Gates celebrates research collaborations with NIH

Global health philanthropist Bill Gates paid tribute to the numerous flourishing partnerships between his family foundation and the NIH, during a recent visit to the Bethesda campus. Research innovations are helping reduce the toll of malaria, tuberculosis, HIV/AIDS and malnutrition, but Gates noted much is left to be accomplished before global health equity is achieved.

Gates said the two organizations are united by their common goals of improving health and understanding the root causes of disease so that effective interventions can be developed. He thanked NIH for the relationship, adding, “It’s great to see that the partnership is growing over time.”

The co-chair of the Bill and Melinda Gates Foundation visited NIH to deliver the annual David E. Barins Global Health Lecture, titled “Why the Future Needs Biomedical Innovation.” The event honors its namesake for his career spent improving health in low-income countries and is co-sponsored by NIH’s National Institute of Dental and Craniofacial Research and Fogarty.

Gates recalled the early days of his interest in global health, when he and his wife, Melinda, learned from an article that hundreds of thousands of children died every year of rotavirus—a diarrheal disease they’d not heard of—mainly in poor countries, and vaccines to protect them were just nearing licensure. Today, one of their foundation’s key goals is to provide disadvantaged children with protection against rotavirus and other killers.

Fogarty marks decade of brain disorders program

Fogarty and its NIH partners will mark a decade of support for brain disorders research and training in developing countries at a three-day symposium on the NIH campus from Feb. 11-13. The meeting, “Frontiers in Neuroscience for Global Health,” will focus on the accomplishments of grantees funded through Fogarty’s Brain Disorders in the Developing World: Research Across the Lifespan (BRAIN) program. The agenda will also feature lessons in research capacity building.

Attendees will share insights on a wide range of topics, including the influence of environmental pollutants and toxins, infectious diseases, trauma and injury, genetics, nutrition and ways to address disorders and deficits with interventions and rehabilitation across the lifespan. The grantees will also discuss ways to address gaps in the current research portfolio, as well as new directions and opportunities for neuroscience in low- and middle-income countries.

The event will be webcast live and archived: http://videocast.nih.gov

Brain Disorders: Research Across the Lifespan

- Fogarty spurs neurological research in developing countries
- Gene in Colombian family holds promise for Alzheimer’s research
- Scientists study brain impact of toxins and pathogens

Read more on pages 8 - 13
Fogarty launches mHealth program

Fogarty has launched a new program to encourage further development of mobile technology and research into how it can be used to improve health, especially in low-resource countries. Although cellphones and other new technologies are increasingly used in research and health care, very limited data are available to determine their impact.

The initiative, Mobile Health: Technology and Outcomes in Low- and Middle-Income Countries (LMICs), aims to support multidisciplinary teams to research possible new mHealth tools or interventions either for chronic diseases or an array of other health issues.

The request for applications encourages research projects that focus on the adaptation, optimization and evaluation of mHealth tools or interventions to prevent, diagnose, manage and treat chronic diseases. Proposals may also involve adapting and evaluating crosscutting mHealth applications that are not disease-specific. Applications should have a strong emphasis on the evaluation of health-related outcomes of the tool or intervention proposed. Technology development and formative research proposals are also acceptable, as long as outcomes-based research is included.

The mHealth technology being developed or adapted should address a well-defined LMIC need and should be appropriate for use in that setting. In addition, interoperability and integration with other health information systems should be considered. As with most Fogarty grants, this program requires partnerships between U.S. and LMIC institutions, which will together build LMIC capacity, through relevant research training, career development, mentoring and technology transfer.

Since mHealth involves many different areas of expertise, the program encourages collaborations among researchers in fields such as behavioral science, engineering, computer science, business, medicine and public health.

NIH partners include the National Cancer Institute, National Institute of Biomedical Imaging and Bioengineering, National Institute of Child Health and Human Development, National Institute of Mental Health and Office of Behavioral and Social Sciences Research. Applicants may request up to $125,000 direct costs per year for up to two years. The first deadline for applications is February 19, 2014.

NIH joins global effort to fund diabetes research

NIH and other members of the Global Alliance for Chronic Diseases (GACD) have jointly announced a new series of research opportunities to tackle the global health burden of Type 2 diabetes, which is growing—especially in low-resource countries where 80 percent of people with the disease reside. This is the second GACD project, following the 2011 launch of grants targeting hypertension.

GACD said research proposals should aim to reduce health inequities in diabetes prevention and treatment, enhance knowledge that can be used for public benefit, and produce scientific data to inform local and national health service providers and policymakers.

NIH is offering three options: Exploratory/developmental research grants may be funded for up to $275,000 over two years, small grant programs for up to $100,000 over two years and research project grants, lasting no longer than five years, with an unspecified funding level. The application deadlines are in February 2014.

NIH participants include Fogarty, the Office of Behavioral and Social Sciences Research, National Institute of Diabetes and Digestive and Kidney Diseases, and National Heart, Lung and Blood Institute.

GACD is a collection of the world’s biggest publicly-funded research agencies, including NIH, that represent more than three-quarters of public health research funding worldwide.
US is losing biomedical research leadership to Asia

The U.S., which has long led the world in biomedical research and development (R&D) spending, is slowly reducing its investments while other countries—particularly in Asia—are boosting theirs, according to an analysis by experts from health care agencies, universities and research groups.

Their report, “Asia’s Ascent—Global Trends in Biomedical R&D Expenditures,” was published recently in the New England Journal of Medicine. In the 2007-2012 period studied, the U.S. share of global public and private biomedical R&D investments slumped from 51 to 45 percent, a change the authors term “remarkable,” especially given that the U.S. not so long ago funded as much as 80 percent of the global activity.

Meanwhile, many Asian countries raised their investments in the same period with double-digit annual growth rates, topped by China’s hefty 33 percent. Japan’s total spending expanded by the biggest absolute dollar amount of any country: $9 billion.

In the year since the study’s cutoff date, the situation has continued to deteriorate for the U.S. as government budget cuts curbed biomedical research funds further. “We are at a crisis point,” said NIH Director Dr. Francis S. Collins in a recent C-SPAN TV broadcast. “In terms of our ability to do research, NIH has received a 25 percent cut, all told, in the past 10 years.”

Collins has underscored to Congress the importance of NIH-funded research to overall U.S. economic activity. It advances scientific products and technologies, creates economic growth, supports high-paying jobs and enhances health and quality of life. “Across the board we need to turn this around,” Collins said, according to a report in The Atlantic. “You look at what a country invests in research and development as part of GDP as an indicator of the health of the [nation’s seriousness]. Right now we are at 2.6 percent. Many other countries are at 3 percent or above—they’re basically out to eat our lunch.”

Most alarming, Collins warned, is the prospect that some lost ground cannot be recovered. NIH now funds only about 15 percent of grant applications, where it traditionally funded about a third, leaving burgeoning numbers of scientists discouraged and more likely to change careers or take their skills overseas. “Research isn’t like a spigot that you turn on and off at will,” he said in his C-SPAN comments. “If we lose scientists, they’re not coming back when things get better.” Damage is also being done to mid-career scientists whose funding is not being renewed, he noted, which means the NIH is losing the impact of its previous research investments as well.

Although the NEJM report showed the U.S. combined private and public biomedical R&D spending in 2012 still dwarfed that of any other individual country, the speed of change is dramatic. Asia-Oceania’s total R&D spending surged by a half between 2007 and 2012.

Contributing to Asia’s blossoming biomedical sector are its cheaper labor costs and higher government subsidies, the NEJM authors wrote, pointing out that U.S. development costs per drug approval have meanwhile “increased considerably.” They called the lack of U.S. national strategy for biomedical R&D “disappointing,” and said if the U.S. hopes to uphold its leadership in the field, it must boost not only NIH funding, but also provide incentives to industry to encourage more R&D investment at home.

RESOURCE

Study reveals drug-resistant mutation in malaria

A newly uncovered mutation in the malaria parasite *Plasmodium falciparum* enables it to survive the most potent antimalarial drug available, artemisinin. This discovery, by an international collaboration that includes NIH’s National Institute of Allergy and Infectious Diseases (NIAID), identifies not only a target for next-generation treatments but also a tool to monitor and help limit the global spread of resistant parasites.

The findings show “important determinants of artemisinin resistance,” the researchers noted in their paper, published recently in *Nature*. Finding genomic changes that cause drug resistance represents “a major advance in the fight against malaria and a significant step toward the eventual eradication of this disease,” according to a press statement by Institut Pasteur, one of the funders. The hunt for genes underlying antimalarial drug resistance has frustrated global health researchers for decades, with the parasite always one step ahead. Over the years, resistance has emerged against nearly all antimalarial drugs, including most recently the latest arrow in the quiver, artemisinin. This loss of effective treatment is threatening malaria control and elimination activities worldwide.

Most cases of artemisinin resistance have appeared in western Cambodia, but clinics have reported instances in Burma, Thailand and Vietnam, according to WHO data. A major concern is that drug-resistant parasites will travel to sub-Saharan Africa, where malaria is most prevalent and deadly.

To search for genetic mutations in *P. falciparum* that enable it to dodge the toxic effects of artemisinin, the international team developed a series of new detection methods involving biological, genomic, clinical and epidemiological approaches. First they induced artemisinin resistance in a parasite strain by exposing it to increasing artemisinin concentrations for 120 reproductive cycles over 5 years. They then sequenced the entire genome of this strain and a similar but nonresistant control strain, and compared the various mutations. Eight had developed in the laboratory, one of which occurred in the so-called “K13-propeller” allele.

The team confirmed this type of mutation occurred in artemisinin-resistant parasites sampled in Cambodia, and then mapped their presence in those patients who had suffered artemisinin-resistant infections. Their analysis confirmed the mutation’s culpability in parasite resistance to artemisinin.

With this result, physicians and scientists now have a molecular marker that quickly detects artemisinin-resistant parasites, so they can efficiently track and contain their spread, as well as tailor patient treatments in real time to save lives and, ultimately, test new antimalarial drugs against these mutant parasites. The researchers are now investigating how the K13-propeller mutations evolve and if similar shields are developing in malarial parasites elsewhere in the world.

WHO urges artemisinin resistance testing

The WHO recently released its 2013 world report on malaria that urges countries to follow standard procedures in routinely testing how well malaria treatments are working, to enhance comparison of national data and allow quicker reaction to the buildup of drug resistance in malaria-causing parasites.

“Continuous monitoring of the efficacy of and resistance to antimalarial drugs is critical, in order to inform treatment policy and ensure early detection of changing patterns of resistance,” the WHO report notes. This practice “can help to detect early changes in *P. falciparum* sensitivity to artemisinin.”

The study reiterates that to contain the risk of artemisinin resistance, health authorities in nine countries permitting artemisinin-based monotherapies should ban the practice and ensure the drug is given only in combination with other malaria treatments to preserve its effectiveness over time.

Full report: http://bit.ly/1gEC110

RESOURCE

Paper abstract: http://1.usa.gov/1htw3TA
Gates celebrates research collaborations with NIH

“Vaccines, after all, are pretty magical,” said Gates, who toured several NIH vaccine labs during his visit. “Over time, the cost of making most vaccines will get down to something like 20 or 25 cents per child treated and yet it can give you lifelong protection.”

Prioritizing research projects is a challenge, he noted, with NIH and the Gates Foundation together accounting for about half of all global health research funding. Gates said his foundation identifies which health areas to support by analyzing how to bring the highest possible disease reduction for each dollar spent. “We want to have as much impact as we can,” he said, noting his funding decisions incorporate the extent to which a particular disease undermines a person’s ability to be productive—a measure known as DALY or disability adjusted life years lost.

Although the foundation focuses on infectious diseases with high DALYs, it also supports research into chronic health conditions with long-term impact, such as child under-nutrition and an often detrimental condition that affects every country in the world—preterm birth. Gates added that if NIH eventually devises a cost-effective intervention for a chronic disease such as cancer or diabetes, “we will get right on making sure that it gets delivered to the poor world. We’re all about health equity.”

Given the enormous value of NIH’s contributions to global health, Gates said he is “disappointed” that its funding is dwindling even as other countries are increasing theirs. Bolstering research spending is a wise decision, he explained. “Investing in research has huge paybacks, paybacks in improving the human condition and paybacks in reducing health costs as you get new tools,” he said. “I am an optimist. I think we’ll be able to convince people that those investments should be restored and grow.”

Gates, whose technological innovations and wealth as co-founder of Microsoft have enabled him to devote billions of dollars to global health, commented on how solutions can be found by harnessing innovations from diverse disciplines. “Sometimes the technology you want to use is not obvious . . . so we need to challenge people from different realms,” he said.

Technology such as Internet access and cellphones can improve global clinical practice in a “phenomenal” way, he noted, for instance in advancing record keeping, measurement and quality of care, monitoring cold storage and providing advice and training to health care workers.

Diagnosis might also be enhanced in some cases by use of digital cameras and processing software, he added.

Yet, new technology should be introduced in a measured way, he cautioned, saying, “In many countries, you don’t want to force [the introduction] prematurely. You’ve got to have a certain level of quality before it becomes a net benefit.”

Gates noted that technology could play an important role in expanding the number of health care professionals trained in countries with heavy disease burden, particularly Africa. “It would be ideal if you can get the scientific knowledge there and the treatment knowledge there to be much higher,” he said. “The gaps are pretty huge and we’re only making modest progress.”

One important way to advance learning is by increased use of free online teaching tools. The Gates Foundation is a significant funder of massive open online courses, or MOOCs. “People watching a video lecture with somebody interesting who’s giving examples and who’s forcing them to answer a few questions to see if they’re gaining the knowledge, that works better than if you’re just throwing them the textbook,” Gates said.

Gates concluded that his foundation will continue to prioritize global health for many decades to come and he welcomes facing the challenges ahead in partnership with NIH.

“Most people are born and die and never see a doctor,” Gates said. “As long as there’s health inequity, poor children have more risk of getting these diseases and there’ll be a lot that we can do.”

RESOURCE

Fogarty Fellow learns skills for global health career

By Arthur Allen

For Dr. Rachel T. Idowu, her Fogarty fellowship in Africa helped her gain the skills needed to conduct research in low-income settings—skills that were immediately useful when she finished the program and began work at the U.S. Centers for Disease Control and Prevention.

As a participant in the Fogarty Global Health Program for Fellows and Scholars, Idowu worked on a project in Kenya designed to evaluate surgical services at the district level by looking at basic outcomes. She collected data with an eye toward helping hospital officials design better decision-making systems. Limited resources and a shortage of surgeons in countries like Kenya mean that patients can face weeks in hospital beds awaiting procedures, which they must pay for in advance. In collaboration with a colleague at Vanderbilt University, Idowu designed an Android-based study questionnaire compatible with an open-source app for smartphones. She hired two Kenyan nurses and trained them to use smartphones to collect data at the study hospitals.

Getting consent and navigating the ethical review process was a challenge. “There were a lot of people dynamics; you’re trying to establish a relationship of trust with strangers and work out a plan for something you think will be of benefit to their country,” said Idowu. “You learn to structure your downtime to get other things done while you’re waiting for approvals.”

Idowu has not had much time to digest her findings. She got off a plane from Nairobi in June 2012 and went to work the next month as an Epidemic Intelligence Service Officer in the International Emergency and Refugee Health Branch of the CDC’s Center for Global Health.

Her Fogarty experience has been extremely useful at the CDC, where she quickly became involved in a number of projects. “The time I spent living and working in Kenya has been very valuable to the job I have now,” said Idowu.

Since joining the CDC, Idowu has helped establish a uniform public health data reporting system in Jordan for health partners administering care inside a large Syrian refugee camp. In South Sudan, her team evaluated the country’s surveillance system for communicable diseases. And in Chad, she was part of a CDC team examining health outcomes for babies at a Sudanese refugee camp, at the request of the U.N. High Commission for Refugees.

These assignments have often involved interacting with health ministries and administrators at regional and local levels, so her work in Kenya was very relevant, Idowu noted. “The Fogarty experience gave me a level of comfort in thinking about which health providers are trained to deliver care and how they can improve the work they do.”

She has also used the mobile technology software systems she learned about in Kenya. The Fogarty-sponsored project was an early example of using mobile data collection tools in combination with a research data management system to accelerate the analysis of health services delivery data in a low-resource setting, observed mentor Dr. Eric Manders, now also at CDC’s Center for Global Health. Manders was previously a bioinformatics expert at Vanderbilt’s Institute for Global Health, where he assisted Idowu in designing her Fogarty study.

Idowu’s decision to embed the data management platform in a respected Kenyan research organization exposed her host country co-investigators to the methodology, building local capacity, according to Manders. “It has been gratifying to observe that in her current role at the CDC, she has transferred her experience with this technology to larger, more complex studies, conducted in remote settings of great humanitarian need.”
Why does the U.S. give priority to global health?
The United States leads on global health because it is perceived to be in U.S. national interests to do so. Fifteen years ago, a significant change occurred in how global health is viewed vis-à-vis U.S. foreign policy. Beginning late in the Clinton Administration, accelerating swiftly post-9/11, and continuing robustly today, there has been recognition at the highest levels that U.S. leadership in advancing global health benefits the U.S. in three critical ways: Investing in American humanitarian values, fostering the stability and security of communities, and undergirding economic growth. It is understood as essential to mitigate specific emerging threats: HIV/AIDS was the most powerful such threat that came into focus in the late 1990s. Malaria and tuberculosis, pandemic influenza and diverse emerging forms of resistance also came to be seen as health security threats warranting heightened attention. A strategic rationale for global health took form, paired with the assumption of real national interests and serious enduring threats. That may seem at odds with a conventional public health or biomedical perspective, but it has been fundamental to spurring sustained U.S. engagement.

What has fueled this leadership?
Operationally, the U.S. role in the past decade and a half has rested on a few key elements: leadership, Congress and resources. Leadership was evidenced by a direct engagement by the President, his White House staff and cabinet officials in supporting the Global Fund to Fight AIDS, Tuberculosis and Malaria, to the tune of at least $4 billion. U.S. leadership has relied both on an unusual bipartisan compact with Congress and a broad societal base of support. Quite remarkably, even as Congress has experienced high turnover, bitter polarization and worsening budgets, it has been possible to preserve a consensus between the executive and Congress on sustaining U.S. efforts in global health. This produced an historic surge of funding—a rise in the aggregate annual investment of roughly $1 billion in 2000 to $8 billion by 2008—along with a concentrated focus on infectious diseases and maternal and child health, concentrated authority in the Office of the Global AIDS Coordinator and impressive gains in efficiency. The population receiving U.S.-supported antiretroviral treatment rose from 1.8 million to 6.8 million over the course of the first five years of the Obama administration, in the midst of a flat budget. That was a powerful factor in convincing Congress to stay the course.

How does NIH research support this effort?
Most fundamentally, through long-term strategic investments in helping answer the questions for which we lack answers—in terms of basic science, trials, product development, and operational research—in the very societies in Africa, Asia and Latin America where the most critical health challenges are concentrated, and where future solutions will be generated. Successful NIH-supported research generates new knowledge, builds R&D capacity in partner countries, creates future health and science leaders, and results in collaborations that enrich and strengthen both U.S. institutions and partner institutions in low- and middle-income countries.

But demonstrating the linkages between R&D and mainstream U.S. global health investments can be tricky and requires a deft form of communication and argumentation. Research investments are often quiet, out of view, very long-term by nature, highly technical and are often uncertain ventures, some of which may succeed while many may not. In the midst of flat or contracting budgets, it becomes that much more imperative to convey effectively the value and dynamism of these investments to nontechnical audiences—in Congress, the media and to the general American people. The Medical Education Partnership Initiative (MEPI) between African and American universities, funded through the President’s Emergency Plan for AIDS Relief (PEPFAR) and administered through the Fogarty International Center, is a powerful creative instance of how the U.S. engagement in infectious disease programs can expand its reach to strengthen U.S.-African research collaborations.

http://csis.org/category/topics/global-health
Brain Disorders: Research Across the Lifespan

Difficult births, poor nutrition and exposure to infectious diseases and toxins mean many children in poor countries lose cognitive function early in their lives and are prevented from achieving their full potential. Others go on to develop epilepsy, causing them to be feared and shunned. For those who manage to survive to old age, they may become afflicted with premature dementia but lack access to diagnosis or treatment.

These and other brain disorders that develop across the lifespan are heartbreaking wherever they occur but pose an enormous burden in low- and middle-income countries where resources are lacking. The physician-to-patient ratio can be as low as one for every 20,000 people, with even fewer psychiatrists and neurologists. That’s why Fogarty began its brain disorders program a decade ago, designed to expand research capacity for dozens of conditions in developing countries. The initiative supports activities that address neurodevelopmental disorders—such as autism, fetal alcohol syndrome and learning disabilities—as well as neurodegenerative diseases including Alzheimer’s and Parkinson’s Diseases, addiction, seizure disorders, neuropsychiatric conditions such as depression and schizophrenia, posttraumatic stress and other disorders. In all, the program has awarded more than 150 grants totaling about $85 million—mostly from NIH partners.

“Many people in developing countries suffer from conditions that affect their brains and devastate their lives, but we don’t have much data documenting the underlying causes of the disorders and interventions that might be effective,” said Fogarty Director Dr. Roger I. Glass. “By supporting research and training in countries where resources are limited, we hope to generate research capacity that could ultimately improve the lives of those suffering from the burden of these neurologic diseases.”

Mental and behavioral disorders are the largest global contributors to Disability Adjusted Life Years (DALYs), according to the Global Burden of Disease Study 2010 from the Institute for Health Metrics and Evaluation.

During the past several decades, global improvements in health care have permitted more children to survive to adulthood, even as they bear the lasting effects of early disease and malnutrition. These can include lower cognitive ability and the development of chronic neurodegenerative disorders. Many causes of developmental disabilities, such as genes, nutrition, infectious diseases, environmental toxins and trauma, are particularly common in resource-poor countries. Sub-Saharan Africa, for instance, carries a especially heavy burden of infectious and parasitic diseases, including HIV, tuberculosis, meningitis and malaria. In many of these countries, very little data exist on the epidemiology, natural history and pathogenesis of neurological problems while at the same time, there exists a dearth of care.

Fogarty’s initiative specifically aims to support teams of researchers from both low- and high-resource institutions as they study brain disorders relevant to developing countries that occur at any stage of life. The projects are intended to provide scientific evidence and also help build the skills needed to research the nervous system and what can undermine it.

To date, research findings have led to publication of 435 peer-reviewed articles and 14 books or book chapters, and the projects have facilitated long-term training of at least 138 scientists.

Over the years, Fogarty has partnered with other NIH Institutes and Centers in a number of its initiatives but the brain disorders program has generated the most trans-NIH support. The eight NIH partners are: the National Institute on Aging, National Institute on Alcohol Abuse and Alcoholism, National Institute of Child Health and Human Development, National Institute on Drug Abuse, National Institute of Environmental Health Sciences, National Institute of Mental Health, National Institute of Neurological Disorders and Stroke and Office of Dietary Supplements. Non-NIH partners include Canada and Mexico.

RESOURCE
Program website: http://1.usa.gov/1bCagAY
Education can curb epilepsy linked to pig parasite

Three-quarters of people with epilepsy live in the developing world and a major cause is a tapeworm infection spread by pigs—known as cysticercosis. Inside humans, the larvae can reach the brain and trigger severe headaches, stroke, hydrocephalus or epilepsy, which occurs in up to 70 percent of those infected.

Researchers investigated the problem in Burkina Faso, with support from Fogarty’s brain disorders program and additional funding from the National Institute of Neurological Disorders and Stroke. The team, led by Dr. Hélène Carabin at the University of Oklahoma, is testing an educational intervention designed to reduce infection. The materials also included information to counteract the stigma of epilepsy.

“Epilepsy is attributed to evil spirits,” Carabin said. “People with it cannot marry or work or share utensils with the family. Often, the family will build them a little hut, not too close.” Before testing their intervention, the researchers gathered data about the prevalence of cysticercosis, measuring antibodies in blood of pigs and humans. Concentrations were highest in villages where pigs roamed freely and lowest in predominantly-Muslim areas where pig farming was negligible.

Armed with these findings, the team produced educational materials and selected 60 villages for their study, half as controls. In the others, they showed a comic book and a movie conveying the importance of using latrines, washing produce and hands, cooking pork meat well, keeping pigs in pens and restricting animal access to human feces.

Preliminary results confirm a very high prevalence of tapeworm infection in pigs; human data are still being analyzed. Carabin, who is on a six-month sabbatical as a Scholar-in-Residence at Fogarty, hopes the intervention successfully changes personal and village hygiene practices, lowers infection rates and ultimately is extended throughout Burkina Faso.

Research shows cassava causes cognitive damage

In impoverished regions of sub-Saharan Africa, some villagers need sticks to walk because of neurological damage from the very food that keeps them from starvation—cassava. Toxins in the tuber can cause sudden and irreversible paralysis and, researchers have learned, also undermine cognitive ability even without physical symptoms.

This problem has widespread public health implications because cassava, also known as yucca, manioc or tapioca, is a dietary staple for more than 600 million people globally. The cyanide it contains as a defense against herbivores and insects is normally removed by processing, but in stressed conditions such as drought, famine and armed conflict, people may eat cassava only partially processed and risk neurological damage.

One country with the highest prevalence of this paralysis is the Democratic Republic of Congo, where the condition is known as konzo and can affect up to 5 percent of people in some villages. A research team decided to investigate the extent of neurological damage from cassava as a first step toward finding interventions to reduce it. Congolese-born U.S. researcher Dr. Desire Tshala-Katumbay of both Oregon Health and Science University and the University of Kinshasa and Dr. Michael Boivin of Michigan State University obtained support from Fogarty’s brain disorders program, with additional funding from the NIH’s National Institute of Environmental Health Sciences.

The team enrolled preteens from villages with and without konzo and gave them standard cognitive and motor proficiency tests. All children in konzo-harboring villages—even without physical symptoms—showed poorer memory than children from konzo-free villages. Those in konzo villages additionally lagged in visual-spatial aptitude and in mental processing. These results suggest that even without physical manifestations from cassava toxins, some children suffer damage. The team is also working on a biomarker to predict deficits in konzo patients and is investigating whether genetic susceptibility or dietary patterns can explain the spate of cases within families.

Tshala-Katumbay said he hopes multidisciplinary teams will focus on remedies, such as projects to educate villagers about adequate cassava processing methods, to reduce related brain injury. “There is more attention to the problem and more research is being done,” he continued. “I hope in time we will get enough expertise to help the government develop the problem and think about interventions.”
Dr. Francisco Lopera was a resident in neurology when the first patient with dementia walked into the San Vicente de Paul hospital in Medellin, Colombia in 1984. “He was 47 years old and he had completely lost his memory over the past three or four years,” Lopera recalled. “What was truly remarkable was, exactly the same thing had happened to his father and grandfather at the same age.”

Over the next several years Lopera visited the man’s family, where he identified several other cases with the same complex of symptoms. He eventually found more patients in nine other mountain villages, as well as in Medellin itself. The families even had a name for the ailment: la bobera, “the idiocy.”

“I didn’t have an investigative program at first,” Lopera recalled. “On the weekends, more out of curiosity than anything else, I went up to the towns and talked to the old people and reconstructed the history of dementia there.” This wasn’t easy, in the midst of the drug wars, but Lopera persevered. Now, with the Medellin area more peaceful than it has been in decades, his work is reaching an important stage. The patients he has examined for the past three decades finally are getting a chance to participate in the trial of a therapy that might help them.

Nearly all of the cases of this heritable variant of early-onset Alzheimer’s disease share a common ancestor. He was a 16th-century Spanish colonist who carried a particularly devastating genetic mutation to Antioquia province, where it spread through isolated villages. To date, Lopera and his colleagues have identified 5,000 patients in 25 families with the mutation.

The area is a mountainous, intensely green region of deep ravines, forests and coffee plantations, ravaged by guerrilla warfare for decades. The conflict sent many gene carriers into the shantytowns in the hills around Medellin, while others stayed behind in the mountains.

In 1991, after Lopera, chief of the neurosciences program at the University of Antioquia, published a case study of this “founder” cohort, Dr. Kenneth Kosik of Harvard got in contact. They began a collaboration that, with assistance from Fogarty’s brain disorders program, has turned what Kosik calls the “natural laboratory” of Antioquia into a leading center for the study of Alzheimer’s disease.

“In this population, we know who’s going to get it and we know when,” says Kosik, now Harriman Professor of Neuroscience at the University of California, Santa Barbara. “The gene does its nasty work like a clock.”

The Lopera-Kosik collaboration, funded by Fogarty and the National Institute on Aging (NIA) since 2004, has taken on added significance in the last few years because of the unique characteristics of the Antioquia population, by far the world’s largest occurrence of early-onset familial Alzheimer’s.

Most Alzheimer’s researchers believe that beta-amyloid protein accumulations in the brain cause the disease. But trials of drugs designed to attack amyloid in sick patients have in recent years failed to slow or reverse its symptoms. Lopera, a co-director of the Colombian trial, is hopeful that these same drugs might be more successful if given to patients before they develop disease symptoms, by preventing the accumulation of the dangerous protein.

The Antioquia cohort presents a unique opportunity to study this hypothesis, because the carriers of the presenilin-1 mutation always develop early-onset disease. No such large, asymptomatic-yet-doomed group of Alzheimer’s patients exists anywhere else in the world.

Lopera, Kosik and other researchers have begun administering Genentech’s drug crenezumab to symptom-free carriers of the mutation in the presenilin-1 gene. The five-year, $100 million trial, funded by Genentech, the NIA and the Banner Institute in...
Researchers are testing a drug to see if it prevents Alzheimer's in a Colombian family with a genetic mutation for the disease.

Phoenix, is the first of its kind: its aim is to determine whether a drug designed to combat Alzheimer's can prevent it from developing in the first place.

The double-blind trial involves 300 patients: 100 asymptomatic carriers will receive the drug, 100 other carriers will get a placebo, as will 100 non-carriers in the same age group. The brains of all patients will be examined using PET scans to detect beta-amyloid. The scientists hope the brain images of those receiving the drug will not show deterioration and the subjects will retain their mental fitness.

If the drug has no effect, says Lopera, the result will also be important, because it may clarify that Alzheimer’s research needs to focus on a target other than beta-amyloid. All of this has been clearly explained to the patients, he said, who can use the information to decide whether to participate.

Dr. Patricia Cardona-Gomez, a professor of cellular and molecular neurobiology at the University of Antioquia and co-PI with Kosik on many studies, trained at the University of Iowa and UCSB’s Neuroscience Institute, supported by a Fogarty grant. Fogarty assistance enabled the University of Antioquia neuroscience department to create a vivarium where rodent models of Alzheimer’s have been studied and housed.

Their research in mice is a long way from any human application, says Cardona-Gomez. Still, employing such cutting-edge work helps put the university’s neurology department in the mainstream of advanced Alzheimer’s research. Several other Antioquia postdocs, Ph.D. and master’s candidates have benefitted from training supported by these grants, and two are currently working in Kosik’s lab.

The partnership and the many years of Lopera’s work in the region have created a degree of trust among researchers and patients that Kosik and Lopera describe as almost unique.

Kosik attributes much of what has been accomplished in Antioquia to Lopera’s “tireless work” doing science, building relations and providing social services to affected families. “He will spend hours and days and weeks going from village to village to collect stories and histories, do neurological exams and make all this happen,” says Kosik, who also praises Fogarty’s role.

“Fogarty has made an enormous contribution,” he says, because by strengthening local capacity it enabled a powerful platform for collaboration between foreign and local scientists. “I can’t emphasize how much that is the key to success of this project. We are not just going down there, taking genes, publishing papers and ignoring the people,” Kosik said. “The Colombian researchers are not just collecting samples, they are thinking and designing experiments at the same level as we are.”

This relationship and its benefits will carry beyond Alzheimer’s research, Kosik says, because the region contains a “treasure trove” of genetic disorders that require careful study. These include the fatal neurological disease Huntington’s, and an inherited disorder that causes young people to suffer strokes.

Alzheimer’s currently afflicts about 5 million Americans, a number expected to triple by 2050. It costs $170 billion to treat each year. Around the world, the estimated 37 million cases of the disease will expand to 115 million by 2050, according to the Alzheimer’s Association.

Cardona-Gomez occasionally meets with patients and relatives in the presenilin-1 cohort, and their plight motivates her. “I feel impotent when I hear some of these stories, but it’s also like a motor that helps me focus more and more on how these problems can be resolved. Not by me, perhaps, but maybe by one of my students.”

Adds Lopera, “Our patients in Antioquia have participated in various studies for almost three decades. They are family to us. They have seen many relatives die of the disease, and they understand that it’s incurable. They are very hopeful about this drug trial, and we also have hopes, but it may do absolutely nothing. Yet even in the worst-case scenario, this information will be important for the future.”

RESOURCE
One of Fogarty’s long-supported capacity building successes comes from a partnership that has generated research expertise, training and scientific findings in Fortaleza, an impoverished area of northeastern Brazil. The collaboration between the University of Virginia (UVA) and Federal University of Ceará began more than 30 years ago and flourished, bringing insight to improve health in Fortaleza’s shantytowns and elsewhere.

One project, for example, led to the astonishing discovery that the “Alzheimer gene,” or APOE4 allele, much maligned for its association with dementia in older age, can provide some benefit. The research was supported by Fogarty’s brain disorders program, with additional funding by NIH’s National Institute of Child Health and Human Development, and led by UVA’s Dr. Richard Guerrant, with UVA child psychologist, Dr. Peter Patrick.

The idea for this investigation was sparked by an earlier NIH study showing a link in children between frequent enteric infections and lower cognitive ability—particularly in tests for semantic fluency, such as naming as many different fruits in a minute as possible. Curious that these functions are similarly compromised in Alzheimer’s patients, Guerrant decided to investigate whether lowest-scoring children carried APOE4.

His international team, led in Brazil by Dr. Aldo Lima with Dr. Reinaldo Oriá, studied 72 Fortaleza children who had been under active surveillance since birth and lived in an environment of heavy enteric infection. The researchers obtained saliva samples for genotyping and collected data on diarrheal history, then conducted tests of verbal fluency, coding aptitude and ability to solve maze puzzles.

Surprising everyone, the children who had APOE4 alleles tested better than those with different alleles, with the gap widest in the highest diarrhea comparison. This suggested that somehow APOE4 protected, rather than harmed, at-risk children’s brains during the critical first two years of life, when neurological development is intense and exposure to diarrhea can be frequent.

“This really is an extraordinary story,” said Guerrant. “It is an obvious advantage to have APOE4 at one state in life while a potential disadvantage at a later stage.” Although exactly how the allele is protective remains unknown. Researchers in Brazil and the U.S. are testing animal models to investigate the mechanisms involved and the impact of interventions using the amino acids glutamine and arginine, or zinc—an essential nutrient. Guerrant’s team is also collaborating to investigate if glutamine speeds repair of the intestine.

When UVA and the University of Ceará began their partnership, research and related training capacity barely existed in Fortaleza. With grants from NIH, especially Fogarty, and various other partners over the past 30 years, the institutions trained and mentored young scientists as they pursued research on topics highly relevant to low-resource areas of the world. Of particular interest in Fortaleza was how chronic enteric and parasitic infections, common in the shantytowns, impact health throughout life, including by compromising absorption of the nutrients needed for physical and mental growth. Research collaborations have also revealed three new and emerging pathogens causing persistent diarrhea in local children.

Today, University of Ceará has four centers of basic science and education and five professional colleges, and is one of the most respected higher learning institutions in Brazil. Many researchers there were trained at UVA and maintain close collaborations on numerous research projects. Capacity building continues, focusing now on developing more expertise for laboratories, clinical trials and genetic epidemiology, all the while gathering data to inform policy and practice on how to control enteric and parasitic infections and prevent their lasting consequences.

A decade ago, Guerrant began applying the lessons learned in Brazil to his newer collaboration in a rural area of South Africa with similar health problems. “There is no more important global health concern,” he said, “than the lasting morbidity of repeated childhood infections leading to malnutrition and impairment of child development.”

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Studies show early intervention is critical for disabled children

By Cathy Kristiansen

Children with intellectual disabilities are commonly regarded as family burdens or sources of shame and pity in Vietnam and many other developing countries. Health and education authorities provide few early intervention services to help these children maximize their skills.

Research can play a key part in changing perceptions by providing evidence that interventions for these children can improve their lives, those of their family members and their communities in general. This prompted Dr. Jin Y. Shin of Hofstra University in New York and her team to demonstrate the impact of personalized therapies on the development of preschool children in two Vietnamese cities. The research received funding from Fogarty’s brain disorders program and the Korea Research Foundation.

“If you don’t educate these mentally disabled children early, it is going to be extremely difficult to get them to fulfill their potential,” Shin said. “But there are very few special education teachers in Vietnam who are qualified to conduct early intervention. This is very necessary research.”

Research can play a key part in changing perceptions and encouraging policymaker action by showing that tailored interventions for these children can improve their lives.

Shin and her colleagues conducted a pilot study at Hue College of Medicine and Pharmacy in central Vietnam, enrolling 30 children with mild-to-severe disabilities tied to conditions such as cerebral palsy, Down’s syndrome and autism. Half the children were placed on a waitlist for intervention and served as controls; for the others, specialized teachers paid weekly home visits and worked on five developmental areas, including communication, social and emotional development, memory, muscle coordination and sensory organization. The study showed that behaviors in children who received intervention improved significantly over the yearlong trial.

An essential part of the pilot project was inclusion of the children’s caretakers. Not only did the teachers conduct developmentally appropriate exercises with the children, but they also showed the caretakers how to do them, so therapy could continue between sessions. “The teachers made sure to allocate some time to train the parents each week, give lots of demonstrations and feedback,” Shin said. “When we finish our study, the parents will be left on their own.”

Shin recalls one single mother who believed her young son with Down’s syndrome would never be able to stand or feed himself. Through various exercises, the boy was coaxed to reach out for rewards at ever increasing heights and distances, and a year later stood, walked, brushed his teeth and could kick a ball. “Parents are very skeptical at first,” Shin said. “When they see their kids are improving, that is the point they start to come around.”

Shin received a second Fogarty grant to expand her study and add not only more data but also training of specialist teachers. Shifting the project to the Department of Psychology and Pedagogy at the Hanoi National University of Education, her team enrolled 80 children of ages 3 to 6 years, with mild developmental delays. They also hired 20 student teachers interested in developmental disabilities who worked with special education experts to learn the home-based early intervention therapy curriculum and receive on-the-job training. The study used low-tech tools such as balls, simple toys and drawing, and again encouraged parent involvement. It is now completed and the results are being prepared for publication.

Fogarty’s brain disorders program supported research that would otherwise be difficult to fund in a low-resource country and enabled the training of more specialized educators and researchers, Shin said. “In Vietnam, you don’t get to see funding for this type of vigorous science that will stimulate rigorous regimes of clinical and educational work. And there are very few special education teachers and researchers for intellectual disabilities, especially 10 years ago,” she said. “Without Fogarty, this type of project was not going to be possible.”

RESOURCES

Papers: http://1.usa.gov/1eszDsh
A congressman recently invited me to speak with him about global health research supported by NIH and Fogarty. He was doubtful about the value of this work and needed ammunition to respond to his constituents, many of whom were unemployed, and concerned that their taxes were not being well spent. I responded directly and asked:

What are the key health concerns of people in your community? Are they worried about the health of their children, the elderly, cancer, heart disease or Alzheimer’s disease?

Children seemed a great starting point so I queried: In most communities, diarrhea is one of the most common causes of hospitalizations among children. Do you have any families with small children in your district who suffer bouts of severe diarrhea?

He nodded yes. I responded, Do you know where the treatment for childhood diarrhea was first discovered and proven to be effective? He was unaware.

In Bangladesh, I responded, cholera is the most severe of the diarrheal diseases, often causing epidemics of huge proportions. NIH and CDC researchers wanted to develop a simple treatment for cholera, the most severe and rapidly fatal diarrheal disease known to man. American and Bangladeshi investigators developed a simple, home-based remedy—a package of oral rehydration salts—that when added to water could exactly replace the fluids and electrolytes lost from the disease and save the patient’s life. This recipe developed through clinical trials in Bangladesh and Calcutta has been adapted to treat the common diarrheal illnesses that we see at home. The medical journal The Lancet touted this as one of the greatest public health breakthroughs of the 20th century and has attributed this treatment to saving one million lives a year.

I queried further if he was worried about the growing problem of Alzheimer’s—as young as 35 years—and its rapid progression to severe senility. If we are to learn by imaging brains with this disease, finding new biomarkers to monitor disease progression over time and testing new treatments to slow down or ultimately halt its progression, this is a key population. We need to conduct some of our research in collaboration with our Colombian colleagues.

The U.S. National Institute on Aging is studying some of these patients and others are being enrolled in clinical trials of new therapeutic agents. So with Alzheimer’s being one of the bank-breaking and evolving pandemics of our time, part of the solution will likely come from research in global health.

I continued and asked if anyone in his constituency had suffered from cancer and received chemotherapy? Did he know where the first link that a virus could cause cancer was found?

Another negative look appeared on his face and I responded. It was in Uganda, when Dr. Dennis Burkitt established the link between a newly discovered virus, the Epstein-Barr virus, and African Lymphoma. Burkitt then visited the U.S. where chemotherapy for cancer was first being developed and brought back a new drug regimen, which he administered to a child with full-blown disease. The tumor melted away in several weeks and became the treatment of choice for this lymphoma, demonstrating that some cancers could be cured.

My time was up so I left him with a final thought. In almost every branch of medicine, research overseas has allowed us to advance our discoveries faster, cheaper and more efficiently than we ever could have at home. We are leaders in global health because we have been able to reach out and engage others to do studies that are locally relevant but can have clear implications for us at home. Global health research truly is the new frontier of science.
Four HIV/AIDS experts win Prince Mahidol Awards
Four renowned experts in HIV/AIDS have been honored with Thailand’s 2013 Prince Mahidol Awards: Drs. Anthony S. Fauci and David D. Ho for medicine, and Drs. Jim Yong Kim and Peter Piot for public health. The award is named after Prince Mahidol of Songkla, who trained in medicine and public health at Harvard in the 1920s.

Fauci and Ho were hailed for research that helped produce HIV/AIDS treatment. Fauci, who directs NIH’s National Institute of Allergy and Infectious Diseases, increased understanding of how HIV destroys the body’s defenses and eventually brings about AIDS.

Ho, who heads the Aaron Diamond AIDS Research Center in New York, pioneered highly active antiretroviral therapy treatment for HIV-infected patients (HAART) that controls viral replication. He has studied HIV/AIDS for 31 years.

Currently president of the World Bank Group, Kim was recognized for his achievements as director of the WHO’s HIV/AIDS Department, which included helping 3 million patients receive antiretroviral therapy and enhancing treatment, prevention and care for HIV/AIDS patients overall.

Piot, who directs the London School of Hygiene and Tropical Medicine, was honored for his success as UNAIDS executive director in raising global HIV/AIDS awareness and championing HIV prevention and low-cost antiretroviral drugs.

Fogarty grantee Pape’s group wins TB award
The organization GHESKIO, founded in 1982 by Dr. J. William Pape and long supported by Fogarty, has been honored with the 2013 Stop TB Partnership Kochon Prize. Haiti’s Group for the Study of Kaposi’s Sarcoma and Opportunistic Infections focuses on HIV/AIDS, TB and sexually transmitted infections.

Fogarty grantee wins child health prize
Dr. Anita Zaidi, a Fogarty principal investigator and head of pediatrics at Aga Khan University in Pakistan, has won a $1 million grant to reduce deaths of children in their first months of life. The Caplow Children’s Prize, named for U.S. philanthropist Ted Caplow, aims to improve child health.

Fogarty’s Breman heads guinea worm panel
An international panel headed by Fogarty scientist emeritus and world expert in infectious diseases, Dr. Joel Breman, has confirmed that the parasite known as guinea worm has been eradicated in Niger. The International Commission for the Certification of Dracunculiasis has approved the results.
Funding Opportunities

Fogarty posts indoor air pollution training resources

With indoor air pollution contributing to nearly 2 million deaths each year, it is a serious health problem, particularly in low-resource settings. NIH recently hosted a workshop to help develop the expertise needed to study exposures and their health impacts, as well as evaluate the effectiveness of possible solutions. Those training materials are now available on the Fogarty website to expand their reach to others interested in this specialized field. Topics include the evolution of cookstoves, ventilation solutions, exposure assessment and possible strategies to encourage adoption of cleaner cooking methods, and others.

Global health groups have launched numerous programs to combat indoor air pollution in low- and middle-income countries, but questions remain about their effectiveness in improving health in the targeted households. More research is essential to maximize success.

NIH participates in the Global Alliance for Clean Cookstoves, a public-private partnership led by the U.N. Foundation to improve livelihoods, empower women and children, and combat climate change by creating a sustainable market for clean and efficient cooking stoves and fuels.

Resources

Training materials: http://1.usa.gov/1eXti6m
Indoor Air Pollution website: http://1.usa.gov/190wm36