings and make plans for their free time that afternoon. Most days they stop at the café at the bottom of the hill to grab a café con leche before continuing to USC's south campus for their medical Spanish class. The walk takes about 20 minutes, which leaves just enough time to pull out their homework, review answers and prepare for the day's lesson.

The class is conducted entirely in Spanish, and the students participate by calling out Spanish names of medical specialties and specific symptoms, then pair off into groups to list qualities that make a good doctor.

This class was the initial appeal of the experience for most of the students, since the specific medical vocabulary is different than that used in typical conversations. As health care professionals, having knowledge of medical terms can make a huge impact on successfully treating Spanish-speaking patients, especially since there is a shortage of Spanish-speaking physicians in the United States.

"We all deserve to have a good relationship and to communicate clearly with our physician," Arnold said, "Through volunteering as an interpreter with JayDoc [Free Health Clinic], I've realized how difficult it is for Spanish-speakers and even non-native English speakers to have that. Being able to serve those patients is my dream."

Desmoineaux's career goal is also to be able to provide speech-language pathology to the growing Latino community in the United States, a demographic that is decid-

edly underserved in Kansas City. For her, the connection is personal since she was raised speaking Spanish in a family originally from Colombia.

Being immersed in the language in class, at the hospital and in daily life helped the students improve.

"The nurses in the hospital use a lot of the same words over and over," Kilgore said. "Once I learned those words, I could understand more of what they were saying."

"Compared to the beginning of the trip, I can understand a bit more when people start talking fast," Vu said. "I still stutter when I'm speaking Spanish but definitely not as much."

PUBLIC HEALTH WORKSHOPS

Several times over the course of the program, the students attend public health workshops to learn how the Spanish public health system is implemented. These workshops vary from lectures on vulnerable populations and insights from a Spanish pharmacist to touring a water treatment facility.

"I think the most eye-opening experience, and the one that I valued the most, was the trip we took to the prison," Arnold said. "The prison directors that we talked to repeatedly said 'This is a rehabilitation-based system, not a punitive system'. To me, that's public health. Caring more about rehabilitation than punishment is a difference that I think would make a huge improvement in the United States."

Another trip the students took was to Sarela Asociación de Dano Cerebral de Compostela, an organization that serves adults who have suffered brain trauma or injury. They joined the residents in group discussions, physical therapy and speech-language pathology sessions. There were also opportunities for reading, art and music therapy, and a sensory room designed specifically for audio/visual therapy.

Another workshop the students took part in was with Celia López Carballido, the president of the Galician branch of Médicos del Mundo (Doctors of the World). She outlined the organization's efforts to educate and serve those who may slip through the cracks of the health system. The students learned about the branch's efforts to focus on education and empowerment rather than charity by using an approach of observing a social context, identifying the leadership and then educating those influential people on better health practices.

CULTURAL PROGRAMS

While learning about the health care system in Spain, the students also had opportunities to engage in traditional Spanish activities and learn more about another culture. The program directors hope to set this trip apart from other study abroad opportunities by creating an immersive experience for the students. This happens through organized cultural programs in which the students can participate, as well as deeper dives like placing the students in host homes for their stay and giving them chances to travel throughout the region.

There are walking tours through the city and hikes through the surrounding mountains. The International Office at USC organized a demonstration of Galician music and dance, where the students learned about the traditional instruments, songs, attire and dance steps. There was also a lecture on literature followed by a reception in the traditional courtyard of one of the university's Old Town buildings. These activities give students a view into a culture different than their own.

The students are also paired with host families who allow the students to stay in their homes and prepare meals for them.

Avery Kilgore and John Perez interact with residents at Sarela Asociación de Dano Cerebral de Compostela, a center for adults with acquired brain trauma.

John Perez reviews his homework with his host mom, Camocha, as she prepares dinner.

"In some programs, the students all live together and tend to just stick in their groups. Living with Spanish families gives them an opportunity to be immersed in the culture," said Alonso Luaces.

John Perez stayed in a newer apartment building with Camocha, his host mom. After the days' activities he would walk to her third-floor flat. He considered himself lucky her building has an elevator, although it's barely big enough to hold more than two people. Some of the other students didn't have the luxury.

The apartment itself was comfortable, but small. Perez usually worked on his homework — there are translations for medical Spanish class and a journal entry in Spanish of the day's events at the hospital — while Camocha prepared their dinner. She moved around the compact kitchen pulling utensils and dishes from various cabinets and drawers. Perez joked with her that she is the most organized person he's ever met.

"My home is very organized," Camocha admitted. "It's like a Tetris game — every piece has its place."

The students had to adjust to the meal schedule in Spain. Lunch is usually between 2 and 3 in the afternoon, and often they don't sit down for dinner with their host families until 9, 10 or even 11 at night.

Although they had to get used to eating later, the students fully embraced the food in Spain. Almost every conversation involved food, either what they liked or what they wanted to try next. Because Santiago de Compostela is so close to the ocean, seafood is the specialty in the area. The students discuss the different ways they had pulpo (octopus) is prepared. They tried the bizarre-looking percebes (Galician goose barnacles) that only grow on the coast in the cold Atlantic waters. Desmoineaux brought back local cheese from an excursion to a nearby village, which the other students eagerly sampled. Most days, Avery Kilgore stopped on the way to the hospital to pick up a fresh-baked tarta de manzana (apple tart).

Like many of the locals, the students walked virtually everywhere while in Santiago de Compostela.

"It's something that you get used to, but it's an adjustment," said Desmoineaux. "I ended up buying new shoes because of the blisters I got the first week."

Alonso Luaces has learned that giving the students time to experience the country is an important part of their experience in Spain.

"This is an academic program, but we've learned the students do need time on their own to explore," she said.

The students used their weekends to see the area. They traveled north to Ons and the coastal town of A Coruña, and south to Porto, Portugal. They also visited the hometown of Ivan, a Spanish student who participated in an international education exchange at KU Medical Center earlier in the year.

The chance to explore and see new sights was one of Perez's favorite parts of the immersion experience.

"I liked all the views," he explained. "We had a lot of opportunities to go to different places. We were able to see the ocean and so many beautiful cities."

A GLOBAL PERSPECTIVE

Like most who have participated in the immersive experience of an international education trip, the firsthand knowledge of a different country's health care system will stay with these five KU Medical Center students as they approach the remainder of their education and into their professional careers.

"As an educational institution, it's part of our responsibility to prepare our students to be culturally aware and to find creative solutions," Connelly said. "International education experiences like the one in Santiago de Compostela are helping to broaden our students' awareness of innovative approaches to health care around the world."

UP TICK

WHAT DO QUESTING BLACK-LEGGED TICKS, MACHIAVELLIAN SPIROCHETES, CATEGORY 5 HURRICANES AND DRUG DEVELOPMENT HAVE IN COMMON? A SWISS SCIENTIST AT THE UNIVERSITY OF KANSAS MEDICAL CENTER MAY HAVE SOME OF THE ANSWERS — ALONG WITH MANY MORE QUESTIONS.

BY KAY HAWES

Wolfram Zückert, Ph.D., professor of microbiology, molecular genetics and immunology at the University of Kansas School of Medicine, is working to solve a complicated puzzle that involves ticks and the bacteria they carry. Zückert has been studying spirochetes since 1988, as he began working toward his master's degree and doctorate in molecular microbiology at the University of Basel in Switzerland. Spirochetes are tightly coiled spiral, double-membrane bacteria with lengthwise flagella that wind around the cell body, producing a twisting motion. They look somewhat alien under a microscope. They also cause nasty diseases, from Lyme disease to rat-bite fever and syphilis.

MACHIAVELLIAN COAT-CHANGING BACTERIA

"Spirochetes are extremely well-engineered," Zückert said.

He should know. Zückert's lab studies several, including the spirochete Borrelia burgdorferi, which causes Lyme disease in North America and Europe. Named after Old Lyme, Connecticut, where the disease was first identified in 1975, Lyme disease now is the most common vector-borne disease in North America.

Lyme disease is spread through the bite of ticks that are infected with the Borrelia bacteria. In most of the United States, the tick carrying Lyme disease is the blacklegged tick (also known as the deer tick). Most people get Lyme disease from the bite of immature ticks called nymphs, which are about the size of a poppy seed and difficult to see.

"They may look just like dirt on your leg," Zückert said. "Until you notice the dirt moving."

Adult deer ticks also can transmit Lyme disease, but they are bigger, about the size of a sesame seed. Since they are easier to see, people are more likely to discover them and remove them before the bacteria can be transmitted, which typically takes 36 to 48 hours. The longer the tick is attached, the greater the risk of acquiring Lyme disease. Unfortunately for the human host, the tick tends to snuggle into warm moist places where they're likely to go unnoticed, like the groin, the scalp or the waistband. The entire life cycle of the tick takes two years, in which it transforms from larvae to a nymph to an adult that lays eggs. Each stage requires a new host and a "blood meal," before it moves on.

According to the Centers for Disease Control and Prevention (CDC), the white-footed mouse, also called the deer mouse, is the primary carrier of Borrelia burgdorferi and a frequent host of deer ticks. This adorable little omnivore scurrying around in the woods is often the

Wolfram Zückert, Ph.D.

first place the ticks encounter Lyme disease. The mouse is both a host for ticks and a reservoir of Lyme disease, connecting the two.

"There is a very complex relationship between the bacterium, the tick and the mammalian hosts," Zückert said.

The adult female ticks (which together with adult males mostly feed on white-tailed deer), drop off the deer after their meal and lay their eggs on the ground. The next year, the eggs hatch into larvae that feed on the mice (or a squirrel or a bird), which are carrying the Lyme disease. The infected larvae then become infected nymphs, lying in wait for humans the next year. Other scientists have studied this symbiotic relationship, which seems aided by the fact that the bacteria-hosting mice have poor grooming habits and don't seem too concerned by either the tick or the bacterium.

Where most of us encounter the tick — and Borrelia burgdorferi — is in walking past the "questing" tick. Ticks cannot fly or jump. Instead, they rest on the tips of grasses and shrubs. While they are questing, ticks secure themselves onto grass or brush with their lower legs, holding their upper legs outstretched and ready to swing up. When a host brushes the grass, the tick scampers on board and starts crawling to a desirable spot.

"The questing tick is ready, waiting for its next host and its next blood meal to come by, sometimes for weeks or months," Zückert said.

While the human is oblivious to the tiny tick soon nestled in a warm spot and attaching a feeding tube to its new host, Zückert noted that the bacterium in the tick perks up the minute it detects the blood meal.

"The bacterium says, 'Ah, this tick is feeding. It's time for me to get out and spread,'" Zückert said. "To get ready for that transition, the bacteria will swap out their surface proteins, in effect changing their coats to have a different appearance."

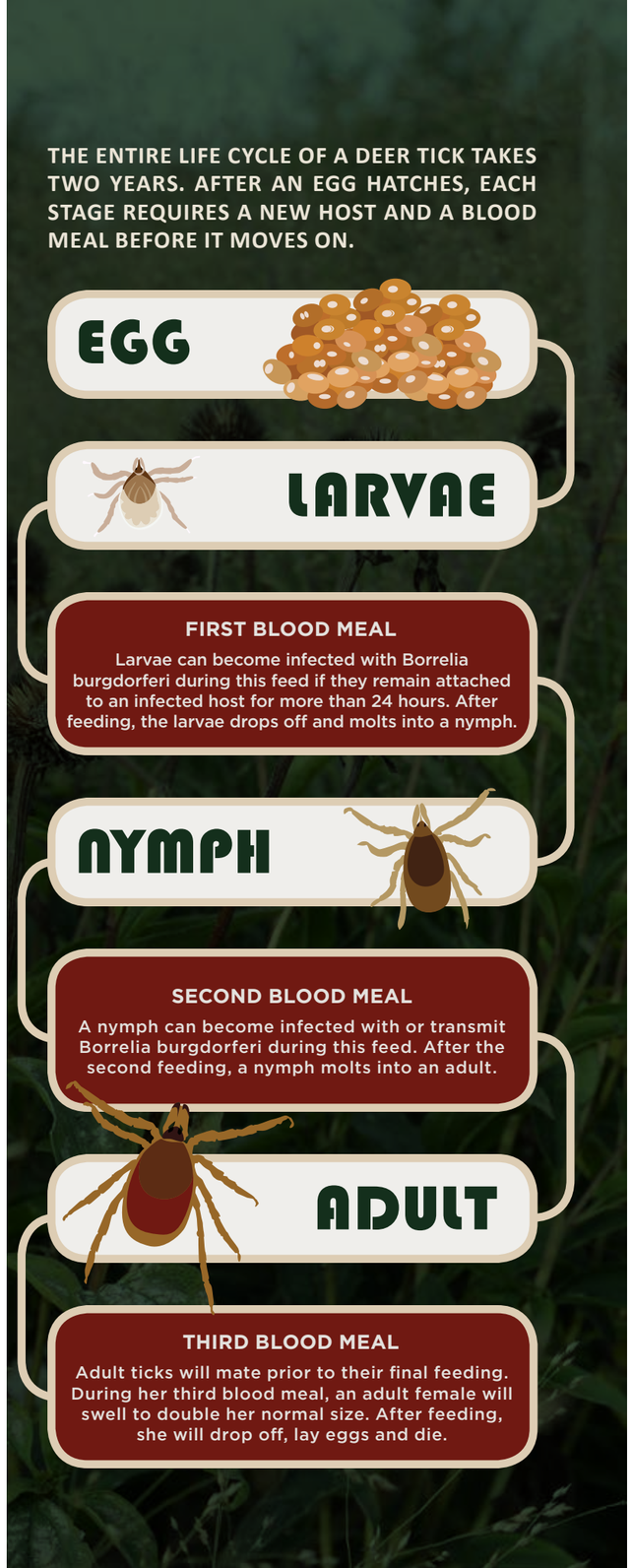
This change begins a process that allows them to escape the immune system of the mammalian host and spread from the skin to other tissues, Zückert explained. "Different surface proteins protect the bacteria in the tick and then allow the bacteria to spread and hide in the mammalian host."

Those proteins are what Zückert is studying. "We want to know how those proteins get to the surface of the bacteria and exactly what they are doing there," he said. Zückert's lab had a major discovery when it identified a large set of surface lipoproteins in the bacteria in 2017. Now, the race is on to figure out more about them. It's not lost on him that the protein coat-changing maneuver is both amazing and frightening, particularly in a bacterium that seems to operate so well as global temperatures rise.

"I tell my students that bacteria are selfish, even Machiavellian," he said. "They want to take over the world."

3-D CRYSTALS AND DRUG DEVELOPMENT

In his role as an educator, Zückert offers concrete advice about the diagnosis and treatment of diseases caused by Borrelia burgdorferi and related spirochetes. In his role as a researcher, Zückert is working to understand more about several different spirochetes. With the expansion of Lyme disease and other pathogens, the day may come when existing antibiotics are no longer effective against Lyme disease or other diseases caused by spirochetes. Zückert is preparing for that.



In June 2019, Zückert published a review article, "Protein Secretion in Spirochetes," in the journal Microbiology Spectrum. His previous work has explored some of the sequence complexities of the Borrelia genome and the lipoproteins virulence factors involved in the pathogenesis of Lyme disease and other Borrelia infections. Now he's working to dissect the export machinery that deploys lipoproteins to the bacterial surface.

"If you can figure out the pathways of lipoprotein secretion, you can look for small molecules that help block that process," Zückert said.

Scott Lovell, Ph.D., director of the Protein Structure Core Laboratory at the University of Kansas in Lawrence, has assisted Zückert in determining protein structure and function.

"My lab is involved in the area of structural biology where we work to determine the three-dimensional structure of proteins using X-ray crystallography," Lovell said.

Lovell first obtains a purified protein sample and subjects it to crystallization experiments. The protein crystals are then used to collect X-ray diffraction data, which allows his lab to ultimately generate a high-resolution structural model. Having structural information for a protein opens the door to additional research. The more you understand a protein, the more you understand how to block it or disrupt it, which is a frequent goal in drug discovery and development.

"Sometimes there are pieces of the puzzle that one can obtain by understanding the protein's structure," Lovell said. "For example, the crystal structure often allows one to ascertain the probable function of a particular protein, which can then be confirmed by conducting additional biochemical experiments."

RISING TEMPERATURES, EXTREME WEATHER AND CHANGING HABITATS

As the world changes, Lyme disease is on the rise. Lyme disease expansion is so closely associated with climate change that the Environmental Protection Agency (EPA) actually tracks the incidence of Lyme disease as a key indicator to document climatic changes.

While ticks do seem to enjoy warm weather and both they and their mammalian hosts are more active during the warmer months, it's the climate rather than the weather that is a concern for the EPA and those who track the spreading range of the deer tick and the rise of Lyme disease.

Weather refers to short-term changes in the atmosphere. Climate refers to the average daily weather over a long period of time. As the National Oceanic and Atmospheric Administration (NOAA) describes it, "Climate is what you expect, weather is what you get." When meteorologists refer to records breaking, that's climate. As the NOAA noted in early October, September 2019 was tied with September 2015 as the second-warmest September on record in the United States at an average of 68.5 degrees, or 3.7 degrees above the 20th century average. Warmer weather means a longer growing season and a warmer ocean, which can lead to small changes, such as more nuts and seeds for the white-footed mouse to munch. It also can lead to larger changes, like extreme weather events and intensified storms, such as Category 5 hurricanes and large-scale flooding.

Zückert notes that all vector-borne diseases — those that result from an infection transmitted to humans (and other mammals) by blood-feeding insects and anthropods, such as mosquitoes, fleas and ticks — are likely to increase and expand their range with a warming climate. Ticks and Lyme disease will benefit greatly.

"Because habitats are changing, with mild winters and lots of acorns, lots of squirrels, lots of mice, lots of deer in the woods, it's a great situation for ticks and for Lyme disease."

Add to that the expansion of suburbs and exurbs where more people can come into contact with more ticks, and it's an ideal environment for more Lyme disease.

"It's already evident that Lyme disease will expand toward the north," Zückert said. "And we will have to see what happens with tick-borne diseases moving up from the south. Ticks generally like temperate climates, but they don't like dry ones."

A study published in November 2018 in the Canadian Journal of Infectious Disease and Medical Microbiology looked at the relationship between climatic variables and the incidence of Lyme disease in 15 U.S. states, concluding that rising temperatures are expected to boost the number of cases of Lyme disease by more than 20% by mid-century.

"Tick-borne diseases are an important public health concern, and the incidence of these infections is increasing in the United States and worldwide," Igor Dumic, M.D., a researcher at the Mayo Clinic College of Medicine and Science who led the study, told Science Daily. "Lyme disease is a classic example of the link between environmental factors and the occurrence and spread of disease."

According to the CDC, there were 42,743 confirmed and probable cases of Lyme disease reported to the CDC in 2017, the most recent year for which it has data. That's a 17% increase over 2016, and the CDC notes that the geographic distribution of the disease seems to be expanding. The CDC also points out that its other studies suggest that the true number of people diagnosed with Lyme disease each year (versus those formally reported to the organization) is actually around 300,000, with 14 states, mostly in the Northeast and upper Midwest, accounting for more than 96% of those cases. As temperatures rise, tick habitat changes, allowing for an expansion of both the ticks and Lyme disease.

WHAT'S NEXT?

Zückert's latest project involves Borrelia mayoni, a type of bacteria identified in 2016 by scientists at the Mayo Clinic and the CDC and Prevention. Borrelia mayoni is the only other known cause of Lyme disease in North America, and current evidence suggests it is only found in the upper Midwest and is closely related to Borrelia burgdorferi. The blacklegged tick can transmit it, and the symptoms are similar to those caused by Borrelia burgdorferi but also can include nausea and vomiting, along with large rashes. Zückert is working with colleagues at the University of Kentucky and the University of North Dakota to take what is currently known about the proteins of Borrelia burgdorferi to learn more about this new species, including figuring out if or how Borrelia mayoni does things differently.

"The Mayo clinic identified a new species that was lurking somewhere on an island or in the woods," Zückert said. "There are probably more out there."

Yes, and perhaps even more as global temperatures rise. The questing tick is perched on the tall grass, waiting to introduce us.

AHEAD OF THE CURVE

MITOCHONDRIA ARE A HOT RESEARCH TOPIC THESE DAYS, INCLUDING AT KU MEDICAL CENTER, WHERE SCIENTISTS BEGAN STUDYING THESE ORGANELLES BEFORE THEY WENT MAINSTREAM.

BY KRISTI BIRCH
ILLUSTRATION BY CHAD HAGEN

In April of 2018, Danny Welch, Ph.D., founding chair of the Department of Cancer Biology at the University of Kansas School of Medicine and associate director of education at The University of Kansas Cancer Center, boarded a plane for Chicago. Loaded on his laptop and backed up on a flash drive in his carry-on were the slides for the presentation he was giving at the annual meeting of the American Association for Cancer Research. It was a talk that Welch had given, in various iterations, numerous times: the role that mitochondria — the tiny structures many of us know from high school as the "powerhouses of the cell" — play in causing cancer to spread from its original location to other places in the body.

Welch focused his talk in Chicago on the latest research from his lab, a study led by then post-doctoral fellow Amanda Brinker, Ph.D., indicating that mitochondria are much more involved in cancer metastasis than previously believed. Cancer is a disease of damaged genes, and most cancer research focuses on the nuclear genome, the DNA in the nucleus of the cell. Mitochondria also contain DNA, just much, much less of it.

Welch explained to the attendees how Brinker exposed a strain of mice engineered to have identical nuclear DNA, but different mitochondrial DNA, to a common breast cancer-causing gene known as HER2. When the mice developed tumors, they metastasized at different times and at different speeds. Since the mitochondria were what differed in the biology of these mice, that meant that mitochondria were what made the differences in how the cancer spread. Brinker's research is a first step toward doctors being able to tailor treatments to individual patients by analyzing their mitochondrial DNA through a blood sample to gauge the cancer's likelihood to metastasize.

At the end of Welch's presentation, around 30 people in the conference room came up to the podium to ask him questions. But that level of interest, he said, was a first. Welch remembers when he, an internationally known researcher who had identified eight of the 30 known nuclear genes for metastasis and deputy editor at the most cited cancer journal in the world, first started presenting his research on mitochondria and there would be just one or two people in the audience. He also recalls the response from the research community when he decided to study mitochondria nine years ago: "People were literally saying, 'You're nuts.'"

It's not a reaction that seems to have surprised him.

"Scientists," Welch added, "are a skeptical lot."

A SLOW MARCH OF SCIENCE

In the history of cell biology, mitochondria arrived late to the game. They weren't discovered until 1886, several decades after the discovery of the nucleus, when a German cytologist named Richard Altmann identified some bean-shaped structures in cells he believed were responsible for cells' metabolic processes — those that create energy — and dubbed them "bioblasts." Twenty years later, biologist Carl Benda renamed them mitochondria ("thread granules" in Greek) because of their tendency to form chains. By the 1950s, scientists knew that the primary function of these organelles is energy production. Mitochondria consume oxygen and combine it with nutrients from food to create energy in the form of a molecule called ATP (adenosine triphosphate). Through that process, mitochondria generate 90% of the energy that cells need to perform all the biological functions that make it possible for the human body to function.

Each year in the United States alone, a few thousand babies are born with "mitochondrial disease," a rare, often inherited disorder in which the mitochondria do not produce enough of that energy. But until the past decade, mitochondria were not widely considered a major player in other diseases. Western medicine focuses on anatomy — if you have a heart problem, you see a heart specialist — rather than non-organ-specific systems like cellular energy metabolism.

Besides that, mitochondria were just too darn small, and few scientists thought they could contribute much to other kinds of illnesses.

"Mitochondria were the bastard stepchildren of the cell nucleus," said Welch, who has a penchant for metaphor. "The nucleus in a human cell has 3 billion base pairs of DNA, whereas mitochondria have just 16,500 base pairs of DNA. So everyone said, 'Oh, that little thing? What could it do?' Well, an Ebola virus is about the same size as a mitochondrion, and it can kill you. Size is not always what matters."

Moreover, it turns out that mitochondria do more than produce energy. They communicate with each other, turn genes on and off in the nucleus, trigger responses in the body's immune and inflammatory systems, and affect communication between neurons in the brain. They can also trigger apoptosis, or cell death.

The difference between researchers like Welch being told they're nuts and being taken seriously did not hinge on one or two big discoveries. There were, to be sure, a few critical basic research findings, such as the discovery in the 1960s that mitochondria have their own DNA. In 1980, researchers found that amazingly, this mitochondrial DNA is inherited only from the mother — a fact that eventually led Welch to study mitochondria. Nine years ago, when he heard a lecture from a researcher who had connected cardiovascular problems to defective mitochondria and cited the maternal inheritance aspect, Welch realized that the same factor might explain different susceptibilities to metastasis.

> "EVERYONE SAID, 'OH, THAT LITTLE THING? WHAT COULD IT DO?' WELL, AN EBOLA VIRUS IS ABOUT THE SAME SIZE AS A MITOCHONDRION, AND IT CAN KILL YOU. SIZE IS NOT ALWAYS WHAT MATTERS."
>
> DANNY WELCH, PH.D.

But even those sorts of revelations, aided by advances in technology such as better ways to track cell respiration and analyze DNA, did not change researcher focuses overnight. Instead, the shift has been the result of the slow march of science, of the gradual accumulation of findings by researchers who studied mitochondria before it was popular, when getting funding to study it was sometimes difficult, and when they might have to present their work to an empty conference room or one full of skeptics.

Today, mitochondria are a hot topic in medicine, especially for diseases for which age is a risk factor. Scientists have discovered that many common age-related diseases also seem to involve dysfunctional mitochondria. In addition to cancer, these diseases include heart disease and stroke, diabetes, and neurodegenerative disorders, especially Alzheimer's disease. Mitochondria are also believed to play a role in aging itself.

Welch is one of a number of researchers studying mitochondria and age-related diseases at KU Medical Center, where mitochondria have been long been a focus. For some researchers, it's been a matter of tuning out the skeptics. For others, it was simply a matter of paying attention to a minuscule organelle that kept making its presence known.

LAYING THE GROUNDWORK

There may be nobody at the University of Kansas who has researched more basic biology related to aging and mitochondria than Mary and Eli Michaelis. Now the University Distinguished Professor of Pharmacology and Toxicology, Eli Michaelis, M.D., Ph.D., arrived as an assistant professor on the Lawrence campus in 1973. Mary Michaelis, Ph.D., an emeritus professor at the University of Kansas, arrived the same year as a graduate student in neurobiology and became a professor after earning her doctorate in 1978.

Neither Michaelis set out to study mitochondria, but their research eventually led them there. In the mid-1990s, the Michaelises were two of the scientists who began a large, 15-year study funded by the National Institutes of Health that focused on aging, the process of losing function in organs that leads to a person's decline and eventual death. Their hypothesis was that two concurrent biological changes were at the root of aging.

One change, oxidative stress, hinged on a theory dating back to the 1950s that over time, cells accumulate unstable oxygen-containing molecules known as reactive oxygen species (ROS) that can damage other parts of the cells, such as DNA and proteins, and eventually cause the cell to weaken or die. Oxidative stress is the progressive accumulation of ROS, also known as free radicals. By the 1970s, scientists also knew that mitochondria were one of the primary producers of oxidative stress; free radicals are a byproduct of the process of converting food into energy.

"That fact eventually helped bring mitochondria into the forefront [of research] again," said Eli Michaelis. "If there are malfunctioning mitochondria, they're going to produce excessive amounts of ROS material, such as superoxide or hydrogen peroxide or nitric oxide. And all those have the potential of being damaging to proteins or DNA."

Russell Swerdlow, M.D., and Danny Welch, Ph.D.

Mary Michaelis, Ph.D., and Eli Michaelis, M.D., Ph.D.

Eli Michaelis's part of the study was focused on determining what parts of the cell these ROS were targeting. Using a mouse model, he found that oxidative stress damages a receptor for glutamate, a major neurotransmitter in the brain that affects memory and learning. Glutamate also allows calcium to get into nerve cells. Cells use calcium to send signals to each other.

That discovery dovetailed nicely with the second biological change they believed caused aging: calcium dysregulation. To function properly, cells must pump enough calcium out in order to let necessary calcium back in. If glutamate receptors are malfunctioning, too much calcium can get in the cell, including in the mitochondria, which can lead to excessive ROS and cell death. Eli Michaelis also found that one of the things that regulates the production of glutamate in nerve cells is glutamate dehydrogenase — a mitochondrial enzyme.

Meanwhile, while her husband's work led him to consider calcium's entrance into the cell, Mary Michaelis was focused on its exit. She had begun studying calcium dysregulation in the early 1980s, with a grant from the National Institute on Aging (NIA). Calcium dysregulation's involvement in aging was also an interest she shared with Zaven Khatchaturian, Ph.D., the man who built the Alzheimer's disease research program at the NIA, and a big supporter of their work.

Mary Michaelis was interested in a tiny pump on the outside membrane of the cell that pushes out calcium. She wanted to see if that pump loses its muscle with age. She found that it did, especially in the brain. And if calcium regulation is impaired, mitochondria can pick up some of the excess calcium and store it.

"If calcium gets overloaded, it could make the mitochondria less effective in generating energy," said Mary Michaelis. "That also kills cells over time."

The Michaelises' research shed light on the biological mechanics of how dysfunctional mitochondria contribute to aging by the gradual damaging of cells over time. Time might heal all wounds, but it also kills us: as we age, diminishing and malfunctioning mitochondria impair and kill cells. And when enough cells die, they take us with them.

Does that mean if scientists could figure out a way to fix bad mitochondria, people could live forever, or even just to, say, 120 years of age? It's not that simple, according to Russell Swerdlow, M.D., who is on the Board of Scientific Councilors at the NIA, which is responsible for reviewing NIA-funded research. Halting aging itself is a bigger, more complicated biological task than treating a specific age-related disease, which is why scientists are closer to achieving the latter. And even if scientists could reverse aging, that doesn't guarantee that the years gained would be healthy ones.

"It raises philosophical issues," Swerdlow said. "How long do we really want to live? And we don't really know yet what arresting aging will look like."

FROM HERESY TO HOPE

If there's anyone at KU whose experience presenting at medical conferences mirrors that of Danny Welch, it's Swerdlow, who is also the director of the University of Kansas Alzheimer's Disease Center, one of 31 NIA-designated Alzheimer's Disease Centers in the country. Established in 2011, the KU Alzheimer's Disease Center is a world leader in the role of mitochondria in Alzheimer's disease.

Sitting in his office at the center he leads with co-director Jeffrey Burns, M.D., a former mentee at the University of Virginia, Swerdlow is candid about his early days of studying mitochondria. He remembers sometimes not being invited to certain meetings, and when he was, he'd encounter criticism and skepticism.

"I'd give a presentation and they'd actually say, 'You're full of [expletive],' or 'This is just dumb,'" said Swerdlow, who is also the Gene and Marge Sweeney Professor of Neurology at the KU Medical Center. (His response to these insults? "Thank you for your opinion.")

His work runs counter to the longstanding hypothesis about the cause of Alzheimer's, the progressive disease that causes thinking and memory problems and usually strikes people age 65 and older. That theory posits that Alzheimer's is caused by a protein known as beta-amyloid, which builds up in the brain to form plaques that inhibit communication between neurons and kills them. These plaques, along with spaghetti-like tangles of protein called tau, are always present with the disease.

But none of the many clinical trials that attacked plaques and tangles has yet proven transformative. Data to date suggest that if there is any potential benefit from these approaches, it will likely be on the level of slowing cognitive decline, rather than fully arresting decline or improving cognitive function.

Swerdlow has long believed that plaques and tangles are more of a symptom of the disease than a cause. Electron microscopy pictures of Alzheimer's disease brains reveal misshapen mitochondria, and some studies have shown that patients with the disease have reduced mitochondrial activity in their brains, fewer mitochondria in their nerve cells, and a reduced ability to utilize glucose for energy. Then there's the simple fact that some people who develop plaques and tangles never develop dementia. Moreover, the amyloid theory has never explained why age is a risk factor for the disease, while defective mitochondria have long been associated with aging.

As a research fellow at the University of Virginia, Swerdlow worked with W. Parker Davis, M.D., one of the first people to claim that defective mitochondria might be contributing to neurodegenerative diseases. They published a series of papers in the 1990s, and in 2004, Swerdlow published The Mitochondrial Cascade Hypothesis, asserting that deficient brain energy and malfunctioning mitochondria precede plaques and tangles and initiate late-onset Alzheimer's.

At the time, his theory was close to heresy. But in the 15 years since his hypothesis was published, scientists at other institutions have published studies consistent with it, demonstrating, for example, that defective mitochondria explain changes outside the brain in the bodies of Alzheimer's patients, while the amyloid hypothesis does not, and that different mitochondrial strains affect the build-up of amyloid in animal brains.

Even though amyloid remains the prevailing culprit according to many, more researchers are looking beyond plaques and tangles and to the work of the KU Alzheimer's Disease Center to find ways to manipulate brain energy metabolism to treat the disease.

REVVING UP THE BRAIN

Researchers already know that exercise, especially aerobic exercise, improves mitochondrial function in muscle. That's why people who exercise develop endurance and get stronger: Exercise improves the muscles' mitochondria, and through this their ability to consume oxygen. The better the oxygen consumption, the better

"IT RAISES PHILOSOPHICAL ISSUES. HOW LONG DO WE REALLY WANT TO LIVE? AND WE DON'T REALLY KNOW YET WHAT ARRESTING AGING WILL LOOK LIKE."

RUSSELL SWERDLOW, M.D.

the muscle cells function. Burns, who is also the Edward H. Hashinger Professor of Neurology at the KU School of Medicine, has done research for 15 years to see if aerobic exercise improves brain cell health the same way it improves muscle health. Burns is teaming up with researchers at the University of Pittsburgh and Northeastern University to conduct the largest, most comprehensive study ever done to determine conclusively if moderate aerobic exercise can improve brain health in older adults and slow cognitive decline and potentially delay the onset of Alzheimer's disease.

Meanwhile, Swerdlow is leading a study to rev up brain energy metabolism with supplements of oxaloacetate (OAA), a natural compound in the cell's energy cycle. Human cells have two energy fluxes: glycolysis (breakdown of glucose) and respiration (converting nutrients to ATP via mitochondria). In many cases when one goes up, the other goes down. Swerdlow and his team want to see if OAA supplements can increase both fluxes to boost brain mitochondrial activity. In the pilot study, people with mild or moderate Alzheimer's disease took a daily OAA dose for a month, and the effects were measured using cognitive tests, blood draws, and scans at the Hoglund Brain Imaging Center. So far, so good.

"We saw what we hoped to see," said Swerdlow. "It appears that oxaloacetate can enhance these energy-producing pathways." The next step is to find the right dose, one that can make a significant cognitive difference while remaining safe.

As a post-doctoral fellow working with Swerdlow, Heather Wilkins, Ph.D., now an assistant professor in the Department of Neurology, published the results of the first therapeutic trial for Alzheimer's disease that targeted and directly measured mitochondrial activity in 2017. Her study specifically targeted the COX enzyme, the part of mitochondria that consumes oxygen to make ATP. It is known to be dysfunctional in Alzheimer's patients.

Wilkins wanted to see if a synthetic estrogen supplement, S-Equol, that had been found to increase brain energy metabolism in rats could stimulate mitochondrial function in people with Alzheimer's. In her trial, 15 women with Alzheimer's disease took S-Equol twice a day for two weeks. According to the blood tests taken before, during and at the end of the study, COX enzyme activity increased in 11 of the 15 participants. Wilkins is now running a second study that includes men and increases the dosage and length of time participants take it.

Wilkins says she can sense a difference in attitude toward mitochondrial research even within the six years she's been at the KU Alzheimer's Disease Center.

"In the beginning, nobody came to my poster sessions," she said. "But this year at the Alzheimer's conferences, it's been invigorating. People are saying we need to look beyond amyloid beta."

BOOSTING MITOCHONDRIAL ENERGY FOR CARDIOVASCULAR HEALTH

The Mitochondrial Genomics and Metabolism Core, which was established when the KU Alzheimer's Disease Center was formed, provides resources and expertise for anyone wanting to study mitochondria, including people elsewhere at the KU Medical Center.

At the KU School of Nursing, Janet Pierce, Ph.D., FAAN, the Christine A. Hartley Centennial Professor of Nursing and University Distinguished Professor, is focusing on improving heart mitochondria to ease the suffering of people with a type of heart condition that accounts for half of all heart failure patients: heart failure with preserved ejection fraction (HFpEF). Heart failure is a condition in which the heart muscle is unable to pump enough blood to meet the body's nutrition and oxygen needs. If the heart pumps normally but is too stiff to fill properly, that's HFpEF. Patients with HFpEF suffer from fatigue, severe lack of energy and shortness of breath. Young patients can develop the disease, but age is a risk factor.

Pierce is looking to boost the energy of these patients with supplements of substances that occur naturally in mitochondria. One supplement is Ubiquinol, a type of coenzyme 10 (CoQ10) that protects cells from damage. Pierce has already conducted studies that found Ubiquinol to be effective in treating people with hemorrhagic shock and traumatic brain injuries.

"This all started because I was looking for ways to use an antioxidant to make cells work better. And people said, 'Ubiquinol,'" she remembered. "Well, it's made in the mitochondria."

Many cardiologists already recommend taking CoQ10 supplements, particularly of ubiquinone, which is the non-active form. CoQ10 is converted to Ubiquinol in the mitochondria. But when that conversion is decreased, Pierce believes, people are at risk to develop heart failure.

In Pierce's NIA-funded clinical trial, patients take supplements of Ubiquinol and D-ribose,

Janet Pierce, Ph.D., FAAN

a sugar that mitochondria use to produce ATP. She hopes to find that one or both can improve mitochondrial function, enhance cellular energy production in the heart and lessen shortness of breath and fatigue.

"One of the things we are focusing on in nursing is the molecular underpinnings of symptoms," she said. "And fatigue, lack of energy, is the perfect thing for mitochondria to combat."

Meanwhile, John Thyfault, Ph.D., professor in the Department of Molecular and Integrative Physiology at the KU School of Medicine, is looking at mitochondria and cardiovascular health from a different angle. He is studying how statins, drugs commonly prescribed to older people to lower cholesterol and ward off heart attack and stroke, can, ironically, interfere with the benefits of aerobic exercise. In 2013, Thyfault led a study that found that people who did moderate aerobic exercise without taking a statin increased their aerobic fitness and their muscle mitochondria, while those who did the same exercise while also taking a daily statin had no increase in their aerobic fitness — and the number of mitochondria in their muscles actually declined.

He is now conducting a study with a researcher at East Carolina University to compare the effects of a lower versus higher dose of statins in hopes of finding that lower doses are better tolerated and won't affect mitochondrial function.

"If we're right, that means some patients could potentially take the low dose of a statin and exercise and get all the benefits of both," said Thyfault. "That seems like a better way to go."

A LONELY SEARCH

In 1999, while conducting a postdoctoral fellowship at Harvard Medical School, Hao Zhu, Ph.D., discovered a gene, Ncb5or, that is linked to lean diabetes, a term for when the disease strikes people with low to normal body weight. An associate professor in the Department of Clinical Laboratory Sciences at the KU School of Health Professions since 2011, Zhu has spent his career studying how this gene, as well as an associated gene called CISD2, leads to diabetes when they are knocked out (deactivated) in the cell.

His most recent work suggests that when these genes are deactivated, cells essential for insulin production cannot distribute iron into the mitochondria and the mitochondria cannot function properly, leading to decreased insulin levels, increased ROS, cell death and ultimately the disease. Lean diabetes, which includes type 1 diabetes, is not an age-related disease, but Zhu points out that the cellular characteristics and mitochondrial defects are nearly the same in type 2 diabetes, and the results of his work should have implications for both. Age is a risk factor for type 2 diabetes, in part because people tend to exercise less and gain weight as they get older.

After discovering and studying Ncb5or for 20 years, Zhu acknowledges that he remains one of the few people who's interested in this gene and its link to diabetes. When more is known about the function of the gene, he said he expects more people will want to study it.

Until then, he is not concerned about the lack of interest.

"Science is often a lonely search in the beginning; this is very normal," he said. "Pioneers are often very lonely, but they are the ones who will make the waves."

MAKING WAVES

So far, there are no FDA-approved drugs that target mitochondria specifically. Meanwhile, the science marches on.

Mary and Eli Michaelis now co-direct the Mitochondrial Genomics and Metabolism Core at the KU Alzheimer's Disease Center, where they are sequencing the mitochondrial DNA from Alzheimer's patients. So far, they have found a few gene mutations that appear to occur at a higher rate in people diagnosed with Alzheimer's. The work before them is figuring out how, mechanistically, these mutations lead to the disease.

"And that will be the difficult part," said Eli Michaelis.

In 2014, Swerdlow founded the Heartland Center for Mitochondrial Medicine, a collaboration for researchers across the region interested in mitochondria and genetics. In 2018, the center held its second symposium, with speakers from research institutions all over the country.

"I may ultimately turn out not to be right, but at least I've turned out not be crazy," Swerdlow joked.

For Welch, the connection between mitochondria and metastasis is about much more than gene mutations. Researchers in his lab and other collaborators are also looking at how mitochondria can change the response to radiation therapy, and how mitochondria can turn nuclear genes on and off. He is excited about how mitochondria can affect the function of the immune system, which can alter the microbiome, the trillions of microbes inside the body, and alter susceptibility to all kinds of disease, of which cancer is just one.

Of all the people who asked Welch questions after his talk at the conference in Chicago last year, one person stands out in his memory: a researcher from the National Institutes of Health whom Welch recognized but did not know, and met for the first time that day.

"He said something like, 'I've heard you present this three or four times now, and I'm finally beginning to believe it,'" remembered Welch. "That made me feel really good."

QUESTIONS

10 QUESTIONS WITH MICHAEL KENNEDY, M.D.

BY DONNA PECK

In May of 2019, the National Rural Health Association announced that Michael Kennedy, M.D., was the recipient of its Outstanding Educator of the Year award. Kennedy is the associate dean for rural health education at the University of Kansas School of Medicine, serves as the assistant dean for student affairs and is the inaugural recipient of the McCann Professorship in Rural Health. We talked with Kennedy about what the award means to him and about his passion for rural health policy and workforce development.

1

Did you always want to practice family medicine?

I was raised in Topeka, Kansas. My father was a KU School of Medicine graduate and my mother was a nurse. I actually went to Arizona State University to study wildlife biology. But while searching for jobs as a wildlife biologist, I started working as a respiratory therapy trainee and caught the bug for medicine. I began medical school at KU in 1986 with the idea of becoming a pulmonary intensivist, but after doing a rural rotation, I knew rural and family medicine was for me.

2

When you got out of medical school, you practiced family medicine in tiny Burlington, Kansas for nine years. What did you love about being a doctor in rural Kansas?

Family physicians in rural settings have a unique opportunity to not only provide medical care to people, but to serve a community. The practice of medicine can be easier in a small town because you get to know many of your patients in the context of their roles in the community.

3

Why did you decide to leave your practice in Burlington in 2002 and return to the KU School of Medicine?

I had been teaching medical students in Burlington and was taking on several students per year in my practice. I loved teaching students about the rewards of practicing rural medicine. Then the KU School of Medicine asked if I would teach the first-year course in clinical skills. I struggled over the decision. Should I continue my deeply rewarding rural practice or should I embark on an academic career? I made the decision to leave Burlington. I took some comfort in knowing that I was also in a stage in my life where my family was in a good position for a move.

4

What are the challenges in getting medical students interested in practicing in a rural or underserved area?

Some students are very solid in their commitment to a career in rural medicine, and there are students from urban backgrounds that would never consider a rural practice. The challenge comes when you have students who are considering rural practice and trying to make up their mind. These students need many positive experiences to plant the seed and then provide soil, sun and water to grow their desire.

5

What kinds of programs does the KU School of Medicine have that help encourage more students to consider a career as a rural physician?

Our programs range from electives to financial programs with a service commitment for repayment. One is the Scholars in Rural Health program which is an assured admission program for juniors in college who commit to rural and primary care practice. STORM (Summer Training Option in Rural Medicine) is an elective in the summer after the first year of medical school which places the student with a rural attending physician for a period of four to seven weeks. Then there is the fourth-year rural preceptorship, a four-week rural preceptorship required for graduation. Since this is a mandatory program, some students approach it with trepidation. However, almost universally, students returned with a new appreciation for rural practice and for the learning opportunities that it presents.

6

Have those programs shown some success?

I think so. In recent surveys from the Association of American Medical Colleges, the KU School of Medicine has ranked in the 98th percentile for graduates choosing family medicine and the 94th percentile for graduates choosing rural practice compared to our peers in allopathic medicine.

7

How has the KU School of Medicine's Salina campus changed the way we train physicians interested in rural practice?

Students from rural areas in central and western Kansas who intend to practice rural medicine now have the option of maintaining their community and family support systems while receiving a medical education. There have only been two classes of graduates that have completed residency education, so it's too early to know for sure if this model is leading our Salina graduates to practice in rural areas. But I definitely think it gives us an additional edge.

8

What did getting the Outstanding Educator Award from the National Rural Health Association mean to you?

It means a lot to me, primarily because I was nominated by my students. It is incredible to be recognized for my primary passion in life. I hope receiving national recognition for my work at the KU School of Medicine will help reinforce to students and faculty the importance of rural health education.

9

You still practice family medicine here in Kansas City. Has working in a larger metropolitan area changed the way you practice medicine from your days as a rural doctor?

At its core the practice family medicine is not very different from rural to urban. It is about developing long-term relationships with your patients, continuity of care, whole person care and broad scope of practice. However, in a rural practice you have a better idea of the other factors that influence your patients' health. In an urban environment, your patients are much more anonymous. I would say that the rural practice has strongly influenced my urban practice because I have resisted that anonymity. And I have continued to make house calls which is much less common in urban areas.

10

What do you enjoy doing in your spare time?

I very much enjoy spending time with my wife of 43 years and my two children, their spouses and our seven grandchildren. I write poetry, and I love to read, especially science fiction and mysteries. I have taken up photography as a hobby. My wife and I love international travel, which lends itself very well to my photography. Lastly, we really enjoy visiting national parks.

Anwaar Saeed, M.D., and Jennifer Klemp, Ph.D.

CAN FISH OIL **PREVENT** COLON CANCER?

BY KRISTI BIRCH

KU Medical Center researchers Anwaar Saeed and Jennifer Klemp are exploring whether omega-3 can help prevent colon cancer in Lynch patients.

Colorectal cancer is the second-leading cause of cancer death in the United States, but for most Americans with access to health care, it's also largely preventable. Regular colonoscopy screenings beginning at age 50 enable doctors to snip out polyps — growths in the colon that sometimes become malignant — before they turn into cancer, or at least find the cancer early enough to be curable.

But for people with Lynch syndrome, an inherited genetic condition that predisposes people to various types of cancers, colorectal cancer poses a much greater threat. While people at average risk for colon cancer have a just under 5% lifetime chance of developing colorectal cancer, people with Lynch syndrome have as much as an 80% chance and typically the disease appears much earlier in life. That was the case with Kansas City Royals pitcher Tim Hill, who discovered he had Lynch syndrome when he was diagnosed with colon cancer at age 25. For these patients, colonoscopy screening is recommended to start as early as age 20 to 25. Because Lynch syndrome accounts for just 3% of colon cancer cases, this high-risk group doesn't always receive as much research attention as the larger average-risk population.

Lynch syndrome, which has no symptoms other than a strong family history of colon, uterine and other gastrointestinal cancers, can be detected by a genetic blood test. So far, a more aggressive screening schedule is the only known safe and effective strategy to fend off colon cancer from developing in these patients. Chemoprevention, the use of a medication or supplements to stop cancer from occurring in the first place, may offer a complementary approach with preventative screening.

"Even though people with Lynch syndrome have the greatest chance of getting the disease, most chemoprevention trials are not focused on patients with a genetic predisposition, but on patients who get the disease spontaneously," said Anwaar Saeed, M.D., assistant professor of medicine and a gastrointestinal oncologist at The University of Kansas Cancer Center.

"There's a huge unmet need to develop more feasible chemoprevention options for Lynch patients."

Saeed is looking to change that. She is launching the first clinical trial to examine the effectiveness of fish oil supplements, which contain omega-3 fatty acids, in protecting against colon cancer for people with Lynch syndrome. Omega-3 fatty acids have anti-inflammatory properties that have been shown to reduce the size and number of tumors in patients with familial adenomatous polyposis, another rare, inherited condition that causes so many polyps to form that patients often need to have their colon removed. Saeed's study is funded by the Cancer Prevention and Survivorship program and the Investigator-Initiated Trial (ITT) Steering Committee, both at the KU Cancer Center.

"This trial is a great opportunity to find a feasible and effective chemopreventive method for this vulnerable population, which is also classified as an orphan population because it accounts for less than 5% of all colorectal cancer patients," said Saeed.

MATCH GAME

For the colon to stay healthy, the cells that line the colon must regenerate themselves every few days. To do that, the cells must replicate their DNA. But sometimes when the DNA is cloning itself, mistakes known as mutations can occur. Luckily, the body has genes that fix the erroneous DNA.

People with Lynch syndrome have damaged versions of one type of those fix-it genes called DNA mismatch repair genes. When these genes are broken and can't do their job, mutated genes accumulate, and the result is runaway cell growth. That's cancer.

Unfortunately, scientists have not yet found a way to repair those resulting mutated genes.

"We can't fix mutations in people," said Dan Dixon, Ph.D., co-leader of the Cancer Prevention and Survivorship program, who is collaborating with Saeed on the omega-3 trial. "So the idea with this study is, what can we control? Well, we can control inflammation."

Inflammation — the immune system's response to an irritant or injury — helps accelerate cancer cells growing out of control. Inflammation also has been shown to increase the number of mutations. Colon cancer is associated with high levels of a lipid (fatty acid) called Prostaglandin E2, which helps activate the body's inflammatory response. More PGE2 generally means more inflammation. And more inflammation for Lynch patients means a greater chance they won't escape colon cancer.

Aspirin, an anti-inflammatory agent, was found to be effective in preventing colorectal cancer in Lynch patients, but aspirin is effective only at high doses, which can cause gastrointestinal bleeding and stomach ulcers.

> THERE'S A HUGE UNMET NEED TO DEVELOP MORE FEASIBLE CHEMOPREVENTION OPTIONS FOR LYNCH PATIENTS.
>
> **ANWAAR SAEED, M.D.**

"We have clinical evidence that aspirin works in this population, but with its side effects, aspirin lacks the universal feasibility," said Saeed. "So we're trying to find an alternative agent that has anti- inflammatory effects but without these side effects."

A SAFE STUDY

The beauty of omega-3 fatty acids in fish oil is that they are expected to curb the production of PGE2 and reduce inflammation without the possibility of harming the patient's gastrointestinal system. That safety is key.

"For a patient with Lynch syndrome, we advise them on more frequent colonoscopies, often suggesting having one every three years, and the importance of removing polyps. But high-risk patients often want to be more proactive than just having cancer screenings," said Jennifer Klemp, Ph.D., a cancer risk counselor and co-leader of the Cancer Prevention and Survivorship program. "If we could recommend a preventive agent that's a natural product, many high-risk patients would find that an attractive option."

Part of Klemp's role in the study is helping identify potential participants with Lynch syndrome to participate in the trial. For 12 months, these study participants will take a daily moderate dose of a prescription fish oil supplement. It can take many years, much longer than the time period of the study, for actual colon cancer to develop, but the researchers will know if the fish oil was effective by monitoring changes in the patients' biomarkers at the beginning and end of the study.

Blood, urine and stool samples will be taken, and colonoscopies will be performed, before and after the 12-month period. The researchers will examine and compare the results to look for reductions in the patients' biological markers of inflammation, cell growth and death and possible tumor development.

If the researchers are right, and the omega-3 fatty acids appear to have a chemopreventive effect, then the next step would be a more comprehensive study over a longer period of time.

"The future longer and larger study could possibly test the same omega-3 fatty acids product in different doses and in combination with other anti-inflammatory drugs like aspirin in lower doses," said Saeed.

"Maybe we find that we can reduce someone's chance of getting colorectal cancer from 80% down to 20%," said Dixon. "Or maybe we could lower the dose of aspirin, so that the person takes both fish oil and baby aspirin."

If they are successful, then people with Lynch would finally have some safe way, other than screening, to protect themselves from cancer.

"Personally, I believe the essence of practicing oncology is to prevent cancer before it becomes clinically visible," said Saeed. "This clinical trial is a low-risk sincere effort to capitalize on prior research developments and to support our mission toward preventing colon cancer in the Lynch population."

TREATING THE MIND AND THE BODY

BY LEILANA MCKINDRA

As a medical student, there was nothing Julie Leber, D.O., loved more than piecing together the puzzle of a new patient's presentation. After completing her psychiatry rotation, she couldn't ignore the strong connection between mental and physical health.

So, Leber decided to specialize in both, and she is now a resident in the rigorous internal medicine/psychiatry program at the University of Kansas School of Medicine.

"I loved the depth of internal medicine and was sure this was the right path for me. I felt like I couldn't be a good internist without a strong foundation in psychiatry," she said. "Throughout my five years of residency, I've learned to see patients with an integrated view and feel well equipped to practice this unique skill set."

That's exactly what dual-training programs in internal medicine, or in some cases family medicine, and psychiatry, are designed to do — train doctors to treat the mind and the body through a skillful blend of core expertise in both medicine and psychiatry.

A TRADITION OF EXCELLENCE

Internal medicine/psychiatry, or med/psych, programs have been around for decades, and the KU School of Medicine is home to one of the best in the nation. Established in 1995, it's one of the longest-running in the country. Credited with 22 alumni since its inception, the program has reliably produced at least one graduate in every year of its existence.

Anchored in both internal medicine and psychiatry — two already strong specialties at the KU School of Medicine with a long, ongoing history of working well together — the med/psych program boasts one of the highest number of dually trained med/psych physicians on the faculty.

"It's played out at least as well as I'd hoped. We've had phenomenal success and outstanding trainees who have gone on and done a lot of great things," said William F. Gabrielli, Jr., M.D., Ph.D., chair of the Department of Psychiatry and Behavioral Sciences and the visionary behind the thriving program. "I think we attract some of the best people in the country. I'm convinced we have a reputation among the best, and we show solidarity with cause and principles better than a lot of the other programs."

Only two residents are accepted into the prestigious program each year out of the 60 who are interviewed and the 150 to 200 who submit applications. Completing the postgraduate course of study leads to dual board certification in both specialties.

"These are great doctors who are very dedicated," said Teresa Long, M.D., who has been the med/psych residency director since the start of the program in 1995.

As part of the highly demanding program, Long said residents are expected to absorb a lifetime of knowledge in five years, compared to three years for internal medicine or four years for psychiatry, before taking their board exams and becoming practitioners who are certified in both specialties.

Leber, a native of Conyers, Georgia, said for her, the wide range of available learning opportunities is where KU's med/psych program separates itself from others.

"We rotated not only at The University of Kansas Health System, but also at the Veterans Affairs medical centers and the Community Mental Health Clinic. We have one of the most robust programs in terms of combined trained faculty," Leber said. "Our academic medical center community is a great thing to be a part of."

Leber took full advantage of all those learning experiences. In 2018, she became the first med/psych resident from the KU School of Medicine to earn the Association of Medicine and Psychiatry's prestigious Martin Fenton Award as the nation's top med/psych resident. The honor, presented to Leber at the association's annual meeting in October 2018 in Chicago, recognizes residents in their final year of training based on outstanding clinical performance, teaching skills, writing and/or research, service to community and leadership.

A BRIGHT FUTURE

Leber, who graduated from the program in June 2019, is currently doing a fifth postgraduate year in internal medicine and psychiatry at the University of Kansas Medical Center. Other alumni of the program have gone on to focus in a variety of areas such as critical care, gastroenterology, cardiology, addiction psychiatry, psychosomatic medicine, geriatric medicine, palliative care and emergency medicine.

"Whether it's community health, mental health, veterans' care or a subspecialty in either psychiatry or general medicine, I think we bring a greater depth to patient issues with the dual training," Long said.

Gabrielli believes the med/psych program is well-positioned for continued success.

"Looking ahead, we will focus on enhancing our top-notch training program by increasing the number of medicine and psychiatry experiences for residents and developing an in-patient med/psych unit," he said.

Emphasizing that mental health is an important part of general medical health, Gabrielli said primary care doctors are continuing to do a lot of behavioral medicine.

"People's minds, behaviors, feelings, perceptions and brain physiology don't exist in a vacuum. It's just that we want to be the specialists in behavioral medicine and we are. That's what makes us unique," Gabrielli said. "It also creates respectability for those doctors. Other colleagues see something there that's different, and that generates a confidence that ultimately results in better communication, better collaboration, and at the end of the day, better patient care."

ALUMNI SPOTLIGHT

Emmanuel John

Associate Professor and Chair,
Department of Physical Therapy
Chapman University, Irvine, California

Emmanuel John, Ph.D., DPT, MBA, associate professor and chair of the Department of Physical Therapy at Chapman University in Irvine, California, is a rising star in the world of academic physical therapy. John was recently elected secretary of the American Council of Academic Physical Therapy, which represents all accredited physical therapy programs in the country.

John, who was born and raised in Nigeria, was one of the first students to receive a doctorate in rehabilitation science from the University of Kansas in 2006. He said the rehabilitation science program at KU was tough, but has paid huge dividends in his career.

"The doctoral program was very rigorous, but it offered a diverse number of learning experiences and mentorship opportunities," John said. "Part of my time at KU was assigned to the Stroke Database Project, where I recruited stroke survivors to volunteer their time and effort to participate in various stroke-related research studies ongoing at KU Medical Center."

John said he has tremendous appreciation for the physical therapy and rehabilitation science faculty who helped shape his educational experience.

"Meeting and learning from people whose research I had read in prestigious scientific journals was such a privilege," he said. "I was also impressed with the diversity within the department's graduate program. I was able to study alongside great minds from countries around the world — and learning about new cultures and values made a tremendous impression on me."

After earning his degree from KU, John served as the director of the Motor Control and Neuromuscular Performance Laboratory at both Howard University and Radford University. Later, he was an associate professor of physical therapy at Touro University in Las Vegas, Nevada.

In 2015, John accepted his current position as chair of the Department of Physical Therapy at Chapman University. The physical therapist education program at Chapman is the oldest in the United States. As chair, John oversees 19 full-time faculty members, more than 35 adjunct faculty and several clinician physical therapist lab assistants serving both the entry-level DPT and transition DPT degree programs. The program currently has 240 entry-level DPT students and about 30 post-professional DPT students.

"The part of my job that I love the most is working to provide innovative solutions to everyday challenges," John said. "I work with our team on strategically planning and positioning us for the future, by creating and strengthening alliances and collaborations within and outside Chapman."

John is also a noted researcher who has published studies on the effects of age, gender and neurological lesions on motor effort; and the impact of brain-drain on physical therapy education in developing countries.

Outside of his professional duties, John has a high-tech hobby.

"I love designing and developing websites for some of my professional associations and other nonprofit organizations located in my home country of Nigeria," he said. "For instance, I designed, developed and now manage websites for the World Confederation for Physical Therapy Africa Region, the Nigeria Physiotherapy Network and the CMUL Physical Therapy Alumni Association. It keeps me busy!"

KU MEDICAL CENTER
The University of Kansas
3901 Rainbow Blvd.
Kansas City, KS 66160

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