END-OF-LIFE FRANKNESS

Rall Lecture Features Host-Guest Swap
BY RICH MCMANUS

Maybe the key to being a longtime successful radio show host is being, oneself, quite interesting. That insight was gently excavated by NIH director Dr. Francis Collins over the course of an hour-long conversation with Diane Rehm at the Rall Cultural Lecture Apr. 7 in Masur Auditorium.

Part of the reason their public dialogue seemed so effortless is that Collins has been Rehm's guest on NPR's The Diane Rehm Show at least 10 times. Rehm said on-air interviews flow most smoothly when guests know their subject fully, and name-checked exemplars from NIH, including Collins, NIAID director Dr. Anthony Fauci and NIAMS director Dr. Stephen Katz.

Collins cheerfully acknowledged that turnabout is fair play at the outset of their conversation. “I step into the role she would normally play,” he said, admitting to feelings of pressure. It was now on him to make a guest feel at ease. He needn’t have fretted.

Collins first asked about Rehm's non-traditional path to journalism. From there, the dominos fell.

A native Washingtonian, Rehm graduated from high school in 1954. Neither of her parents thought college was for girls, so she became a secretary at the D.C. department of highways, deploying workers to fill the potholes her boss had noticed on his commute to work.

Recruited to another secretarial position at the U.S. Department of State, she found herself “surrounded by intellectuals,” including a particularly learned and handsome young man named John Rehm. “He became my teacher,” Rehm said, and eventually her husband.

She spent 14 years at home rearing two

NIH director Dr. Francis Collins interviews Diane Rehm at Rall Lecture.

NIAID Researchers Move Closer to Universal Flu Vaccine
BY ERIC BOCK

Flu viruses mutate from year to year—sometimes gradually, sometimes suddenly. By mutating, they make it harder for the immune system to eliminate them. Two NIAID scientists are attempting to learn more about how the viruses function so they can develop better vaccines. They reviewed their findings at a Clinical Center Grand Rounds lecture in Lipsett Amphitheater recently.

‘FARMACEUTICALS’

Studies Find Certain Foods May Lower Risk of Some Cancers
BY DANA TALESNIK

We eat for energy and sustenance and tend to choose foods we consider tasty. Growing evidence shows that a plant-based dietary pattern is associated with a lower risk of many cancers. Many plant foods are not only nutritious, but also may have specific anticancer properties. Researchers at Ohio State University are studying how certain

Maryland governor visits NIH, inn. See p. 12.

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Pride Month Events, May 25-June 30
The Office of Equity, Diversity, and Inclusion, along with the Sexual & Gender Minority Research Office and the National Institute on Minority Health and Health Disparities, is sponsoring several events to celebrate Pride Month.

The theme for this year is “Telling Our Stories, Claiming Our Power, Standing in Our Truth.” Four events will take place on campus between May 25 and June 30:

- May 25 (10-11:30 a.m.) Heeding the ManDate - Project Healthy Living, Porter Bldg., Rm. 640
- June 8 (1-3 p.m.) Catalyzing Efforts to Collect Sexual and Gender Minority Health Research and Workforce Data, Natcher Bldg., Balcony A
- June 14 (1-2:30 p.m.) Fostering an Inviting Workplace for Transgender & Gender Nonconforming Employees (training), Bldg. 31, C Wing Rm. 7
- June 30 (10-11:30 a.m.) Health Care and Research for the Transgender Community, Bldg. 10, Masur Auditorium

For more information contact Ryan Mahon at ryan.mahon@nih.gov.

Take a Hike Day, June 2
The 9th annual NIH Take a Hike Day will be held Thursday, June 2 from 11:30 a.m. to 1:30 p.m. in front of Bldg. 1.

Join guests including Shellie Pfohl, executive director of the President's Council on Fitness, Sports and Nutrition, at the event. All NIH staff are invited to walk or run around the perimeter of campus—about 3.25 miles from start to finish—rain or shine.

The event also launches the U.S. surgeon general’s “Step It Up” campaign at NIH. Commissioned Corps officers at NIH are responding to surgeon general Dr. Vivek Murthy’s call to action to promote walking and walkable communities by promoting taking the stairs at NIH workplaces. Make every day a “Take a Hike Day” by taking the stairs and “Step It Up!”

Submit Ideas for Cancer Moonshot Initiative
As part of the Vice President’s National Cancer Moonshot Initiative, the National Cancer Institute has launched an online engagement platform to enable the research community and the public to submit cancer research ideas to a blue ribbon panel of scientific experts.

Any member of the public is encouraged to submit ideas for reducing the incidence of cancer and developing better ways to prevent, treat and cure all types of cancer.

Research ideas may be submitted in the following areas: cancer clinical trials; data sharing; dissemination & population sciences; immunotherapy & immunoprevention; pediatric cancer; tumor evolution & progression; other exceptional opportunities.

To submit your scientific research ideas to the Moonshot Initiative visit http://CancerResearchIdeas.cancer.gov/.

Scientific ideas can also be submitted to cancerresearch@nih.gov or by phone to the Cancer Information Service at 1-800-4-CANCER.

To sign up for updates on the engagement platform and other aspects of the National Cancer Moonshot Initiative, visit www.cancer.gov/moonshot-cancer-initiative.

Re-Opening of Bldg. 1 Café
The Bldg. 1 Café re-opened on April 18 under new management by Eurest Dining Services, which operates the coffee bars in Bldgs. 10/CRC and 35.

Located on the third floor, the Bldg. 1 Café serves breakfast, lunch and snack items with an emphasis on healthy options. It is open from 7:30 a.m. to 3:30 p.m., Monday-Friday. The daily menu features Starbucks coffees, pastries, juices, paninis, soups and sushi, as well as the popular On-the-Go salad and sandwich options. The café, open to all NIH staff and visitors, is a service of the Office of Research Services’ Division of Amenities and Transportation Services. For more information, contact the DATS food team at (301) 402-8180 or visit the NIH Food/Concession Program Services page at www.ors.od.nih.gov/food.
Berman To Give NIAAA’s Mendelson Lecture, May 25

Dr. Marlene Oscar Berman will deliver the 2016 Jack Mendelson Honorary Lecture on Wednesday, May 25 at 1:30 p.m. in Lipsett Amphitheater, Bldg. 10. Her talk will be on “Brain Mechanisms Underlying the Perceptual, Emotional and Cognitive Impairments Associated with Chronic Alcohol Use Disorder.”

Berman is professor of neurology, psychiatry and anatomy & neurobiology and director of the Laboratory of Neuropsychology at Boston University School of Medicine, as well as a career research scientist in the Department of Veterans Affairs Healthcare System in Boston.

Through her more than 40 years as a researcher and educator, Berman has advanced our understanding of the brain mechanisms underlying the perceptual, emotional and cognitive impairments associated with chronic alcohol use disorder (AUD). Her research addresses abnormalities in brain circuits controlling emotional perception and regulation and the impact of brain damage on the course of AUD development. One of her many seminal contributions was to characterize the syndrome of severe amnesia for events occurring after the onset of extensive brain damage produced by alcoholism, known as Korsakoff’s syndrome.

Currently, Berman uses neurobehavioral tests and neuroimaging measures of brain structure and function to assess how emotional dysregulation may underlie addiction problems like AUD. She also explores how AUD-related abnormalities in the brain circuits that control emotional perception and regulation may differ for men and women. These differences can directly affect how people make economic, social and health-related decisions, such as whether to continue to drink.

Berman has published some 250 peer-reviewed manuscripts, invited reviews and book chapters. She also has mentored more than 60 graduate students, postdocs and students on their way to medical or graduate school.

She received her doctorate in psychology from the University of Connecticut and her master’s degree in psychology from Bryn Mawr College. Her permanent teaching and research home since 1970 has been Boston University School of Medicine.

Berman has received many honors and awards, including the 2004 Massachusetts Neuropsychological Society Lifetime Achievement Award; a Fulbright Senior Scholar Award in 1991; the 2011 Henri Begleiter Excellence in Research Award from the Research Society on Alcoholism; and the 2012 Distinguished Career Award from the International Neuropsychological Society. Berman received a Senior Scientist Research and Mentorship Award for 2007-2015 from NIAAA. NIAAA established the lecture series as a tribute to Dr. Jack Mendelson, who made remarkable contributions to the field of clinical alcohol research. Each spring, the series features a lecture by an outstanding alcohol investigator whose clinical research makes a substantial contribution to our understanding of alcohol susceptibility, alcohol’s effects on the brain and other organs and the prevention and treatment of alcohol use disorder.

Harvard’s Mongan Fellows Visit NIH

The National Institute on Minority Health and Health Disparities recently hosted a visit by the Harvard University Commonwealth Fund Mongan fellows in minority health policy. “I’ve actually been hosting this for about 5 to 6 years now,” she said, “and I really enjoy it.”

PHOTO: WHITNEY ANDERSON

Harvard’s Mongan Fellows Visit NIH

The National Institute on Minority Health and Health Disparities recently hosted a visit by the Harvard University Commonwealth Fund Mongan fellows in minority health policy. The event capped the fellows’ week-long Washington, D.C., tour.

The 1-year fellowship is designed for minority physicians to prepare them for leadership roles in health care delivery.

This year’s visiting fellows included five physicians, each with different disciplines and backgrounds.

Dr. Jane Atkinson, chief of NIDCR’s Center for Clinical Research, said the best indication of a person’s lack of health is unfulfilled cavities, often seen in people of lower socioeconomic status and minority groups. One of the most pressing disparities in the field, she said, is oral cancer. While improvements have been made to reduce mortality, African-American men continue to have a lower survival rate than that of their Caucasian counterparts.

Dr. Pamela Collins, director of NIMH’s Office for Research on Disparities and Global Mental Health, said a major disparity in the U.S. is untreated psychosis. Many who experience this illness won’t seek immediate medical help, going without a diagnosis and subsequent treatment for more than a year.

“In the U.S., people actually spend a year and a half without seeking medical care,” Collins said.

Dr. Lawrence Agooda, director of NIDDK’s Office of Minority Health Research Coordination, discussed his institute’s participation in the Step Up program and the overall goal to diversify the biomedical research field.

Dr. Brett Miller, director of NICHD’s Reading, Writing and Related Learning Disabilities Program, emphasized his group’s focus on childhood normative development and the risks of not achieving that development due to abuse and neglect.

Dr. Leah Miller, a research program officer in the Office of Research on Women’s Health, discussed ORWH’s emphasis on the inclusion of sex as a biological variable when conducting medical research.—Whitney Anderson

ON THE COVER: Representation of the surface of the Zika virus with protruding envelope glycoproteins (red) showing

IMAGE: KUHN & ROSSMANN RESEARCH GROUPS, PURDUE UNIVERSITY

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the major carotenoid that gives tomatoes their red color—may reduce the risk of prostate cancer. Whether one consumes tomato juice, sauce or soup, said Clinton, carotenoids and other bioactive compounds in these foods enter the blood and alter concentrations in the target tissue.

In a recent OSU study, rodents fed tomatoes had increased lycopene levels and decreased cancer risk. But in a control group where 80 percent of the animals developed cancer, when certain carotenoid enzymes such as lycopene were eliminated, efficacy declined.

“We’re beginning to see in an animal model, very carefully controlled, how a genetic variation, as extreme as it may be, can alter how a dietary component impacts the cancer risk,” said Clinton, also the John B. and Jane T. McCoy chair in cancer research at the OSU Comprehensive Cancer Center. “We’re seeing dramatic and interactive effects between the tomato components, androgens [hormones that stimulate prostate cancer cell growth] and gene expression patterns.”

Through the magic of food science, technology and plant genetics, OSU investigators created a tomato juice with soy protein, teaming up to choose tomatoes that are easy to process, free of pesticides and rich in carotenoids. Clinton admitted it took quite a few iterations to make this tomato-soy juice taste good.

Each 6-ounce can of their tomato-soy juice has 22 mg of lycopene and 33 mg of soy isoflavones (plant-based estrogens). In several mouse models, tomato products reduced the incidence of prostate cancer and its progression. In human studies where men consumed 2 cans daily over several weeks, prostate cancer risk decreased. Tomato phytochemicals also affected pathways related to androgen signaling, mimicking what happens when doctors put men on hormone therapy, said Clinton.

Studies are ongoing to evaluate the hundreds of metabolites and dozens of genes in tomatoes. There’s great interest in the tangerine tomato, which has polycyst lycopene that rodents and humans seem to more readily absorb.

“There’s enormous variety in bioavailability and metabolism,” said Clinton, much of which may be due to genetic heterogeneity of the population. Research is now progressing rapidly in human studies that extract carotenoids to evaluate their absorption and distribution.

OSU lab studies show that soy inhibits prostate and bladder cancer in animal models. Some studies show compounds in soy actually inhibit critical processes related to cancer progression.

The researchers also created a soy bread. Clinton noted there were challenges upscaling production to make hundreds of loaves in uniform batches for clinical trials. Then came numerous tests to optimize appearance, taste and overall consumer acceptability.

The lab’s soy bread contains 60 mg of soy isoflavone in 2 slices. The team has a tasty soy-almond version as well, since almonds allow for cleavage of soy isoflavones during cooking that may aid in nutrient absorption.

Data from one human study revealed how people metabolize soy; men consuming the bread showed positive immune outcomes.

The team also created a yeast-based soy bread. Yeast makes more vitamin D when exposed to light, said Clinton, and vitamin D may affect colon carcinogenesis.

“If we make our bread whole wheat soy-vitamin D bread, now you also have this amazing opportunity to manipulate possibly the colonic microbiome in a way that potentiates the anticancer immune effects that may be there from both soy and vitamin D,” said Clinton.

Another OSU horticulture project is the black raspberry, which happens to grow well in Ohio. Black raspberries are rich in polyphenols—which may stop cancer cells from spreading—and anthocyanins, plant pigments with antioxidant effects.

Several animal studies have shown that black raspberries, whether eaten or applied topically, have oral cancer-fighting properties. The berries inhibited oral carcinogenesis significantly in the hamster cheek pouch and rat tongue model.

“By and large, black raspberries, regardless of the genes, the time of harvesting and location, all contain substantial bioactives,” said Clinton. “But they are impacted statistically and significantly by genetics as well as growing conditions and stages of ripeness.”

Investigators also created a sweet treat—black raspberry confections, including gummies, hard candies and white chocolate-coated candies that, Clinton said, have made great Christmas gifts.

But the focus of the berry studies is a nectar. An OSU team harvests the black raspberries, freeze-dries and vacuum-packs them into sterile containers so the nectar doesn’t require refrigeration. Thus preserved, it can

**“All of these issues are going to be part of deciphering how a food product impacts the cancer process.”**

-DR. STEVEN CLINTON
NIEHS Breaks Ground for ‘Net Zero Energy’ Warehouse

BY KELLY LENOX

A rarely visited portion of the NIEHS campus in Research Triangle Park, N.C., was the scene of the Apr. 15 groundbreaking for a new warehouse. Scheduled for completion in 2017, the building is designed to be net zero energy, which means it will generate as much or more power than it uses. It will be the first net zero facility for the entire Department of Health and Human Services.

And with warehouse operations separate from the rest of campus, the facility will meet stringent security guidelines for federal buildings.

About three dozen people gathered for the event, including NIEHS and NIH leadership and staff, local dignitaries and representatives from the architectural and contracting firms that designed and will build the warehouse.

“Today’s groundbreaking is really a team celebration, recognizing the hard work and partnership of many, many individuals from across NIH and the department,” said Dr. Linda Birnbaum, director of NIEHS and the National Toxicology Program.

“This secure warehouse will allow us to route commercial delivery vehicles away from the majority of the institute’s population, research activities, child care center and critical campus infrastructure,” she said, noting that the site will be equipped with a vehicle inspection station.

The planning team set high standards for sustainable building and operations. “It is targeted to be a LEED Platinum facility, the highest sustainability rating provided by the U.S. Green Building Council,” Birnbaum told the group.

Dan Wheeland, director of the NIH Office of Research Facilities, was on hand to mark the occasion. “In tough budgetary times, only the most meritorious projects survive the scrutiny that is involved,” he said of the approval and funding process. According to Wheeland, features of the plant that contributed to its approval included improving security, reducing operating costs, consolidating operations closer to the customer and reducing greenhouse gas emissions.

“This is not just a project per se,” Wheeland said. “It’s emblematic of what we’re trying to do across the Department of Health and Human Services and it’s exactly consistent with the NIEHS mission.”

Rep. David Price (D-NC), whose district includes NIEHS, was also on hand. He echoed Wheeland’s observation on the good fit with the institute’s mission. “It means that you are not only promoting environmental research and environmental stewardship, you are actually demonstrating it by the example that you set,” he said.

After a year of warehouse operation, the U.S. Green Building Council will evaluate such data as energy use and power generation and assign a LEED rating. Designers targeted platinum status by including a wide variety of features including energy conservation and generation, water efficiency, use of recycled and regionally sourced materials, habitat protection, reduction in light pollution and others.

MIT’s Hammond To Give 2016 Pittman Lecture, May 26

Dr. Paula Hammond of the Massachusetts Institute of Technology will give the annual NIH Director’s Margaret Pittman Lecture on Thursday, May 26 from 3 to 4 p.m. in Masur Auditorium, Bldg. 10. Her topic is, “Nanolayered drug-release systems for regenerative medicine and targeted nanotherapies.”

Hammond is the David H. Koch chair professor of engineering in the chemical engineering department, which she heads, at MIT and a member of MIT’s Koch Institute for Integrative Cancer Research. She uses electrostatics and other complementary interactions to generate functional polymer materials with highly controlled architecture. Her research in nanotechnology encompasses the development of new biomaterials to enable drug delivery from surfaces with spatiotemporal control. She also investigates novel responsive polymer architectures for targeted nanoparticle drug and gene delivery and self-assembled materials systems for electrochemical energy devices.

The lecture honors Pittman, NIH’s first female lab chief, who made significant contributions to microbiology and vaccine development, particularly in the areas of pertussis and tetanus, during her long career at NIAID.

The lecture is part of the Wednesday Afternoon Lecture series. For more information and reasonable accommodation, contact Jacqueline Roberts, (301) 594-6747 or robertsjm@od.nih.gov.
children before realizing, in 1973, that with kids growing up, she needed something to do.

Rehm enrolled in a class called “New Horizons for Women” at George Washington University, joining 19 other women who were segregated, by prior education, from the top of the building (graduate-level education) to the basement (where Rehm found herself, with other high school grads).

“They all said, ‘You really ought to be in broadcasting.’ I thought that was the craziest thing I’d ever heard,” said Rehm.

Within 2 weeks of finishing the course, Rehm talked with a friend who volunteered at a tiny radio station at American University. She encouraged Rehm to join her there.

The station was housed in a Quonset hut on campus. “If you went off the curb, you lost the signal,” Rehm joked. “This was when NPR was in absolute infancy.”

Offered a volunteer position, Rehm said, “A little light bulb went off in my head, and I accepted.”

On her first day on the job, the manager met her with bad news—the host was sick.

“I thought she was going to send me back home, but she said, ‘I want you to come in the studio with me.’ For 90 minutes, we interviewed a representative of the dairy council… Well, I knew about butter…”

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Rehm remained at the station as a volunteer for 10 more months, then spent 2 years as associate producer on the program, developing two health-related shows during that same period. She left that position to do some television and then was hired by the Associated Press as a freelance reporter specializing in medical research.

Rehm’s mother had died of liver cancer when Diane was 19, and her father died 11 months later, “literally of a broken heart. I wanted to know why.”

John Rehm’s father became diabetic, suffered from retinopathy and committed suicide; his wife, too, later killed herself.

“Death and illness and medicine have always been something I’ve had great interest in,” said Rehm.

She returned to WAMU as a full-time salaried employee in 1979, hosting the morning talk show Kaleidoscope, which was renamed The Diane Rehm Show in 1984.

In the mid-1990s, Rehm began experiencing problems with her voice. “I felt my voice clutching and clamping. It started with a tiny little cough.”

It became repetitive, and guests, including Sen. Barbara Mikulski (D-MD), noticed it. Rehm recalls, “I couldn’t do the show [with Mikulski]. I had tears in my eyes. And she said, ‘If you need help, I’ll get you to NIH.’”

By February 1998, Rehm’s voice had become a choked stutter and she left the air. For 4 months, she sat at home “not answering the phone, not speaking to anyone except my husband, not leaving the house.”

A neurologist and an otolaryngologist at Johns Hopkins diagnosed her with spasmodic dysphonia, a vocal cord problem amenable to treatment with the then-new therapy of Botox injections. Ironically, the same neurologist who made this discovery also diagnosed her husband’s Parkinson’s disease.

While waiting for her voice to return after the Botox injection, Rehm was invited by Slate to keep a diary of her recovery, which proved to be therapeutic.

That skill served her most acutely as she came to grips with her husband’s advancing illness.

“At the end, John Rehm could no longer use his hands, no longer feed himself, stand, walk to the bathroom or care for himself in any way.” The family gathered to hear his decision: “I am ready to die.”

John asked his doctor to help him die, but the doctor said he could do nothing, noting that it was against Maryland law.

“Only you can make this happen,” said the doctor, advising him to suspend food, water and medication.

“We all left, not knowing what John’s decision was going to be,” Rehm recalled. The next day, Rehm took him a photo album she had long ago created of his early years in
Paris, where he was born, through his prep school years in New York.

“He looked so well that day. He said he had not eaten or had anything to drink or taken any medication, ‘And I feel great!’

“I know why he felt great—he felt like he had taken his life back into his own hands.”

Rehm and her husband, who was 6 years older, had spoken a great deal about end-of-life issues and had promised that they would help each other die when the time came.

Assured that he was doing what he wanted, Rehm stood by his side as he proceeded on his end-of-life journey.

“For the next 2 days, his face was pink and he looked wonderful,” Rehm said. “At the end of the second day, he fell asleep and never woke again.”

Rehm addressed the audience: “I ask all of you—have you talked with your family about what you want?”

Rehm, who has written a book—On My Own—about losing her husband, says she’s not an advocate of anything other than having the discussion about the end of life, regardless of faith or other considerations.

“In St. Louis, there’s now a group called Coffee & Death,” she said. “These are friends and neighbors who gather to talk about exactly what they want [at the end of life]. Everyone in the neighborhood knows, not just family and friends.

“This country has been death-averse,” she charged, urging Collins and the medical profession to find ways to surrender the heal-at-all-costs mindset. “We need to talk more openly,” Rehm said, noting that several states have already adopted right-to-die statutes.

For his own part, Collins said he was grieving Rehm’s decision to retire The Diane Rehm Show after the 2016 elections. He asked her why.

“Because I turned 79 last September,” she said. “It struck me that 80 was a good time...I’ve had that real estate for 37 years, 2 hours a day. Dr. Collins, don’t you think that’s enough?”

After she leaves the microphone, Rehm plans to “talk a great deal about the right to die, also about Alzheimer’s disease and Parkinson’s disease.”

The audience gave her a standing ovation as she left the stage. The entire conversation is archived at https://videocast.nih.gov/summary.asp?Live=18852&bhcp=1.

Indo-U.S. Diabetes Research Collaboration Celebrates Progress

NIDDK director Dr. Griffin Rodgers and staff met with Dr. Soumya Swaminathan, secretary of the Department of Health Research and director general of the Indian Council of Medical Research (ICMR) on Apr. 15 to discuss joint accomplishments and future opportunities in diabetes research under an agreement signed by the U.S. and India in 2012.

Earlier this year, collaborative teams of U.S. and Indian scientists received bilateral awards from NIDDK and ICMR to study diabetes in youth, genetics of diabetes in South Asians and the role of environmental pollutants in diabetes risk. These inaugural awards stem from efforts following a 2013 diabetes research workshop in New Delhi co-led by NIDDK and ICMR.

For more about the collaboration, visit the news page at www.niddk.nih.gov.

Panel Explores Deficits of Wealthy Nation

The National Heart, Lung, and Blood Institute recently convened a think tank panel meeting on “Understanding Health Disadvantages Across High-Income Countries.” The 2-day meeting, led by NHLBI’s Center for Translation Research and Implementation Science, explored why the United States is experiencing a health disadvantage characterized by worse health outcomes across all groups—rich/poor, urban/rural and among vulnerable populations—compared to other high-income countries.

Experts from the U.S. (including representatives from NHLBI, NCI, NIDDK, NINDS, NCATS, NIMHD, FIC, CDC, academia and foundations), the United Kingdom, Canada, New Zealand, Australia, Finland and Sweden discussed research that may tackle the underpinnings of health disadvantages in the U.S.

For more information about the meeting and next steps, contact Dr. Luis Alejandro Salicrup, (301) 451-1073, salicrup@mail.nih.gov.
Dr. Matthew Memoli, director of the clinical studies unit in the Laboratory of Infectious Diseases, described work in his lab to understand how the flu virus causes disease. Dr. Jeffery Taubenberger, chief of the viral pathogenesis and evolution section in LID, reviewed efforts to develop a vaccine that protects against multiple flu strains.

Memoli observed how healthy volunteers respond to type A flu infections in his lab. The viruses were created in the lab, but “are genetically identical to the types of flu you could catch walking around on the street.” He then studies how volunteers respond to the infection. These are called challenge studies.

Challenge studies allow Memoli to gather precise information that he couldn’t obtain by studying people who come down with the flu by natural means. He can, for example, control who gets infected and with what type of virus. This allows determination of the minimum viral dose to produce illness, when participants are contagious, how long they are sick and when they develop an immune response to overcome the virus.

In natural settings, it’s difficult to study a single strain of the virus because flu viruses often change every year, he added. The only downside to challenge studies is the “route of inoculation is unnatural.”

Memoli explained that there are two proteins on the surface of flu viruses: hemagglutinin (HA) and neuraminidase (NA). HA helps the virus bind and enter red blood cells found in the respiratory system. NA helps control who gets infected and with what type of flu strain.

**“We’ve shown, amazingly, we get some very broad protection in animal studies...[In one study] “we were able to get 94 percent survival with lethal challenge with 8 different subtypes, including a variety of subtypes not in the vaccine.””**

—DR. JEFFERY TAUBENBERGER

In one recent study, Memoli infected two groups of volunteers with the flu to learn more precisely what a protective level of antibodies really is. One group had low levels of HA antibodies while the other had high levels of HA antibodies. The patients with higher HA antibodies had developed them because they either had the flu or received a vaccination.

The group with higher levels of HA antibodies had a lower chance of developing mild to moderate symptoms and of spreading the virus to others. Patients with higher NA antibody levels didn’t get severe symptoms, suggesting NA antibodies might better predict the severity of flu-like symptoms and reduce symptoms.

Memoli said his findings are just the “tip of the challenge iceberg.” He hopes to find more information—on the genes involved in responding to the flu and on how the immune system responds to flu viruses—that will lead to the development of vaccines that protect against many strains.

Next, Taubenberger described progress toward a universal flu vaccine, one that “would provide broader protection than a vaccine against a particular flu strain.”

He said influenza A viruses originate in wild birds. The viruses can spill over and “permanently adapt” to wild and domestic animals. He compared predicting the strain that will cause the next pandemic to the complexity and uncertainty involved in picking the winner of the NCAA basketball tournament.

“Pandemics are very unpredictable,” in terms of when they appear, the strains involved and the routes by which they spread. There have been 4 pandemics in the last 100 years, Taubenberger added. “All these viruses share some genetic relationship to an ancestry from the 1918 virus,” which killed at least 50 million people worldwide.

Instead of attempting to guess the next pandemic or seasonal flu virus, Taubenberger tried something different. His laboratory created a virus-like particle (VLP) vaccine cocktail that contains the HA proteins of four strains of flu: H1, H3, H5 and H7. Over the past 10 years, these strains have “caused significant outbreaks,” in people and animals. Made up of characteristic molecules from viruses, VLP vaccines stimulate an immune system response but don’t cause an infection.

They vaccinated mice with the cocktail, which targets HA, and then infected them with lethal strains of flu not tailored to the cocktail.

“We’ve shown, amazingly, we get some very broad protection in animal studies,” he said. In one study, “we were able to get 94 percent survival with lethal challenge with 8 different subtypes, including a variety of subtypes not in the vaccine.”

The vaccine was effective for at least 6 months and in older mice. While the results are encouraging, more testing must be done. Right now, Taubenberger is testing the vaccine in ferrets. If the results are successful, the cocktail could be subsequently tested in Memoli’s clinical challenge studies.

NIAAA Seeks Study Subjects

NIAAA is seeking healthy volunteers and volunteers with and without alcohol use disorder and/or early life stress, 21-65 years of age, to participate in a study researching whether people with alcohol dependence have more difficulty learning to feel calm or learn to fear things more easily. They also want to study how early life stress affects the ability to learn to feel calm. Compensation may be provided. For more information: Office of Patient Recruitment, 1-866-444-2214 (TTY 1-866-411-1010). Refer to study 15-AA-0127.
Ketamine Lifts Depression via a Byproduct of Its Metabolism

A chemical byproduct, or metabolite, created as the body breaks down ketamine likely holds the secret to its rapid antidepressant action, NIH scientists and grantees have discovered. This metabolite singularly reversed depression-like behaviors in mice without triggering any of the anesthetic, dissociative or addictive side effects associated with ketamine.

“This discovery fundamentally changes our understanding of how this rapid antidepressant mechanism works and holds promise for development of more robust and safer treatments,” said NIH’s Dr. Carlos Zarate, a study co-author and a pioneer of research using ketamine to treat depression. “By using a team approach, researchers were able to reverse-engineer ketamine’s workings from the clinic to the lab to pinpoint what makes it so unique.”

NIH grantee Dr. Todd Gould of the University of Maryland School of Medicine, in collaboration with Zarate and other colleagues, reported the findings May 4 in Nature. The team also included researchers at NCATS, NIA and the University of North Carolina.

“Now that we know that ketamine’s antidepressant actions in mice are due to a metabolite, not ketamine itself, the next steps are to confirm that it works similarly in humans and determine if it can lead to improved therapies for patients,” explained Gould.

Clinical trials by Zarate and others have shown that ketamine can lift depression in hours, or even minutes—much faster than the most commonly used antidepressant medications now available, which often require weeks to take effect. Further, the antidepressant effects of a single dose can last for a week or longer. However, despite legitimate medical uses, ketamine also has dissociative, euphoric and addictive properties, making it a potential drug of abuse and limiting its usefulness as a depression medication.

NIH Creates Atlas of Human Malformation Syndromes

Researchers with NHGRI have collaborated with physicians and medical geneticists around the world to create the Atlas of Human Malformation Syndromes in Diverse Populations. Health care providers can use the new atlas to diagnose diverse patients with inherited diseases by comparing physical traits (called phenotypes) and written descriptions of their symptoms with photos and descriptions of people with the same condition and ancestry. Previously, the only available diagnostic atlas featured photos of patients with northern European ancestry, which often does not represent the characteristics of these diseases in patients from other parts of the world. The free electronic atlas was announced online in Genetics in Medicine.

“This atlas is long overdue and much needed,” said Dr. Daniel Kastner, NHGRI scientific director. “The impact of such a resource will be immediate and profound for all health care providers who are diagnosing and treating birth defects and genetic diseases in people of diverse ancestry.”

Congenital malformations, also known as birth defects, are the leading cause of infant deaths and diseases worldwide. Examples include heart defects, such as missing or misshaped valves; abnormal limbs, such as a clubfoot; neural tube defects, such as spina bifida; and problems related to the growth and development of the brain and spinal cord. Birth defects can be caused by genes not working properly, missing or extra chromosomes or mothers’ exposure to medications and chemicals during pregnancy.

Rapid-Response Immune Cells Are Fully Prepared Before Invasion Strikes

Through the use of powerful genomic techniques, researchers at NIAMS have found that the development of immune cells, called innate lymphoid cells (ILCs), gradually prepares these cells for rapid response to infection. This work, which appeared online May 5 in Cell, sheds light on the development and function of a cell type that is increasingly recognized as having an important role in the body’s immune defense.

“Up until now, researchers have focused on T cells—another type of immune cell,” said NIAMS scientific director Dr. John O’Shea, senior author of the paper. “ILCs are coming into the spotlight because they appear to have a critical role in defending the body’s barrier regions, such as the skin, lungs and gut, where microbes must first pass to make their way into the body.”

Our immune system has two arms—innate and adaptive. ILCs are innate immune cells that respond quickly against pathogens at the first site of invasion. They release small molecules called cytokines that transmit signals to fight infection.

Elevated Bladder Cancer Risk Tied to Arsenic in Water from Private Wells

A new study has found that drinking water from private wells, particularly dug wells established during the first half of the 20th century, may have contributed to the elevated risk of bladder cancer that has been observed in Maine, New Hampshire and Vermont for more than 50 years. Other risk factors for bladder cancer, such as smoking and occupational exposures, did not explain the excess risk in this region. The study—by researchers at NCI and colleagues at Geisel School of Medicine at Dartmouth; the departments of health for Maine, New Hampshire and Vermont; and the U.S. Geological Survey—appeared May 2 in the Journal of the National Cancer Institute.

Bladder cancer mortality rates have been elevated in northern New England for more than half a century. The incidence of bladder cancer in Maine, New Hampshire and Vermont has been about 20 percent higher than that in the United States overall. Rates are elevated among both men and women. A unique feature of this region is the high proportion of the population using private wells for their drinking water, which are not maintained by municipalities and are not subject to federal regulations. These wells may contain arsenic, generally at low to moderate levels. Previous studies have shown that consumption of water containing high concentrations of arsenic increases the risk of bladder cancer.

There are two possible sources of arsenic in the well water in northern New England. Arsenic can occur naturally, releasing from rock deep in the Earth, and arsenic-based pesticides that were used extensively on crops such as blueberries, apples and potatoes in the 1920s through the 1950s.
NIH's Rosner Ends Half-Century NIH Career

BY RICH MCMANUS

Dr. Judah Leon “Lee” Rosner, a senior investigator in the molecular genetics section of NIDDK's Laboratory of Molecular Biology, concluded a 50-year NIH career on Apr. 29 with an afternoon-long scientific seminar in Wilson Hall that featured his many collaborations and the breadth of his involvement with the NIH community.

Rosner was a Ph.D. student at Yale University, after having studied zoology as an undergraduate at Columbia College, when he was recruited to NIH in 1965 by Dr. Michael Yarmolinsky of the Laboratory of Molecular Biology (LMB). Two years later, he had earned his Yale degree and was well along in establishing the hallmarks of his NIH tenure—science, friendship, humor, service and social engagement.

Rosner, who will continue his work in Bldg. 5 as a special volunteer, is an all-access NIH’er. He wrote papers in his specialty of bacterial genetics with colleagues all over the world; he traveled extensively to recruit minorities to science careers at NIH; he helped lead an NIH committee that protested the Vietnam War (and invited prominent anti-war spokesman Dr. Benjamin Spock to speak at NIH); he gave his 100th blood donation at NIH in 1992, is now up to his 220th donation and still gives regularly; he supported NIH R&W activities generously, including long stints as a softball player in both the men’s league (Heartbreakers) and coed league (Cloneheads).

And he was a loyal member of the Lambda Lunch, perhaps NIH’s longest-running debate society/journal club. His retirement seminar included hallmarks of the LL—high-minded intellectual battle on the topic of “struggles for the soul of biology.”

Rosner, who studied lambda phage in *E. coli*, even drove a car with license plates that read “Eco Lee.”

NIDDK scientist emeritus Dr. Bob Martin said he and Rosner were “NIH’s odd couple.” They did science by day—publishing some 30 papers together—but also took bagel-making classes and learned Italian, among other adventures. “Lee trained as many people of color as the rest of NIH combined,” said Martin, adding that in the 1970s and 1980s, Rosner was one of few NIH’ers recruiting talent to NIH from historically black colleges and universities.

Martin encountered in Rosner a person “not satisfied until every nuance [of an intellectual argument] was analyzed from every angle…He is still brimming with scientific ideas and criticisms.” Lately, said Martin, Rosner has been advocating for first-aid courses to be taught in public schools.

Dr. Michael Gottesman, NIH deputy director for intramural research, was a member of LMB from 1971 to 1974, and recalls that “Lee was the leader of the welcome wagon there.” The two published a paper in *PNAS* in 1975 describing the new transposon, Trn9. “I’m grateful to Lee for introducing me to the field [of antibiotic resistance].”

Yarmolinsky, “It suggests that the story is told, not just well-begun…Impact is not to be confused with importance,” he said, decrying the rise of “impactitis.”

“I’m really overwhelmed,” said Rosner, at the seminar’s conclusion. He called himself a product of LMB and the Lambda Lunch. “Those two places taught me to cooperate, be friendly, share and struggle for the truth…It really does take a village to produce a good scientist, he concluded. “I was surrounded by great scientists, great human beings and great friends.”

“Lee was one of the people in Bldg. 2 who made us feel at home. We knew that Lee was there to fall back on when we didn’t know what to do.”

-DR. SUSAN GOTTEMSMAN

PHOTOS: BILL BRANSON

Surrounding Rosner (front, second from l) are speakers at the Apr. 29 LMB/Lambda Lunch seminar in his honor. They are (front, from l) Dr. Michael Gottesman, Dr. Max Gottesman of Columbia University, NCI’s Dr. Sankar Adhya. At rear are (from l) Dr. Martin Gellert, LMB chief Dr. Susan Buchanan, Dr. Susan Gottesman, Dr. Michael Yarmolinsky and Dr. Bob Martin.

PHOTOS: BILL BRANSON
Dr. Robert Nussenblatt, chief of the Laboratory of Immunology at the National Eye Institute, died of cancer on Apr. 17 at age 67. He came to NIH in 1977 and proved to be a tireless scientist, research leader, mentor, clinician and patient advocate.

Nussenblatt was a world-renowned expert on inflammatory diseases affecting the eye, including uveitis. He literally wrote the book on the subject—Uveitis: Fundamentals and Clinical Practice—now in its fourth edition. He authored several other books and more than 600 articles in scientific journals.

Many patients with ocular inflammatory disease endure long-term treatment with medications that have unwanted and sometimes intolerable side effects. Nussenblatt dedicated his career to understanding the mechanisms of uveitis and improving treatment. One of his major accomplishments was demonstrating that cyclosporine was effective as a steroid-sparing agent, which has since become the standard of care for non-infectious uveitis. He also led research to test the biologic agent daclizumab as a treatment for uveitis and helped pave the way for its use in treating some types of multiple sclerosis.

His leadership roles at NIH included clinical director and scientific director of NEI. He was also a senior advisor to the deputy director of the NIH Intramural Research Program, associate director (clinical director) of the NIH Center for Human Immunology and acting scientific director of the National Center for Complementary and Alternative Medicine from 2004 to 2012. Nussenblatt pursued team science at an international scale. He led the UNITE consortium, which partners NEI with sites in the United Kingdom, South China and Hong Kong in the study of ocular inflammatory diseases. He had honorary degrees from around the world.

Nussenblatt’s commitment to his patients was remarkable. He always put patients first, never hesitating to drop everything to tend to their needs. He routinely exceeded the expectations of patients and families. He always made time to talk and had an uncanny ability to remember almost anyone he met, even acquaintances he had not seen for decades.

By training other clinicians, Nussenblatt influenced patient care worldwide. Over the span of his 39 years at NIH, he mentored more than 67 fellows who are now practicing around the globe. He received the American Academy of Ophthalmology’s Life Achievement Honor Award in 2011. Additionally, he had spoken at more than 66 invited lectureships around the world. He was recently nominated to become a distinguished NIH investigator.

One of his visions was development of large public databases such as the Lung Imaging Database Consortium and Reference Image Database for Evaluation of Response. These have been valuable for benchmarking quantitative imaging tools for measuring response to therapy. This led to creation of the Quantitative Imaging Network in 2008, in which imaging scientists and oncologists from universities across the country participate in the development of tools and methods to extract reliable quantitative information from medical images in order to predict or measure patients’ response to cancer therapies.

Clarke was a long-standing fellow of the American Association of Physicists in Medicine and a recently inducted fellow in SPIE, the international society for optics and photonics. In addition, the American Institute for Medical and Biological Engineering inducted him into its college of fellows for outstanding contributions to the advancement of biomedical imaging, especially in the realm of cancer diagnosis and treatment.

Clarke is survived by his wife, Alice; daughters Allisun and Laura; sons-in-law Edward Sfeir and Edward Jose and four grandchildren.
Gov. Hogan Visits NIH, Children’s Inn
PHOTOS: ERNIE BRANSON

Gov. Larry Hogan (R-MD) visited NIH on the afternoon of Apr. 28, stopping first at the Clinical Center, where he toured the laboratory of Dr. Louis Staudt, co-chief of NCI’s Lymphoid Malignancies Branch. The governor then proceeded to the Children’s Inn at NIH, where he met patients and their families. Above, he converses with the Middleton family, along with NIH director Dr. Francis Collins and former Rep. Connie Morella (R-MD), seated at right.

ABOVE: NIH director Dr. Francis Collins (l) points out features of the CRC model in the hospital atrium.