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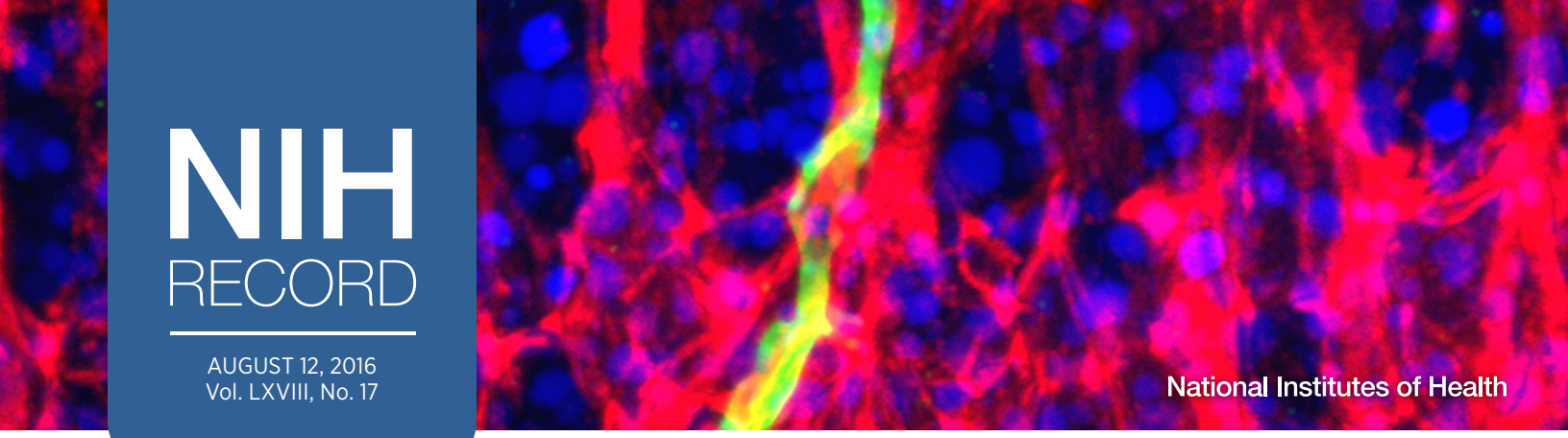


Science Gets Closer to Clarity On Genome

BY RICH MCMANUS

It appears that the actors that regulate the function of DNA in humans—and everything else that lives—behave much like human society: friends talk to friends, where you come from matters, family is important and memory is crucial—no one forgets their roots. It is a world where being turned on, and turned off, is the only thing that matters. Could DNA regulation be a metaphor for Saturday night on U St., or browsing on Tinder?

Such mysteries were plumbed at depth by Dr. John Stamatoyannopoulos, professor of genome sciences and medicine at the University of Washington School of Medicine and director of the Altius Institute for Biomedical Sciences, who spoke recently at the Wednesday Afternoon Lecture Series. Undeterred by the seeming impossibility of the task before him, he offered both the history of, and predictions about, the field in medicine that currently holds most hope—and most technological horsepower: the genome.

When the Human Genome Project announced success in the early 2000s, the real work had only just begun. Sure, we've got the letters, but what do they mean? How does the parts manual stand up and breathe?

Stamatoyannopoulos walked the audience through a timeline starting in the mid-1970s, when the link between chromatin structure and gene activation was established. That led to the development of DNA and RNA detection techniques, sometimes

SEE **GENOME**, PAGE 4

Dr. John Stamatoyannopoulos lectures at NIH.

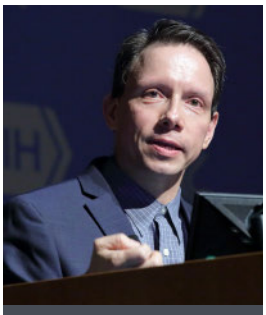
Who made a surprise appearance at the NIH Director's Awards recently? See p. 7.

ALSO THIS ISSUE

Biological Clock Can Help Researchers Understand Aging Process

BY ERIC BOCK

Dr. Steve Horvath believes he's built a biological clock that's even more accurate than the candles on a birthday cake.



Dr. Steve Horvath

The clock is an algorithm that estimates a tissue sample's biological age by measuring DNA methylation patterns, he explained at a recent Wednesday Afternoon Lecture. DNA methylation is a natural chemical process in which compounds known as methyl groups are attached to DNA.

SEE **HORVATH**, PAGE 6

Scientist Studies Brain Damage from Excessive Alcohol Use

BY DANA TALESNIK

An evening of one drink too many can have dizzying effects. Some of the cognitive deficits from consuming too much alcohol—such as slower reaction times and impaired memory—can be especially profound among chronic, heavy alcohol users.

Dr. Marlene O. Berman

Dr. Marlene Oscar Berman has studied alcohol's effects on the brain for more than 40 years. While in graduate school, she started out studying memory impairment in rhesus monkeys.

SEE **BERMAN**, PAGE 8

Ornament of a Moment

The Fogarty International Center held a picnic July 26 at Bldg. 16. Event organizer Bruce Butrum waved a wand around to make bubbles, one of which was appropriately magical as it held a reflection of Bldg. 16—affectionately called Stone House—on its thin, shimmering and very fragile surface.

PHOTO: KARIN ZEITVOGEL

Employee Rights: Race, Religion and...Restrooms?

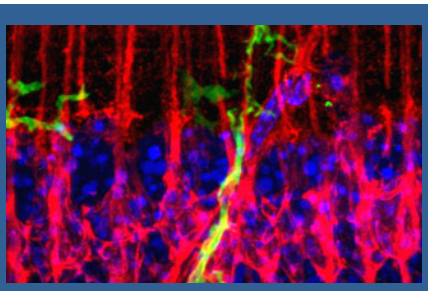
In a recent decision by the Equal Employment Opportunity Commission, Lusardi v. Department of Defense, the EEOC addressed two issues involving the rights of transgender employees. Can an agency deny a transgender employee who has transitioned to the opposite gender the use of restroom facilities that correspond with his or her gender? And can the intentional use of an employee's former gender pronoun and name constitute a hostile work environment?

Tamara Lusardi was a civilian employee with the Department of the Army at Redstone Arsenal in Huntsville, Ala. She agreed to use a private restroom during the initial period of her transition. On two occasions, when the private restroom was unavailable, Lusardi used the women's restroom. Both times she was confronted by a supervisor who informed her that she was required to use the private restroom until she could show proof of having undergone "final surgery." Lusardi's supervisor also repeatedly referred to her by her former male name and male pronoun in the presence of others in a manner intended to mock or humiliate her.

The EEOC established that Title VII of the Civil Rights Act of 1964, a federal law that prohibits employers from discriminating against employees on the basis of sex, race, color, national origin and religion, does not require an employee to provide proof of a medical procedure as a prerequisite for equal opportunity. Therefore, an agency may not determine access to facilities on the basis of the completion of medical procedures that will establish proof of an employee's gender. The EEOC also determined that in this case the intentional use of an employee's former gender pronoun and name can constitute a sex-based hostile work environment.

In March, North Carolina's legislature passed House Bill 2, a law that prevents transgender individuals from using bathrooms corresponding to the gender with which they identify. NIH, in accordance with federal law, asserts that denying transgender individuals access to restrooms and other workplace facilities consistent with their gender identity is a violation of Title VII. HB2 has no bearing on NIH employment or operations.

For more information on preventing and addressing workplace harassment, visit http://edi.nih.gov/consulting/guidance/toolkits. To reach out to the EDI Guidance team about NIH workplace concerns, visit http://edi.nih.gov/consulting/guidance/dear-guidance.



ON THE COVER: *Close-up of an inflamed mouse retina showing a microglial cell (green) clinging to radial Muller cell processes (red). Microglia are involved in inflammation.*

IMAGE: MINHUA WANG, NEI

The NIH Record

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Editor: Rich McManus
Rich.McManus@nih.gov

Associate Editor: Carla Garnett
Carla.Garnett@nih.gov

Staff Writers:
Eric Bock • *Eric.Bock@nih.gov*
Dana Talesnik • *Dana.Talesnik@nih.gov*

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Outdoor Film Festival at Strathmore, Aug. 20-22

The 20th Comcast Outdoor Film Festival will take place Aug. 20-22 on the lawn at Strathmore. Bring your blanket, chairs (low ones only) and anyone who loves movies. The movies are free. Food, wine and beer will be available to purchase. There will also be a raffle to help raise funds for the NIH Charities (Friends of Patients at the NIH, the Children's Inn and Camp Fantastic/Special Love); donations are accepted as well.

This year's films will be:

Aug. 20 *Jurassic World*

Aug. 21 *Minions*

Aug. 22 *The Wizard of Oz*

CC Hospital Board Holds First Meeting

NIH director Dr. Francis Collins (front, c) welcomes members of the NIH Clinical Center hospital board to its inaugural meeting. The board includes (front row, from l) chair Dr. Laura Forese, Beatrice Bowie; in the second row are Dr. Richard Shannon, Dr. Carolyn Clancy and Paul O'Neill. At rear are Jeanette Erickson, Dr. Reed Tuckson and Ellen Berty.

PHOTO: BILL BRANSON

On July 15, the new NIH Clinical Center hospital board held its first day-long meeting to begin to define a path forward for the hospital. Planning for the future was to be based on the Red Team recommendations, and included an effort to hear directly about the experiences of physicians and caregivers who serve patients in the CC. The Red Team was originally formed to look at problems identified in the CC's pharmaceutical development section (PDS). After that review, the team suggested the formation of the hospital board last April as part of 11 recommendations concerning hospital operations that were accepted by NIH director Dr. Francis Collins on Apr. 21.

At the inaugural meeting, everyone around the table agreed that perfection is a worthy goal, that no blame need be assigned and that a hospital whose governance was determined in the 1950s and 1960s is ripe for renovation. But there are many roads to perfection and a consensus will need to be reached as to the route.

The board, which meets quarterly, reports to Collins. He provided an overview of the CC's 63 years of distinguished achievement, citing its "proud history of tackling the world's public health problems," including, most recently, Ebola virus and Zika virus infections.

"Unquestionably, the NIH Clinical Center has done amazing work over these years and its value to the nation has been truly profound," he said. "Our goal is to strengthen and enhance the Clinical Center's already stellar reputation and role as a true national treasure."

New board chair Dr. Laura Forese added, "There is not a hospital in the world that thinks 'We're happy and we're going to stand still.' If one goes around the country and looks at the practice of medicine, which I've done quite a bit, I dare say there is no perfect place. We're here to help you pursue perfect."

Membership of New CC Hospital Board

The board is led by chair Dr. Laura Forese, a pediatric orthopedist who is executive vice president and chief operating officer at New York-Presbyterian Hospital.

Executive director is Dr. Lawrence Tabak, NIH principal deputy director. NIH director Dr. Francis Collins, to whom the board reports, is an *ex-officio* member.

Other members are Ellen Berty, special education teacher, book author and former NIH research participant; Beatrice Bowie, facilitator, Shady Grove Adventist Medical Center sickle cell support group and board member of the NIH patient advisory group; Ruth Brinkley of KentuckyOne Health; Brig. Gen. James Burks, director, Manpower, Personnel and Resources, and chief of the Medical Service Corps, U.S. Air Force; Dr. Carolyn Clancy, deputy under-secretary for health for organizational excellence at the Veterans Health Administration and former director of the Agency for Health Care Research and Quality; Jeanette Erickson, senior vice president for patient care services and chief nurse, Massachusetts General Hospital; Paul O'Neill, former Treasury secretary and OMB deputy director who is now non-executive chairman at Value Capture LLC; Dr. Peter Pronovost, director, Armstrong Institute for Patient Safety and Quality and senior vice president for safety and quality at Johns Hopkins University; Dr. Richard Shannon, executive vice president for health affairs and professor of medicine, University of Virginia Health System; Dr. Reed Tuckson, former ACD member and managing partner, Tuckson Health Connections.

Board member Dr. Richard Shannon of the University of Virginia said, "The overwhelming majority of health care delivery systems in America are undergoing the very same introspection and review that we are partaking in here." He said the complexity of human disease is increasing substantially and that upgrades are essential in the face of this reality.

"I don't think that any of us want to have any part in finger-pointing, blame or pushing people into a defensive posture," said board member Dr. Reed Tuckson, who recently concluded service on the advisory committee to the NIH director.

"We certainly welcome the opportunity to get better," said CC director Dr. John Gallin, who has held that post for 22 years. "It's not that we're an unsafe hospital, it's that we're a place that we think can get better."

Gallin said the CC budget, currently at around $420 million annually, has been hampered over the past dozen years by failure to keep up with inflation, resulting in a shortfall of roughly $46 million over that time. Add to that potential Red Team remediation costs estimated at $50 million, and "you could say that we're $100 million from where we ought to be," he said.

Dr. Henry Masur, chief of the CC's critical care medicine department, said he and his fellow department heads think the problems uncovered in the PDS exemplify two concepts: "The institutes provide the CC with inadequate funds to deliver the services they expect for their research portfolios. And governance and decision-making would benefit from greater input from staff with recent clinical and hospital management experience."

He added, "We think we provide superior care." But there are outliers, he said, "where quality is not where we wish it would be. But that is not the culture, that is not what we condone, that is not what we encourage. We are proud of what we do and we want to make that eminently clear."

"The board is not here to push people to implement the Red Team's suggestions," said Forese. "I think we're going to learn a lot—all of American medicine is. This is going to be hard, but it's going to be worth it."

The board's public session is archived at https://videocast.nih.gov/summary.asp?Live=19412&bhcp=1.

Genome

CONTINUED FROM PAGE 1

known as "footprinting."

By around 1980, science discovered that native regulatory elements are marked by altered chromatin structure. For the next two decades, investigators discovered and mapped about 300 human regulatory elements.

"Then there came a burst of activity with genome-scale technology," said Stamatoyannopoulos. Projects like NHGRI's ENCODE and the Roadmap Epigenomics Program flooded public databases with an enormous amount of information involving more than 500 cell and tissue types.

A single cell, it turns out, activates some 150,000 regulatory elements, or about 1 percent of the human genome.

It is now appreciated that there are about 60,000 genes in the human genome, Stamatoyannopoulos said, including around 21,000 traditional genes that code for proteins, 40,000 non-coding genes and about 1 million non-coding RNAs.

As of 2016, more than 3 million regulatory regions have been discovered and more than

★ ★ ★

"...We will have more than 90 percent of human regulatory DNA mapped by 2020."

–DR. JOHN STAMATOYANNOPOULOS

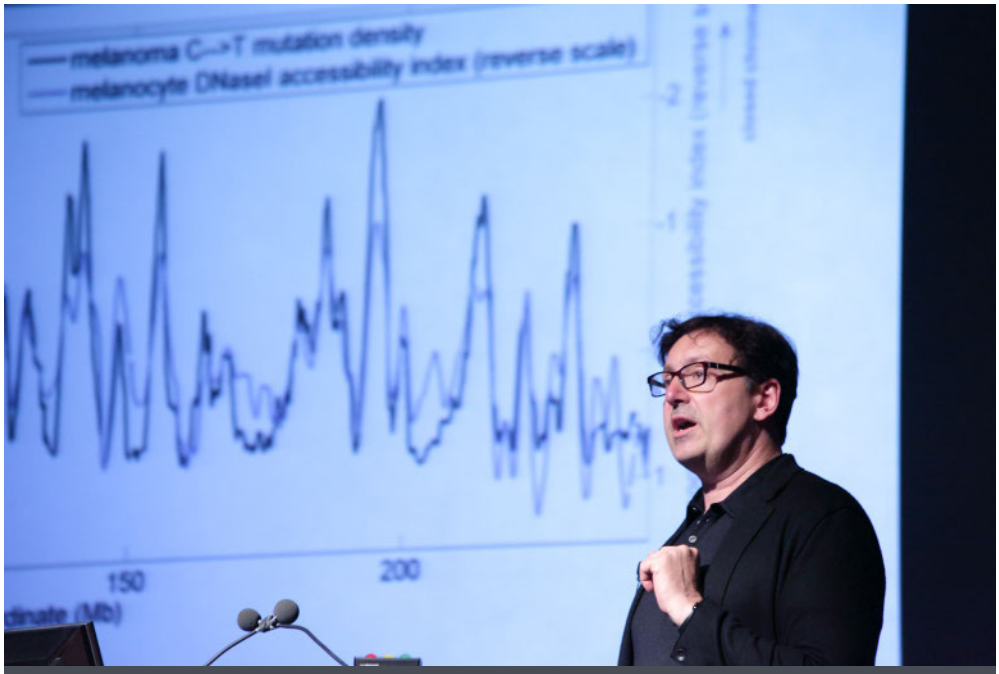
★ ★ ★

15 million transcription factor recognition elements have been found.

Categorizing that information is, however, "enormously complicated. It's like we're staring at this big forest, with no clear path forward...We are talking about millions of [regulatory] elements times thousands of cell states."

Nonetheless, generalizations are emerging from this mass of information, including that cells, as they go from primitive to definitive states, appear to remember where they came from.

Also, for many common diseases, disease- and trait-associated variants are now known to be concentrated in regulatory DNA. This finding helps scientists interpret the significance of disease-associated variants that, prior to this, had no clear functional role, i.e., they were not in a promoter or a gene or anything obvious.



Stamatoyannopoulos said he was a postbac in Bldg. 10 years ago. "I have a lot of fond memories here," he recalls.

PHOTOS: BILL BRANSON

In cancer, it has been found that cells reactivate primitive developmental programs. "Old stuff gets flipped on in haphazard ways," said Stamatoyannopoulos. "We can now figure out the cell of origin of cancer."

This is the fruit, he said, of the transition from a few maps to "lots and lots of maps" over the past 5-7 years.

Stamatoyannopoulos believes that, within 5 years, we will know where all the regulatory DNA is in the human genome. "I think we will have more than 90 percent of human regulatory DNA mapped by 2020," he said. Within the same timeframe, about half of that regulatory DNA will be associated with its target gene, he predicted.

By the early 2020s, Stamatoyannopoulos envisions science's ability to begin completing the important trifecta—from discovery, to detection to clinical translation.

The full lecture is archived at https://videocast.nih.gov/summary.asp?Live=19267&bhcp=1.

Deadline Oct. 7

Pfizer's Centers for Therapeutic Innovation Proposal Portal Opens Sept. 6

The National Center for Advancing Translational Sciences continues to manage NIH's collaboration with Pfizer's Centers for Therapeutic Innovation (CTI) network. The next call for proposals opens on Sept. 6; the submission deadline is Oct. 7.

The Pfizer CTI program at NIH is designed to help bridge the gap between early scientific discovery and its translation into new medicines through public-private resource sharing. It pairs leading NIH intramural researchers with Pfizer resources to pursue scientific and medical advances through joint therapeutic development. Goals include identifying biologic compounds with activity in a pathway or target of interest to both NIH and Pfizer and then together moving the compounds into the clinic to test them.

The CTI model is the first NIH-wide biologics initiative with a pharmaceutical partner that NCATS coordinates on behalf of all NIH intramural researchers. For more information, visit https://ncats.nih.gov/cti/proposals and https://ncats.nih.gov/cti. To set up a meeting that can include non-confidential discussion about pre-proposal ideas, contact Pfizer CTI representative Dr. Nader Halim at Nader.Halim@pfizer.com and copy NIH-PfizerCTI@mail.nih.gov.

NIDCR Director Hits Ground Running

Ever have the urge to run from work? NIDCR director Dr. Martha Somerman does.

In any weather, no matter the season, Somerman regularly runs home. It's a 3½- to 5-mile trip, depending on the route she chooses. On a typical workday, she leaves NIH at 6 p.m. and runs through several neighborhoods and local trails. In the winter months, she takes a more direct path but is out there nonetheless.

NIDCR director Dr. Martha Somerman prepares to run.

Somerman has always been an avid runner but never liked running on a treadmill. She prefers to exercise outdoors—running, biking and hiking—even on hot days and in the winter. Most weekends, she tries to fit in at least one 20-mile bike ride.

"Many people [contemplate] the best way to deal with stress," Somerman said. "For me, exercising outdoors is an important part of my life."

Originally from New York, Somerman came to NIH to head NIDCR 5 years ago, after a 9-year stint in Seattle as dean of the University of Washington's School of Dentistry. But she was no stranger to NIH. She first came to NIH as a postdoc in the 1980s and, soon after, received her first NIH research grant. In those days, she participated in the annual NIH run and some fun runs with colleagues at NIH.

There was plenty of snow where Somerman did her doctoral work—the University of Rochester in upstate New York. While there, she took up cross-country skiing. When she first came to NIH, she remembers skiing on a golf course in Rockville after a big snow. Nobody at the course seemed to mind, she said.

Always an active person, Somerman also played tennis for many years. In fact, that's how she met her husband.

"Once lodging is booked for Dr. Somerman's travel, she will always seek out a park or other space nearby where she can run," said Suzanne New, Somerman's executive assistant. "Sometimes she'll even send us photos from her runs. She's taken some beautiful photos during runs at sunrise."

Most days, Somerman takes Metro to work and runs home. On days when she drives, she tries to fit in a run during the day.

"Running relaxes me," Somerman said. "And it's a great alternative commute." For more, visit https://www.youtube.com/watch?v=7HFpUVy-F7tY.—**Dana Talesnik**

POKÉMON GO

Postdoc Trains His PI in New Game

NIH has not been exempt from the tech fad Pokémon Go, which has swept the country in recent weeks.

"Like many others, our lab has started participating in this addictive game of catching rodents, among other digital animals, not unlike the daily routine of scientists around campus," said Dr. Ernesto Perez-Chanona, a postdoctoral fellow in the laboratory of Dr. Giorgio Trinchieri, cancer immunobiology section, NCI. "It also makes the sunny journey between Bldg. 37 and the Belkaid lab—our collaborators at NIAID [in Bldg. 4]—far more exciting than it has ever been before."

One driving force behind NIH's involvement is that the Silvio Conte Bldg. and Bldg. 10 have been designated as Pokémon "gyms" where throughout the day, postdocs, postbacs, staff and summer students release pent up frustration from finicky experiments by battling one another so that their team gains possession of the building.

The teams include Mystic (blue), Instinct (yellow) and Valor (red), a favorite among NCI researchers and staff in Bldg. 37.

"For a brief period of time, my most well-trained Pokémon—named after my PI—was in charge (see image)," said Perez-Chanona. "However, other members of the lab are also represented in my Pokémon collection.

"One great part of the game," he says, "is the Pokémon Stops, which provide trainers with in-game goodies, but also highlight some of the hidden gems on campus, such as the Pyramid Between Heaven and Earth by Keith Allen Haring, the Asclepiades Mural, the Frog of the Anita B. Roberts Garden and countless plaques dedicated to past contributors to the NIH community.

"As always, be alert when walking around," says Perez-Chanona, "and happy hunting!"

NINR's Henderson Named AAN Fellow

Dr. Wendy Henderson, chief of the digestive disorders unit in NINR's Division of Intramural Research, has been selected as a fellow of the American Academy of Nursing. The academy will honor the 164 nurse leaders selected in the 2016 class of fellows during its annual policy conference Oct. 20-22 in Washington, D.C. AAN fellows are nurse leaders who have made significant contributions to nursing and health care. Henderson's research interest is in the mechanisms involved in symptom distress related to digestive disorders, specifically the biobehavioral relationships between brain-gut microbiota axis and patient symptoms. For more on her work visit www.ninr.nih.gov/researchandfunding/dir/whenderson.

Horvath

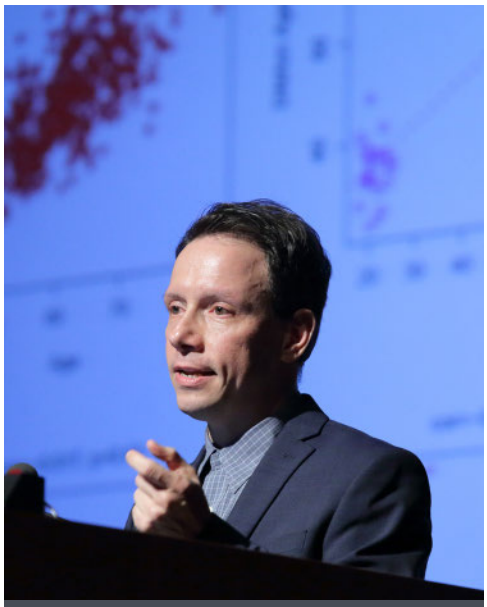
CONTINUED FROM PAGE 1

"The clock is a very accurate measure of tissue age," said Horvath, professor of human genetics and biostatistics at the University of California, Los Angeles. "It's associated with many age-related conditions, it's a prognostic of mortality and it allows you to contrast the ages of different tissues."

He can, for example, use the algorithm to compare heart and lung tissue samples from a middle-aged man. "I could say his heart is 50 years old and his lungs are 30 years old," he said. Doctors might eventually be able to use this information to develop an individualized treatment plan for the patient.

To develop the clock, Horvath studied more than 8,000 samples from 82 open-source DNA methylation data sets. He identified 353 markers from 51 different types of tissue samples and looked at how DNA methylation changes during a person's life.

The result of the clock is "literally an age estimate. And that age estimate is referred to as epigenetic age," he said.



Horvath describes his research group's approach to aging's "biological clock."

PHOTOS: ERNIE BRANSON

The clock applies to the whole life span from prenatal samples to old age. In young people, it measures "development" whereas in older people it measures "aging."

The clock ticks fastest in people under 20 years old. Once a person reaches adulthood, the clock slows down to a more constant ticking rate, Horvath noted. Over time, stress factors, whether they are environmental or genetic, influence the clock. That's why the heart of a 30-year-old can be older than other parts of the body.

There are several diseases that age brain and blood tissue faster than normal, according to the clock's results. Down syndrome, Parkinson's disease, HIV infection and Alzheimer's disease are just a few examples. Horvath isn't sure why this is the case.

He has also analyzed obesity's effect on blood, liver and adipose tissue. He found the higher a person's body mass index, the higher the age of his or her liver. Blood and adipose tissue didn't age much. "That already teaches us something," he said. "Stress factors that age you probably will age you in a tissue-specific manner."

He studied tissue samples from obese people who had bariatric surgery, an operation that helps patients with extreme obesity lose weight. Over the course of 9 months, most patients who have the surgery lose weight rapidly.

"The depressing news is once your liver's age is accelerated due to obesity, an intervention will not reset the age—at least not in the short term," he said.

Some parts of the body age slower than the rest. In a study of centenarians—those older than 100—and supercentenarians—those older than 110—he found that the cerebellum, a part of the brain that regulates motor control, is usually the youngest part of the brain.

"If we can figure out why the cerebellum stays young, maybe we [can] find a way to keep the rest of the brain young as well," he said.

The clock, however, isn't perfect. Female breast tissue "almost always overestimates [chronological] age." Breast tissue may simply be older than the rest of the body or the clock is "poorly calibrated," which means the clock may lead to higher error. Hormone exposure might explain this, but Horvath isn't certain.

And, in general, he said the presence of cancer can both increase and decrease the methylation-dependent age of affected tissue. "The epigenetic clock is broken in cancer tissue," he declared.

The results from Horvath's clock are preliminary. More research needs to be done to understand how tissue's epigenetic age relates to the cause and effect of disease.

Insights from the clock could eventually lead to the development of anti-aging treatments. If aging's effects can be reduced by as little as 20 percent, he said, it could save $3 trillion in major entitlement spending over the next 50 years.

"Biological aging clocks give rise to a straightforward approach for finding anti-aging interventions," Horvath concluded.

• • •

"If we can figure out why the cerebellum stays young, maybe we [can] find a way to keep the rest of the brain young as well."

-DR. STEVE HORVATH

• • •

Register Now For NINR Anniversary Event

Registration is now open for NINR's scientific symposium "Advancing Science, Improving Lives: A Window to the Future," which will take place on Sept. 14 from 3 to 5:45 p.m. at the Washington Hilton. The symposium, one of NINR's 30th anniversary events, will bring together scientists, health care professionals and members of the public to examine the advancements in nursing science that build the foundation for clinical practice and enhance the health of the nation.

The symposium will feature distinguished scientific speakers and include panel discussions on the topics of sleep and omics science. The event is free, but registration is required. For more information and to register, visit www.ninr.nih.gov/30years.

U.S. Sen. Mark Warner (D-VA) surprises the audience at the NIH Director's Awards Ceremony, which was held in Kirschstein Auditorium, Natcher Bldg.

PHOTOS ABOVE: BILL BRANSON, ERNIE BRANSON

Senator a Surprise Guest at Director's Awards

U.S. Sen. Mark Warner (D-VA) made a surprise guest appearance at the NIH Director's Awards Ceremony on July 19. On campus for an afternoon tour and science briefing, the lawmaker asked to address the assembly briefly after learning that the awards program would be held at the same time as his visit.

At the event, NIH director Dr. Francis Collins introduced Warner as a constant and loyal friend of scientific research and NIH in particular. Warner thanked Collins and congratulated awardees for their outstanding accomplishments. The senator noted that he's had close personal ties to medical research for many years, with a keen interest especially in work on Alzheimer's disease and type 1 diabetes— his mom died of AD in 2010 and one of his children was diagnosed with diabetes as a youngster.

Concluding his remarks, in which he denounced sequestration as "stupid," Warner pledged to continue to work with colleagues in Congress to appropriate more funds for NIH.

While on campus he also met with Dr. James Anderson, NIH deputy director for program coordination, planning and strategic initiatives, who gave an NIH overview. Warner, Anderson and Dr. Elizabeth Wilder, director of the Office of Strategic Coordination, discussed the Gabriella Miller Kids First Pediatric Research Program.

The senator toured the lab of Dr. Terry Fry, head of the hematologic malignancies section in NCI's Pediatric Oncology Branch. POB acting chief Dr. Brigitte Widemann participated in that session. Lastly Warner talked with Dr. Susan Resnick, senior investigator in the Laboratory of Behavioral Neuroscience at the National Institute on Aging.

Warner, Collins and NCI acting director Dr. Doug Lowy later posted on social media about the visit.

Social Media Tells the Story. Twitter posts by NCI acting director Dr. Doug Lowy (image at left) and Warner offer visual details about the senator's NIH visit.

Berman discusses the brain damage caused by long-standing alcohol abuse.

PHOTOS: ERNIE BRANSON

Berman

CONTINUED FROM PAGE 1

She then turned to brain damage in people. A professor at Boston University, and a career scientist with Boston's Department of Veterans Affairs, her NIH and VA-funded research continues to examine brain changes in people with chronic alcohol use disorder.

"I've always been fascinated with the way in which the brain controls behavior," said Berman, director of the neuropsychology lab at Boston University School of Medicine, who delivered NIAAA's 8th annual Jack Mendelson Honorary Lecture recently. Her foray into understanding alcohol's effects on the brain began with patients who had Korsakoff's syndrome, a memory disorder commonly caused by long-standing alcohol abuse.

Korsakoff patients had severe short-term memory loss but excellent memory for events that occurred before their brain damage, explained Berman, and they also would repeatedly tell the same stories.

"I was struck by the repetitious behaviors of Korsakoff patients in the wards," she said, "and together with their memory impairment, I realized there were certain similarities in the behaviors of the patients and the monkeys I'd studied as a student." The monkeys with bilateral frontal lobe lesions also had a short-term memory impairment on performance tasks and walked around in circles incessantly.

In earlier research, before the advent of neuroimaging technologies, her lab conducted performance tests to observe behavioral abnormalities beyond amnesia in Korsakoff patients.

"By comparing behavioral deficits in humans to well-documented deficits in monkeys with known damage to a specific brain region, we could infer whether patients had similar damage and dysfunction," said Berman, employing an approach called comparative neuropsychology.

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"By comparing behavioral deficits in humans to well-documented deficits in monkeys with known damage to a specific brain region, we could infer whether patients had similar damage and dysfunction."

-DR. MARLENE OSCAR BERMAN

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On basic memory and perception tasks, Korsakoff patients performed worse than both healthy control subjects and uncomplicated alcoholics (who didn't have Korsakoff syndrome, all of whom had abstained for a month or more). For one test in which patients had to choose the correct colors or sounds to get a reward, the Korsakoff patients needed much more time and made more errors.

"We were able not only to quantify clear indications of prefrontal cortical damage, such as short-term memory deficits and abnormal perseverative behavior in alcoholic Korsakoff patients," said Berman, "we also showed they had reduced perceptual processing abilities and, in later experiments, we observed deficits in attention, problem-solving difficulties, lower arousal levels and reduced sensitivity to the effects of rewards."

Korsakoff patients' brain damage causes impairments beyond short-term memory loss and repetitive responses. Berman's studies showed their brain damage was more extensive than in uncomplicated alcoholics. They also showed deficits on every emotional function test, including tests using such visual and auditory cues as identifying emotion on faces or the inflection of a voice. Recent functional MRI studies have confirmed widespread cortical atrophy and other brain damage in Korsakoff patients.

"Importantly, we saw alcoholics without the severe impairments characteristic of Korsakoff patients who nonetheless did have perceptual, cognitive and inhibitory deficits compared to nonalcoholic controls," Berman said. The activation levels of the amygdala (emotion) and hippocampus (memory) were significantly blunted in the long-term alcoholic patients.

Interestingly, when patients had to pace their responses at time intervals, the uncomplicated alcoholics responded well early on but showed abnormal perseverative behavior later in the exercise.

Berman said some experts have posited that alcoholism may modify brain structure without killing neurons, which begs the question of whether neuron repair could occur with sustained abstinence. Her lab has seen evidence of the brain's resilience and flexibility among the alcoholic group. The prefrontal brain regions may at times use alternative networks while performing cognitive tasks to compensate for decreased processing by other parts of the brain.

"Alcoholism likely affects selective brain systems, leaving other regions relatively

intact," Berman said. "The intact regions then can serve as substitute places in the brain for reassigning functions of the affected areas."

There were also differences between men and women. Berman's ongoing studies are showing alcoholic men to have a thinner cerebral cortex and less cerebral white and grey matter volume than the alcoholic women, said Berman. In men, the severity of damage directly correlated to the duration of heavy drinking but in alcoholic women, only a couple of brain regions were affected by duration of drinking.

When examining the size of the extended reward and oversight system (EROS), one large study showed the total EROS was significantly less in alcoholic men than women, particularly in the dorsolateral prefrontal cortex, which controls executive function.

"There's more and more converging evidence showing not only that alcohol use disorders reflect a damaged brain," said Berman, "but also that the clinical and functional appearance associated with alcoholism—such as loss of self-control, repetition of compulsive and impulsive behaviors and disinhibition—are tied to an accumulation of abnormalities in multiple interconnected brain systems and at multiple levels of the nervous system."

NIDA Hosts Winners Of Addiction Science Awards

NIDA director Dr. Nora Volkow (l) with (from l) second place winner Lindsay Poulos, third place winner Rachel Mashal, and first place winner Kashfia Rahman, and Dr. William Dewey, chair, Friends of NIDA

The winners of NIDA's 2016 Addiction Science Awards, part of the Intel International Science and Engineering Fair (ISEF), presented their projects to NIDA director Dr. Nora Volkow and other NIDA scientists on July 19. Following the presentation, the awardees toured the NIH campus. The Addiction Science Awards are coordinated by NIDA as well as Friends of NIDA, a private group dedicated to furthering NIDA's mission. ISEF is the world's largest science competition for high school students.

First place went to Kashfia Rahman, a sophomore at Brookings High School in Brookings, S. Dak., and the recipient of last year's third place Addiction Science Award. Her project found a direct correlation between a teen's negative outlook on stress and a negative physical stress response that adversely affects sleep quality, emotion and cognition. Rahman was able to show that how a teen handles stress can affect how vulnerable he or she is to drug use and addiction.

Second place went to 15-year-old Lindsay Poulos, a sophomore at the Episcopal School of Jacksonville in Jacksonville, Fla., who explored the concept that e-cigarettes might be a healthier alternative to traditional cigarettes. Her project found that fruit flies exposed to e-cigarette vapor showed evidence of gene mutations, suggesting that health risks exist with e-cigarette nicotine delivery systems.

Winning third place was 18-year-old Rachel Mashal, a senior at John F. Kennedy High School in Bellmore, N.Y. Her project found that dietary changes protected adult fruit flies from the negative effects of caffeine. She found that male fruit flies are more vulnerable to some of the negative effects of caffeine during development and in adulthood than are the female flies, suggesting that diet can influence males and females differently in response to a substance like caffeine. Further research might show that diet can influence how people respond to different drugs of abuse, Mashal said.

NIAMS Roundtable Focuses on Ichthyosis Research

NIH-supported basic, translational and clinical researchers recently met with NIAMS leadership and staff to discuss research gaps and unmet needs related to ichthyoses, a group of genetic skin disorders. The meeting also included representatives from other ICs, the Food and Drug Administration, a patient advocacy organization and industry. The full-day roundtable informs the institute's scientific planning process. The group addressed topics including ichthyosis course and co-morbidities; disease pathogenesis; outcome measures to gauge disease severity; new therapeutics; and how best to engage new investigators, patients and patient advocacy organizations in ichthyosis research.

Participants included NIAMS director Dr. Stephen Katz (seated, third from r), deputy director Dr. Robert Carter (seated, second from r), director of the Division of Skin and Rheumatic Diseases Dr. Susana Serrate-Sztein (back, second from r), and staff members Drs. Carl Baker (seated, l) and Ricardo Cibotti (back, third from r). The meeting was co-chaired by Katz along with NIAMS grantees Drs. Amy Paller (seated, third from l) and Keith Choate (seated, second from l).

PHOTO: ELIZABETH BOURAS

Researchers Identify Brain Circuits that Help People Cope with Stress

Research has identified brain patterns in humans that appear to underlie "resilient coping."

NIH-supported research has identified brain patterns in humans that appear to underlie "resilient coping," the healthy emotional and behavioral responses to stress that help some people handle stressful situations better than others.

People encounter stressful situations and stimuli everywhere, every day, and studies have shown that long-term stress can contribute to a broad array of health problems. However, some people cope with stress better than others and scientists have long wondered why. The new study, by a team of researchers at Yale University, is now online in the *Proceedings of the National Academy of Sciences.*

"This important finding points to specific brain adaptations that predict resilient responses to stress," said Dr. George Koob, director of the National Institute on Alcohol Abuse and Alcoholism, a supporter of the study. "The findings also indicate that we might be able to predict maladaptive stress responses that contribute to excessive drinking, anger and other unhealthy reactions to stress."

In a study of human volunteers, scientists led by Dr. Rajita Sinha and Dr. Dongju Seo used a brain scanning technique called functional magnetic resonance imaging to measure localized changes in brain activation during stress.

In addition to NIAAA, the study was supported by the NIH Common Fund, the National Institute on Drug Abuse and the National Institute of Diabetes and Digestive and Kidney Diseases.

New Medication Shows Promise Against Liver Fibrosis

A new drug developed by scientists at NIAAA limits the progression of liver fibrosis in mice, a hopeful advance against a condition for which there is no current treatment and that often leads to serious liver disease in people with chronic alcoholism and other common diseases.

"This study represents an important step towards an effective treatment for liver fibrosis," said NIAAA director Dr. George Koob. A report of the study is now online in *JCI Insight*.

Liver fibrosis is a gradual scarring of the liver that puts people at risk for progressive liver disease and liver failure. It may develop as a late consequence of chronic alcoholism, viral hepatitis, obesity or diabetes and can progress to cirrhosis and liver cancer, yet currently there is no therapy approved by the Food and Drug Administration.

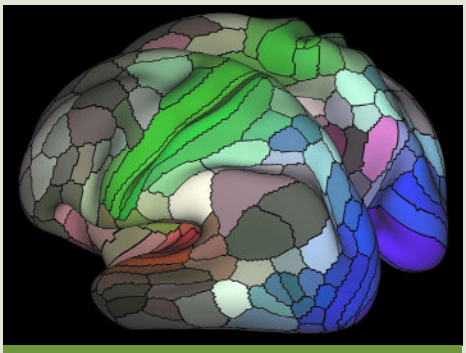
The new compound is a chemically modified version of ibipinapant, a brain-penetrating cannabinoid type 1 (CB-1) receptor antagonist used in scientific research. Senior author and NIAAA scientific director Dr. George Kunos' team modified its structure to reduce its ability to penetrate the brain and to include a molecular group that directly inhibits iNOS, the enzyme responsible for generating nitrogen compounds that promote inflammation.

"Fibrosis is a multifactorial, complex disorder that can benefit from simultaneous targeting of more than one cellular process," Kunos explained.

Kunos and his NIAAA team developed a new medication that concurrently inhibits both CB-1 receptors and iNOS. The new compound was designed to have only very limited ability to enter the brain in order to avoid the psychiatric side effects that limit the usefulness of currently available, brain-penetrant CB-1 receptor-blocking compounds.

Connectome Map More Than Doubles Human Cortex's Known Regions

Researchers have mapped 180 distinct areas in our brain's outer mantle, or cortex—more than twice the number previously known. They have also developed software that automatically detects the "fingerprint" of each of these areas in an individual's brain scans. Funded by NIH through its Human Connectome Project, this software correctly mapped the areas by incorporating data from multiple non-invasive brain imaging measures that corroborated each other.



Researchers discovered that our brain's cortex is composed of 180 distinct areas per hemisphere. For example, the image above shows areas connected to the three main senses—hearing (red), touch (green), vision (blue) and opposing cognitive systems (light and dark). The map is based on data from resting state fMRI scans performed as part of the Human Connectome Project.

IMAGE: MATTHEW GLASSER & DAVID VAN ESSEN

"These new insights and tools should help to explain how our cortex evolved and the roles of its specialized areas in health and disease and could eventually hold promise for unprecedented precision in brain surgery and clinical work-ups," said Dr. Bruce Cuthbert, acting director of the National Institute of Mental Health, which co-funded the research as part of the HCP.

The new study identified—with a nearly 97 percent detection rate—97 new cortex areas per hemisphere, in addition to confirming 83 that were previously known.

NIMH grantees Dr. David Van Essen and Dr. Matthew Glasser, both of Washington University in St. Louis, and colleagues at six other research centers, reported on their discoveries July 20 in the journal *Nature*.

Dr. George Koob delivers remarks after receiving French Legion of Honor award from French Ambassador Gerard Araud (r).

PHOTO: BILL BRANSON

NIAAA Director Receives French Legion of Honor

In a June 30 ceremony at the Washington, D.C., residence of French Ambassador Gerard Araud, NIAAA director Dr. George Koob became a knight of the French Legion of Honor in recognition of his leadership in developing scientific collaborations between France and the United States.

"I am extremely grateful for, and humbled by, this recognition," said Koob, who has served as NIAAA director since January 2014. "My collaborations and interactions with scientists in France have been deeply gratifying, both personally and professionally, and I look forward to ongoing scientific camaraderie between our countries in the years ahead."

The Legion of Honor, France's premier award, was founded by Napoleon Bonaparte in 1802 to recognize eminent accomplishments of service to France.

Among previous American recipients of the award are hundreds of veterans of World War II, former Surgeon General C. Everett Koop, former NIH director Dr. Elias Zerhouni and many leaders in academia, politics and the arts. Ambassador Araud presented the award to Koob on behalf of French President François Hollande.

Koob is recognized as one of the founders of the field of addiction research and is internationally renowned for his expertise on alcohol and stress and the neurobiology of alcohol and drug addiction.

The author of hundreds of articles published in international journals, Koob has had a long collaborative relationship with Dr. Michel Le Moal, professor emeritus of neuroscience at the University of Bordeaux, France, and a fellow of the French National Academy of Sciences.

With Le Moal, Koob co-authored *Neurobiology of Addiction* in 2006 and *Drugs, Addiction and the Brain* in 2014, both of which are regarded as major reference books in the field of addiction research.

Through his association with Le Moal and other eminent French scientists, Koob has been able to share his expertise and knowledge of the mechanisms underlying addiction and other psychiatric diseases and behavioral disorders with many French investigators.

Throughout his career, Koob has created strong links between French and American researchers and he has hosted and trained a large number of young scientists from France, including 13 postdoctoral fellows.—**John Bowersox**

Dr. Francisco Sy

Sy Retires After 12 Years at NIMHD

Dr. Francisco Sy, a program director and AIDS coordinator in the Division of Extramural Scientific Programs at NIMHD, retired recently after 12 years of service.

Sy served in various leadership positions including: director, Office of Community-Based Participatory Research and Collaboration; director, Office of Extramural Research Administration; and director, Division of Extramural Activities and Scientific Programs. He also served as president of the NIH Asian Pacific American Organization.

"At NIMHD, Dr. Sy was always a loyal and trusted colleague with energy to address challenging tasks and the strength to always do the right thing in the face of adversity," said NIMHD director Dr. Eliseo Pérez-Stable.

Prior to NIH, Sy was a senior health scientist in the Division of HIV/AIDS Prevention for 4 years at the Centers for Disease Control and Prevention. In 2003, he volunteered and led the CDC severe acute respiratory syndrome community outreach team in Asian communities in the U.S. to mitigate the fear and stigma associated with SARS.

He also was founding president of the Association of Asian Pacific Islander Employees of CDC and the Agency for Toxic Substances and Disease Registry. He taught and conducted research in infectious disease epidemiology for 15 years at the University of South Carolina School of Public Health. Sy has been editor of *AIDS Education and Prevention: An Interdisciplinary Journal* for 28 years.

In recognition of his contributions, Sy has received numerous awards including: the 2015 NIH Director's Award for catalyzing the advancement of sexual and gender minority research; 2012 Harvard School of Public Health Outstanding Alumnus for Leadership in Public Health Practice; the 2012 NIH Director's Award for coordinating LGBT research at NIH; the 2004 HHS Secretary's Award for Distinguished Service in CDC's SARS outbreak investigation; and the 1991 James Keith Excellence in Teaching Award from USC.

Sy earned his Ph.D. in immunology and infectious diseases from Johns Hopkins University, M.S. in tropical public health from Harvard University and M.D. from the University of the Philippines.

He was recently appointed chair of the department of environmental and occupational health in the School of Community Health Sciences at the University of Nevada, Las Vegas.

"Dr. Sy's contributions, commitment and dedication to the research mission and vision of NIMHD is unparalleled," said NIMHD deputy director Dr. Joyce Hunter. "His integrity and leadership ability are recognized throughout the NIH community by those who have worked with him. Dr. Sy's vast knowledge of minority health and health disparities and his experience at NIH will no doubt be of significant benefit to the University of Nevada."—**Gerda Gallop-Goodman**

At left, NIH director Dr. Francis Collins enjoys the ballgame July 19 with his granddaughter Norah Fraker, visiting from Tecumseh, Mich., and HHS Secretary Sylvia Mathews Burwell. At right, Burwell delivers the game's first pitch before the official start, as a grounds crewman looks on.

'Night at Ballpark' Proves Boon to Patients, Family

The Murrays from Mississippi know more about pediatricians than they do about pitchers. For the past decade, the family of four has been coming to NIH to participate in studies of a rare adrenal disorder. Common family outings, like sporting events, aren't so common for them. Dad, Christian, and mom, Gina, their two children, Chandler, 16, and Hunter, 12, had never been to a major league baseball game. Until HHS Night at the Ballpark on July 19 at Nationals Park in Washington, D.C.

"We are so excited," said Gina, decked out in a red Ks for Kids shirt outside the Children's Inn at NIH as she and her family left for the game.

Hunter, whose illness limits his sports activities, eagerly climbed atop the dugout for his big announcement over the PA system. He had been practicing, he said.

"It's time for Nationals baseball. Let's play ball," Hunter bellowed, dragging out the last word.

Team mascot Screech gave him a fist bump—the first of many from fans and Nationals staff. All the way to his seat, Hunter was greeted with high-fives and kudos.

The Nationals ended up losing to the Los Angeles Dodgers, but more than 5,000 HHS employees, including NIH director Dr. Francis Collins, attended the game.

Asked what they enjoyed most about the game, Hunter and Chandler chimed together, "Everything."

They both participate in studies conducted by researchers at the National Institute of Child Health and Human Development. These studies aim to evaluate potential treatments for congenital adrenal hyperplasia, a rare disorder in which the body does not produce the hormone cortisol. Cortisol affects energy levels, blood sugar, blood pressure and the body's response to stress, illness and injury.—**Meredith Carlson Daly**

ABOVE: At left, Burwell (r) meets Hunter, sister Chandler and mom Gina, looking proud. At right, Burwell and Hunter, 12, (l) sister Chandler, 16, and parents Gina and Christian Murray pose on the field before the game.

PHOTOS: ROSALINA BRAY, CHRIS SMITH