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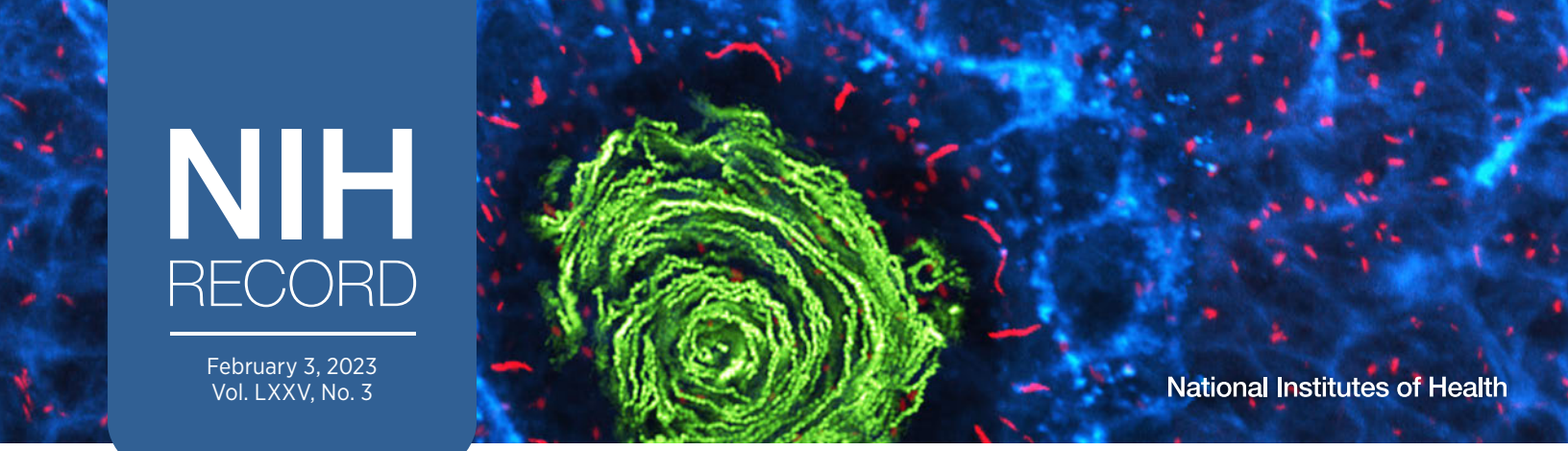


ENSURING 'FERTILE SOIL' EVERYWHERE

Stress, Adversity in Early Life Have Impact Across Lifespan

BY ERIC BOCK

Our environment and experiences over the first 1,000 days of life have an enormous influence on our growing brain and long-term wellbeing, said Dr. Laura Stroud at the annual Stephen E. Straus Distinguished Lecture in the Science of Complementary Therapies.

"Things that happen to us when we're very young have a much larger impact. This is a sensitive period of brain development and lifelong health," said Stroud, director of the COBRE Center for Stress, Trauma and Resilience (STAR) at the Miriam Hospital and professor of psychiatry and human behavior at the Warren Alpert Medical School of Brown University. "If we can have an impact here early, we may be able to change the course of health and disease."

Stress during pregnancy has a very profound impact on a child's lifespan. Differences in stress and nutrition alter both mother's as well as fetus's biology, leading to differences in brain development and physiologic system formation in the offspring. This concept is known as "prenatal programming." One way a mother communicates with her fetus is through the placenta, an organ that develops in the uterus during pregnancy.

Research has revealed that sensitive periods of development, including the fetal-infant transition, affect our brain and overall longterm health.

SEE **STROUD**, PAGE 4

PERSPECTIVE MATTERS

Rare Cancer Survivor, Oncologist Discuss the Patient Experience

BY DANA TALESNIK

Deanna Fournier

Frustrated. Isolated. Angry. Anxious, yet determined and hopeful. These are among the many emotions experienced by patients with rare cancers. Deanna Fournier knows firsthand.

Fournier was just 6 years old when she was diagnosed with a rare cancer. The prognosis was bleak, but she survived. Looking back, "I had to grow up rather quickly," said Fournier, director of the Histiocytosis

SEE **RARE CANCER**, PAGE 6

REGROWING THE RETINA

Researcher Uncovers 'Roadmap' to RPE Regeneration

BY AMBER SNYDER

Dr. Katia Del Rio-Tsonis

What if we could cure diseases such as age-related macular degeneration (AMD) by regrowing the damaged parts of the eye? Researchers like Dr. Katia Del Rio-Tsonis of Miami University are working to make it possible.

In her recent lecture, "Uncovering the Roadmap Toward Retinal Regeneration via RPE Reprogramming," Del Rio-Tsonis

SEE **RPE**, PAGE 8

Grantees look into lessening PFAS. See p. 3.

ALSO THIS ISSUE

UNLOCK NEW CAREER PATHS
Management Intern Program Holds Info Sessions

Have you heard of the NIH Management Intern (MI) Program? It is a highly competitive, two-year career development program for current NIH employees. MIs come from a variety of job backgrounds, including both scientific and administrative fields. Recent MIs have joined the program from positions as diverse as an intramural program specialist, police officer, contract specialist, high-voltage electrician and extramural support assistant.

MIs rotate through different administrative career fields to gain invaluable insight into NIH while contributing through targeted assignments and challenging projects. After two years and upon completion of the program, MIs transition into an administrative-management career in one of many areas throughout NIH.

NIH's MI vacancy announcement will be posted in USAJobs on Mar. 1-10. To learn more about the program or to view a recording of a recent information session, visit https://bit.ly/3CVprMn.

Organizers also will hold new sessions on Tuesday, Feb. 14 from 10 to 11:30 a.m. and Thursday, Feb. 16 from 1:30 to 3 p.m. Also, there will be an opportunity to speak directly to current MIs who will answer questions at a Coffee with an MI session on Wednesday, Feb. 22 from 12:30 to 2 p.m.

If you are interested in attending any of these events, email mi_info@od.nih.gov.

BRAIN To Host Webinar, Feb. 15

Join the Brain Research Through Advancing Innovative Neurotechnologies (BRAIN) Initiative for a webinar about the BRAIN Circuits Program and team science approaches on Wednesday, Feb. 15 at noon ET.

Register for the webinar at https://bit.ly/3JhKop2.

For details about BRAIN, visit Braininitiative.nih.gov.

Learn about funding opportunities that support teams of scientists and how to apply for team science grants such as the U01 and U19. Add distinct and diverse perspectives to improve the quality and value of brain research.

Develop innovative conceptual frameworks, approaches and technologies.

Build and strengthen a collaborative network of multidisciplinary researchers.

NIH Public Health Service Commissioned Corps officers participated in the Wreaths Across America event at Arlington National Cemetery in December.

PHOTO: JAMARR HUMPHREY

NIH'ers Volunteer for Wreaths Across America

National Wreaths Across America Day happens every December to remember, honor and teach. There are coordinated wreath-laying ceremonies across more than 3,700 locations, in all 50 U.S. states, at sea and abroad.

NIH Public Health Service Commissioned Corps officers participated in the event held in 2022 at Arlington National Cemetery along with more than a dozen other officers stationed in the D.C. metropolitan region. Participants gathered in the early morning hours and stayed until the mission was complete—to place a wreath on every hero's grave.

Veterans Day is in the Fall and Memorial Day is in the Spring. Service members sacrifice their time and safety every single day of the year to preserve our freedom. We will never forget those who have served and those who have made the ultimate sacrifice.

The officers who volunteered their time during this past holiday season helped enhance the visibility of the Commissioned Corps, promoted camaraderie and placed a spotlight on why we serve.

Visit the website at: www.wreathsacrossamerica.org/ to read more about Wreaths Across America.—**Jing Tassone**

NIEHS Influences National Effort to Solve PFAS Problems

BY CAROL KELLY

As science on per- and polyfluoroalkyl substances (PFAS) develops, the National Institute of Environmental Health Sciences (NIEHS) continually plays a substantive role.

A group of more than 9,000 manmade chemicals, PFAS have been used for decades in a variety of industrial and consumer products. Now found in drinking water, soil and dust, researchers estimate PFAS can be detected in 98% of Americans.

Dr. Susie Dai of Texas A&M in the lab

PHOTO: MICHAEL MILLER/TEXAS A&M AGRILIFE

PFAS stay in the environment, rather than breaking down, due to chemical bonds within the molecules that are hard to split.

NIEHS partnered with the Agency for Toxic Substances and Disease Registry to commission a study on health effects related to PFAS by the National Academies of Sciences, Engineering and Medicine.

The resulting report notes that all 50 states have some PFAS contamination, but not all of this contamination is at a level that calls for health warnings. People are mainly exposed to PFAS through consuming contaminated water and food, according to the report.

"NIEHS-funded scientists are currently assessing different kinds of PFAS and supporting the development of methods to screen for, monitor and remediate these substances, among many other efforts," said NIEHS Director Dr. Rick Woychik.

Health effects from PFAS exposure are a concern. The report asserts there is sufficient evidence of association between such exposure and increased chance of a decreased antibody response in adults and children, decreased infant and fetal growth, abnormally high cholesterol and kidney cancer in adults.

The report, coupled with NIEHS-supported research, can be used to help clinicians better test, diagnose and provide care to patients exposed to PFAS.

Although PFAS are difficult and expensive to clean up, promising cost-effective technologies are underway. Novel remediation methods are being developed with grant funding from NIEHS's Superfund Research Program.

Successful remediation requires an initial crack of hard-to-break bonds in the PFAS molecule followed by destruction of any harmful secondary molecules. Some PFAS or their byproducts of removal are buried or burned, which leads to other environmental concerns. Cleaner methods are needed.

At the University of California, Riverside, NIEHS grant recipients demonstrated how microbes can break down certain PFAS into smaller, non-toxic molecules. Investigators also showed that some PFAS can be more easily degraded than others.

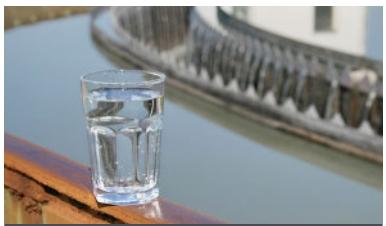
At Texas A&M University, NIEHS grantees discovered a plant-derived material that adsorbs and disposes of certain PFAS with microbial fungi that literally eat these chemicals. Adsorption is the process of molecules sticking to a surface.

"The plant's cell wall material serves as a framework to adsorb the PFAS," stated Dr. Susie Dai, Texas A&M associate professor. "Then this material and the adsorbed chemical serve as food for a microbial fungus. The fungus eats it, it's gone and you don't have the disposal problem. Basically, the fungus is doing the detoxification process."

Knowledge of the effects of PFAS exposure and potential treatments has grown, thanks to recent research. But there is more work to do, and those efforts involve preparing science to handle future discovery of other harmful chemicals.

In addition to PFAS, there are certain other chemical compounds that have attracted national attention because they have been found in water sources. Called "contaminants of emerging concern," these pollutants come from everyday consumer products, industrial manufacturing processes and agricultural practices. But they have been traditionally difficult to detect in drinking water.

In response, the White House Office of Science and Technology Policy (OSTP) issued the National Emerging Contaminants Research Initiative report this past August. The document establishes a vision to provide access to clean and plentiful drinking water for every person in the country. Strategic goals that address critical research gaps are outlined.



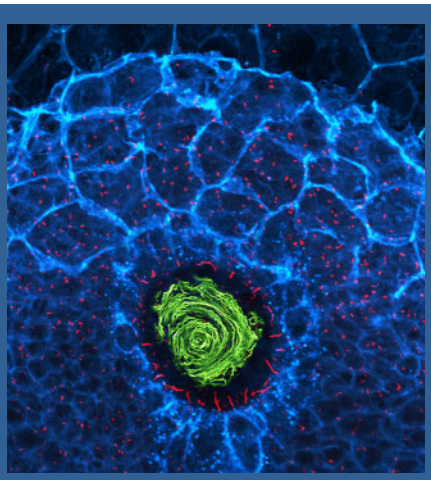
Information from the National Emerging Contaminants Research Initiative will inform future drinking water standards.

PHOTO: BORIS CHAMICEVYC/SHUTTERSTOCK

NIEHS staff shaped the report as leading members of the interagency working group.

"The working group aimed to identify critical research priorities for analyzing, monitoring and treating emerging contaminants in drinking water," said working group member Dr. David Balshaw, acting director of NIEHS's Division of Extramural Research and Training. "Integrating the work of federal agencies is necessary to address data gaps and to protect public health."

This year, OSTP and federal partners will coordinate to support implementation of this initiative. R



ON THE COVER: *NHLBI-supported researchers are reporting new insights into how hair-like cellular structures called cilia are able to sense biomechanical forces to shape the heart and other organs during embryo development. The findings, published in the journal* Science*, could lead to better ways to diagnose and treat congenital heart disease. Shown is a fluorescent microscope image of a zebrafish embryo highlighting cilia (red), fluid flow (green) and the plasma membrane (blue) inside a small cluster of cells called the left-right organizer. February is American Heart Month. Congenital Heart Disease Awareness Week is Feb. 7-14.*

IMAGE: SHIAULOU YUAN (MASSACHUSETTS GENERAL HOSPITAL AND HARVARD MEDICAL SCHOOL) AND ZHAOXIA SUN (YALE UNIVERSITY)

The NIH Record

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NIH National Institutes of Health
Turning Discovery Into Health

Dr. Laura Stroud (l) and colleagues focused on revealing the earliest intergenerational transmission of maternal experiences and behaviors.

Stroud

CONTINUED FROM PAGE 1

Stroud said adverse childhood experiences are related to long-term health. Examples include emotional and sexual abuse, parental substance use, exposure to domestic violence, physical and emotional neglect, homelessness and parental divorce. Beyond the immediate household, adverse community events like poverty, discrimination, poor housing quality and violence can have lifelong consequences in children.

The long-term impacts of stress and adversity in early life affect a child physically and mentally, she noted. Exposure to these experiences can also lead to an earlier death.

"In the wake of the pandemic, we know that even more children and families are experiencing stress and trauma, and there's been an unprecedented level of mental health problems in children and parents," Stroud said. "It's even more important to understand how we can build resilience in those who are exposed to stress and trauma."

Protective experiences may prevent or mitigate some of these harmful effects, she suggested. Nourishing relationships help lead to optimal neurodevelopment and positive social, emotional and cognitive function. Examples include unconditional love from one person, helping others, having a trusted best friend or being part a group. Healthy behavior can also help children achieve milestones.

In terms of environmental influences, tobacco is one of the most common substances fetuses are exposed to in utero, she said. Rates of smoking are highest in younger mothers with lower incomes and in the South and Midwest. It is associated with poor outcomes across a child's development.

In newborns, exposure to tobacco products is causally associated with sudden infant death syndrome, low birthweight and prematurity. In older children, obesity, disruptive behaviors and attention deficit disorder are also linked to smoking. Children with mothers who smoke are more likely to smoke and develop a nicotine addiction themselves.

New tobacco products such as e-cigarettes are also used during pregnancy, Stroud found. Many people perceive them as a safer alternative to traditional cigarettes. However, research suggests that e-cigarette use is associated with similar birth outcomes because nicotine, the addictive chemical found in tobacco, is present. These are even more pronounced in babies whose mothers smoke marijuana in addition to tobacco products.

Stroud's research has shown that newborn babies with mothers who smoke show signs of stress and muscle tension. A month later, they were more irritable, had a harder time self-soothing and had a decreased attention span.

Subtle differences in behavior have even been detected during fetal development. Fetuses exposed to tobacco are more aroused and active compared to fetuses who have a mother who doesn't smoke.

"Smoking is not a random exposure," she said. "Mothers who smoke during pregnancy are less likely to receive adequate prenatal care, more likely to use other harmful substances, have higher stress levels and more problematic relationships, are more likely to have an unplanned pregnancy with or without a supportive partner and have multiple children."

Pregnancy is a "window of opportunity for resilience," the researcher suggested.

★★★

"Pregnancy is a window of opportunity to foster resilience in two generations."

–DR. LAURA STROUD

★★★

Women are more likely to quit smoking when they are expecting than at any other time in their lives. Those who successfully quit reported higher levels of attachment to their baby during pregnancy. Quitting reverses many of the early effects, like low birthweight and prematurity. Expectant mothers also go to the doctor's office for medical care more often.

A member of Stroud's lab observes how an infant responds to a variety of different situations designed to mirror everyday tasks, such as seeing a new toy.

Stroud said it's important to look beyond what builds resilience at the individual and family level to community and structural levels. It is also critical to maintain resilience and support families in the postpartum period. Right now, she and her colleagues are studying how to best support parents during the most

Emerging evidence suggests stress and adversity may be transmitted from one generation to the next. However, protective experiences may prevent or mitigate these effects, Stroud said.

important period of a child's life so that health outcomes improve.

"Pregnancy is a window of opportunity to foster resilience in two generations," she emphasized.

There are many theories in psychology, for example, based on individuals who have blossomed despite growing up in difficult circumstances, she noted. Researchers must work with communities to change society so that all children have an opportunity to succeed.

She likened it to scientists studying one flower that grows through a crack in concrete.

"We're starting to be aware that we need to make fertile soil so that all flowers can bloom, instead of focusing on the one flower that's able to bloom despite all the obstacles," Stroud said.

The yearly lecture honors the founding director of NCCIH (formerly the National Center for Complementary and Alternative Medicine), Dr. Stephen E. Straus. The event is supported by the Foundation for the National Institutes of Health with a gift from Bernard and Barbro Osher.

View the full lecture at https://bit.ly/3H7KPiG.

Rural Health Seminar Addresses Dissemination, Implementation

BY ANDREW ERON AND MARK GIFFORD

NIH recently held the fourth annual Rural Health Day Seminar, "Improving Rural Health Through Research Dissemination and Implementation."

Dr. Lawrence Tabak, performing the duties of NIH director, opened the seminar by listing several obstacles: higher percentage of older adults, higher poverty rates, less accessible health care providers and facilities and the disproportionate impact of the Covid-19 and opioid misuse epidemics. He noted that the work of all 27 institutes and centers relates to the needs of rural communities, with mental health, health promotion, pain management, obesity, diabetes, hypertension, dental health, eye health and cancer currently representing emphasis areas for researchers interested in rural populations.

Dr. Shannon Zenk, director of the National Institute of Nursing Research, identified the intersection of rurality and social determinants of health as particularly important in successful dissemination and implementation of research findings. To underscore this understanding within NIH, she spotlighted several ongoing NIH efforts—in particular ComPASS (Community Partnerships to Advance Science for Society) and the NIH HEAL (Helping to End Addiction Long-term) Initiative.

The seminar included panelist presentations and discussion, moderated by Sarah Young of the Health Resources and Services Administration's Federal Office of Rural Health Policy. She discussed the higher rates of all-cause mortality in rural communities and the continued growth of the gap between rural and urban residents—not only for all-cause mortality but also for each of the leading causes of mortality.

Panelists were Dr. Rima Afifi of the University of Iowa College of Public Health, Dr. Julie Fritz of the University of Utah College of Health, and Dr. Tiffany Haynes of the University of Arkansas for Medical Sciences.

Afifi proposed reimagining rurality to shift the prevailing understanding away from the status quo, which she described as metro-normative, urban-centric, monolithic, minimalist and deficit-based.

Fritz outlined the foundational principles for her community partnerships and implementation efforts: shared goals, shared resources, shared data and mutual respect for expertise.

Haynes shared the impetus for her research: conversations with community members, such as a pastor from the Arkansas Delta, which has the highest percentage of rural residents and African-American residents in the state, about his congregation's struggles with depression and suicide. These talks resulted in the REJOICE intervention, which Haynes's team co-created with community members in response to the notable imbalance of need for and access to health services.

Audience questions covered a range of topics, including ways in which rurality intersects with bias and prejudice; strategies for outreach, participation and engagement; and the intentional use of language. Panelists emphasized the importance of sustaining the work, connections and relationships in the community; and understanding the unique needs of individual communities.

Concluding the seminar, Dr. Monica Webb Hooper, deputy director of the National Institute on Minority Health and Health Disparities (NIMHD), synthesized the myriad themes addressed. She reflected on the progress achieved while acknowledging the severity of the disparities between urban and rural health outcomes, and the relationship of those worsening disparities with adverse social factors that combine to negatively impact health.

Webb Hooper tasked researchers to continue creating and cultivating meritorious science projects to address rural health challenges, noting that NIMHD has a history of encouraging and funding paradigm-shifting research.

For more on the seminar, visit https://bit.ly/3WElVgu. To watch the recorded videocast, go to https://bit.ly/3H7y6fU.

Rare Cancer

CONTINUED FROM PAGE 1

Association. She shared her journey at a recent NCI Office of Cancer Survivorship lecture that also featured Dr. Eli Diamond, a neuro-oncologist at Memorial Sloan Kettering Cancer Center.

The symptoms Fournier had experienced—back pain, prolonged constipation, difficulty walking and a droopy eyelid—were not necessarily indicative of rare cancer. But when symptoms didn't improve, doctors took a biopsy of a lesion on her spine and diagnosed her with Langerhans cell histiocytosis (LCH).

Looking back, "I think about the feelings my parents and I felt, this burden of navigating this journey alone, [of a disease] we had never heard of before," said Fournier. The uncertainty was terrifying. Would treatment work? What quality of life would she have?

Fournier's family contacted a doctor who offered the most advanced treatment available at the time, but they faced a distressing choice. The new treatment "possibly would be incredibly toxic and lead to negative outcomes," she said. Fortunately, she had a positive outcome.

"But the journey doesn't end when the disease goes into remission," said Fournier. She continued experiencing mobility challenges and inflammatory responses to certain stimuli. The threat of relapse loomed. There are still many unanswered questions.

"Sometimes we don't even know what questions to ask," she said, "and we're afraid of asking too many, fearful of the burden on our care partners, our family and friends."

As with any rare cancer, the burdens are tough to navigate, from chronic pain to anxiety over treatment cost to the lack of information and resources.

"Patient research can really help with this so we can better understand all the gaps and challenges in the patient journey," she said.

That's what Diamond has come to work on—partnering with rare cancer patients and their caregivers to help manage the burden of living with rare cancer—while researching treatments for these diseases.

"I want to emphasize that, while individual rare cancers are of course rare, in aggregate, they are not rare," said Diamond. "Probably about one in five individuals with cancer has a rare cancer, so what we learn about a single rare cancer really reverberates to other affected individuals."

Dr. Eli Diamond consults with a patient.

PHOTO COURTESY OF MEMORIAL SLOAN KETTERING CANCER CENTER

Histiocytic cancers (HC) are blood cancers caused by an excess amount of histiocytes—a type of white blood cell—within tissues. Symptoms are severe.

LCH, the kind that afflicted Fournier, can affect different organs—liver, lung, spleen—as well as lymph nodes, skin and bones of the spine and hips.

"I cannot overstate this," said Diamond. "This disease can cause the most excruciating pain in all types of areas—the mouth, the groin, the skin, all over. It can be dreadful."

In milder cases, affected areas can be surgically removed followed by radiation and observation. In more severe LCH cases, before gene-targeted therapies were discovered, chemotherapy was curative for some. Others needed many lines of chemo over years; a fraction went into remission.

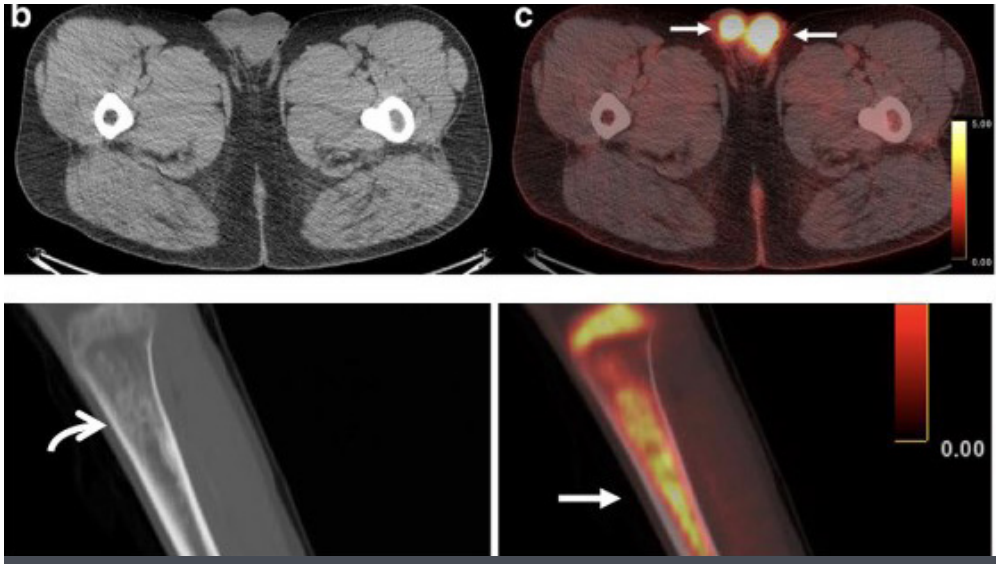
Diamond focuses primarily on patients with another HC called Erdheim-Chester Disease (ECD), a multi-system disorder that's also extremely painful. ECD causes tumors in the legs, organ dysfunction and uncontrolled inflammation, and often a range of neurological symptoms.

Research advances have led to newer medications—some with FDA approval and others in clinical trials—to help manage symptoms, though they come with serious side effects.

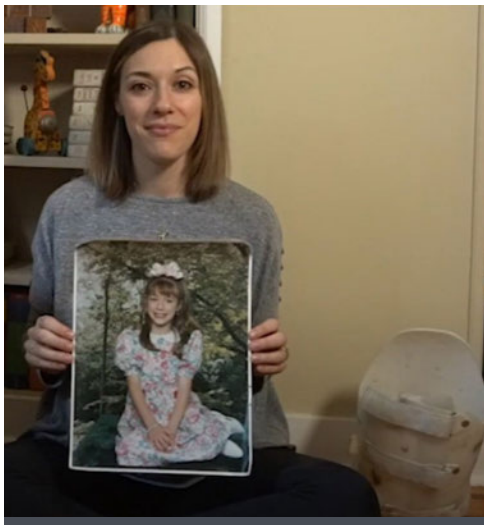
One such drug called Cobimetinib, approved by the FDA in recent months, worked wonders in almost all patients but side effects included heart problems, gastrointestinal issues, body rash, muscle problems and fatigue. For another approved drug, a third of patients in the clinical trial had to stop taking it due to intolerance.

Medications are "halting mortality, on the one hand, but have very difficult side effects on the other," said Diamond. Only a tiny fraction of patients are cured without enduring effects. For most people, stopping treatment leads to relapse. "So it's acting like an off switch, but it's not a cure."

And that is the conundrum, Diamond noted. "Many patients with these diseases now have this managed but incurable, chronic illness, balancing suppressing their



In pre-treatment scans from 50 ECD patients, PET (r) detected 94% of tumors versus 34% by CT scan.



Fournier holds a photo of herself as a child. Beside her is the back brace she wore for several months following treatment, as a lesion had collapsed her vertebrae.

disease on the one hand and side effects on the other."

To better understand the burdens and challenges of rare cancer patients and their caregivers, Diamond started a registry for ECD patients.

"We on the clinician-scientist side came up with 27 symptoms that patients with this disease could possibly have," said Diamond. After reviewing patient responses from focus groups and interviews, they ended up with more than 60 different symptoms.

Fournier and Diamond participate in a Q&A during the virtual lecture.

Learning more about the array of symptoms has helped Diamond advocate better for his patients.

"Being able to report the frequency and severity of disabling pain and fatigue has allowed me to secure disability benefits for patients even when they don't meet the conventional criteria," he said.

The registry also helped highlight the importance of PET scans—which detected almost every tumor—in fully evaluating and treating patients.

Diamond's team then did a deeper dive with a subset of patients, conducting more detailed surveys and interviews.

"Patients in the study always said fatigue and pain were co-travelers," he said. They described their fatigue as intrusive and exhausting; every little thing takes effort. The pain is "electrical."

Further, he said, "it was sobering to learn that whether someone's disease was in remission or what kind of treatment they were on did not have any association with more or less frequent pain." The chronic symptoms make palliative care especially important.

"In the cancer caregiving world, [a vital coping factor] is how individuals are able to find meaning and purpose in the experience of providing care," Diamond said.

A study his team conducted of 92 caregivers to patients with ECD and other histiocytic disorders revealed most of the caregivers had one and often multiple unmet needs, from resources to emotional support.

It's a vicious cycle. The lack of information and expertise about the rare disease leads to unmet needs for the patient and caregiver, while both must navigate long-term symptom management amid an uncertain future. All of it creates "this unfortunate loop of decreased meaning and purpose" and rising anxiety for the caregiver.

"We need more longitudinal studies to test interventions to help incorporate patient-reported outcomes into trials, more symptom-directed interventions themselves," as well as more informational and social support for caregivers, said Diamond.

"There is hope on the horizon," added Fournier. "We have gratitude for the dedicated clinicians and researchers who are adamant about getting us ever closer to a cure."

To view upcoming lectures in the series, see: https://bit.ly/3De7zg1.

Gaillard Named NIGMS Division Director

Dr. Shawn Drew Gaillard recently became the new director of NIGMS's Division of Genetics and Molecular, Cellular, and Developmental Biology (GMCDB). She had been GMCDB acting director since February 2022.

Dr. Shawn Drew Gaillard

"GMCDB-funded researchers pursue a variety of important questions, ranging from how cells repair DNA to how microbial diversity affects human health," said NIGMS Director Dr. Jon Lorsch. "Dr. Gaillard's extensive scientific background and her expertise in managing a wide range of research and training programs make her an ideal choice for directing this division."

Gaillard joined GMCDB as chief of the Developmental and Cellular Processes Branch in 2019, overseeing grants focused on organismal response to environmental stressors.

Prior to this role, she was the research training officer at NIAID. Before that, she was a program director in the NIGMS Division of Training, Workforce Development and Diversity and former Division of Genetics and Developmental Biology. Her experience also includes serving as a science education fellow at the Howard Hughes Medical Institute and directing what is now the NIH Academy on Health Disparities.

Gaillard has received numerous NIH and NIGMS honors and has participated on several high-profile committees, including having co-chaired NIGMS's striving towards racial inclusion, diversity and equity committee.

"I am deeply committed to NIGMS and excited to serve as the GMCDB director," Gaillard said. "I look forward to working with staff and extramural scientists on exciting breakthroughs that shed light on the molecular basis of gene regulation, developmental processes and cellular function."

Gaillard earned a bachelor's degree in natural sciences with a concentration in chemistry from Spelman College in Atlanta and a Ph.D. in biology from Howard University in Washington, D.C. She performed predoctoral and postdoctoral research at NIDDK.

RPE

CONTINUED FROM PAGE 1

discussed her research as part of the NEI Audacious Goals seminar series in neuroregeneration. The talks explore regenerative neuroscience and medicine with special emphasis on the visual system.

The RPE is the retinal pigment epithelium, a structure in the eye composed of a single layer of cells at the outermost layer of the retina. In AMD, the RPE begins to degenerate, causing vision loss. RPE reprogramming is "the window to the future of the [Audacious Goals Initiative]," said seminar host Dr. Tom Greenwell, acting associate director of NEI's Office of Regenerative Medicine.

Del Rio-Tsonis's research focuses on the cellular and molecular events that occur during retina and lens regeneration. She uses animal models such as newts, frogs and chickens as well as human-induced pluripotent stem cells (iPSCs).

Some adult salamanders have the remarkable ability to regrow their lens and retina (and just about any other bodily tissue) after removal—a feat that is unheard of for most adult animals, Del Rio-Tsonis said.

Regrowing the retina in newts occurs through RPE cell de-differentiation. Cells "reprogram" and transform into two kinds of progenitor cells (descendants of stem cells that can further change into specialized cell types). Neural progenitor cells replace the neural retina (one of two layers that form the complete retina) and RPE progenitors replace the RPE itself.

The ability to transition from one adult cell type to another is unique and involves specific regulation at the gene level. Del Rio-Tsonis wants to learn how to harness that regenerative power for humans, to be applied to conditions such as AMD.

Early-stage embryos also can regrow body parts under the right conditions. Del Rio-Tsonis studies the phenomenon in embryonic chickens (chicks). She has found that, within a narrow window of time, the chicks can regrow their retina after its removal (retinectomy) by reprogramming the RPE.

In her research, she removes the retina from a four-day-old chick embryo, leaving the RPE and ciliary margin intact. Adding fibroblast growth factor 2 (FGF2) induces "robust regeneration," with RPE cells

Del Rio-Tsonis discussed her research as part of the NEI Audacious Goals seminar series in neuroregeneration.

reprogramming into a neuroepithelium, which eventually differentiates into mature retina neurons and muller glia. FGF2 is vital to this process—without it, the retina does not regenerate.

Additionally, Del Rio-Tsonis has learned that there is only a small window of opportunity for embryonic RPE regeneration. The RPE is considered "plastic," or able to reprogram, at embryonic day four (called "E4"), but that plasticity is lost at day five, or E5.

"The RPE will not reprogram, even with FGF2," she explained. At E5, the RPE becomes "fate-restricted" rather than plastic.

Del Rio-Tsonis also studies the genetics of RPE regeneration. She observed that the "RPE genetic landscape changes as it responds to injury and FGF2."

She examined the genetic profiles of chick RPEs within 6 hours of removal—with and without adding FGF2. She found that "key neural transcription factors [including genes like VSX2 and SIX6] remain FGF2-inducible past the window of RPE competency restriction."

This is not true for all transcription factors in the RPE, though; the RPE functional program present at E5 is not disrupted with FGF2 and this program is driven by key transcription factors such as OTX2 and MITF.

Through single nuclei RNAseq, she identified several novel players that could dictate RPE regeneration competence. These genes may be helpful for future research for prompting RPE regeneration past E4.

Future steps, Del Rio-Tsonis said, include expanding these gene expression studies to human iPSC-derived RPE model systems.

A recording of the lecture is available at https://bit.ly/3Dbilnc. R

Feb. 9

Vanderbilt's Wilkins To Give NIMHD Black History Month Presentation

For Black History Month, the NIMHD Director's Seminar Series lecture will feature Dr. Consuelo Wilkins, senior vice president and senior associate dean for health equity and inclusive excellence at Vanderbilt University Medical Center, on Thursday, Feb. 9 at 2 p.m. ET. Her talk, "The Intractability of Health Disparities: Where Do We Go from Here?" will be virtual.

Dr. Consuelo Wilkins

Visit https://bit.ly/3DaNXcL to learn more about NIMHD seminars.

Save the Date: Rare Disease Day

Rare Disease Day (RDD) is an annual NIH event, co-sponsored by NIH's National Center for Advancing Translational Sciences (NCATS) and the Clinical Center. This year, the hybrid event will take place on Tuesday, Feb. 28 from 9 a.m. to 5 p.m. ET in the Natcher Conference Center and will be livestreamed and archived on videocast.nih.gov

RDD aims to raise awareness about rare diseases, the people they affect and NIH research collaborations that address scientific challenges and advance research for new treatments. The event features patients, patient advocates, health care providers, researchers, trainees, students, industry representatives and government employees.

For more information, including the agenda and a link to register for the event, see: https://bit.ly/400JSBE.

Study Links Specific Air Pollutants to Asthma Attacks in Children

An NIH-funded study found that moderate levels of two outdoor air pollutants—ozone and fine particulate matter—are associated with non-viral asthma attacks in children and adolescents who live in low-income urban areas.

PHOTO: ROMAN-DZIUBALO/SHUTTERSTOCK

The observational study is one of the first to link elevated levels of specific outdoor air pollutants in particular cities to distinct changes in the airways during asthma attacks not triggered by respiratory viruses. Findings were published in *The Lancet Planetary Health.*

In the study, conducted by the NIAID-funded Inner City Asthma Consortium, investigators examined the relationship between air pollutant levels and asthma attacks among 208 children ages 6 to 17 years who had attack-prone asthma and lived in low-income neighborhoods in one of nine U.S. cities. The researchers validated the associations they found in an independent cohort of 189 children ages 6 to 20 years with persistent asthma who also lived in low-income neighborhoods in four U.S. cities.

The investigators followed the children prospectively for up to two respiratory illnesses or six months, whichever came first. They matched each illness with air quality index values and levels of individual air pollutants recorded by the Environmental Protection Agency in the relevant city on the dates surrounding the illness. They subsequently adjusted their data for city and season to decrease the impact of these variables on the findings.

The scientists found that asthma attacks had a non-viral cause in nearly 30% of children, two to three times the proportion seen in non-urban children, according to previously published reports. The study also identifies links between exposure to the two pollutants and molecular changes in the children's airways during non-viral asthma attacks, suggesting potential mechanisms for those attacks.

Could a Blood Test Detect Alzheimer's Earlier?

One of the first stages of Alzheimer's disease involves formation of toxic aggregates, called oligomers, of the protein amyloid beta (Aβ). Oligomers can start to form more than a decade before symptoms and other known disease markers appear. The ability to detect these oligomers could enable earlier diagnosis and the potential to intervene before irreparable brain damage occurs.

An NIH-funded team led by researchers at the University of Washington developed a method to detect toxic Aβ oligomers in patients' blood. They tested the assay, called the soluble oligomer binding assay (SOBA), on nearly 400 banked human blood plasma samples. Results appeared in the *Proceedings of the National Academy of Sciences.*

When the team applied SOBA to a cerebrospinal fluid sample from a person with Alzheimer's disease, they detected Aβ oligomers. They did not detect oligomers in cerebrospinal fluid from a person who had no cognitive impairment.

Next, the researchers tested whether SOBA could detect Aβ oligomers in blood samples. The samples came from more than 300 people. SOBA detected toxic oligomers in 52 of 53 people with Alzheimer's disease or mild cognitive impairment. It did not detect oligomers in most of the control samples.

Ten of these positive samples came from people who later developed mild cognitive impairment. This shows that the SOBA test detected the toxic Aβ oligomer before Alzheimer's symptoms appeared. The team also measured conventional Alzheimer's disease biomarkers in cerebrospinal fluid samples from the same people. None of these correlated with disease state as well as the SOBA method did.

SOBA distinguished Alzheimer's disease from other forms of cognitive impairment. The team designed SOBA to detect only oligomers of Aβ and not of other proteins. Consistent with this, samples from people with other forms of cognitive impairment tested negative.

Other neurodegenerative diseases, such as Parkinson's disease, also involve toxic protein oligomers. The team showed that SOBA could be modified to detect Parkinson's disease and Lewy body dementia.

These results suggest that SOBA could detect toxic oligomers in the blood even before cognitive impairment occurs.—adapted from *NIH Research Matters*

Adolescent Substance Use Holds Steady in 2022

The percentage of adolescents reporting substance use in 2022 largely held steady after declining significantly in 2021, according to the latest results from Monitoring the Future, a survey of substance use behaviors and related attitudes among eighth, 10th and 12th graders nationwide.

In 2022, reported use of any illicit drug within the past year remained at or significantly below pre-pandemic levels for all grades, with 11% of eighth graders, 21.5% of 10th graders, and 32.6% of 12th graders reporting any illicit drug use in the past year.

Monitoring the Future, conducted annually by researchers at the University of Michigan, Ann Arbor, is funded by NIDA.

"It is encouraging that we did not observe a significant increase in substance use in 2022, even as young people largely returned to in-person school, extracurricular activities and other social engagements," said NIDA Director Dr. Nora Volkow.

For the survey, students self-report their substance use behaviors over various time periods, such as past 30 days, past 12 months and lifetime. The survey also documents students' perception of harm, disapproval of use and perceived availability of drugs. Notably, the survey results are released the same year the data are collected.

From February through June 2022, investigators collected 31,438 surveys from students enrolled across 308 public and private schools across the country. All participating students took the survey online, with 95-99% of respondents taking the survey in-person in school.

Adolescents most commonly reported use of alcohol, nicotine vaping and cannabis in the past year. Compared to levels observed in 2021, data reported in 2022 showed that nicotine vaping and cannabis use remained stable for all three grades surveyed. Alcohol use remained stable for eighth and 10th graders but returned to pre-pandemic levels for 12th graders in 2022, with 51.9% of 12th graders reporting alcohol use in the past year.

Illicit drug use, other than marijuana, also remained stable for all three grades surveyed. These data build on long-term trends documenting low and fairly steady teen use of cocaine, heroin, amphetamines and nonmedical use of prescription drugs, generally. Meanwhile, use of narcotics other than heroin, including opioids, increased slightly among 12th graders between 2021 and 2022.

For more data from this survey—including student responses to perceived harmfulness—see: https://monitoringthefuture.org/results/.

NIH Chief Information Officer Norris Retires

NIH Chief Information Officer Andrea Norris, who also served as director of the Center for Information Technology (CIT), retired on Dec. 31. For more than a decade, she led a $1.6 billion technology portfolio that supports the research of the agency's 27 institutes and centers as well as researchers at more than 2,500 universities and medical centers across the country that receive NIH funding.

NIH CIO Andrea Norris at her retirement party

"I have relied heavily on Andrea over the years for her expert advice on a range of information technology issues," said Dr. Lawrence Tabak, performing the duties of NIH director. "Her guidance is frequently sought not only by NIH leadership but also by leaders from across HHS and the federal government on IT and data science matters that could significantly impact NIH. We are grateful for the many ways she has enabled the advancement of the NIH mission."

Norris's career leading national management and technology programs and operations in the public sector stretches back 40 years. She came to NIH after prior senior leadership roles at the National Science Foundation (NSF) and NASA, bringing invaluable management experience on a wide variety of agency technology initiatives.

"It has been an exciting time to be at NIH and I'm so proud of the many ways that technology has helped to catalyze and enable NIH's accomplishments over the last decade," Norris said.

NIH benefited enormously from her deep knowledge in strategic planning, business management and technology. She established the Science and Technology Research Infrastructure for Discovery, Experimentation and Sustainability (STRIDES) Initiative, which accelerated adoption of cloud computing by the NIH-supported biomedical research community.

"Our cloud-based STRIDES program allows investigators to access and analyze more than 200 petabytes of research data from more than 1,200 science institutions and programs," she explained.

Other tech achievements under Norris's watch include building and sustaining a modern network that supports transit of up to 6 petabytes of data each day; expansion of Biowulf, the world's largest high-performance computational resource focused on biomedical research; and developing modern platforms and tools to enable the NIH workforce to work from anywhere at any time with excellence.

The Biowulf expansion alone resulted in a 500% increase in computing capacity and significant modernization of NIH's overall computing and networking environment.

"Most recently," Norris reflected, "I've had the privilege of co-chairing an effort to develop NIH's first digital strategic plan with [NLM Director] Dr. Patti Brennan and a committee of talented individuals from across NIH. The strategy proposes a new and more synergistic approach for technology decision-making and describes a cohesive framework to guide how NIH prioritizes and delivers high-priority, high-value capabilities over the next five years. Most importantly, it recommends new ways of working together to ensure NIH has the capabilities necessary to advance discoveries in the years ahead."

"True to Andrea's exceptional ability to work across large organizations, she ensured that this effort broadly engaged all of NIH, focused on future needs, and addressed all functions of NIH ranging from grants management, to building management, to the conduct of science," Brennan observed. "I am extremely proud to have co-chaired this effort with Andrea and to have worked side by side with someone who demonstrates such commitment, wisdom, and leadership. Andrea has not only left an indelible footprint on this new strategic vision but also on all the work she has led during her tenure at NIH."

Norris (second from r) is joined by (from l) NIH Acting Chief of Staff John Burklow, NIH Acting Principal Deputy Director Dr. Tara Schwetz and Dr. Lawrence Tabak, performing the duties of NIH director.

PHOTOS: MARLEEN VAN DEN NESTE

Norris said, "We should continue to experiment and exploit opportunities to use technology more strategically to accelerate what we do, which is to turn knowledge into discovery, and accelerate impacts on health and disease for people around the world. I'm proud and happy to have been a small part of these amazing advances. I can't wait to hear about all of NIH's continued successes."

During her NIH tenure, Andrea was selected as a fellow in the National Academy of Public Administration and received the Theodore Roosevelt Government Leadership Award. She also was recognized twice with the Presidential Rank Award, once at NIH and once at NSF, for meritorious service for delivering exceptional public sector leadership and high-impact results.

"Andrea Norris is an outstanding example of a woman leader in health information technology," said Brennan. "She is a visionary and well-respected leader—one who possesses deep technical knowledge, experience, creativity, and thoughtfulness. I have had the good fortune to work closely with Andrea and consider her to be one of my closest colleagues at NIH."

Norris also steered implementation of a 100-gigabit high-speed networking infrastructure to support public access to health and science information and connect researchers around the world.

Under her leadership, communication and digital capabilities for NIH staff were significantly expanded, including a broad range of NIH IT systems and services that support research and operational activities.

In addition, NIH's Cybersecurity Program was significantly bolstered under Norris's leadership to reduce high-impact risks, including maturing the cyber tool infrastructure with multiple layers of defensive software and implementing state-of-the-market secure identity and access technologies to support more than 300,000 researchers who access NIH data resources and systems.

Above the rewarding work and collegial atmosphere at NIH, Norris said she will miss her colleagues and the exceptional collaborations the community affords.

"It has been an incredible honor and privilege to work with the people in CIT and the Office of the CIO—the leadership and management team, federal staff, contractors and business partners who work so hard to support the technology needs of the NIH community," she said. "They never miss a beat and always do whatever it takes to support the NIH mission with excellence. It has also been a pleasure to work with thousands of individuals from the Office of the Director and the institutes and centers on myriad cross-NIH technology efforts. NIH colleagues are always generous with their time, expertise and support. I will truly miss working with and learning from such smart, talented and dedicated individuals."

Norris looks to plotting out her post-NIH chapter with a bit more leisure.

"Initially I want to take some time to relax a bit, spend more time with my family and be thoughtful about what's next without the pressures of everyday work responsibilities," she concluded.

"I have a three-year-old granddaughter and a new grandson due in March, and I can't wait to have fun with them. Although I am retiring from federal service, I will likely continue to work on initiatives that have meaning and purpose where I can contribute my skills and experiences in new ways. It's what I love doing. And the list of personal goals I want to accomplish keeps getting longer! I'm going to try and make the next 10 years be as special as the last 10 have been for me here at NIH."

ODS Acting Director Betz Retires After 33 Years

BY ANN JAMISON

Dr. Joseph M. Betz retired on Dec. 31, after serving as the Office of Dietary Supplements (ODS) acting director for 4½ years. He worked for 33 years in the federal government—20 at ODS.

Dr. Joseph Betz

Betz joined ODS in 2002 as the first director of the Analytical Methods and Reference Materials (AMRM) Program, where he oversaw several large intra- and extra-governmental initiatives that provided robust, validated analytical methods and reference materials for accurately and reliably measuring the composition of natural products in research, industry and regulatory settings.

In June 2018, he was appointed ODS acting director, guiding staff through:

- elevation of ODS to an office reporting to the director of the NIH Office of the Director's Division of Program Coordination, Planning, and Strategic Initiatives (DPCPSI)
- successful transition to remote work due to the Covid-19 pandemic
- drafting of a new strategic plan and producing ODS's 25th anniversary symposium
- launch of a new dietary supplement research coordinating committee.

"I would like to acknowledge and express my appreciation for the outstanding leadership that Joe has provided to ODS," said Dr. Robert Eisinger, DPCPSI acting director. "We wish him the best of health and happiness as he begins this next phase of his life and career."

Betz during a virtual lecture

An internationally recognized pharmacognosist, Betz is an expert on botanical identification and phytochemistry. In graduate school in the 1980s his doctoral research was on natural product drug discovery.

While in grad school, he also worked with the nascent herbal goods industry to develop analytical methods for ginseng products to distinguish between authentic Panax species and species falsely sold as ginseng.

After earning his doctorate in pharmacognosy, he spent 12 years as a research chemist in the Division of Natural Products at the U.S. Food and Drug Administration (FDA) Center for Food Safety and Applied Nutrition. While at FDA, Betz led a team that worked closely with the Centers for Disease Control and Prevention to identify a dangerous contaminant in L-tryptophan supplements.

In addition, after FDA identified serious adverse events associated with Ephedra supplements, Betz developed analytical methods to be used for enforcement actions on products containing ephedrine. He created and directed FDA's Natural Toxicants in Food Plants Program and expanded the program to include development of analytical methods for bioactive substances in dietary supplements.

Before joining ODS, he was vice president for scientific and technical affairs at the American Herbal Products Association, where he worked to improve industry supply chain transparency and traceability.

When Congress mandated that ODS support collaborative efforts to validate analytical methods and develop reference materials for dietary supplement ingredients, Betz joined ODS to build and manage AMRM.

Betz is an adjunct associate professor in the department of pharmacology and physiology at the Georgetown University School of Medicine. His research has included developing analytical methods for botanical quality and determining bioactive plant secondary metabolites. He's well versed in food law, drug law, dietary supplement regulations and good manufacturing practices.

Betz has authored more than 100 peer-reviewed articles and book chapters, has lectured extensively and has been a member of many expert committees. He is a member of the American Society of Pharmacognosy, a fellow of the Association of Official Analytical Collaboration (AOAC International), past chair of the editorial board for the *Journal of AOAC International* and a member of the U.S. Pharmacopeia's expert committee on dietary supplements. He also serves on expert scientific advisory committees for the governments of Canada and Hong Kong.

Betz earned numerous awards, including the Norman R. Farnsworth Award for Excellence in Botanical Research, the Varro E. Tyler Prize for outstanding scientific contributions to the field of dietary supplements, the Herbal Insight Award for contributions to the botanical sciences, the AOAC International Harvey W. Wiley Award for Excellence and Development of Analytical Methods and the G.H. Neil Towers Award.

He received an Office of the Director Honor Award for contributions toward establishing and developing the ODS Vitamin D Standardization Program.

"We know Joe as a thoughtful and dedicated mentor, and a compassionate leader," concluded ODS colleagues. "He's also a wearer of bowties and a collector of lawn and desktop flamingoes. We're fortunate to have enjoyed working with Joe and have benefited from his leadership for the past 4.5 years."

Betz now serves as an NIH special volunteer and can be located in the global email directory.

Dr. Gerhard Ehrenspeck

Former SRO Ehrenspeck Is Mourned

BY SYED AMIR

Dr. Gerhard Ehrenspeck, 81, retired scientific review officer, Center for Scientific Review (CSR), passed away on Jan. 3 from complications of cancer treatment. He managed CSR's cellular biology and physiology study section before retiring in 2006.

Born in Munich, Germany, Ehrenspeck and his family migrated to the U.S. when he was 12. He earned a Ph.D. in biophysics at Penn State University (1969). After pursuing postdoctoral studies at the Max Planck Institute for Molecular Genetics in West Berlin (1971), and later the Max Planck Institute for Biophysics in Frankfurt, he returned to the U.S. in 1974 to take a fellowship at the Mount Sinai Medical School in New York City. Before coming to NIH in 1988, he had a research and teaching appointment at Case Western Reserve University, Cleveland.

Besides his professional activities, Ehrenspeck had a variety of hobbies. A superb photographer, he took spectacular pictures of natural life subjects—birds, spiders and bees—in their native milieu. He was also an avid collector of toy trains and had set up in his basement a miniature railroad exhibition, complete with tracks, signals and stations. Occasionally, he entertained his friends, giving them a tour of his basement wonderland.

A fluent speaker of German, Ehrenspeck maintained contact with his extended family in Bavaria, and frequently went to visit them. He was also an enthusiastic traveler and had visited countries in South America, Europe and the Middle East, bringing back fascinating pictures and exotic stories about their history and culture. Only the Covid-19 pandemic stymied his travels—something his physical infirmities could not do.

GLOBAL MODEL FOR REGISTRIES

SEER Marks 50 Years of Turning Cancer Data into Discovery

In 1971, the National Cancer Act (NCA) expanded National Cancer Institute (NCI) authority. As a direct result, the newly established National Cancer Program created a data bank to collect, store, analyze and disseminate data that would support research on prevention, diagnosis and treatment.

This marked the birth of the Surveillance, Epidemiology and End Results (SEER) Program, the main strategy NCI uses to support activities that monitor trends in cancer diagnosis and outcomes. Data collection for SEER began in January 1973 with diagnoses in the U.S. and its territories. Geographic area and demographic coverage have expanded over the past 50 years to represent nearly half the U.S. population today.

SEER comprises 18 population-based central cancer registries that submit data to NCI and 10 additional registries providing research support.

A cancer registry is an information system that collects, stores and manages data on all people with cancer who reside within the registry catchment area. Registries are the backbone of surveillance, tracking progress of efforts to reduce the cancer burden. The data are used to plan and evaluate cancer prevention and control efforts nationally and at the state level.

De-identified surveillance data also represent a source to support a broad set of cancer research.

Dr. Lynne Penberthy

"The [SEER] program serves two really important purposes," said Dr. Lynne Penberthy, associate director of NCI's Surveillance Research Program. It "provides population-based estimates on incidence, mortality and survival for cancer in the U.S. and monitors the progress of how we're improving cancer outcomes over time. The second major purpose is to support cancer research through the controlled access to different de-identified SEER data products."

SEER is an authoritative source of information on cancer rates and trends nationwide. It also supports multiple types of cancer-related research by providing information on outcomes to evaluate the effectiveness of new treatments among patients outside the clinical trial setting (in the real world) and providing controlled access to various SEER data that support other types of epidemiologic studies.

More than 17,000 publications have included SEER data as part of their primary analysis. Each year more than 4,500 people download the SEER data file.

Throughout its history, SEER has adapted to the changing needs of the cancer research community. For example, cancer surveillance at NCI has expanded to include evaluating patterns and trends in cancer-related risk factors, health behaviors and health services and their effects on trends in cancer incidence, morbidity, mortality and patient survival.

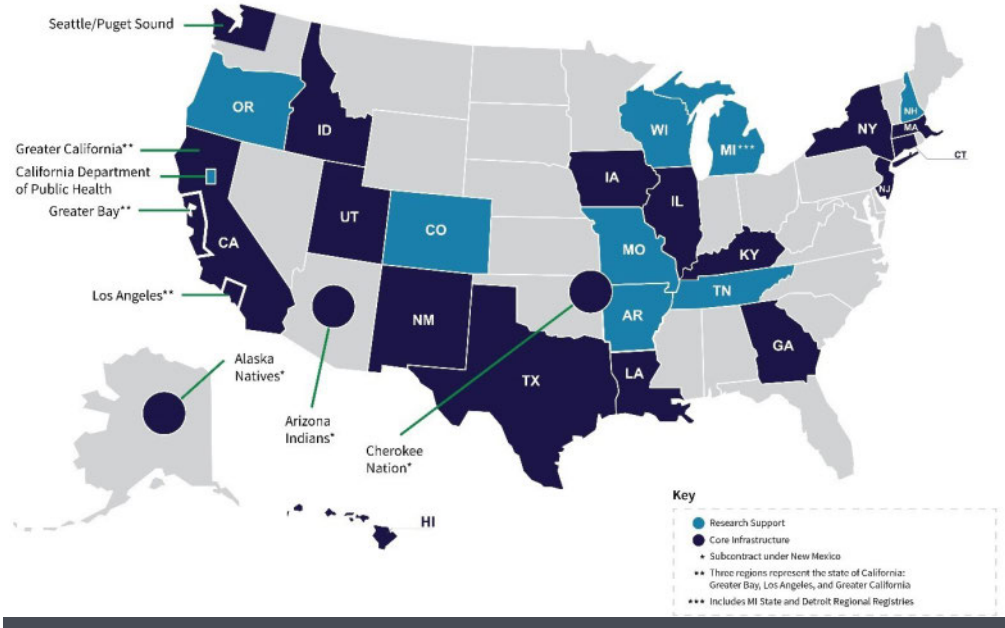
Studies focus on developing and improving methods for cancer-related surveillance research and promoting and facilitating their use among investigators within the extramural community and federal agencies.

Until relatively recently, cancer registrars had to manually enter cancer data into a patient record. Now, patients have electronic health records that require registrars to consolidate information from multiple sources and review it for accuracy.

The SEER Program now works with many health care provider data sources, such as pharmacies and genomic testing laboratories, to enable centralized links to cancer registries, offering comprehensive data with clinical information often not accessible through traditional reporting mechanisms.

And the program has prioritized adjusting to the changing landscape. SEER is moving toward more automation where possible to improve consistency and reduce the delay in cancer reporting.

Given its emphasis on quality control since its inception, longstanding commitment to representing all segments of the population, and recent progress in supporting research advances, the SEER Program provides a model for cancer registries around the world.



SEER began collecting data on cancer cases on January 1, 1973, in the states of Connecticut, Iowa, New Mexico, Utah, and Hawaii and the metropolitan areas of Detroit and San Francisco-Oakland. Since then, the SEER Program has expanded to cover numerous additional areas.