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PROGRESS PAUSED

Scientists Describe Research **Reboot After Covid Shutdown**

BY CARLA GARNETT

Imagine laboring many months toward a rare goal. All the planning, all the prep work and your team finally finds itself poised, with the objective within reach, when suddenly the journey is halted in its tracks. That's how one longtime intramural scientist describes NIH's recent 13-week lab shutdown due to the global coronavirus pandemic.

"It's like climbing Mount Everest," said senior investigator Dr. Charles Venditti, who heads NHGRI's organic acid research section. "It's just a long, long struggle, just trying to get to base camp. And then when



Shown BC (before covid), NCI's Laboratory of Cell Biology, led by NIH deputy director for intramural research Dr. Michael Gottesman (front), returned to campus as part of Group A.

you get there, the team has to coordinate to go for the summit. The summit is the sort of major accomplishment we try to achieve for a scientific program. Usually, it's a manuscript or a set of experiments that are going to make a major advance...Well, a lot of us were at base camp. Then came covid, and we had to just stop everything. Now we're just dwindling; we can't have everybody come in and we can't

have the team assembled. It's been difficult for us to keep our projects advancing in the laboratory. No one knows when we're going to come back full speed and that really affects our ability to get our science to the top of Mount Everest. The covid pause has introduced a major, major setback."

Shutting Down

Beginning Mar. 20, to reduce the risk of coronavirus transmission, NIH shut down all but mission-critical functions in all its laboratories and facilities nationwide. More than 3 months later, on June 22, the first labs-those with specific functions that could not be performed elsewhere and designated "Group A"-began returning to physical worksites under strict safety guidelines and with significant restrictions.

Days later, several scientists in Group A described the unprecedented period from a researcher's perspective.

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Dr. Fauci tosses first pitch at Nats Park, p. 12.

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CORONAVIRUS AVALANCHE

Covid-19 Lessons from the Austrian Alps

BY RICH MCMANUS



of Ischgl in the Austrian Alps was hosting a lively aprèsski nightlife. It was early March 2020, and busloads of vacationers from nearby slopes were

Two or 3 years

that-the town

ago-at least

it feels like

town's bars, boosting a normal population of 1,867 residents into something north of

SEE VON LAER, PAGE 4

flocking to the

'A HUGE SANDBOX'

How Computational Tools Can Guide Us Through a Pandemic

BY DANA TALESNIK



There's a flood of epidemiological data pouring in daily on Covid-19. The challenge is figuring out how to integrate this deluge of data with all its variables into a useable format. That's where statistical modeling and

machine learning come in.

"There's a huge sandbox with regard to how much data we've got and how much is

SEE HOLMES, PAGE 10

Webinar on Dietary Assessment Methodology for Risk of Chronic Disease

The Office of Disease Prevention (ODP) will hold a Methods: Mind the Gap webinar with Dr. Katherine L. Tucker on the issues in dietary assessment methodology for determining risk of chronic disease. It will take place on Wednesday, Aug. 12 at 11 a.m.

The current epidemic of chronic disease, which is growing globally, is clearly associated with adequacy of dietary intake. However, limitations in dietary assessment mean that uncertainty remains for many aspects of diet and health. Improving dietary assessment methods is, therefore, a major priority.

Tucker is a professor of nutritional epidemiology



in the department of biomedical and nutritional sciences and director of the Center for Population Health at UMass Lowell's Zuckerberg College of Health Sciences, with an adjunct appointment at University of Massachusetts Medical School. Her research focuses on dietary intake and risk of chronic disease, including osteoporosis, cognitive decline, obesity, metabolic syndrome and heart disease, with an emphasis on health disparities.

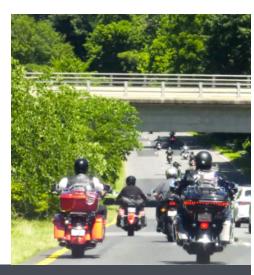
Registration is required at prevention.nih. gov/education-training/methods-mind-gap/issues-dietary-assessment-methodology-assessing-risk-chronic-disease. The webinar will be recorded and available on the ODP website within about a week.

FAES Endocrinology Course Set

The Foundation for Advanced Education in the Sciences endocrinology update review course will be held virtually Oct. 5-9. This fully online class will cover the development of efficient and cost-effective approaches to the clinical, laboratory and radiologic diagnosis of endocrine diseases, with emphasis on recent advances. The course will provide case studies as well as examples of exam questions.

The weeklong review will include presentations and problem sets from experts in the field. Tentative speakers include Dr. Beverly Biller of Massachusetts General Hospital, Dr Ranganath Munivappa of





Collins Participates in Motorcycle Ride for Charity

NIH director Dr. Francis Collins recently "had a great time meeting up on my Harley with more than a dozen motorcycle riders as part of a recent charity event that raised more than \$5,000 for the Federal Employees Education and Assistance Fund and Friends of Patients at the NIH. The fundraising drive, held on June 26, started in Fairfax, Va., rolled into Montgomery County and made its way to Washington, D.C.'s Rock Creek Park for lunch and ceremonies." At left, Collins says hello to Narisu Narisu (I), a bioinformatics scientist with the National Human Genome Research Institute, and Darryl Leja (r), NHGRI's visual information specialist. The photo at right shows the group out for a ride. For more on the event, visit https://federalnewsnetwork.com/tom-temin-federal-drive/2020/07/the-nih-director-an-inside-the-beltway-superstar-with-an-m-d-ph-d-and-a-harley/.

NIDDK, Dr. Robert D. Shamburek of NHLBI and Dr. Lee Weinstein of NIDDK.

Registration is required and can be found at https://faes.org/events/ENDO-2020.

NCATS's 'Green Champion' Reduces Plastic Waste in Labs

Even the most routine NIH science experiments can leave behind a big environmental footprint—from high-powered equipment running around the clock to non-reusable lab supplies. This is especially true of experiments happening at NCATS.



One of the center's major programs involves high-throughput screening (HTS), an approach that lets scientists test the potential usefulness of thousands of compounds at a time. While HTS can significantly speed up the search for potential new drugs, it produces a lot of waste. It uses

nearly a billion pieces of single-use plastic plates and pipette tips every year, costing money and producing tons of trash. Although HTS is used in labs across the country, little has been done to decrease its material waste, partly because the number of plastic products used in each HTS experiment could not be reduced. The best way to cut the overall use of plastic products was to develop a way to reuse them. Carleen Klumpp-Thomas, research services core (RSC) and automation lead for NCATS's intramural program, did just that.

She spent 5 years optimizing and improving protocols for various applications by running experiments with the RSC team utilizing different detergents, instruments and washing processes. Once she found the best cleaning protocols, she worked closely with NCATS biologists to ensure the reused HTS products performed just as well as new ones. In fact, her results were so impressive that the reused plastic products occasionally outperformed the new ones. An added bonus: The cleaning techniques didn't require any new equipment.

"Carleen has essentially turned what were once consumables into resources that can be used multiple times, saving NCATS thousands of dollars that have been reinvested into experimentation as opposed to buying more consumables," said NCATS director Dr. Christopher Austin.

For these reasons, Klumpp-Thomas was selected as a Department of Health and Human Services Green Champion for Operational Efficiency.

For more information about her work, emails can be sent to carleen.klumpp-thomas@nih.gov.



Trainee Writes Children's **Book About Viruses**

BY DANA TALESNIK

Most of us rarely think about viruses until these microscopic nuisances upend our lives. These past few months have been fraught with confusion and frustration and, as the Covid-19 pandemic rages on, we continue grappling with uncertainties. It's hard enough for adults to make sense of it all, let alone explaining it to children.



For kids wondering why their school shut down, why everyone is suddenly wearing masks and why they can't hug grandma, there's a new resource. Hannah Margolis, a 2020 Dartmouth College graduate who's now a postbaccalaureate fellow at NIH. has written a children's book titled What Is a Virus?, available for free online.

"When the pandemic started, I was very frus-

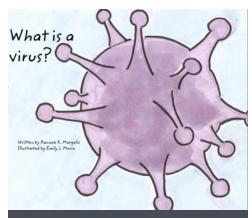
trated because my school shut down and I knew all these other schools were shutting down as well. So, there were all these kids and families stuck at home who might not necessarily understand why," said Margolis, who wrote the book as a positive outlet for her frustration in between finishing her Dartmouth coursework remotely.

"I think a lot of the problems we've had in the U.S. with people not wearing masks or washing their hands or following other scientific guidelines are partially because people just don't understand where the advice is coming from, and that makes [covid] really hard to combat. Because you can't see a virus, it's really difficult to convince people it's there."

In the book, illustrated by Dartmouth classmate Emily Morin, Margolis explains how a virus makes us sick and how our bodies can fight back even better if we take care of ourselves. She devoted three pages to proper handwashing. In the colorful spread, she explained that soap destroys the protein and fat outer layer of the virus so it can no longer infect cells.

"Knowing some basic science can really go a long way to help reinforce the safety standards we need to slow down infection rates and get things back to normal," she said.

Margolis hopes her book will inform people of all



Cover of Margolis's online children's book shows the spiky coronavirus. Another illustration appears below.

ages. She wrote it with younger kids in mind but included informative sidebars—on SARS-CoV-2, DNA/RNA, the history of microscopes, the importance of vaccines—for the more inquisitive older kids. Parents may learn a few things too.

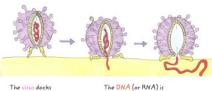
The information "is not necessarily difficult to understand," said Margolis. "It's just stuff that you might not have heard since high school biology or maybe you didn't learn it at all. Even as an adult, it can be helpful to have a basic refresher on viruses right now."

Raised in a small town in Nevada, Margolis writes a regular guest column for her hometown paper, the Elko Daily Free Press. She wasn't sure if people back home would be interested in the science behind the pandemic, but they were.

"There's been this incredible public outcry of people wanting to understand this information," she said. Questions began pouring in, inspiring her to write a series on Covid-19, with topics ranging from wearing masks to herd immunity and her favorite science field, structural biology.

Eager to do some lab work before applying to

The different proteins on the coat allow the virus to dock onto receptors on your cells



The virus docks

graduate school, Margolis arrived at NIH as an IRTA fellow and teamed up with Dr. Naoko Mizuno's lab at NHLBI. The lab had moved to NIH from Germany in January, a few weeks before Covid-19 would suspend lab operations across NIH. Now, they're busy setting up to get experiments underway. Although Margolis does not work on SARS-CoV-2, the tools and methods used in studying proteins could be applied to viruses.

"It's really incredible. Proteins are smaller than a

wavelength of light, yet they're responsible for everything that keeps our bodies moving and healthy," she said. "Being able to see them on a molecular level is very important right now. The structures of the SARS-CoV-2 viral protein are being used to help with drug targeting and trying to determine how to inactivate the virus."

Margolis wants her book to convey that viruses can be scary, amazing and cool all at the same time.

"I want kids to be excited by this stuff," she said. Covid-19 "has real implications in the world and we need to take it seriously. But it's also okay to sit back, enjoy the illustrations and think: virus structures are really cool-looking."

The free online book is available at https:// digitalcommons.dartmouth.edu/cgi/viewcontent. cgi?article=1000&context=student projects.



ON THE COVER: Mouse, trachea, scanning electron microscopy. Cilia (turquoise) microvilli on ciliated cells (yellow) goblet cells (red).

IMAGE: DAN SACKETT, NHGRI; JOHN BURKE, NHGRI; PATRICIA ZERFAS, ORS; ERINA HE, ORS

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Von Laer

CONTINUED FROM PAGE 1

10,000. Before the month was out, more than 10,000 people would be infected with SARS-CoV-2 in Ischgl, or by someone who had visited there.

But astonishingly, only two people in Ischgl would die of Covid-19, the disease caused by the virus, even though a subsequent study by researchers at Innsbruck Medical University would show that more than 42 percent of those living in Ischgl carried coronavirus antibodies, among the highest rates of seroprevalence ever detected [Bergamo, in Italy, had rates of more than 60 percent].

As virologist Dr. Dorothee von Laer of the university walked an NIH Covid-19 scientific interest group lecture audience through a virtual reenactment of these events on July 1, the virus was raging uncontrolled: more than 10 million cases worldwide, another 8 million to 10 million cases not yet diagnosed, half a million confirmed deaths and more than 160,000 daily new infections, as of that date.

"It's remarkable how this little particle of around 10 nanometers can have such a devastating effect," she said, noting that it is estimated that 1 infected cell can produce thousands of new virions in only 12 hours.

Europe's pandemic began in France and Italy, then spread to Germany and the rest of Europe, said von Laer. "Ischgl was a gateway. It set off a coronavirus avalanche."

Early in March, tourists returning from Ischgl (pronounced "ISH-guel") to Iceland started coming down with Covid-19. On Mar. 5, authorities in Tyrol state posted a notice of risk. Five days later, all of the town's bars were closed.

"There was a big exodus—everyone left town in 3 days, Mar. 11-13," said von Laer. On Mar. 14, the ski resort shut down. "From Mar. 13 through the end of April, the whole valley was quarantined. Forty percent of all Covid-19 cases in Austria were traced to Ischgl."

Cellphone tracking data confirmed that Ischgl was an epicenter of Covid-19, she said.

"We are not very experienced with big clinical trials at my medical center," von Laer admitted, "but we do have a big diagnostic institute."

She and her colleagues set out to

"[Ischgl] is a party hot-spot. People come in buses, hundreds every evening. It's a very good place for a virus...The music is very loud, people are shouting, they are in a closed space and they're there all night."

~DR. DOROTHEE VON LAER



determine the seroprevalence of the virus, the incidence of cases, the number of children infected and to trace the history of the outbreak, using mathematical models.

They enrolled 1,536 people, or 82 percent of all residents in Ischgl, testing blood for viral antibodies with 4 different assays, using PCR tests on samples from throat swabs and collecting questionnaires. Testing positive were 624 people, or 42 percent of the study population. Blood samples from the community taken in 2019, pre-pandemic, served as controls.

The researchers also did a household analysis that included 136 children and 184 adults from 78 homes, 22 of which experienced no infections.

"It was absolutely not the case that the virus would sweep through the household," von Laer reported. "We find this very interesting...This group of people that were highly exposed but not infected is a population of interest to us."

In couples where only one person was infected, Covid-19 was transmitted to the other only about half the time.

"That shows us that the virus is not as



nold analysis

n_ nouseholds	%		n_ tested	n_ IgG pos
1	1.28	0 to <6 years	35	10
13	16.67	6 to <10 years	36	7
46	58.97	10 to<14 years	32	8
18	23.08	14 to<18 years	33	11
		Children	136	36

"It's remarkable how this little particle of around 10 nanometers can have such a devastating effect," said Von Laer, who spoke from her lab in Austria.

contagious as one would have thought," she said.

Out of all seropositive adults in the study, only a few needed hospitalization, von Laer continued; 83 percent did not know that they had a previous coronavirus infection. Children, in general, became less ill than adults.

"The crucial event in the control of super-spreading was closure of the bars," she concluded. "There was a strong decline in Rt [a measure of how fast a virus is growing in a population] after the bars closed."

As routine interventions such as social distancing and mask-wearing helped control virus spread, mathematical models conclude that the high seroprevalence significantly contributed to the drastic decline of new infections during April, said von Laer. Yet herd immunity has not yet been reached, "despite very good virus control."

During a Q&A session, she noted that Ischgl's high infection rate is much higher than in the nearby ski resorts, which tend to have a quieter nightlife.

"[Ischgl] is a party hot-spot," she said.
"People come in buses, hundreds every

evening. It's a very good place for a virus...The music is very loud, people are shouting, they are in a closed space and they're there all night."

Von Laer was also asked if it is worthwhile to achieve herd immunity without a vaccine, as has been proposed in Sweden.

"That is an ethical and political question, not a question for virologists," she said. "But to achieve herd immunity, there would be at least 25,000 deaths in a country as small as Austria. As a doctor, I think that preventive measures are necessary and important. But if improving the economy is worth it to you, you can let 25,000 people die so we can go out and buy all sorts of stuff we don't need."

The full lecture is available at https://videocast.nih.gov/watch=38084.



PROGRESS VIA PARTNERSHIP

NINDS, Nonprofits Gather Virtually

BY SHANNON E. GARNETT

NINDS recently held its 14th nonprofit forum, "Progress through Partnership," drawing its largest crowd, albeit virtually, to date. More than 200 participants gathered in cyberspace via Zoom on June 29-30 for the event that provided an opportunity for patient advocacy groups to connect with and learn more about NINDS, NIH and each other.

"This is probably the most important meeting of the year for us," said NINDS director Dr. Walter Koroshetz. "It's a meeting where we exchange ideas with nonprofits—the organizations that represent the patients we serve. We go to scientific meetings where we hear about the great science, but NINDS is not an institute that's founded to improve the lot of scientists. It's an institute that's trying to improve the lot of people who suffer from neurological disorders. So, the scientists, the NINDS folks and the people on this meeting are really partners in this struggle to bring new treatments to patients with neurological disorders and also to prevent them."

Koroshetz updated attendees on the current status of NINDS amid the Covid-19 pandemic. "NINDS is open for business," he said. "We are on schedule in terms of reviewing grants and sending out funds to scientists all over the country to perform research. The problem is that research itself is on hold because of the pandemic. Some labs here at NIH are starting to reopen, but in terms of review and moving the research forward with funding, we are on our usual schedule."

The meeting kicked off with a forum favorite—a nonprofit's success story in therapeutic development. In her keynote presentation, "How CureSMA has made progress by building community and collaborations," Dr. Jill Jarecki, chief scientific officer of CureSMA, shared the remarkable scientific progress that has been made in SMA drug development.

Spinal muscular atrophy, or SMA, refers to a group of genetic diseases that destroy motor neurons. Currently there are two FDA-approved drugs to treat SMA—Spinraza and Zolgensma. Jarecki sald a third drug, Risdiplam, should be approved in August.

"One of the most important roles I think an advocacy group can have is encouraging collaboration and bringing different groups together," she said. She provided examples of ways CureSMA has pursued collaboration: having annual SMA conferences, creating working groups from academia and medicine and working with industry partners.

Two members of the forum's executive planning committee—Geraldine Bliss, president and co-founder of CureSHANK, and Paul Gross, chairman and founder of the Cerebral Palsy Research Network—led a session on "Covid Challenges"





NINDS director Dr. Walter Koroshetz gives welcome remarks at Nonprofit Forum. Monica Weldon of the nonprofit executive planning committee moderates a panel discussion.

in Nonprofit and Research
Communities," which focused on
results from a survey the committee
launched among the nonprofit
community in the weeks leading up
to the forum. The survey looked at
the impact of Covid-19 on research,
patient support and nonprofit
revenue.

"Many of our organizations are realizing reductions in revenue at this time and it comes at such a complex time when researchers need our support," Bliss said. "Their labs have been closed or scaled down, clinical

trials and clinical research studies have been paused and our patients need us more than ever."

The meeting also featured two panel discussions on innovative therapeutic developments for rare disorders and ways to develop clinical trials for rare diseases. The sessions, "Challenges in Therapeutic Development" and "Clinical Trials: Precision Approaches to Rare and Not So Rare Disorders," stressed the importance of building registries, developing natural history studies, sharing data and engaging industry and pharmaceutical companies.

The next morning, NINDS deputy director Dr. Nina Schor provided an overview of NINDS's current strategic planning process.

"It takes a village to do this," she said. "The thing about strategic planning is that the process is almost more important than the outcome. The way people get together and hear each other's views and get each other's input and troubleshoot together to work out the problems and the issues and the challenges really changes an organization going forward." She welcomed input on the plan from the nonprofit community.

Nonprofit representatives got an opportunity to meet informally with NINDS program staff in breakout sessions on both days.

"We travel this road together," said Koroshetz. "We are all science advocates. We are all pushing to improve the understanding of the brain and nervous system so we can get new therapies and we do that together."

and defined them as

"believable charac-

ters experiencing

meaningful events

who must cope with

the consequences."

Recordings of both days of the forum are available on NIH Videocast—https://videocast.nih.gov/watch=38056 and https://videocast.nih.gov/watch=38058.

Added Workshop Touts Power of Storytelling

This year's nonprofit forum featured an additional workshop titled "The Power of Storytelling," held on July 16; it emphasized the importance of personalizing narratives in research, medicine and patient care.

The virtual session included a presentation by Liz Neely, executive director of The Story Collider, a nonprofit organization devoted to telling true, personal stories about science. She described stories as "powerful framing devices that help humans make sense of the world,"



Dr. Sonia Vallabh of the Broad Institute, with her husband Dr. Eric Minikel, shares her story during the "The Power of Storytelling" virtual workshop. The two spoke to an NIH audience in December; see https://nihrecord.nih.gov/2020/01/24/coupleturns-hand-fate-hand-hope.



Liz Neely discusses the importance of personal narratives in science.

Neely encouraged nonprofit representatives to add stories to their strategic communication toolkits. "Stories are what help humans connect," she explained. "We all have stories. I hope you tell them and I hope you tell them well."

A special highlight during the workshop was a story shared by Dr. Sonia Vallabh, an associate scientist at the Broad Institute, of how a genetic prion disease inspired her and husband Dr. Eric Minikel to switch their career paths to become biomedical research scientists focused on developing preventive drugs for prion disease.

Reboot

CONTINUED FROM PAGE 1

Like Venditti, staff scientist Dr. Dave Kupferschmidt of NINDS's integrative neuroscience section was at a crucial moment when the shutdown was announced.

"Our lab had to shut down experiments just as projects were beginning to crest," he said. "Technical details of many experiments had recently been streamlined and we were about to enter a particularly productive phase. Our experiments also require complex breeding of various transgenic mice and often last 6-7 months from start



Dr. Dave Kupferschmidt

to finish. The shutdown meant that we couldn't advance these projects enough in time to present meaningful stories at [virtual] conferences that many of us were poised to attend."

His lab, which studies the neural

circuit basis of normal and disordered cognition, had several initiatives underway when NIH entered lockdown mode.

"Many of these projects involved longterm neuronal recordings from mice with genetic mutations relevant to schizophrenia as they performed tests of cognitive function," Kupferschmidt explained. "Others involved monitoring and manipulating the activity of discrete neuronal populations in the mouse brain to study how their connections might be altered to counteract disordered connectivity seen in our disease-related models."

In-person work stoppage came at an inopportune time for NHGRI's Dr. Mike Erdos, too. He's a staff scientist in NIH director Dr. Francis Collins's lab.

"I was one of the last people in the lab at the time of closure because I had a new instrument, with an engineer on site, being installed," Erdos said. "We have not gotten to use it yet. The install was completed on Mar. 19. Mar. 20 was our first official shutdown day. We have two major projects in the lab-understanding the molecular genetics of type 2 diabetes pancreatic function using single-cell analyses and development of

potential therapeutics to treat the premature aging Hutchinson-Gilford progeria syndrome (HGPS)."

Biggest impact

Research chemist Dr. Rob Robey of NCI's Laboratory of Cell Biology, where NIH deputy



director for intramural research Dr. Michael Gottesman is chief, also experienced "sudden progress interruptus."

"One of the most frustrating things about shutting down was lost time on a project that started getting really interesting just before Covid-19 hit," he shared. "We work on drug resistance in cancer and we had done RNA sequencing on a cell line that had been selected for resistance to a drug we have been studying. We had some candidate genes that we were exploring as potential resistance mechanisms and one of my colleagues sent me a paper that implicated one of the genes we had been looking at-a real 'Aha!' moment-just about a week before we had to shut down. Even worse, the gene is poorly characterized, so there are only a handful of papers about it on PubMed. So for 3 months I could only dream up experiments and not actually do any of them-very frustrating for a scientist in general, but even more so in this instance. I am making progress on this now, but the 3 months lost is just annoying."

Some research elements can be stored, of course, but the loss of time-particularly with outside collaborators, and for early-career trainees and students-is harder to quantify and recoup.

"As we have learned from government shutdowns in the past, everything can be brought down to some level-cell lines



frozen, experiments ceased-which we did for a number of ongoing experiments," NHGRI's Erdos said. "However, not everything can be brought to a halt. We have valuable mouse experiments in our mouse model for progeria with a very encouraging DNA-editing treatment that has been going on for over a year that continued through the sequester. One HGPS bone development cell culture experiment was in the middle of a 30-day differentiation [phase], which was able to be completed during the sequester. We also had one very detailed collaborative experiment with the New York Stem Cell Foundation that we were able to get to a stopping point, but then everything required freezing down."

"I had to freeze all my cell lines down," agreed Dr. Darawalee Wangsa Zong, NCI

research biologist in the Genetics Branch. "A few of my colleagues had single-cell cultures growing and it was difficult for them to freeze those down. One of my experiments needed to be finished ASAP since my collaborator was waiting on just that



Zong

one result before publishing. I managed to finish the experiment one day before we shut down."

At NIH since 2004, she's 1 of 19 people in that lab; half the staff consists of students.

"Our lab works with different types of cancer, particularly that of colon, breast and cervix," Wangsa Zong said. "I was working on two projects of my own, but since our lab specializes in spectral karyotyping, we also have many outside collaborations that were put on hold."

Senior investigator Dr. Daniel Reich of NINDS conducts studies of multiple sclerosis, including neuroimaging, pathology, biomarkers and RNA sequencing.

"Fortunately, we had no experiments that were lost," he said. The major impact of the shutdown was "loss of ability to do our normal clinical studies-mostly natural history studies in multiple sclerosis-and our nonhuman primate studies, which require teams of people working together over a several-month period."



Creative Safekeeping

Some labs found innovative ways to preserve what they could.

"I am fortunate to work with a very talented and creative group of scientists, and when it was

clear that a shutdown was imminent, we worked hard to ensure a creative continuity of operations even if we couldn't be on site," explained NINDS staff scientist Dr. Ben Free. "We were lucky to have not lost any valuable reagents. We were able to transition the synthesis of some analogs to an overseas contract research organization that remained open as an essential business. The company then synthesized compounds under our direction so they would all be ready for us to test upon return to the lab.

"Furthermore," he explained, "we were able to contract to another commercial research organization to run some selectivity testing on some lead compounds. This is an example of how we were able to continue some laboratory operations with the help of industry partners. This greatly prevented

loss of time and resources as this portion of our work was able to continue and be highly productive."

NCI senior associate scientist Dr. Art Shaffer said he "typically does daily experiments to move our lymphoma research forward. We do lots of benchwork experiments that we try to translate quickly to the clinic with our associated Clinical Center team...We do a fair amount of cell culture experiments that tend to run for weeks. We froze what we could, but some things in-progress were lost, probably about three-fourths of what we were doing. We were also stymied by not being able to do any mouse work. We need to test drug combinations to treat cancer in mice, and that was not approved to move ahead. Much like a budget shutdown, 1 week lost equals 3 weeks to restore/revive. That means we've got 9 months of work ahead to recover to the point where we were in March, assuming everyone can come back every day soon."

Unrecoverable: Time, Experiences

Erdos lamented what can't be recovered. "The biggest impact is losing the day-to-day interaction and discussions with our colleagues in the lab. Focusing while working home alone is a good thing, but much creativity comes from intangible thought

_ivia's portrait of

mouse technician

Darwin Romero



interactions
with other
curious minds
that lead to
innovative and
productive
developments
in research."
Venditti
thought of

people and their families who schedule appointments up to a year in advance to visit NIH, and who couldn't come during shutdown.

"We have two natural history studies that are very, very active on rare metabolic disorders that affect mainly pediatric patients," he explained. "Our laboratory does research to try and develop new treatments for these children. These are grave conditions and we are following hundreds of patients from all around the world, and for them, visiting NIH for an assessment is almost like an interventional clinical trial. Most of our patients are being treated with best intentions because there are no real evidence-based practices, as is typical for patients with rare disorders. Many of the children we take care of are managed with dietary protein restriction, cofactors and supplements. They're teetering between health and illness. We often provide advice and guidance when they participate in our natural history studies."

Reich, whose research also involves patients, agreed. "We aren't open—we still can't do our natural history studies, which is frustrating both to us and to the patients. We hope to be able to restart our nonhuman primate studies with Group B, but we're nervous about how that will go."

Regarding his lab's work with animals, Venditti saluted the dedication and diligence of a technician who cared for the mice while everyone else teleworked. [See sidebar.]

"In addition to losing the ability to perform physical experiments," Kupferschmidt noted, "we experienced a hit in our work efficiency as a result of the shift to telework. Our data analysis demands considerable computational power, and equipping ourselves for this capability from home unfortunately spanned a large chunk of the shutdown. All lab members and IT staff worked diligently to best facilitate this transition, but the massive scale of this

CONTINUED ON PAGE 8

SKETCH AMID SHUTDOWN

Research Champion Immortalized

Dr. Charles Venditti's NHGRI lab includes a translational research program that conducts natural history studies on rare metabolic disorders. A large part of their work involves breeding and treating very sick—and very valuable—mice. It's a vital research component that is difficult to halt mid-stream—even when a pandemic unexpectedly comes calling. Fortunately, devoted animal caretakers like Darwin Romero, a Kelly contractor to NHGRI and Venditti lab mouse technician, rose to the occasion.

"Our mouse technician has just been an absolute hero for our research program," Venditti said. "He's in there saving our precious mice, even on weekends. Helping us with our critical gene therapy experiments. Acting as a missionary for our scientists to help them try to keep the science going



Dr. Charles Venditti and his daughter, artist Livia, age 14

remotely. It's been amazing to see people step up and we've made real progress, despite the covid crisis, because of his efforts."

So impressed with Romero's work ethic was Venditti that his enthusiastic praise while teleworking inspired his youngest daughter, Livia, an artist, to render a portrait of the tech. The scientist plans to present the portrait to the aptly named science technician Darwin soon.

"Without the tireless efforts of our animal caretakers/vets and especially mouse technicians—like Darwin in this time of crisis—our precious animal disease models, and eventually the patients they help, would have been utterly decimated," Venditti concluded.

CONTINUED FROM PAGE 7

shutdown created unforeseen hurdles and unavoidable backlogs."

Considering next-generation scientists, Free observed, "One effect on our program was the lost opportunity and knowledge transfer for our trainees." His lab had two postbaccalaureate IRTA fellows who had to leave the lab in the last days of the shutdown en route to graduate and medical school.

"These outstanding students were at NIH to learn hands-on application of science, designing and running experiments and contributing to overarching research projects," he said.

Both students worked hard for 2 years, Free noted, only to have their projects rapidly cut short before they could see them through. "The [Office

of Intramural Training and Education] did a fantastic job of providing resources for these trainees during the last few months to continue learning and being engaged, but the cut-off of the projects has been particularly tragic for them...We also had to cancel travel to two scientific conferences. These conferences, while extremely important for all scientists, are particularly valuable to trainees for cementing future relationships and furthering their careers. It was a shame that both conferences were canceled and the trainees who have since left the lab will not have the opportunity to make up those experiences."

Daniel Bronder, an NCI predoctoral fellow, focuses on taking away the positive from the time away from the bench.

"[The forced downtime] offered the opportunity to take a step back from pipetting and

reflecting on all the work I have done up to this point," he said. "It has really provided me with an opportunity to take a more global look at the body of my work to scrutinize what I have got thus far and evaluate which experiments will be the most impactful to

Daniel Bronder

bring my story to completion. I also had the opportunity to start writing up the results of my work, so going forward I will be in a better position to slot results into place more easily."

NCI research fellow Dr. Sarah Clatterbuck Soper reported, "Our lab is a combination wet/ computational cancer genomics

lab with a focus on osteosarcoma. I am mainly on the wet side, though I do some computational work. I study alternative telomere maintenance in osteosarcoma. I work in cell lines, so I was able to freeze

lines, so I was able to freeze down my work. While there has been a ramp-up process on

return, it has been pretty smooth, basically just getting my cells going again. I should be able to begin collecting data again [soon]. It was perhaps comparable to taking a long vacation. While shut down, I was not able to move my 'main' wet lab project forward at all. That's a big impact and obviously frustrating."



In calmer times, principal investigator and NIMH director Dr. Joshua Gordon (back, 2nd from r) and his NINDS lab gather for a photo op. These days, they're returning to onsite work in stages and shifts, says Kupferschmidt (front, r).

restraints necessary for a thoughtful and safe return."

Says Shaffer, "Jumping back in is impossible under the 'Group A-B-C-D' plan. We can only be at about one-third strength in the lab, which for us means you can't be here every day. A typical lab week had been 6-7 days a week; now it's only 3. Plus, NCI cores—sequencing, cell sorting, etc.—are not running at capacity, which also severely limits everything we can do."

Creating a New Normal

Dr. Sarah Clatterbuck Soper

Free, whose lab studies development of new medications for dopamine-related neurological disorders such as Parkinson's disease and psychosis,

said he's grateful that continuity of operations plans with industry partners allowed the scientists to "have compounds ready to go as soon as we were allowed back in the lab. It will take a few weeks to get our assays back up and running at anything near full capacity, but we are thankfully able to be productive right away. Schedule limitations have been a challenge, as we have had to think carefully about what assays we can feasibly get back online with any given personnel. We keep in very close daily contact and tweak our scheduling as necessary to ensure maximum workflow under the prescribed

"Everybody is hyper aware of wearing masks and keeping distance, I would say. It's still a little awkward to share data in person..."

~DR. ROB ROBEY

* * *

"There have been and will continue to be stages to our safe re-opening,"
Kupferschmidt said of the lab led by principal investigator and NIMH director Dr. Joshua Gordon. "Currently only a few lab members are coming on site with any significant frequency. Mouse breeding is now being ramped up to re-derive our colonies of experimental mice. We hope to soon be able to restart the extended experimental clock on many of our lab's projects."

"Since I'm in charge of getting the lab supplies, etc., my first week or so involved taking inventory, getting the lab ready for everyone to return, [obtaining] masks,



etc.," Wangsa Zong noted. "We even had an equipment breakdown while we were away, so we're trying to get that solved as well."

Adjusting to a new covid-conscious climate, Erdos cautioned that "jumping right back in has the same caveats as shutting things down. Thawing cells and getting them to be conditioned for experiments again takes a little time. But it is necessary and also allows for us to get accustomed to the new regulations for distancing and safety. Being in the lab only about 50 percent of the time, and only one-third of the lab occupancy at any one time, requires extra attention to coordination and organization. Breeding animals for experiments also takes some lead time, about 2-3 months to get colonies back up to normal."

"For us at least, things have been pretty smooth," said Robey. "Everybody is hyper aware of wearing masks and keeping distance, I would say. It's still a little awkward to share data in person—I actually made a PowerPoint file with recently acquired data and printed it out so my colleague and I could go over the data from a safe distance—but we all seem to be managing! Quite frankly, even though everybody is at one-third capacity, it still feels completely dead. I rarely see anybody in the halls; it's just eerie."

Those returning onsite should expect a very different workplace than they left. Auditoriums, shuttlebuses and cafeterias all are functioning on limited schedules, according to safety guidelines.

"Conference space will be utilized when NIH is at a phase where in-person meetings can be conducted safely either with proper physical distancing or because the pandemic has subsided," said Brad Moss of the Office of Research Services. "Until such time, the use of remote conference capabilities continues to be the recommended method for conducting meetings at this time. ORS will continue to analyze the population on campus to see what food service operations we can open safely as additional groups return to work."

An assessment of conditions followed the first wave of returnees. NIH director Collins announced on July 13 that Group B could return the week of July 20, which happened as scheduled. However, not all individuals within these groups have actually returned, despite the all-clear.

Outdoor Light Linked with Teens' Sleep, Mental Health

Research shows that adolescents who live in areas that have high levels of artificial light at night tend to get less sleep and are more likely to have a mood disorder relative to teens who live in areas with low levels of night-time light. The research was funded by NIMH and was published in *JAMA Psychiatry*.



"These findings illustrate the importance of joint consideration of both broader environmental-level and individual-level exposures in mental health and sleep research," says study author Dr. Diana Paksarian, a postdoctoral research fellow at NIMH.

Daily rhythms, including the circadian rhythms that drive our sleep-wake cycles, are thought to be important factors that contribute to physical and mental health. The presence of artificial light at night can disrupt these rhythms, altering the light-dark cycle that influences hormonal, cellular and other biological processes. Researchers have investigated associations among indoor artificial light, daily rhythms and mental health, but the impact of outdoor artificial light has received relatively little attention, especially in teens.

In this study, Paksarian, Dr. Kathleen Merikangas, senior investigator and chief of NIMH's Genetic Epidemiology Research Branch and co-authors examined data from a nationally representative sample of adolescents in the United States.

To gauge the teens' exposure to outdoor artificial light at night, the researchers used satellite imagery data to calculate the average artificial light levels for each census block group in the U.S. As expected, levels of artificial light at night varied according to certain neighborhood-level factors, such as urbanicity, socioeconomic levels and population density.

Importantly, teens who lived in areas with high levels of artificial light at night tended to report later weeknight bedtimes and shorter weeknight sleep duration. The analyses showed that, on average, teens in areas with the highest levels of outdoor light went to bed about 29 minutes later and got 11 fewer minutes of sleep than did teens in areas with the lowest levels.

"Although environmental light exposure is only one factor in a more complex network of influences on sleep and behavior, it is likely to be an important target for prevention and interventions in adolescent health," says Merikangas.

NIH Researchers Reframe Dog-to-Human Aging Comparisons

One of the most common misconceptions is that 1 human year equals 7 dog years in terms of aging. However, this equivalency is misleading and has been consistently dismissed by veterinarians. A recent study, published in *Cell Systems*, lays out a new framework for comparing dog-to-human aging.

In one such comparison, the researchers found the first 8 weeks of a dog's life is comparable to the first



9 months of human infancy, but the ratio changes over time. The research used epigenetics, a process by which modifications occur in the genome, as a biological marker to study the aging process. By comparing when and what epigenetic changes mark certain developmental periods in humans and dogs, researchers hope to gain specific insight into human aging as well.

Researchers performed a comprehensive analysis and quantitatively compared the progression of aging between two mammals, dogs and

humans. Scientists at NHGRI and collaborators at the University of California, San Diego, UC Davis and the University of Pittsburgh School of Medicine carried out the research.

All mammals experience the same overarching developmental timeline: birth, infancy, youth, puberty, adulthood and death. But researchers have long sought specific biological events that govern when such life stages take place. One means to study such a progression involves epigenetics—gene expression changes caused by factors other than the DNA sequence itself. Recent findings have shown that epigenetic changes are linked to specific stages of aging and that these are shared among species.

"Dogs experience the same biological hallmarks of aging as humans, but do so in a compressed period, around 10 to 15 years on average, versus over 70 years in humans. This makes dogs invaluable for studying the genetics of aging across mammals, including humans," said Dr. Elaine Ostrander, NIH distinguished investigator and co-author of the paper.

The group acknowledges that the dog-to-human years formula that they developed is largely based on data from Labrador retrievers alone. Hence, future studies with other dog breeds will be required to test the formula's generalizability. Because dog breeds have different life spans, the formula may be different among breeds.



Holmes

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being produced daily," said Dr. John Holmes, professor and associate director, Institute for Biomedical Informatics, University of Pennsylvania Perelman School of Medicine. "Computational methods are being rethought and re-engineered and new ones are being introduced [all the time]."

Holmes, who spoke virtually at NLM's inaugural Ada Lovelace computational health lecture on June 24, had returned days earlier from a 6-month sabbatical in Italy. He discussed how different data models help us analyze contagion and predict outcomes, which can guide research and policy.

Italy, where Holmes was a visiting professor at the University of Pavia in Lombardy, had the world's highest Covid-19 mortality rate during the first months of the pandemic. A confluence of environmental

and demographic factors contributed to the country's dire numbers, from muggy weather and pollution to an aging population, many of whom live in nursing homes that have become hotbeds of infection.

The densely populated region of Lombardy was the hardest hit. On Mar. 9, the entire country went into lockdown. "I knew enough about this at that point to realize that we're in big trouble and I'm not going home," said Holmes.

Contagion Dynamics

Data models are handy

tools for managing all the moving parts of an evolving pandemic, providing a window into contagion dynamics. "This is really important because a pandemic occurs over time," said Holmes, and the dynamics "give us a sense for the rate of spread and identify co-variance. And, from all of this, we

want to develop and evaluate methods for containment and mitigation."

Traditional computational methods—such as epidemic curves that plot the number of cases along a timeline—track disease transmission and identify hot-spots. These curves rely on reporting, which can be spotty and delayed, noted Holmes, but they do paint a useful picture of contagion dynamics.

"The early exponential rise in these curves indicates the point in time where the strain on existing health care systems is the highest," he said. Some countries did a better job than others of flattening the curve, spreading cases over time to reduce the burden on hospitals.

Other tools, including compartment models such as the SEIR—susceptible, exposed, infected and recovered—chart how people progress through each "compartment," information that can be used

to simulate the effects of the pandemic on hospital capacity. These models can give us rate equations, such as the reproduction number, or R-naught, representing the average number of people each person infects during an outbreak.

The day before Holmes's lecture, Italy reported only 122 Covid-19 cases over a 24-hour period. "The R-naught for Italy right now is far less than 1; the infection is dying out," he said. "That's very exciting, to say the least, given that the case count was typically in the thousands daily for months."

Some statistical models have had mixed track records.

The better ones, said Holmes, consider multiple elements, such as a model his colleagues have been working on with the Policy Lab at Children's Hospital of Philadelphia that incorporates census data, behavioral risk surveys and environmental factors.

"There's no better example of a dynamical system than a pandemic like covid," said Holmes. "There's a certain underlying chaotic function."

Artificial Intelligence

Other computational tools use machine learning to mine epidemiological data and predict outcomes. Setting confirmed covid cases as the outcome, a group of researchers used computer-generated algorithms to examine the impact of environmental factors on covid transmission in four cities in Italy.

"These methods came up with population



Three medieval towers, erected in the 11th and 12th centuries, on the main campus of the University of Pavia, Italy, where Holmes was a visiting professor earlier this year

density and humidity being the strongest predictors of Covid-19 spread," said Holmes. "I've heard humidity come up time and again, in a number of different covid projects that I've been working on."

Another study simulated parameters intended for contact tracers and decision-makers who need such real-time assessments. Researchers used a feature map plugged into past mobile crowd-sensing data to model mobility patterns.

"They found that 2 weeks after the first confirmed case in the city under the risk of community spread, AI-enabled mobilization of assessment centers can [dramatically] reduce the unassessed population size,"



The lecture's namesake, Ada Lovelace, was an English mathematician who lived in the early 19th century.

IMAGE: NATIONAL PORTRAIT GALLERY, LONDON

MILESTONES



AI in the Age of COVID-19: Computational Tools for a Pandemic



"...robust methods drawn from field of artificial intelligence ... a us to model more accurately an more quickly the population an disease dynamics that are centred developing policies for preventi detection, and treatment. We vexplore these approaches, inclusome that are currently in use a as a proposal for novel, next-generation machine learning to epidemiologic investigation."

said Holmes. This became a useful tool for updating policy guidelines.

Another predictive approach is looking at what's trending online. Internet search behavior can serve as an early-warning system for incidence of covid or other infectious diseases, said Holmes, who noted exponential increases in online searches for handwashing, hand sanitizer and antiseptics early in the pandemic.

Social media can also compute incidence early on. In China, the Wiebo social media platform aggregated and compared 15 million covid-related posts across the country. Reports of symptoms and diagnosis of cases significantly predicted the daily case counts compared with official statistics, noted Holmes.

Beyond case counts, a more varied picture can come from agent-based models, which simulate behaviors, allowing researchers to see the potential effects as they tweak the parameters individually or combined with other agents.

Researchers recently modeled infection spread in nursing homes in Italy by setting up risk parameters using a new, multi-agent platform called NetLogo. "They found useful information and strategies for reducing transmission risks," said Holmes. With this model, "you can certainly implement some interventions, perhaps masking or no-visitation policy in the nursing home... and see how much that would reduce cases."

The question remains: how can we best use the abundance of data now available to researchers?

"Hopefully," said Holmes, "it feeds into policy and behavior change, and a reduction in the impact of a pandemic like this in the future." B

CSR's Chaitin Retires

BY PAULA WHITACRE

Dr. Michael Chaitin's last day at NIH did not go as expected when he first announced his retirement after 20 years as a scientific review officer at the Center for Scientific Review. Working at home on the last day of March during the



Dr. Michael Chaitin

Covid-19 pandemic, he closed his laptop at the end of the afternoon, walked into another room and announced to his wife, "I am retired." A send-off with colleagues-via Zoom-took place earlier that day. As of this writing, he has not cleaned out his office, much less seen colleagues in person.

That anticlimax, which he acknowledged was "a little surreal," does not reflect his career advancing the vision sciences in many capacities in and outside of NIH. Born in New York City and raised on Long Island, Chaitin majored in physics at the State University of New York at Albany as an undergraduate. However, he migrated to cell biology to undertake retina and retinal degeneration research, in part because of his own experience with retinitis pigmentosa, a genetic condition that initially affects peripheral and night vision.

Chaitin obtained his Ph.D. in molecular biophysics at Florida State University but was able to conduct his thesis work in a retina research laboratory at UCLA. He also did postdoctoral work in retina research, supported by fellowships from the National Eye Institute, in the department of pathology at Yale and at the Jules Stein Eye Institute at UCLA. His research focused on the photoreceptor cells in the retina that mediate the absorption of light and how these cells keep themselves healthy or can cause diseases that affect vision.

Chaitin served on the faculties of the University of Miami School of Medicine and the University of North Texas Health Science Center at Fort Worth. In 2000, he decided to move into scientific administration at NIH when the opportunity arose to manage what was then called visual sciences A study section, followed by other eye-specific study sections.

"Mike managed the biology of the visual system study section with exceptionally high standards for himself and his reviewers," said Dr. Noni Byrnes, CSR director and his former division director and review group chief. "Not only was he an asset to CSR and to NIH due to his competence in review, but also he was active in outreach at the annual meetings of the Association for Research in Vision and Ophthalmology [ARVO]."

Dr. Magsood Wani, his supervisor as chief of the cell biology integrated review group, emphasized Chaitin's long track record of service to the vision community. "Because he was so involved, he was able to convene the highest caliber of reviewers to give the fairest reviews," Wani said. He noted that the workshops and networking he did at the annual ARVO meetings particularly helped junior investigators.

Precautions related to Covid-19, for now, have affected Chaitin's original retirement plans to travel and spend time with family and friends. On the other hand, his son, a journalist in Washington, and daughter, a music teacher in Prince George's County, are temporarily sheltering in place at the family's Rockville home. One advantage of retirement amid the pandemic: His daughter is teaching him to play the piano, something he has wanted to do for a long time.

NIGMS Branch Chief Smith Mourned

Dr. Ward Smith, chief of NIGMS's Biomedical Technology Branch in the Division of Biophysics, Biomedical Technology, and Computational Biology, passed away in early July.

Smith first joined NIGMS in 2007 as a program director in the former Division of Cell Biology and

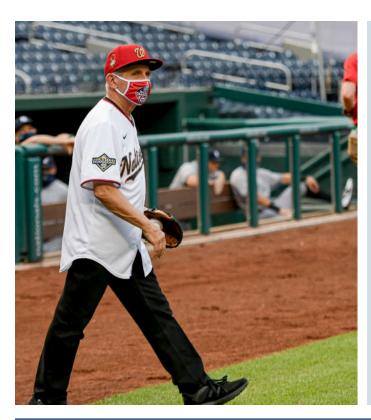


Biophysics. Among his major contributions to NIGMS were his management of the Protein Structure Initiative, for which he was honored with an NIH Director's Award, and of the NIHsupported synchrotron facilities. Smith also oversaw a large portfolio of grants in biomedical

technology. The recipient of several NIGMS awards, he will be remembered as a well-liked colleague who was generous with his time and was wiling to help others.

Prior to coming to NIGMS, Smith had an illustrious career in academia and industry. After receiving his Ph.D. at the University of Michigan, where he worked in the lab with Dr. Martha Ludwig, he joined Dr. David Eisenberg's lab at the University of California, Los Angeles, where he conducted structural studies on ribulose-1,5-biphosphate carboxylase/oxygenase, a photosynthetic enzyme essential to the global carbon cycle. He went on to spend most of his career in industry where he applied his crystallography expertise and served in leadership positions.

Major contributions included crystallizing the enzyme that's the target of glyphosate (an active ingredient in weedkillers) and solving the structure of thymidylate synthase with 5-fluorouracil, one of the first examples of the structure of a drug bound to its target. Other work helped launch the paradigm of structure-based drug design. B



'True Champion' Fauci Throws First Pitch on Opening Day

NIAID director Dr. Anthony Fauci threw the ceremonial first pitch on Major League Baseball's Opening Day July 23 at Nationals Park.



Calling him a "Nats super-fan," the Washington Nationals said in a statement, "Dr. Fauci has been a true champion for our country during the Covid-19 pandemic and throughout his distinguished career, so it is only fitting that we honor him as we kick off the 2020 season and defend our World Series Championship title."

The Topps limited edition baseball trading card featuring Fauci's toss—on sale for just 24 hours—set an all-time record print run, selling 51,512 cards. That scorched

the previous record of 19,396 cards sold in honor of Vladimir Guerrero Jr.'s debut hit for the Toronto Blue Jays in 2019.

Owing to the pandemic and to limit spread of the coronavirus, Opening Day was nearly 4 months later than normal and stadium stands were virtually empty as the 2020 60-game season will be played without in-person audiences until further notice.

The Nats dropped their first game, and first series, to the New York Yankees.



Pandemic Projects Occupy NIH'ers' Free Time

NIH employees, notoriously accomplished in their free time, were recently asked to share with us their creative projects, undertaken during those hours when a commute would normally occupy their time. Since the global coronavirus pandemic has made telework mandatory for many, we asked to see what's been going on outside of work hours. Here is some of the harvest. Feel free to submit your project to the editors by Aug. 24.

"I am sharing these chalk drawings my husband and I did at the beginning of all this for our kids," said Neyal Ammary-Risch of NHLBI's communications office. "Because I'm a nerdy public health educator married to a professional artist, we took it as an opportunity to help explain things in a fun way (and use up some of hundreds of pieces of sidewalk chalk we've accumulated). I had a few more punny ideas but ran out of driveway!"









