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Author Recounts How Opioids Took Hold in America

BY DANA TALESNIK

In 2012, Sam Quinones, a crime reporter for the *Los Angeles Times*, almost couldn't find a publisher for his book on the opioid epidemic. Overdoses were ravaging communities across America. Yet this addiction to opioids—from prescription painkillers to heroin—that has killed tens of thousands of Americans had long eluded the public's radar.

At first, Quinones couldn't find people to interview. No one wanted to talk.

"One guy told me that all across this country there are thousands and thousands of families, parents going to bed every night crying themselves to sleep, their arms around a photo album," said Quinones, author of *Dreamland: The True Tale of America's Opiate Epidemic,* who spoke at a recent NIDA event in Wilson Hall. "The worst fear they have is people finding out why their loved ones really died. There was a silence."

Quinones, whose presentation took the form of a conversation with Dr. Jack Stein, director of NIDA's Office of Science Policy and Communications, said people were fabricating relatives' obituaries. They were ashamed and didn't want exposure. "If you don't have families on board, the media isn't paying much attention...and politicians aren't really in tune with it," he said.

But eventually people began breaking their silence. "People gained encouragement from each other a little bit and began to realize they were not alone."

Once There Was a Dreamland

When Quinones started writing *Dreamland*, he admittedly knew nothing

SEE **QUINONES**, PAGE 6

Sam Quinones, author of *Dreamland: The True Tale of America's Opiate Epidemic*

SYMPTOM MANAGEMENT

Armstrong Surveys Rare Cancer Patients

BY DANA TALESNIK

NCI's Dr. Terri Armstrong

Getting diagnosed with cancer is a frightening, uncertain experience. Already anxious about their prognosis, patients also must brace themselves for intensive and sometimes lengthy treatment and the potential for serious side effects from therapy and symptoms of the disease. For cancer patients, the overall care they receive is crucial.

SEE **ARMSTRONG**, PAGE 8

'MINUTES TO DIE'

Film Illustrates the Ruin of Snakebite

BY RICH MCMANUS

Filmmaker James Reid

In an effort to draw the world's wavering attention to the problem of snakebite—"the most neglected of the world's neglected tropical diseases"—filmmaker James Reid brought his documentary *Minutes to Die* to Lipsett Amphitheater recently.

Sponsored by NIH's global health interest group, the viewing, a 62-minute version of a longer film, was followed by a

SEE **SNAKEBITE**, PAGE 4

WHO director-general comes to NIH; see p. 7.

ALSO THIS ISSUE

11th Annual Take a Hike Day — June 7

Join the Office of Research Services for the 11th annual Take a Hike Day, a non-competitive fun walk/run on Thursday, June 7, from 11:30 a.m. to 1:30 p.m. in front of Bldg. 1, rain or shine. Activities will begin at 11:30, followed by opening remarks from NIH leadership. The walk/run will start promptly at 12:15. Not on campus? No problem. You can participate in Take a Hike Day at the following off-campus locations: Executive Plaza, Fishers Lane, Rockledge and Shady Grove. To register, visit https://go.usa.gov/xQ4GR.

Lace up your walking shoes. Collect a co-worker or two and take a break from all of the hustle and bustle for a leisurely stroll or jog around the perimeter of the NIH campus (total distance of 3.25 miles). No matter how fast you walk or how far you run, the ultimate goals are to begin or continue a regular habit of physical activity and create a foundation for long-term behavior changes for a healthier lifestyle.

More than 15,500 employees have participated in Take a Hike Day over the past 10 years, so let's continue the tradition. Remember to bring your NIH ID badge to get back on campus at the conclusion of the walk/run.

Through the end of June, NIH is highlighting wellness-supporting events through the "Spring into Wellness" campaign. To learn more about NIH-sponsored events that support your financial, social, career, physical and community well-being, check out the campaign website at https://go.usa.gov/xXsea.

Venter To Speak at NLM Conference

Dr. Craig Venter, founder, chairman and CEO of the J. Craig Venter Institute, will be among the speakers at a conference, "Data Science Innovation at the Intersection of Biomedical Research and the Library," June 13-14 in Lister Hill Auditorium, Bldg. 38A. The event is cosponsored by the National Library of Medicine and the Friends of the NLM.

The conference will bring together key stakeholders including researchers, government, industry, publishers and health care consumer representatives, to provide a forum for presentations and discussions around supporting data sharing, the changing role of journals and peer review, use of "FAIR" (findable, accessible, interoperable and reusable) data sets, trends in mining big data to yield knowledge, opportunities for trans-NIH data science activities and more. The constructive and practical outcomes will benefit producers as well as users of scientific discoveries.

Rep. Raskin Tours Clinical Center

Rep. Jamie Raskin (D-MD) visited NIH on Apr. 6, meeting with agency leadership for an overview of clinical trials participation and taking a tour of the Clinical Center. Above at left, he meets NIH director Dr. Francis Collins and at right takes in the hospital atrium with Dr. James Gilman, CEO of the CC. His tour included a stop at the NIDCD Audiology Clinic (right), where research audiologist Dr. Chris Zalewski gave a presentation. Also orienting him to NIH was NIH principal deputy director Dr. Lawrence Tabak.

PHOTOS: MARLEEN VAN DEN NESTE

Register at fnlm.org. The full speaker list can be found at http://hosted.verticalresponse.com/842329/e799571d63/1573012165/7cb269a6c9/.

Webinar on Assessing Impact of Public Health Laws, May 22

Join the NIH Office of Disease Prevention for a Mind the Gap webinar with Dr. Jamie Chriqui on design and analysis considerations for assessing the implementation and impact of obesity and tobacco-related law and policy on communities, organizations and individuals. The webinar will start at 11 a.m. on Tuesday, May 22.

Dr. Jamie Chriqui

Chriqui is professor of health policy and administration and co-director of the Health Policy Center in the Institute for Health Research and Policy in the School of Public Health at the University of Illinois at Chicago. She has more than 27 years of experience conducting public health policy research, evaluation and analysis. She is considered a national expert on evaluating laws and policies on communities, systems and population health with an emphasis on chronic disease issues including obesity, substance abuse and tobacco control.

Chriqui will accept questions during the webinar via WebEx and Twitter. Use #NIHMtG.

Registration is required and can be done at https://nih.webex.com/nih/onstage/g.php?MTID=efa86469e4da43bd6790545b3e6ccfb1d.

'All of Us' Begins Nationwide Enrollment

Exactly 2 months shy of the second anniversary of its founding on July 6, 2016, the All of Us Research Program (formerly known as the Precision Medicine Initiative Cohort Program) opened enrollment nationwide on May 6. The event was marked by community events in seven cities across the country.

The program intends to partner with 1 million or more people across the United States who will share information over time to help build the world's largest and most diverse data resources for health research. Initially, enrollees will have to be 18 or older, but the program hopes to begin accepting children in summer 2019.

"This might have seemed like a pipe dream 15 years ago, but today it is a reality," said NIH director Dr. Francis Collins at a May 1 media telebriefing. He called All of Us a historic, unprecedented and unique program that will last at least a decade if not longer.

"This will be a massive public resource," he said. "It is among the most ambitious research efforts our nation has ever undertaken...The possibilities are pretty limitless."

Eric Dishman, director of All of Us, said the program "is incredibly personal to me." Diagnosed with a rare kidney cancer, he underwent 23 years of treatment and endured 57 rounds of "imprecise medicine" before benefiting from cutting-edge therapy. "It ought to be personal to you, too."

He expects the program will reach its goal of 1 million participant/partners in 5-6 years, "but if 10 million sign up on May 6, we'd be very happy."

Researchers of all kinds, including citizen scientists, will be able to request access to All of Us information to conduct studies to inform how individual differences affect health and disease. The research portal is expected to open in 2019, Dishman said.

"We won't wait until the end of the study to make data available—we want to let thousands of flowers bloom." Findings from these studies may lead to more tailored health care approaches in the future.

Enrollees may provide physical measurements including blood pressure, body mass index, heart rate, height, hip circumference, waist circumference and weight. Biosamples to be collected include blood (or saliva if blood draw is unsuccessful) and urine.

In the past 2 years, All of Us has reached the following milestones:

• Version 1 protocol tested and Institutional Review Board-approved; a beta phase is already well under way

• Built network of 100+ academic, provider, technology and community partners

• Established partnerships with 25 community, provider, advocacy organizations and the National Library of Medicine to help educate and engage diverse populations

• Developed participant-friendly and bilingual (English and Spanish) enrollment website, participant portal and call center

• Constructed biobank building/robotic capability with 24-hour shipping process; currently storing more than 800,000 frozen vials with capacity for more than 35 million vials

• Developed data warehouse with infrastructure to collect, clean, curate, de-identify and eventually share the data

• Completed end-to-end security & usability testing; obtained Authority to Operate

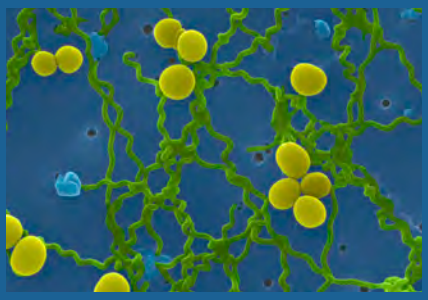
• Developed innovative pilots for testing EHR (electronic health record) & wearables strategies (Fitbit pilot)

• Launched 129 clinics across the country to begin enrolling participants, with "pop-up" clinics planned for distant areas

• Already, more than 45,000 participants started protocol; more than 27,000 completed all available protocol.

Those interested in joining the program can do so by visiting, www.JoinAllofUs.org.

The All of Us Research Program aims to engage a diverse community of participants, especially those who have been underrepresented in research in the past. "We know that the research transgressions of the past have made some people skeptical, but we can and we will do better," said Dr. Dara Richardson-Heron, the program's chief engagement officer.



ON THE COVER: Leptospira *(shown in green) is a type (genus) of elongated, spiral-shaped bacteria. Infection can cause Weil's disease, a kind of jaundice, in humans*
IMAGE: TINA CARVALHO, UNIVERSITY OF HAWAII, MANOA (FUNDED BY NIGMS)

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Snakebite

CONTINUED FROM PAGE 1

panel discussion with Reid and Dr. Claire Komives, a professor at San Jose State University. She is working on a "tiny ribosomal peptide" harvested from opossum serum that broadly neutralizes snake venom. Opossums are naturally immune from most American snake venoms, which are toxic stews relying primarily on metalloproteases to do their damage.

Scale of Problem

Five million people a year are bitten by snakes, mainly in the tropics, and hundreds die daily. Snakebite kills 125,000 people a year—the entire population of Topeka, Kan., or Bern, Switzerland, for example—and often imposes economic ruin on victims and their families, whether or not they survive. As many as 2 to 3 times that number are maimed, disfigured or suffer amputation due to snakebite. According to the film, as many people die from bites in a month as died during the 26 months of the last African Ebola crisis.

"It is the world's most ignored way to die, and it will continue until the world takes notice," says film narrator Mike Rowe, known to local audiences for his TV ad work and as host of the Discovery Channel's *Dirty Jobs* and CNN's *Somebody's Gotta Do It*. "It's a fixable problem—the solution is not complicated."

Back in 2009, snakebite made the World Health Organization's neglected tropical diseases (NTD) list, but it was removed shortly thereafter, said Reid. It recently was restored to the list, making it eligible for research funds from WHO-sponsored donors.

The vast majority of those bitten by snakes go to traditional healers and medicine men in their villages—that's the only available health care, in many cases. But that only delays effective medical care, which can sometimes be days away by foot or vehicle. Victims are usually impoverished farmers or herdsmen; city dwellers in many affected countries "are genuinely ignorant of their plight," according to the film.

In the tropics, snakebite is more feared than tuberculosis, malaria and HIV/AIDS, the film maintains. Even tsunamis are considered less of a threat. Yet snakes do offer a service—they keep rodents from destroying farms.

Anti-venom is effective, if administered in time, but drug companies find it unprofitable to manufacture and stores of it are depleted in rural Africa and India, where the need is greatest.

Snake venoms fall into one of three categories: hemotoxins, which cause uncontrolled bleeding; neurotoxins, which paralyze breathing; and cytotoxins, which destroy tissue. There is no universal anti-venom.

From 1894 until the present, the standard way to obtain anti-venom has been to inoculate horses with venom, wait a time for antibodies to develop, then draw plasma from the animals, from which antibodies are purified. It is a labor-intensive undertaking and causes pain to the horses, but it works.

Yet in India, where some 46,000 people die from snakebite yearly, the ministry of health believes only about 1,300 people are killed, hence stores of anti-venom are low. "The central government doesn't want to admit the magnitude of the problem," said Reid.

According to one African physician in the film, snakebite doesn't get the financial resources that malaria, TB and AIDS get—treatments for those diseases are often free.

Help from Unexpected Quarters

The last half of the film, which Reid made for the Lillian Lincoln Foundation, offered hope from some unexpected quarters. Researchers at Liverpool School of Tropical Medicine are working to create a single therapy for the 21 species of venomous snakes in Africa. The University of Costa Rica is a world leader in the production of anti-venom; researchers there consider its availability a human right.

Said one, "For us it is not an economic decision...We're using science for what it should be used for—helping people."

At Port Moresby General Hospital in Papua New Guinea, a model effort to develop affordable therapies against bites by the Taipan snake—common in the Pacific islands—is expected to deliver a product in 2019.

"If it can work in resource-poor Papua New Guinea, it can work anywhere in the world," said one researcher.

Other solutions to the problem of snakebite include improvements in transportation to rural hospitals, since the time that elapses between bite and therapy is so crucial. A single ambulance truck outfitted with ventilators, monitors and the capability to perform roadside intubation can save 60-100 people yearly who would otherwise die, but it costs about $300,000.

Another way to build a bridge to survival is to create a field antidote that can slow venom's effects for long enough to allow a victim to reach care. The compound varespladib (also known as LY315920), originally developed for heart disease, has been tested at Yale University, where it outperformed 400 other agents. Crucially, it can be taken

After the film, director Reid and Dr. Claire Komives of San Jose State University took questions from the audience on issues raised by *Minutes to Die*.

PHOTOS: MARLEEN VAN DEN NESTE

orally and needs no refrigeration.

Researchers tested varespladib, which Komives described as a phospholipase A2 inhibitor, on mice and found that, against 35 venoms from 6 continents, it proved effective in 28 of them.

Komives is working on a "tiny ribosomal peptide" harvested from opossum serum that broadly neutralizes snake venom.

"It delays the death of the mice, so in people it should give them time to get to the hospital," she said. It could be delivered in pill form, an epi-pen or maybe even as a liquid, like cough syrup. "But it's only buying you time. My fear is that people will think they're fine. They still need to go to the hospital for anti-venom."

Komives has a strategy in mind that would capitalize on the opossum, whose serum contains immunoglobulin-like proteins that protect against snake venom. "I believe there is a way it could be done," she said, and for as little as 6 cents a dose to produce.

There are also global education campaigns, ramped up during monsoon season, when bites are most common. People are urged to wear shoes and trousers, which can prevent bites, and to lay victims on their sides in ambulances, so that they don't choke on a paralyzed tongue.

'No Excuses Anymore'

There are no excuses anymore, the film concludes. "We've got the science, the technology and the heart...We just need investments in countries. Ministers of health and governments must make it a priority, so the WHO can direct donor help."

Minutes to Die has screened some 50-60 times throughout the world, in 4 languages, said Reid during a Q&A session after the movie. He said the WHO, which restored snakebite to the NTD list in 2017 after an 8-year absence, will release in May a roadmap report detailing, country-by-country, the game plan against snakebite.

"I can just see the snowball getting bigger," he said.

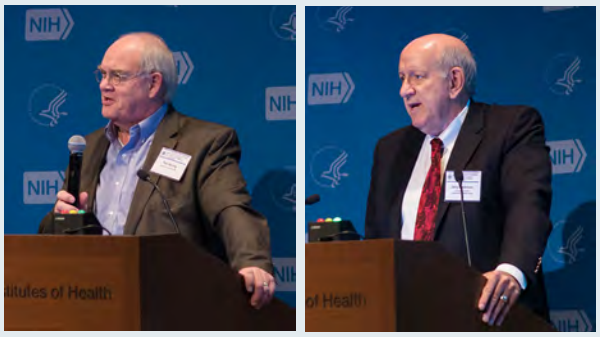
For more information on the issue, visit www.minutestodie.com. R

MORE TO COME

NEI 50th Anniversary Events

NEI recently hosted "Vision and Immunology: Partners in an Ambiguous Relationship," the second in a series of day-long symposia honoring the institute's 50th anniversary.

"The immune system is pretty remarkable. It keeps us going every day despite all the environmental threats, etc., that we face," said NEI director Dr. Paul Sieving. But in the eye, where the immune system can easily wreak havoc on vision, a tightly balanced control of immune cells makes for a dance between factors that protect against pathogens and factors that protect against inflammation.



NEI director Dr. Paul Sieving (l) and Dr. Jerry Niederkorn, University of Texas Southwestern Medical Center

"Immune privilege—there are two sides to that sword," said Dr. Jerry Niederkorn of the University of Texas Southwestern Medical Center. Ordinarily, the eye keeps a tight lid on the immune system, dampening the activity of immune cells that enter it. This makes the eye, like the brain, an immune-privileged site, which is crucial because inflammation in the eye (uveitis) can damage the eye's light-sensitive retina and affect vision. Immune privilege also enables transplantation of tissues like the cornea with low risk of immune rejection.

But immune function, the sword's other edge, is still needed to fight off viral and bacterial infections. Several speakers discussed potential ways to help clear infections while preventing damage to the eye. Others addressed transplantation, autoimmunity, age-related macular degeneration and genetic disorders that affect the eye.

Upcoming NEI 50th anniversary symposia on campus include Low Vision and Vision Rehabilitation, June 29 and Future of Vision Research, Oct 18.

NEI on Capitol Hill

NIH staff joined members of Congress and research leaders at another recent event on Capitol Hill recognizing NEI's progress over the past 50 years in understanding vision and preventing and treating eye disease. The Alliance for Eye and Vision Research hosted the event.

Due in large part to clinical trials funded by NEI, the incidence of severe vision loss from diabetic retinopathy has decreased by 90 percent, said Sieving. Today, NEI is at the forefront of regenerative medicine, he said, citing the NEI Audacious Goals Initiative, which supports research to image the visual system and identify biological factors that allow retinal neurons to regenerate.

NIH director Dr. Francis Collins addresses the group while Rep. Pete Sessions looks on. At right, Dr. Rachel Caspi, chief, NEI Laboratory of Immunology, organized a symposium.

NIH director Dr. Francis Collins reflected on the contributions vision research has made to the rest of medicine: "NEI-supported researchers have led the way in advancing common disease genetics and gene and stem cell therapies." And this year, an NEI team is poised to launch the first U.S. clinical trial of tissues derived from induced pluripotent stem cells, he noted. The stem cell therapy aims to replace diseased cells of the retina to treat age-related macular degeneration.

Rep. Pete Sessions (R-TX), a steadfast advocate for publicly funded vision research, noted that cutting-edge research funded by NEI helped lead to the first FDA-approved gene therapy for an eye disease. Visit the NEI web site for more information about 50th anniversary events and activities at https://nei.nih.gov/neiat50.

Quinones says he's more comfortable talking to prisoners than politicians.

PHOTOS: LISA HELFERT

Quinones

CONTINUED FROM PAGE 1

about addiction or pain management, but he'd been reporting extensively on Mexican drug trafficking. Why, he wondered, are Mexican heroin traffickers doing such big business in America?

As Quinones discussed his research, coincidentally, NIH director Dr. Francis Collins was launching the administration's opioid initiative in Ohio, the state where this story unfolds.

Dreamland was a huge community pool in Portsmouth, Ohio. Generations of families regularly hung out there; it was the soul of this bustling town. But in the 1980s, economic hardship set in; factories closed and half the population left. Dreamland had been "this essential thing that kept people in a community," said Quinones. In 1993, it closed.

"Dreamland became a metaphor for America," he said. "Nobody goes outside [anymore]. Everyone becomes cloistered indoors."

Gateway to a Crisis

As the economy declined, doctors in Portsmouth were dispensing oxycodone and other prescription painkillers like candy, without warning of possible addiction. As people got hooked and couldn't get more or enough, they started turning to heroin, an opiate derivative, for their fix.

"The problem starts with very potent legal drugs," Quinones said. "If you unleash a powerful new legal supply of drugs on the population, the consequences will be pretty scary and certainly unpredictable."

A decade ago, Quinones first heard stories of people in Huntington, W.Va., switching from pain pills to a type of potent, cheap heroin and dying in large numbers. He started investigating how this black-tar heroin, which is only made in Mexico in this hemisphere, arrived in lethal quantities in a state east of the Mississippi where few Mexicans lived.

Quinones learned that, in the small town of Xalisco, Mexico, drug traffickers developed a refined system to sell black-tar heroin across the United States. He likened it to a pizza delivery service: convenient, regular delivery to satisfy the cravings of addicts, who had a customer service number they could call to order more. Quinones began to unravel the pain connection and discovered that the problem was endemic, from Rust Belt states to rich suburbs.

Prescription painkillers were cheap, available and initially underused, said Quinones. Some published research suggested narcotics were nonaddictive in supervised amounts, and the problem spiraled from there. "Patients were demanding to be fixed," he said. "The easy answer is pills for everybody in large amounts over a long period of time."

The opioid crisis grew from over-prescription and excess availability of legal opioids in this country. "Demand doesn't come from Mafia or street peddlers," he said. "It comes from doctors being pressured and pushed...they unleash collectively a supply of pain pills on this country that's astounding and continues to be; prescribing is dropping, but it's still outrageously high."

In January, Quinones testified about the opioid crisis before the Senate. "It was the most surreal moment of my life," he said. "I'm a crime reporter; I don't function well in the halls of power. I prefer to talk to folks in prison."

For his book, Quinones interviewed

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"Heroin is scary as hell. It's a national catastrophe, but there's also within it the seeds of enormous opportunity and rebirth."

–SAM QUINONES

• • •

Set in Bldg. 1's Wilson Hall, Quinones's presentation took the form of a conversation with Dr. Jack Stein (l), director of NIDA's Office of Science Policy and Communications.

imprisoned traffickers, addicts and their families, prosecutors, drug enforcement agents, pain specialists, doctors and rehab counselors. To lure readers, he structured the book like a compelling television series such as *The Wire* or *Breaking Bad*, he said, treating each short chapter like a scene.

There are multiple themes, but they all circle back to the sense of community that existed at Dreamland. "It was not just pharmaceutical marketing, not just Mexican trafficking," said Quinones. "It was our own increasing isolation and the crushing destruction of entities that'd really brought us together as Americans. This became easily the main theme of the book."

Toward a Solution: More Cuddling?

A group of neonatal nurses in a New Hampshire hospital once told Quinones that drug-addicted newborns need, above all, cuddling.

"Those little babies are showing us the fundamentals of this whole problem," he said. "They're all alone; they don't want to feel alone, so you have cuddlers rocking them to sleep." Addicts need a variety of services, but they also need to feel part of a community.

"We have a way forward," he said, "working against that very pernicious, corrosive tendency toward isolation in our culture."

Quinones advocates expanding addiction research across the Ohio Valley and involving more recovering addicts in research. Many are eager to help solve the problem, he said.

"Heroin is scary as hell. It's a national catastrophe," said Quinones, "but there's also within it the seeds of enormous opportunity and rebirth." To dig out of the opioid crisis will require massive grants and loans, he said, on par with the Marshall Plan that helped rebuild postwar Europe.

Anyone can get involved in helping end the isolation that breeds addiction. Join a community task force, for example, recommended Quinones. Our personal consumer decisions also matter.

"It's incumbent on all of us," he said, "to be accountable for our own wellness and, therefore, when we are [well], whatever decisions the pharmaceutical companies want to make about what to market to us will have far less importance and power." R

Dr. Tedros Adhanom Ghebreysus (at center of table on left), director-general of the World Health Organization, visits NIH on Apr. 20, when he met NIH leadership at Stone House.

WHO Director-General 'Tedros' Visits NIH

Dr. Tedros Adhanom Ghebreysus, director-general of the World Health Organization, visited NIH on Apr. 20, when he met NIH leadership at Stone House. Known widely as Tedros, he participated in a group discussion (above) with NIH senior leadership and the institute and center directors. Later, in the Stone House library, he signed a memorandum of understanding between NIAID and WHO to enhance future collaborations on research activities conducted in response to emerging infectious disease outbreaks and public health emergencies. The MOU includes the intent to establish an NIAID-WHO Collaborating Center for Emerging Infectious Disease Response Research and Preparedness.

Above, Tedros and NIAID director Dr. Anthony Fauci sign the document. Below, Tedros chats with NIH director Dr. Francis Collins (l) and Fogarty International Center director Dr. Roger Glass.

PHOTOS: CHIA-CHI CHARLIE CHANG

NCI's Armstrong gives CCR Grands Rounds; below, she chats with attendees.
PHOTOS: CHIA-CHI CHARLIE CHANG

Armstrong

CONTINUED FROM PAGE 1

"Sometimes it's the journey that tells you more about that experience with cancer than the actual diagnosis does," said Dr. Terri Armstrong, senior investigator in NCI's Neuro-Oncology Branch (NOB), at the Center for Cancer Research Grand Rounds held recently in Lipsett Amphitheater.

Armstrong's research focuses on predicting and managing symptoms better, an interest she developed early in her career while observing patients experience significant symptoms from the cancer itself, compounded by those associated with treatment such as nausea, vomiting, diarrhea and fevers.

"Every day, I saw the impact of both the disease and the treatment on the patients we were caring for," said Armstrong. Some of those patients were close relatives.

While Armstrong was in college, her mother was diagnosed with cancer. Soon after, her grandmother, great-grandmother and two maternal aunts were in the same fix.

"I lost some of the most important women in my life during that time and that truly influenced my perspective," Armstrong said.

Over the years, she has learned the importance of letting patients define their own reality and what life quality means to them. Doctors should weigh in, she said, but ultimately the patients' wishes and goals should guide treatment.

Armstrong primarily works with people who have central nervous system (CNS) tumors. This type of cancer is rare, about 2 percent of all cancers, but most of these patients have a poor prognosis.

Some 700,000 Americans are currently living with a primary CNS tumor. From the time of diagnosis, the majority are unable to work and, during the course of the illness, half of them have as many as 10 current symptoms at any one time; 40 percent report at least 3 ongoing symptoms they described as moderate to severe in intensity. One large patient sample showed that CNS tumor patients have stress, fatigue and sleep disturbances at the same level as patients having other high-risk cancers.

"The symptom burden has an impact on functional status, disease progression and survival," said Armstrong.

There is increasing recognition in those providing care and in the drug approval process that understanding how a treatment affects how a patient feels or functions is an important consideration when evaluating its effect.

Quality of life is also important, but some patients had reported their quality of life as being very good, despite their serious symptoms. Armstrong said she then realized that many factors, beyond biological ones, influence a patient's quality of life, including family support, social interactions, financial situation and emotional well-being. This led to her focus on symptoms, which may be a closer surrogate of the impact of the disease and treatment.

To gauge symptoms and their effect on daily life, she developed a short, simple questionnaire that, along with neuropsychological testing, has been adopted by many brain tumor clinical trials.

In a phase 2 clinical study, the drugs lapatinib and temozolomide (TMZ) were given to highly symptomatic patients with recurrent ependymoma tumors. Most patients on this treatment had stable disease on imaging, while their weakness, pain and numbness significantly lessened. Armstrong said the trial showed the prospects of controlling tumor growth while ameliorating patients' symptoms.

To reach even more patients with rare CNS tumors, Armstrong and her colleagues started a web-based study to reach patients where they live and not be dependent on them being seen in a specific hospital. Armstrong led the ependymoma outcomes project for the CERN (Collaborative Ependymoma Research Network) Foundation to help share information and improve care among rare tumor populations. This work also included collecting clinically annotated tumor samples to learn more about the predictors of survival and outcome in patients with ependymoma.

The investigators published one of the largest studies exploring survival outcomes, important preliminary work that, along with seminal work by other researchers, has led to the identification of subtypes of ependymoma.

Armstrong is now partnering with other researchers, including Drs. Michael Scheurer

and Cari Kitihara, collecting germline DNA and environmental exposure history to explore why people develop this rare cancer.

Meanwhile, Armstrong leads NOB's natural history study, enrolling all CNS tumor patients undergoing longitudinal follow-up at NIH. In just over a year, the program has enrolled at least 340 patients and will continue gathering clinical outcomes, molecular tumor analyses and other relevant data.

Armstrong also aims to better predict symptom risk. Current symptom management, she said, involves reducing doses or stopping treatment, or providing prophylaxis to all patients receiving treatment or waiting for symptoms to occur and trying to mitigate them.

"What if instead we can understand who is at predisposed risk of developing the toxicity and target that or not expose patients at undue risk to that agent?" Armstrong asked. "Or, if we understand the biological process, then we target that process, and perhaps we can keep the symptom or toxicity from occurring altogether."

The most common therapies for primary brain tumors are radiation and TMZ chemotherapy. A significant symptom with TMZ is myelosuppression, which dampens the immune system. One study found women at heightened risk for toxicity with TMZ.

In a second study, 80 percent of patients reported fatigue and hypersomnia during cranial radiation therapy. The team found two genes associated with inflammation and the circadian clock—BMAL and PER2—that may be inducing fatigue in brain tumor patients, said Armstrong.

Studying the biological basis of symptoms will allow doctors to change approaches to prevent symptoms in at-risk patients and increase therapies in those not at risk.

It's also important to remember, said Armstrong, to remain optimistic, because there are novel treatments and patients who beat the odds. One such patient, after learning he had 6 months to live, enrolled in a clinical trial and is alive and well more than 20 years later.

"Statistics are just statistics and they mean almost nothing for our individual patients," said Armstrong. "They provide a framework, but none of us know what the future will be."

13-lined ground squirrel

PHOTO: NEI

'Hibernation in a Dish'

Researchers at NEI have discovered cellular mechanisms that help the 13-lined ground squirrel survive hibernation. Their findings could be a step to extending storage of human donor tissues awaiting transplantation and protecting traumatic brain injury patients who undergo induced hypothermia. The findings were published in the May 3 issue of *Cell*.

During hibernation, the 13-lined ground squirrel endures near freezing temperatures, dramatically slowing its heart rate and respiration. How the squirrel's tissues adapt to the cold and metabolic stress has confounded researchers.

A structure in cells known to be vulnerable to cold is the microtubule cytoskeleton. This network of small tubes within a cell provides structural support and acts as a kind of inner cellular railway system, transporting organelles and molecular complexes vital for a cell's survival.

In a series of experiments, the research team led by Dr. Wei Li, a senior investigator in the NEI retinal neurophysiology section, and Dr. Jingxing Ou, a postdoctoral scientist in Li's lab, compared cells from non-hibernators to cells from the ground squirrel to determine differences in their response to cold. They found that in ground squirrel neurons, the microtubule cytoskeleton remains intact while it deteriorates in the neurons of humans and other non-hibernating animals, including rats.

To investigate the biological factors supporting the squirrel's cold adaptation, researchers created "hibernation in a dish." They took cells from a newborn ground squirrel and reprogrammed them to become stem cells, which are undifferentiated cells capable of becoming any type of tissue in the body.

Importantly, these lab-made cells, also known as induced pluripotent stem cells, retained the intrinsic cold-adaptive characteristics of the adult squirrel's cells, thus providing a type of platform for studying how various kinds of the rodent's cells adapt to the cold.

ALS Researchers Recreate Human Spinal Cords on a Chip

Aided by advanced stem cell technology and tissue chips, NIH-funded researchers used stem cells originally derived from a person's skin to recreate interactions between blood vessels and neurons that may occur early in the formation of the fetal human spinal cord. The results published in the Apr. 10 *Stem Cell Reports* suggest that the system can mimic critical parts of the human nervous system, raising the possibility that it may one day be used to test personalized treatments of neurological disorders.

The research was funded in part by NCATS and NINDS.

Led by Dr. Samuel Sances and Dr. Clive Svendsen, both of Cedars-Sinai Board of Governors Regenerative Medicine Institute in Los Angeles, the researchers first converted the stem cells into newborn spinal cord neurons or epithelial cells that line walls of brain blood vessels.

In most experiments, each cell type was then injected into one of two chambers embedded side-by-side in thumb-sized, plastic tissue chips and allowed to grow. Six days after injections, the researchers found that the growing neurons exclusively filled their chambers while the growing blood vessel cells not only lined their chamber in a cobblestone pattern reminiscent of vessels in the body, but also snuck through the perforations in the chamber walls and contacted the neurons. This appeared to enhance maturation of both cell types, causing the neurons to fire more often and both cell types to be marked by some gene activity found in fetal spinal cord cells.

Bacteria Therapy for Eczema?

Topical treatment with live *Roseomonas mucosa*—a bacterium naturally present on the skin—was safe for adults and children with atopic dermatitis (eczema) and was associated with reduced disease severity, according to initial findings from an ongoing early-phase clinical trial at NIH. Preclinical work in a mouse model of atopic dermatitis had suggested that *R. mucosa* strains collected from healthy skin can relieve disease symptoms. The new findings, published May 3 in *JCI Insight*, support further evaluation of this potential new therapy.

Atopic dermatitis is an inflammatory skin disease that can make skin dry and itchy, cause rashes and lead to skin infections.

"Living with atopic dermatitis can be physically and emotionally challenging," said Dr. Anthony Fauci, director of NIAID. "While treatment can help manage the symptoms, currently available therapies can be time-consuming—requiring multiple daily applications—and costly. New, inexpensive therapies that require less frequent application are needed to expand the options available for atopic dermatitis treatment."

Have a question about some aspect of working at NIH? You can post anonymous queries at https://nihrecord.nih.gov/ (click on the Feedback tab) and we'll try to provide answers.

Feedback: What is the status of the construction project at Center and Wilson Drives? It seems as though the big machinery never moves.

Response from the Office of Research Facilities: The major construction project you reference, to upgrade utility infrastructure, is scheduled to be completed the first week of July. However, the site will begin to visually change by the end of May as the hole will be backfilled with soil and most of the heavy equipment will be moved offsite. The sidewalk, curb and gutter, and asphalt will be rebuilt in late June and sod and other landscaping will be completed by the last week of June. By the second week of July, the roadway and surrounding area should return to normal operations.

Shown from Bldg. 31A with Bldg. 2 at right, the utility infrastructure upgrade going on at the intersection of Center and Wilson Drives is nearly complete. Road and sidewalk repairs as well as landscaping are all planned for early summer.

Snyder Retires from OER

BY ERIC BOCK

Dr. Margaret Snyder retired Mar. 30 from NIH's Office of Extramural Research, where she was Freedom of Information Act coordinator, senior advisor to the deputy director, animal research advisory committee member and privacy coordinator.

"NIH is a marvelous place," she said. "It was a privilege and honor to have worked here."

In her position, she advised or drafted responses to public inquiries and official correspondence. Snyder described her job as a "diverse smorgasbord of interesting and challenging activities." She was also the "bingo baroness" at OER employee picnics, calling out numbers in bingo games.

After obtaining her doctoral degree, Snyder became an academic counselor for first-year students interested in majoring in pre-veterinary science at Ohio State University. She's also worked at Ohio State's research foundation, a zoo and a non-profit foundation.

Snyder had applied to work at NIH

Dr. Margaret Snyder retired Mar. 30.

PHOTO: CHIA-CHI CHARLIE CHANG

At left, recent awardee Dr. George Giacoia; at right, on hand at a recent meeting of the Association of American Physicians are (from l) Dr. Darryl Zeldin, NIEHS scientific director; Dr. Stephen Chanock, director of NCI's Division of Cancer Epidemiology and Genetics; Dr. Hannah Valantine, chief officer for scientific workforce diversity; Dr. Luigi Ferrucci, NIA scientific director; and NICHD's Dr. Constantine Stratakis. Valantine, Ferrucci and Stratakis were elected to the association.

NICHD Scientists Receive Honors

Two NICHD scientists have received distinguished honors. Dr. Constantine Stratakis, NICHD's scientific director, was elected recently to the Association of American Physicians. Leader of the Division of Intramural Research and its section on genetics and endocrinology, he has identified genetic causes of several adrenal disorders, including Cushing syndrome.

In addition, Dr. George Giacoia, a medical officer at NICHD, received the 2018 Sumner J. Yaffe Lifetime Achievement Award in Pediatric Pharmacology and Therapeutics from the Pediatric Pharmacy Association. The award is given annually in recognition of significant contributions toward the improvement of children's health through pediatric pharmacology and therapeutics.

Giacoia has developed numerous programs during his 20-year career at NIH, most notably the U.S. Pediatric Therapeutics Initiative under the Best Pharmaceuticals for Children Act, which aims to prioritize therapeutic areas and advance clinical trials of on- and off-patent drugs that need further study in children.

three times. Her first two applications were unsuccessful. However, the third time was the charm. Her experience between applications prepared her for her eventual position at NIH.

"I wasn't ready and wasn't seasoned enough," Snyder said. "Sometimes, rejection is a good thing."

On Friday, Aug. 13, 2001, she and her husband packed up their car and a trailer and drove to Bethesda. Although the date was ominous, "There was no bad luck associated" with the move, she said.

Snyder had regularly given blood to the American Red Cross. Shortly after she began at NIH, the NIH Blood Bank emailed employees, in desperate need of donors. She decided to donate because, "How do you say no when you feel somebody's life depended on your donation?"

On her first visit to the bank, she saw a monitor featuring photos of donors who have given at least 100 times. She thought to herself, "Boy, that's commendable. I'll never do that." Back then, Snyder rarely—if ever—saw a woman's photograph among the rotating images.

One donation led to another. And "the next thing you know I was counting down the number of donations to 100." She wasn't sure if she'd make it before she retired.

"I got 102 donations going out the door," she said. "I'm pleased and proud that I donated blood."

Although Snyder won't be giving at NIH anymore, she'll continue to give elsewhere—"It doesn't cost but a little time for such a valuable donation."

Snyder said her 17 years at NIH have given her wonderful memories, including working on committees with some of the top scientists in the world from NIH's intramural community and getting to know a few of them.

"I am proud to have worked with the administrators and staff of many scientific programs, Freedom of Information offices and various offices within OER," she said. "The NIH community is truly committed and dedicated to our mission."

Varmus Portrait Unveiled at FNIH Ceremony

A portrait of Dr. Harold Varmus was unveiled Apr. 26 in recognition of his service as director of the National Cancer Institute from 2010 to 2015. It joins a gallery of former NCI directors displayed on the 11th floor of Bldg. 31. The collection dates back to the first NCI director; portraits of all 14 former directors mark the leadership of cancer research efforts in the United States. Artist Jon Friedman, who has painted Varmus several times, including his NIH director portrait in Bldg. 1, was on hand for the ceremony at the Cloister. The portrait was commissioned by the Foundation for the National Institutes of Health, which also hosted the event. On hand for the ceremony were (above, from l) current NCI director Dr. Ned Sharpless, FNIH president and executive director Dr. Maria Freire, Varmus and Dr. Doug Lowy, NCI deputy director. At left, Varmus enjoys remarks at the occasion.

PHOTOS: CHIA-CHI CHARLIE CHANG

Healthy Volunteers Needed

NIAID researchers seek healthy volunteers, 18-60 years old, for a study at the Clinical Center to examine safety and tolerability of an investigational product targeting Ebola. You cannot get Ebola from this product. Financial compensation is provided. For more information, call 1-866-444-2214 (TTY 1-866-411-1010). Read more at https://clinicaltrials.gov/ct2/show/NCT03478891.

People with Anxiety Sought

NIMH is studying people with anxiety and how they respond to stressful events. Researchers are seeking those with general anxiety, panic and/or social anxiety disorder. Study requires 1 to 2 outpatient visits to the Clinical Center. Compensation will be provided. For more information, call 1-866-444-2214 (TTY 1-866-411-1010) and refer to study 03-M-0093.

Vaccine Study Seeks Healthy Vols

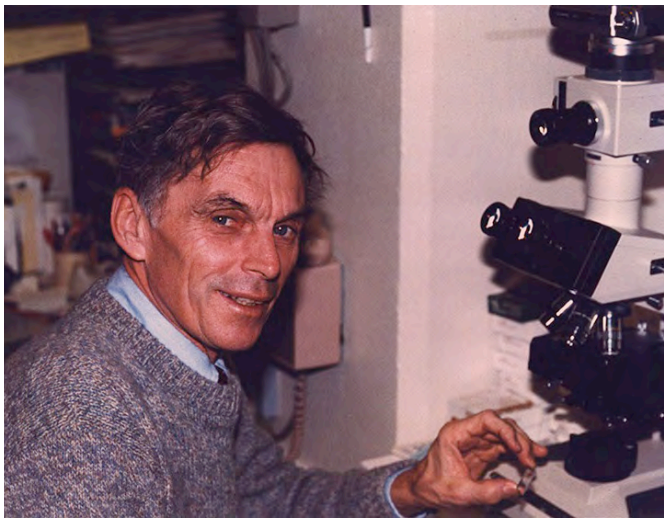
Researchers at NIAID's Vaccine Research Center need healthy volunteers 18-60 who are living with HIV for a research study. The study evaluates an investigational product targeting the HIV virus to determine if it is safe and can generate an immune response. Compensation is provided. For more information call the Office of Patient Recruitment at 1-866-444-2214 (TTY 1-866-411-1010) or email vaccines@nih.gov. Se habla español. Refer to study 18-I-0030.

Stress Study Recruits Volunteers

NIMH is studying how the brain and body respond to stressful events. Researchers are seeking healthy volunteers without mental health disorders. Study requires four outpatient visits to the Clinical Center. Compensation will be provided. For more information, call (301) 402-4961 (TTY 1-866-411-1010) and refer to study 17-M-0046.

RSV Challenge Study Looking for Healthy Volunteers

NIAID researchers are seeking healthy volunteers, 18-50 years old, to participate in a respiratory syncytial virus (RSV) challenge study at the Clinical Center. Participants will receive one dose of the RSV virus. Afterwards they will be required to stay in the hospital from 9 to 16 days or more and return for follow-up visits about 1 and 2 months after infection. They may develop mild or medium cold symptoms. Researchers will use what they learn to test new antivirals to treat and vaccines to prevent RSV in the future. Compensation is provided. For more information, call 1-866-444-2214 (TTY 1-866-411-1010) or go online to https://go.usa.gov/xnpZD.



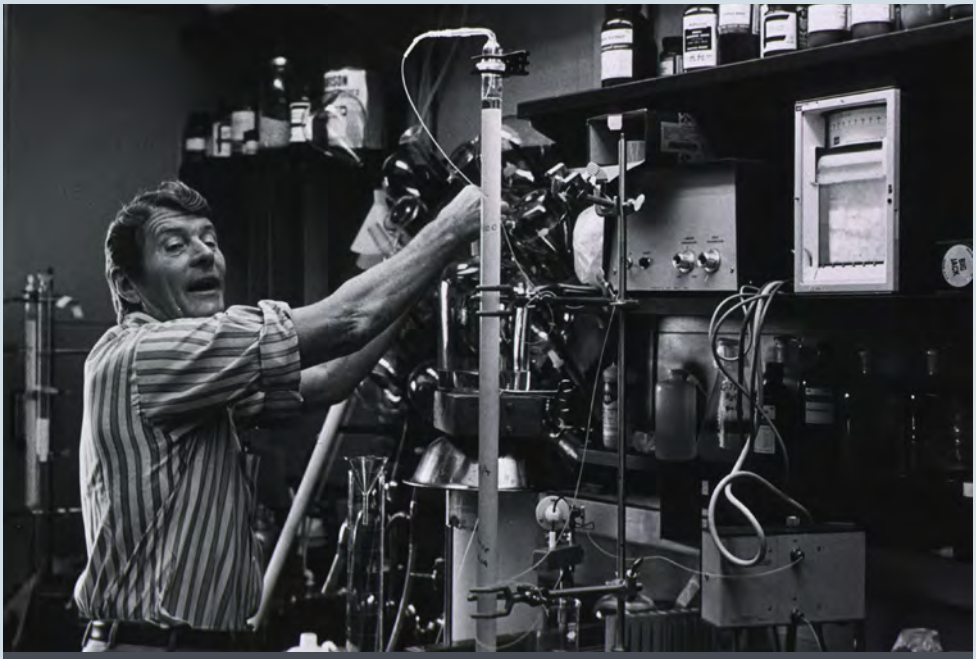
At left, Dr. Michael Potter poses with a tumor sample at the microscope where he spent much of his time. The microscope is included in the new display about Potter. At right are the exhibits (Anfinsen at left and Potter at right) at the fabricator, prior to delivery.

Twin Clinical Center Exhibits Honor NIH Scientists

BY MICHELE LYONS

The Office of NIH History and Stetten Museum opened twin historical exhibits in the Clinical Center in May honoring two NIH greats: Dr. Christian Anfinsen, who shared the 1972 Nobel Prize in chemistry; and Dr. Michael Potter, winner of a 1984 Lasker Award. Anfinsen and Potter began their careers at NIH in the 1950s, when molecular biology and genetics were new fields. They expanded both fields by asking questions that led to deeper understanding of basic biological functions. Their commitment to science influenced their personal lives as well.

The exhibit "Christian Boehmer Anfinsen: Protein Folding and the Nobel Prize" shows how Anfinsen answered the questions: How do amino acids come together to create proteins? How do proteins then fold into their specific shapes? What do those shapes have to do with the actual function of a protein? Anfinsen answered those questions as he learned how to unfold and refold proteins to determine their amino acid chains and created the first enzyme synthesized in a laboratory.



In this photo taken for the Nov. 7, 1972, issue of the *NIH Record*, Dr. Christian Anfinsen recreated what he was doing when he learned that he had won the Nobel Prize. The photo is part of a new installation in the Clinical Center central corridor.

He believed that discovering how proteins work in the body was as important as breaking the genetic code because, after all, the entire purpose of DNA is to encode the production of proteins from amino acids. He stated the bold idea in his 1959 book, *The Molecular Basis of Evolution*, that comparative protein chemistry combined with genetics would provide insights into evolution. He aimed to take basic molecular biology to what he called "molecular engineering."

The exhibit "Curiosity and Collaboration: The Work of Michael Potter" shows how answering basic questions motivated Potter as well: How does the body defend itself from bacteria, viruses and foreign cells? And what causes cancer? Potter and his collaborators discovered how immunoglobulins work, how genes and viruses can interact to cause cancer and how to grow cancerous cells in a petri dish to study, instead of in an animal. He prepared the field for the discovery of monoclonal antibodies, one of the most important tools today in medical research. Generous with his material, Potter believed that knowledge, instead of acknowledgement, was the goal of science.

The twin exhibits also present personal glimpses of each man's life. One of the objects in the Anfinsen exhibit is his typewriter and some of the letters he wrote in support of scientists around the world. Potter's love of the natural world, particularly the beach, and some examples of his artistic talent are displayed.

The history office's goal is to present a glimpse into NIH's rich history of achievements that have been important for basic and clinical research. The exhibits were developed and designed by the NIH Stetten Museum with sponsorship from NCI, NIDDK and NHLBI. Some of the images and objects were generously loaned by NLM.