As scientific findings began to accumulate during the spring of 2020 about SARS-CoV-2, the virus that causes COVID-19, two facts became increasingly apparent: that it can be transmitted even by people who are asymptomatic, and that transmission occurs primarily through the air. What was less clear was how a person who is neither coughing nor sneezing might still be able to put virus particles into the air for others to inhale, and what could be done about the problem. NIDDK intramural scientists used an innovative approach to answer both questions. A person spoke into an opening in one side of a box, and a camera was placed on the opposite side. The researchers projected a sheet of laser light into the box through a slit in one of the other sides, so that droplets of fluid coming from a person's mouth would be visible as they passed through the light, so they could be recorded by the camera. A researcher spoke the words "stay healthy" into the box, and video from the camera captured the results: droplets generated in the act of speaking showed up as bright flashes of light as they passed through the laser sheet. Those two words alone were enough to generate hundreds of "speech droplets." When the researchers covered the speaker's mouth with a damp cloth, simulating use of a mask, the number of speech-generated droplets dropped virtually to zero. These experiments showed that speech is an important potential means of transmitting the virus and showed one way that the use of masks can be valuable for helping limit viral transmission. The image shown is from one of the videos at the moment when the highest number of speech droplets (shown in green) were visible in a single frame. The spots of light vary in brightness because of the differences in the size of the droplets, with the largest causing the brightest flashes. (The bright spot at the end of a curving line near the bottom left of the image is not a speech droplet: it corresponds to the tip of a very thin wire positioned near the light sheet and used as a reference for focusing the camera.) The complete video is available at: *www.nejm.org/doi/full/10.1056/nejmc2007800*.

Cross-Cutting Science

Medical advances are not usually achieved in great, intuitive leaps. More often, new prevention strategies, treatments, and cures result from a long, gradual accumulation of knowledge from years of scientific research. Insights into the fundamental biologic building blocks and processes of an organism—its genes, the proteins they encode, the inner workings of cells, and the ways cells communicate with each other—can have broad and far-reaching implications. Indeed, many significant advances in our knowledge of disease and disease treatment can be traced to laboratory studies whose relevance to health could not have been fully known or appreciated at the time they were conducted.

There are also moments when the biomedical research enterprise is called upon to rapidly harness knowledge, resources, and expertise across many fields to meet extraordinary and urgent challenges that threaten the public health. This past year has seen the emergence of a pandemic new viral disease, COVID-19, whose short- and long-term impacts on human health are still being discovered as the NIH and others strive to develop effective vaccines and treatments as quickly as possible. At the same time, events highlighting racial injustice in this country have drawn fresh and much-needed attention to the burden of health disparities on communities that are also most heavily affected by COVID-19 and by chronic diseases within the NIDDK mission.

Described in this chapter are NIDDK research-related efforts to overcome these critical challenges, as well as a feature celebrating 70 years of NIDDK-supported accomplishments and continued research for the betterment of public health today and into the future.

COVID-19

The COVID-19 pandemic has brought illness, disability, and death for many in the United States and around the world, while upending lives and normal activities. COVID-19 is caused by a novel respiratory virus, SARS-coronavirus-2, or SARS-CoV-2, that uses a cell surface receptor, called angiotensin-converting enzyme 2 (ACE2), to enter and replicate within cells in the body. Disease symptoms range from mild to severe. While the majority of people with severe COVID-19 disease suffer respiratory symptoms, the virus can cause damage throughout the body, with many other serious and life-threatening effects.[1]

Although people of any age or state of health can contract the virus, those with chronic diseases such as type 2 diabetes, obesity, and chronic kidney disease are at higher risk of developing severe disease leading to hospitalization and death,[2] as are older adults and people with depressed immune systems. Alarmingly, many people who become infected with SARS-CoV-2 do not develop obvious symptoms themselves but can still spread the disease to others—including those at high risk. Researchers have just recently begun to gain insights into genetic and other factors that could help explain and hopefully help predict the observed variability in COVID-19 disease severity.[3] At the same time, as researchers are examining people in recovery from COVID-19, they are finding evidence of damage to the heart and other organs even in people with mild or asymptomatic infections, suggesting that the

[1] *Gupta A, et al. Nat Med 26: 1017-1032, 2020.*

[2] *Centers for Disease Control and Prevention: www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/evidence-table.html. Accessed October 29, 2020.*

[3] *Zhang Q, et al. Science 370: eabd4570, 2020; Bastard P, et al. Science 370: eabd4585, 2020.*

virus can cause silent damage to the body whose permanence is yet unknown as the disease is so new.[4]

Multifaceted Research Response

The NIH has undertaken a multi-pronged approach to rapidly establish studies aimed at vaccine development and testing, improved COVID-19 testing strategies, more effective treatments, and better understanding of COVID-19 disease and the virus that causes it. These efforts are detailed on the NIH website at: *www.nih.gov/coronavirus*. The NIDDK and other NIH components have also undertaken specific efforts to support research that can address the many facets of this novel disease. For example, the NIDDK has provided funding supplements to grantees who proposed revisions to ongoing projects aimed at achieving insights into the relationship between COVID-19 and preexisting or new-onset kidney, metabolic, and gastrointestinal diseases and that may lead to rapid translation and impact in the COVID-19 emergency. The NIDDK has also solicited new applications for research funding that would support projects focused on basic and clinical mechanistic studies of SARS-CoV-2 and COVID-19 susceptibility, routes of infection, course of disease, morbidity and mortality in people with preexisting diseases, or adverse acute or chronic outcomes in organs, tissues, and biological systems within the Institute's purview.

Another key aspect of the NIDDK's response has been to work toward alleviating the burden imposed by the COVID-19 pandemic on the biomedical research enterprise: as businesses, government and community agencies, and academic institutions shuttered to protect staff and employees and prevent spread of SARS-CoV-2 in the early days of the pandemic, many biomedical research efforts not directly involved in COVID-19 studies mostly ground to a halt. Many NIDDK clinical studies were halted due to concerns regarding face-to-face clinic visits and closures of academic clinical research facilities, and thousands of NIDDK-supported researchers suspended laboratory-based investigations. Subsequent efforts by institutions to begin conducting research activities anew underscored novel challenges and hurdles posed by COVID-19. As the timeline for a return to "normal" is unknown, this disruption to research has had tremendous ripple effects on scientific progress, careers, and prospects for funding, especially for younger investigators. To obtain greater insight on the challenges "on the ground" and possible solutions, the NIDDK solicited input from its National Advisory Council—whose members include scientific luminaries, academic leaders, and representatives from health advocacy groups and professional societies—on the scope of the pandemic's impact on Institute-supported research. Both NIH-wide policy changes and NIDDK efforts have enabled the Institute to implement several of the Council's recommendations, including strategies for "re-starting" research activities that were affected by the pandemic.

NIDDK intramural researchers were also affected by the disruptions to onsite laboratory research. However, as part of a nimble public health response, the NIH asked its scientists to propose studies germane to COVID-19, which could be pursued within careful parameters at NIH research campuses as local caseloads, conditions, and safety measures allowed. Numerous NIDDK investigators proposed such studies and many are under way, ranging from fundamental studies of the virus and potential vaccine targets to clinical studies of viral detection, organ impact, and possible symptom prevention. For example, NIDDK investigators published findings from one set of studies early in the pandemic that have proven critical in establishing an evidence base for measures to prevent viral spread, as detailed below.

Through all of these efforts, as the Nation continues its struggle with COVID-19, the NIDDK continues to strive toward ensuring the health and safety of researchers, study volunteers, and patients while also helping to maintain research progress and a robust scientific workforce across all of the areas within its research mission.

More details and updates on the NIDDK response to COVID-19 can be found at: *www.niddk.nih.gov/research-funding/research-programs/niddk-covid-19-research-response*.

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[4] Puntmann VO, et al. JAMA Cardiol 5: 1265-1273, 2020; Oran DP and Topol EJ. Ann Intern Med 173: 362-367, 2020.

Speaking of COVID-19…

A series of experiments by NIDDK intramural investigators shows how speech might promote the spread of the virus that causes COVID-19 even from people who have no apparent symptoms of the disease—results that underscore the importance of mask-wearing to stem the pandemic. Any of a wide variety of respiratory infections are known to spread from person to person through sneezing and coughing, both of which generate a mist of potentially pathogen-containing small droplets of saliva and mucous that can be inhaled by people nearby. This is one important way that the virus that causes COVID-19 is transmitted. However, a growing body of evidence suggests that the virus may also spread easily from infected people who feel well and are neither coughing nor sneezing—but how? Some suggestive evidence has raised the possibility that normal speech might play a role. Speaking is also known to generate droplets that can harbor viruses; moreover, many of these droplets are smaller than those produced by coughing and sneezing, which means they have the potential to remain airborne for longer. But how many such droplets are produced during speech, how long they last, and how far they travel have been open questions.

To provide answers, NIDDK intramural researchers developed a clever tool for quantifying speech-generated droplets and following their fates. They used a specially designed lens to spread the narrow beam of a laser into a thin sheet of light, which they projected through a slit in a carboard box of about 18x20x25 inches in size, painted black inside to prevent the light from reflecting off the sides. Droplets generated by speaking the words "stay healthy" through a hole in the box caused visible flashes when they passed through the light sheet. Using the video camera feature of a mobile phone to record these flashes allowed the scientists to determine not only how many droplets were created—about 2,600 per second of speech—but also to estimate their size (from the intensity of the flash) and to find out how long they continued to circulate within the enclosed box. The louder the words were spoken, the more droplets they generated; also, certain sounds, particularly the "th" sound in "healthy," produced more droplets than others. While the largest droplets disappeared quickly, likely falling to the bottom of the box, thousands of smaller droplets persisted far longer, often continuing to circulate within the enclosed box for 14 minutes or more. In fact, many of the tiniest droplets rapidly dried out to form particles that were still circulating in the box over an hour later. Importantly, one set of experiments showed that covering the mouth with a damp cloth—analogous to wearing a mask—virtually eliminated movement of speech-generated droplets into the box. As a high proportion of people with COVID-19 harbor potentially transmissible virus yet initially have no symptoms—and indeed may never develop a severe form of the illness—this experiment highlights one way that using masks in public spaces is important for limiting the spread of COVID-19.

Anfinrud P, Stadnytskyi V, Bax CE, and Bax A. Visualizing speech-generated oral fluid droplets with laser light scattering. N Engl J Med 382: 2061-2063, 2020.

Stadnytskyi V, Bax CE, Bax A, and Anfinrud P. The airborne lifetime of small speech droplets and their potential importance in SARS-CoV-2 transmission. Proc Natl Acad Sci USA 117: 11875-11877, 2020.

NIDDK EFFORTS TOWARD ACHIEVING HEALTH EQUITY

As the United States has grappled with the impact of the COVID-19 pandemic, heartbreaking events have been highlighting racial injustice in the Nation. This injustice falls heavily on people who are simultaneously burdened by health disparities. In fact, disparities in COVID-19 outcomes are exacerbated by chronic diseases, such as obesity, diabetes, and kidney disease, that disproportionately affect U.S. minority groups. Because combating these conditions is central to the NIDDK mission, the Institute is firmly committed to research programs aimed at reducing COVID-19 disparities. For example, the NIDDK is participating in an NIH-wide program called Rapid Acceleration of Diagnostics-Underserved Populations, which is working to understand the factors associated with disparities in COVID-19 morbidity and mortality and to lay the foundation to reduce disparities for those underserved and vulnerable populations who are disproportionately affected by, have the highest infection rates of, and/or are most at risk for complications or poor outcomes from the COVID-19 pandemic. Moreover, because many NIDDK mission diseases and disorders place disparate burdens on

minority groups and people with limited resources, and because the Institute believes health equity is integral to social justice, the NIDDK has reaffirmed its commitment to combating health disparities—whether pandemic related or not—through basic, translational, and clinical research.

NIDDK Approaches Toward Advancing Health Equity In Its Mission Diseases

The NIDDK is pursuing four main strategies to help advance the cause of health equity:

- *Continue vigorous efforts to recruit diverse study cohorts inclusive of those most affected*, which often means reaching out to underserved segments of the population.

- Because having people from disproportionately affected backgrounds conduct and guide research helps address health disparities most effectively, the NIDDK seeks to *open doors for young people from underrepresented groups* through training, support, and inspiration to pursue research careers.

- Engaging clinical trial participants more broadly in the research enterprise can help advance scientific inquiry; thus, the NIDDK is now implementing strategies to *promote participant engagement*, not only as study volunteers, but also in study design, recruitment, and consent.

- The Institute is *supporting research to identify the causes of health disparities*, fueling clinical research by yielding testable hypotheses. Disparities may stem partly from biological differences, such as genetic risk factors more prevalent in one population than in another. Disparities that stem from systematic differences in access to care, environmental exposures, and other external factors are of equal interest; for this reason, the NIDDK also supports research on social determinants of health, which are conditions in the places where people learn, live, play, and work that affect health risks and outcomes. Research on social determinants of health is crucial for lighting a path toward health equity and is a vital complement to studying biological factors that contribute to health disparities.

Mutually Reinforcing Approaches Toward Health Equity

The four approaches outlined above can interact and bolster one another, as illustrated by the NIDDK-supported APOL1 Long-term Kidney Transplantation Outcomes Network (APOLLO). Groundbreaking NIDDK research demonstrated a key biological factor contributing to the elevated rates of end-stage renal disease (ESRD), sometimes known as kidney failure, in people of African descent: specific variants of a gene called *APOL1*, found almost exclusively in people of recent African ancestry, are associated with significantly elevated ESRD risk. Based on this discovery, the NIDDK led the development of the APOLLO research network to determine the impact of *APOL1* genetic variants on kidney transplant outcomes for 2,614 pairs of living African American donors and the recipients of their kidneys. APOLLO is also pioneering the Institute's approach to participant engagement via its Community Advisory Council (CAC). Composed of African American transplant recipients, kidney donors, and individuals on dialysis, the CAC provides input and guidance on study design, including recruitment, retention, implementation of protocols, and return of results. Thus, APOLLO integrates three approaches to overcoming disparities: it proceeds from a seminal discovery about a health disparity's cause, is composed of a large and representative group of those most affected, and is demonstrating the value of engaging participants in research.

Promoting Diversity in the Scientific Workforce

While NIDDK researchers from every race and ethnicity are striving to reduce health disparities, the NIDDK recognizes that these vital efforts would benefit substantially from having a scientific workforce that better reflects the diverse backgrounds and experiences of the U.S. population. Indeed, the overall biomedical research enterprise would be greatly strengthened by the scientific ideas and talent of people currently underrepresented in research. While scientific talent is surely well represented across all groups, opportunity is not. Therefore, it is important to ensure that young people are exposed to the challenges, joys, and opportunities of science and are provided needed mentoring.

The NIDDK's approach to overcoming the dearth of minority scientists therefore begins in grade school and continues through support and mentorship for minority investigators early in their careers. For

example, each year the High School Short-Term Research Experience for Underrepresented Persons (STEP-UP) program provides a stimulating, rigorous summer opportunity to discover experimental science for about 100 African American, Latino/Hispanic, and American Indian or Alaska Native students, as well as students from U.S. territories. STEP-UP also supports undergraduates interested in conducting NIDDK-supported research. Complementing this effort, the NIDDK Diversity Summer Research Training Program (DSRTP) brings college students from minority groups to the NIH campus for mentored research experiences. Both DSRTP and STEP-UP are intended to help build and sustain a diverse biomedical, behavioral, clinical, and social science researcher pipeline focused on NIDDK mission areas. NIDDK support for minority investigators continues through graduate school and into faculty positions. For example, the Network of Minority Health Research Investigators (NMRI) connects postdoctoral and junior faculty investigators with more senior researchers who mentor and serve as role models for them.

Information on NIDDK programs designed to increase the number of minority investigators—and foster their success—may be found on the NIDDK website at: *www.niddk.nih.gov/research-funding/research-programs/diversity-programs*.

The NIDDK's Role in Promoting Better Health Across American Society

Systemic changes across many U.S. sectors will be needed to achieve health equity. While many changes are beyond the missions of the NIH, the NIDDK's approaches to the problem proceed from the recognition that research can play a valuable role in advancing these goals. The programs described here are just a sample of the NIDDK's ongoing efforts toward health equity and toward ensuring that NIDDK-supported research benefits all of America—especially those most burdened by the diseases and disorders in its mission.

(Adapted from an article by Dr. Griffin P. Rodgers, NIDDK Director, and Dr. B. Tibor Roberts, NIDDK Office of Scientific Program and Policy Analysis, J Clin Invest 130: 5036-5038, 2020.)

Celebrating the Past and Planning for the Future: The 70th Anniversary of the NIDDK

In 2020, the NIDDK celebrated 70 years since its founding in August 1950 (see "History of the NIDDK" inset). Over the course of its history, the Institute that is known today as the National Institute of Diabetes and Digestive and Kidney Diseases is proud to have supported and conducted research on many of the Nation's most serious chronic diseases. Affecting people of all ages and racial and ethnic groups, the diseases and disorders within the NIDDK research mission encompass some of the most common, costly, and disabling conditions, as well as less prevalent but nonetheless debilitating diseases affecting Americans today: endocrine and metabolic diseases and disorders such as diabetes and obesity, digestive diseases such as nonalcoholic fatty liver disease and inflammatory bowel disease, chronic kidney disease and kidney failure, urologic diseases such as interstitial cystitis/bladder pain syndrome and benign prostate enlargement, and blood diseases such as anemias.

The research advances made possible through 70 years of NIDDK support have saved lives, improved quality of life, and laid the foundation for future progress. The Institute has supported a number of winners of the world's most prestigious scientific honors, including the Nobel Prize in Physiology or Medicine, the Nobel Prize in Chemistry, and the Lasker Awards. These honorees include extramural scientists at universities and other research institutions across the country who have been supported by the NIDDK, as well as scientists within the Institute's Intramural Research Program.

As part of activities to mark its 70th anniversary, in the summer of 2020 the NIDDK highlighted important research accomplishments supported over the past seven decades and showcased how these advancements inform the Institute's current activities and guide its vision for the future. These communications are highlighted on the NIDDK

History of the NIDDK: On August 15, 1950, President Harry S. Truman signed into law the Omnibus Medical Research Act, establishing the National Institute of Arthritis and Metabolic Diseases (NIAMD)—which would become today's NIDDK. The new Institute incorporated the laboratories of the Experimental Biology and Medicine Institute and expanded to include clinical investigation in rheumatic diseases, diabetes, and a number of metabolic, endocrine, and gastrointestinal diseases. That same year, the NIAMD Council held its first meeting and recommended approval of NIAMD's first grants. Over the years, the NIAMD evolved into the National Institute of Arthritis, Metabolism, and Digestive Diseases (in 1972) and the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (in 1981). In 1986, the Institute's Division of Arthritis, Musculoskeletal and Skin Diseases became the core of a new, independent Institute. The NIDDK then acquired its current name—the National Institute of Diabetes and Digestive and Kidney Diseases.

website (*www.niddk.nih.gov/about-niddk/70th-anniversary*) and in social media, and additional communications took place through such venues as the "Healthy Moments" radio broadcast featuring the NIDDK Director, Dr. Griffin P. Rodgers. During the 70th anniversary year, the NIDDK also embarked upon the development of an Institute-wide strategic plan, which will complement disease-specific planning efforts and help guide research planning across its mission. External input is key to this effort. The NIDDK invited broad external input with a public Request for Information, which was open for several months; the Institute is also gaining input from its Advisory Council and strategic plan Working Group and will seek further external input during the planning process.

In addition to celebrating seven decades of substantial research accomplishments, 2020 brought remarkable challenges as a global pandemic upended life as we knew it. NIDDK staff, grantees, and trainees rose to those challenges, seeking ways to combat COVID-19 while keeping research operations running smoothly and safely, despite many uncertainties. With a strengthened spirit in 2021, we now embark upon the next 70 years of research with compassion and dedication to advance public health.