Throughout 2010, SUNY Downstate is marking its sesquicentennial. Among the many reasons to celebrate this anniversary, one is particularly salient: for 150 years, SUNY Downstate faculty members have engaged in basic, translational, and clinical research with the goal of alleviating suffering and restoring health.

Some of these investigations have directly transformed medicine, while others produced insights into human physiology and pathology that opened new avenues of research that years later resulted in new ways of preventing or treating illnesses.

This issue of Profiles in Innovation features an article highlighting some of the most important scientific and medical advances made by SUNY Downstate faculty over the 150 years. These medical milestones span a range of health problems, from heart disease and kidney failure to Marfan's syndrome and low self-esteem.

Not unexpectedly, many of these advances have changed more than one field of medicine. Dr. Robert Furchgott’s Nobel Prize-winning discovery of nitric oxide’s role in the body is the basis for finding new ways to treat heart disease, dementia, cancer, lung disease, inflammatory joint disease, and other medical problems that affect, literally, hundreds of millions of people worldwide.

Today, SUNY Downstate basic scientists, behavioral scientists, clinicians, and public health experts are expanding our knowledge of a broad range of healthcare topics. In this issue, you can read about bench research being conducted to understand how brain cells communicate; find ways to boost HDL, or “good,” cholesterol; create a mouse model to study the effects of maternal crack bingeing on babies; and elucidate the genetic mechanism by which sleep disturbances increase the risk of cardiovascular disease.

You can also read about research aimed at translating scientific discoveries into new medical interventions. Downstate researchers are harnessing the power of computing and their knowledge of the brain to create a prosthetic hand that works like the real one and testing the blood of heart surgery patients for an antibody that they suspect causes a damaging inflammatory response after surgery.

Working in Brooklyn, members of the Downstate community are keenly aware of the health problems of inner-city residents. Two new research projects—one examining the reasons for the overuse of emergency room care, the other exploring the causes of health disparities among residents of the borough—are highlighted in this edition of Profiles in Innovation. By finding solutions to these problems, Downstate can contribute to solving important challenges confronting our nation.

In another way, Downstate is already taking lessons learned in Brooklyn and using them to help people elsewhere. Brooklyn’s diversity is key to the success of Downstate’s International Emergency Medical Program, which trains emergency medicine residents to work in other countries and to provide humanitarian relief.

In this issue, you can also learn about the SUNY Eye Institute, whose goal is to advance basic, translational, and clinical research in the field by creating a collaborative research program among three SUNY campuses—Downstate, Upstate, and the State College of Optometry. And, finally, on its tenth anniversary, you can read about the remarkable success of Downstate’s Biotech Park as a scientific enterprise, economic engine, and workforce development initiative.

Ian Taylor, MD, PhD
Senior Vice President, Biomedical Education and Research
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A Century and a Half of Innovation

The Collegiate Division of the Long Island College Hospital (LICH), the predecessor to today’s SUNY Downstate Medical Center, was launched on March 29, 1860, in the City of Brooklyn at a time when formal medical education was still largely theoretical and lecture-based. LICH’s founding proved to be a seminal event in U.S. medical history. The college, one of 47 medical schools in the country at the time (there are now 132), was the first in the country to integrate direct patient care with lectures and classroom study. “The Long Island College Hospital,” wrote the Brooklyn Eagle newspaper the day after LICH’s opening, “starts with means which will enable them not only to succor the afflicted, but to establish a College for instruction, the benefits of which will be experienced by the whole country, and reflect distinction on the city in which it is located.”

That article was prescient. Since the medical school’s beginnings in Brooklyn Heights in the spring of 1860, its faculty has contributed to the transformation of medical practice around the world. Among its researchers and clinicians are a Nobel Prize winner, the developer of a revolutionary imaging technology, a pioneer in the use of the heart-lung machine, and the inventor of a kind of microsurgery that has allowed for corneal transplants, to name just a few.

Among Downstate’s researchers and clinicians are a Nobel Prize winner, the developer of a revolutionary imaging technology, a pioneer in the use of the heart-lung machine, and the inventor of a kind of microsurgery that has allowed for corneal transplants, to name just a few.


downstate's tradition of medical innovation goes back to its very beginnings, with LICH faculty member Austin Flint, Sr., MD. “Austin Flint’s name is forever attached to a heart murmur,” the so-called Flint murmur, says Jason Lazar, MD, director of Downstate’s cardiovascular training program. “But Austin Flint had considerably greater achievements.”

At a time when infectious diseases claimed thousands of lives and epidemics were common, the widely published and respected Dr. Flint was an early advocate of germ theory, the idea that microorganisms spread many forms of infectious disease. “In an era when surgeons were still performing operations bare-handed, he was a tireless proponent of hand washing,” Dr. Lazar notes. Still, Dr. Flint’s biggest innovation was his popularization of the stethoscope and the listening to heart and lung sounds for diagnostic purposes. “Because of Flint’s influence,” Dr. Lazar says, “the stethoscope became an important tool in medical practice and remains one to this day.”

Among the next generation of innovators at the medical college was its own 1863 alumnus Alexander Skene, MD, LLD. A leader in American gynecology, he wrote a textbook, Treatise on the Diseases of Women, that was described in 1894 as the “best work ever written”

A Century and a Half of Innovation

The writer is indebted to Kathleen Powderly, CNM, PhD, acting director of Downstate’s Division of Humanities in Medicine, for her original research on Downstate’s history and for her assistance with this article.

Dr. Powderly and Jack Termine, former DMC archivist, John Zubrovich and Aaron Cormier of Biomedical Communications have compiled a lively online timeline of Downstate’s 150-year history. It can be viewed at www.downstate.edu/sesquicentennial/index.html
the capacity of Brooklyn’s only academic medical center that in October 1954 President Dwight David Eisenhower laid the cornerstone for the Basic Sciences Building on Clarkson Avenue.

Chandler McCuskey Brooks, PhD, chaired the Department of Physiology then. A renaissance man with interests in theology and philosophy, he made significant contributions to the study of cardiac and neuronal electrophysiology, neuroendocrinology, and the autonomic nervous system. Dr. Brooks was also the first dean of Downstate’s School of Graduate Studies, which opened in 1966. His experiments uncovered how changes in the heart’s electrical activity can lead to fatal arrhythmias. And his research laid the groundwork for the development of the cardiac pacemaker. “He was a physiologist of the body, not of a cell, an enzyme, or a molecule,” write his collaborators Kiyomi Koizumi, MD, PhD, and Mario Vassalle, MD, in a memorial essay. “He was a true physiologist who wanted to understand the secret mechanisms of the extraordinary human machine.”

Dr. Brooks’s contemporary Evelyn Witkin, PhD, who worked at Downstate from 1955 until 1971, “was a transformative figure in science,” says Graham Walker, PhD, the American Cancer Society Research Professor at MIT. She studied the cellular responses to DNA damage. The human body undergoes tens of thousands of genetic insults daily, and such injury can result in health problems that include cancer, neurological disorders, immunological illnesses, and accelerated aging.

Dr. Witkin was one of the first women elected to the National Academy of Sciences. Dr. Witkin established that cells can become resistant to radiation, and, working alone in her lab, later went on to identify proteins that can repair DNA damage. Says Dr. Walker, “Evelyn Witkin played a key, early role in helping us understand that cellular responses to DNA damage have enormous implications for human health.”

The record of innovation at SUNY Downstate during this period attracted Clarence Dennis, MD, a pioneer in the development of the heart-lung machine. Beginning in the late 1930s, while at the University of Minnesota, Dr. Dennis and his colleagues had begun designing a machine that could perform the functions of the heart and the lungs, thereby making open-heart surgery possible. In 1951, Dr. Dennis performed the world’s first open-heart operation. Though the machine worked perfectly, the patient did not survive, due to the complexity of his condition. In 1955, after moving to Downstate, Dr. Dennis again performed open-heart surgery using a heart-lung machine, and this time the patient survived. It was the world’s second successful operation using a heart-lung machine. “Creating a machine that could substitute for the heart and the lungs was a technical tour de force,” says Jeffrey Borer, MD, chair of the Department of Medicine and chief of cardiovascular medicine at Downstate. Dr. Dennis’s contributions to the field, Dr. Borer says, “made possible a type of cardiac repair that was previously unimaginable.”

The 1950s, ’60s, and ’70s were the period in which ophthalmologist Richard C. Troutman, MD, spearheaded the development of sophisticated ophthalmic instruments and complex surgical techniques that are still in use today. Among them: corneal transplants, intraocular lens implantation, in which an eye’s clouded lens is replaced by a clear plastic one, and refractive surgery for improved eyesight. These accomplishments are all the more remarkable given that Dr. Troutman began his work during an era when eye surgery was still performed without magnification. Collaborating with microscope manufacturers, he developed the first high-precision microscopes for surgical use, thereby founding the field of ophthalmic microsurgery. “He gave ophthalmology the push it needed to enter the modern era,” says Douglas Lazzaro, MD, professor...
The 1998 Nobel Prize winner Robert Furchgott, PhD, chair of the Department of Pharmacology from 1956 to 1988, had a similarly profound impact on the world of cardiology. In 1980, Dr. Furchgott discovered that a then-unidentified “endothelium-derived relaxing factor” allows for the relaxation of the muscle cells in blood vessels’ walls, and plays a crucial role in the regulation of blood pressure. In 1986, Dr. Furchgott established that EDRF was the gas nitric oxide. The nitric oxide pathway is now being explored as a treatment for a host of illnesses, including heart disease and pulmonary hypertension. “The discovery of nitric oxide and its function,” said Dr. Valentin Fuster, then president of the American Heart Association, in a 1998 interview, “is one of the most important in the history of cardiovascular medicine.”

In the late 1980s, a post-doctoral student at Downstate, Brendan Lee, MD, PhD, was part of a team of researchers who discovered the genetic mutation that causes Marfan syndrome, a sometimes fatal disease of the body’s connective tissue. Dr. Lee was also the first to clone the gene — an incredible technical achievement at that time. That cloning confirmed the link between the genetic mutation and Marfan syndrome. “These discoveries were major breakthroughs for the entire field of connective tissue disease,” says Josephine Grima, PhD, the National Marfan Foundation’s vice president of research and legislative affairs.

A century and a half after its beginnings at LIC, SUNY Downstate continues this tradition of innovation. In fields as diverse as HIV and diabetic retinopathy, the brain’s extracellular matrix and angiogenesis, among many others, its faculty makes discoveries and invents devices that change the way medicine is practiced. Since 2006, many of these world-changing researchers have been featured in this annual publication. Like their predecessors, Downstate’s current faculty offer “succor to the afflicted,” and their research generates benefits that will be experienced, in years to come, across the country and around the world.
A Biotech Park Grows in Brooklyn

Despite its wealth of scientific and biomedical talent, New York City has long lagged behind areas like Boston and San Francisco in attracting and retaining small and mid-sized biotechnology companies.

The reason is simple, says Eva Cramer, PhD, Downstate’s vice president of biotechnology and scientific affairs and a distinguished service professor of cell biology. “There’s a lack of affordable lab space.”

Envisioning a solution that could benefit emerging biotech firms, and Downstate and New York City scientists as well, Dr. Cramer and colleagues devised in 2000 a plan for a biotechnology incubator, a lab facility that provides already-built bench and office space at reasonable prices. “We started with no real estate, no money, just the idea that we could capitalize on the synergy between companies and our faculty and students,” Dr. Cramer recalls.

That idea has grown into a Biotechnology Park adjacent to the campus, a larger facility on the Brooklyn waterfront called BioBAT, plus an educational program that prepares college science majors for jobs in biotechnology.

The Biotechnology Park, featured in a March 2010 article in Crain’s New York Business, is one of only two biotech incubators in the whole of New York City. It includes the 24,000-square-foot Advanced Biotechnology Incubator and a state-of-the-art synthetic chemistry facility. The proximity of both helps facilitate interactions between the companies and Downstate’s faculty and students. BioBAT, a 486,000 square-foot facility for more mature biotech companies, is based at the former Brooklyn Army Terminal. Tenants include the International AIDS Vaccine Initiative, a developer of HIV vaccines; BioCangen, which designs assays for cancer detection; and Bio-Signal Group, a producer of devices that record brainwaves. “Having these different kinds of spaces means we can provide smaller companies with larger facilities as they grow,” Dr.Cramer says.

Because “science courses do not adequately equip science majors for employment in biotech labs,” Dr. Cramer says, the incubator’s one-month workforce development component teaches undergraduate students biotech job skills. To date, the program has helped more than 90 students find work in the field.

“These students are well received by a wide range of employers, from the City’s Medical Examiner’s Office and the New York Blood Center, to the American Museum of Natural History,” Dr. Cramer says. A number of graduates are employed at the incubator itself.

“Faculty members now have a place to pursue their entrepreneurial projects right next to the school,” Dr. Cramer says. “Our medical and graduate students can experience the excitement of working at biotech start-ups. And the dream we had ten years ago has been built, and continues to grow, right here in Brooklyn.”

A New Prescription for Eye Research: Collaboration

With more faculty, there’s more collaboration, and more possibilities.” So says William Brunken, PhD, professor of cell biology and ophthalmology about the recently launched SUNY Eye Institute. Dr. Brunken co-directs the Eye Institute with John Hoeper, MD, chair of ophthalmology at the Upstate Medical University in Syracuse, and David Troilo, PhD, vice-president of SUNY State College of Optometry. The program is a collaboration among the faculty of these schools as well as faculty from Stony Brook University’s School of Medicine and the University at Buffalo School of Medicine & Biomedical Sciences. Through the sharing of resources and intellectual capital, the Eye Institute is poised to turn New York’s State University system into one of the nation’s powerhouses in basic, translational, and clinical vision research.
The Eye Institute’s most important achievement to date is the creation of a mechanism for collaboration and communication where none existed before. “In the past, a lot of our vision researchers worked in their own silos,” explains Douglas Lazzaro, MD, chairman of Downstate’s Department of Ophthalmology. “Now, using our listserv and our Web site—sunyeye.org—‘we’ll be able to communicate much more efficiently with our colleagues about the scientific questions we’re pursuing and the resources we have to offer each other.”

One of these resources is the patient population that receives care at SUNY-affiliated hospitals. “Collectively, that’s between 250,000 and 300,000 patients,” Dr. Brunken explains. “With the appropriate ethical guidelines in place, this offers a powerful tool for research that cuts across a wide demographic spectrum.”

The Eye Institute’s investigators also hope that their new collaboration will attract to the field of vision research investigators in related disciplines such as biochemistry, material science, and epidemiology. “The problems we’re looking at — diseases of the retina and neurodegeneration — are big problems,” Dr. Brunken says. “They’ll benefit from the involvement of researchers with other areas of expertise.”

Already, the establishment of the Eye Institute helped attract nationally renowned glaucoma researcher John Danias, MD, PhD, to Downstate. “I was excited with the prospect of working with a number of diverse investigators and expanding my clinical and translational research,” Dr. Danias says. “Downstate provided those opportunities and the Eye Institute expanded them further.”

The Eye Institute also represents a model for similar research programs in the large SUNY system. Plans for collaboration and cooperation, such as those at the foundation of the Eye Institute, are at the heart of Chancellor Nancy Zimpher’s new vision for SUNY.

Not long after Haiti’s devastating earthquake this winter, ten Downstate medical faculty, residents, and nurses were on the ground at the University Hospital in Port-au-Prince, providing around-the-clock emergency room care. “The hospital was having trouble getting 24-hour staffing in the ER, and we were willing and available to do that,” explains Christina Bloem, MD, MPH, clinical assistant professor of emergency medicine.

The group’s effort was an example of the medical school’s International Emergency Medical Program in action. “Shortly before the earthquake, we had begun collaborating with a clinic in the town of Terrier Rouge, in northern Haiti, helping them build capacity,” says Dr. Bloem, the program’s director. “And this work became part of what I hope will be multi-year project now.” In fact, the group returned to Haiti in April.

International emergency medicine is the newest subspecialty in Downstate’s nationally renowned Emergency Medicine Department. Established in 2006, the International Emergency Medicine Program trains residents in what Dr. Bloem identifies as the two branches of international emergency medicine: “One is humanitarian relief, disaster relief. The other is more academic, developing emergency medicine as a specialty in other countries.”

In fact, emergency care like that provided in the United States is scarce in most parts of the world. “A lot of places don’t have pre-hospital systems. They don’t have ambulances,” Dr. Bloem notes. In many countries, physicians who staff ERs have none of the specialized training in trauma and other emergent conditions that emergency medicine doctors in developed nations have. “One of the things we teach our residents is how to share their medical expertise and their knowledge about structuring emergency medical systems,” Dr. Bloem says.

To date, the Emergency Medicine Department’s faculty and residents have established collaborations with medical facilities in Jamaica, Turkey, South Africa, Romania, Lesotho, India, and Brazil, as well as in Haiti. “When we were there,” says Dr. Bloem of the department’s relief work this winter, “we were able to utilize the many skills we have learned in central Brooklyn: handling large volumes of patients, working with diverse populations.”

“At Downstate,” she adds, “you learn to be open to other cultures and other methods of healthcare delivery. That serves us well, in Brooklyn and in our international endeavors.”

Around-the-World Emergency Care

IEM members (from left): Ernest Garnier, MD, clinical assistant professor; Debra Barrow, RN; Robert Gore, MD, clinical assistant professor; Dr. Christina Bloem; Marie France Senat-Zephir, RN.
There’s a joke among people whose primary language isn’t English,” says Humberto Brown, MA, director of health disparities/new constituency development for the Arthur Ashe Institute for Urban Health (AAIUH). “If you tell a medical provider you’re not good at English,” Mr. Brown quips, “he or she will speak very loudly, as if the volume will solve the communication problem.”

The Ashe Institute, which has an office on the Downstate campus, works closely with faculty and staff on programs dedicated to improving the well-being of vulnerable urban populations. A study the Institute conducted found many older Latinos didn’t access healthcare that was available to them because “their issues were talked about at a volume that allowed everybody to hear.”

This finding and Mr. Brown’s anecdote illustrate one reason why health disparities exist in the United States and in Brooklyn in particular. A recent survey by the Robert Wood Johnson Foundation found that Brooklyn ranked 58th out of 62 New York State counties in terms of health outcomes. Residents of New York City’s poorest neighborhoods, including many who live in the areas surrounding Downstate, have life expectancies four years shorter than those in the city’s most affluent districts. “In Brooklyn, we see severe disparities in the areas of cardiovascular disease, infant mortality, HIV and AIDS, asthma, and other chronic health conditions,” notes Brooklyn’s Deputy Borough President Yvonne J. Graham.

To help understand the causes of these disparities and to provide solutions, Downstate, the Arthur Ashe Institute, and the Borough President’s Office leveraged their long-term relationships to establish, in 2004, the Brooklyn Health Disparities Center (BHDC). “The BHDC is the place that brings together researchers and advocates who work both within the University and outside of it to pursue common goals,” says Center Director Clinton Brown, MD, an associate professor of clinical medicine at Downstate.

Since the Center’s founding, its faculty has trained Downstate cardiovascular fellows in health disparities research. It established the Summer Institute Program to Increase Diversity in Cardiovascular Health Disparities Research, which instructs junior scientists from around the country in those same research issues. It developed innovative curricula to train hair stylists to become lay health advocates who can teach their customers about cardiovascular health and disease, and it has built

Members of the Brooklyn Health Disparities Center (from left): Humberto Brown; Dr. Clinton Brown; Dr. Tracey Wilson; Kweli Henry; Dr. Marilyn Fraser White; Girardin Jean-Louis, PhD, co-director, Research Core, associate professor of medicine; Dr. Ruth Browne; and Ferdinand Zizi, MBA, clinical instructor of health sciences.

Hispanics Who Speak Spanish as Primary Language Have More Problems Communicating with Their Physicians

Deaths Due to Diabetes: Racial/Ethnic Disparities are Widening

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<tr>
<th>Race/ethnicity</th>
<th>Deaths per 100,000 adults</th>
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<tr>
<td>White</td>
<td>30.0</td>
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<td>Black</td>
<td>40.0</td>
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<tr>
<td>Hispanic</td>
<td>43.0</td>
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Rates are age-adjusted.
Sources: Bureau of Vital Statistics, NYC DOHMH; U.S. Census 1990 and 2000/NYC Department of City Planning
a strong network of community-based organizations that advises the Center on community health issues.

Now, with funding from the NIH’s National Center on Minority Health and Health Disparities (NCMHHHD), “the BHDC is laying the groundwork for future research and policy recommendations to combat health disparities,” says Tracey Wilson, PhD, the Center’s research core co-director and associate professor of community health sciences.

To achieve these ends, the Health Disparities Center is enhancing its already existing relationships. “This is really a capacity-building grant,” explains Ashe Institute CEO Ruth Browne, ScD, MPH, who is also co-director of the Center. The Center is now designing a curriculum on health disparities research for high school students who participate in the Institute's Health Sciences Academy. “The Academy is a program we run here on the Downstate campus,” Dr. Browne explains, “where faculty and graduate students teach talented minority students in a three-year, after-school science enrichment program, coupled with an urban public health program.” The NCMHHHD funding will also enable the Center to place these students in paid summer internships at local community-based organizations “to conduct surveys and needs assessments and to disseminate information,” she adds. Also strengthened by this grant is the BHDC’s involvement with community-based organizations, such as the Caribbean Women’s Health Association, the Arab-American Family Support Center, and the Haitian Centers Council. “These groups really have their fingers on the pulse of their communities,” explains Marilyn Fraser White, MD, the BHDC’s co-director of community engagement and the AAIUH’s associate director of research and training.

The Center staff has begun training 40 such organizations in community-based participatory research, in which members of the communities affected by conditions or issues under study act as full participants in the research process. “We believe that this community involvement is key to identifying reasons for health disparities,” Dr. White says.

To further its policy-change goals, the Center is “teaching community-based organizations how to make recommendations to legislators and other policy makers,” says BHDC policy analyst Kweli Henry, MPH.

All of these efforts can lead to the elimination of the health disparities that prevent many in Brooklyn from living long and healthy lives.

### A Tale of Two Neighborhoods: Access to Healthcare in Brooklyn

<table>
<thead>
<tr>
<th>Percent of adults not receiving needed medical care in the past year:</th>
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<tr>
<td>Central Brooklyn (Bedford-Stuyvesant, Crown Heights)</td>
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<tr>
<td>Northwest Brooklyn (Brooklyn Heights, Park Slope)</td>
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Percent are age-adjusted. Source: NYC Community Health Survey, 2002

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### Partners in Care:

**Acute Care Overuse Meets Its Match**

Residents of northern and central Brooklyn suffer from startlingly high rates of infant mortality, HIV/AIDS, cardiovascular disease, and other illnesses. They also overutilize high-cost emergency room (ER) and inpatient care. One measure of this overutilization is highlighted by this fact: the ER at University Hospital of Brooklyn (UHB), Downstate’s teaching hospital, was designed, in 2001, to treat as many as 25,000 patients annually but in 2009 saw 73,000.

What is the connection between these two phenomena?

Grace Wong, MBA, MPH, Downstate’s vice-president for managed care and clinical business, has decided to find out.

She is motivated by a belief that Brooklyn's healthcare resources can be employed in ways that can improve residents' health while keeping medical costs down. And her ambitious Brooklyn Healthcare Improvement Project (BHIP), supported by a New York Healthcare Efficiency and Affordability Law grant, is designed to make that happen. The project will, first, investigate the factors that impact health and healthcare provision in its 15 zip-code, mid-Brooklyn study area. Then, employing a unique public/private/community partnership, it will develop recommendations and solutions that can benefit residents, healthcare providers, and insurers alike.

In this endeavor, Ms. Wong is joined by two groups: an advisory panel made up of community leaders, government representatives, health insurers, and business owners; and a team of academics. Her colleagues include Jeanne Stellman, PhD, a professor of environmental and occupational health sciences in the Department of Preventive Medicine, Michael Lucchesi, MD, chair of the Department of Emergency Medicine and medical director at University Hospital of Brooklyn; Howard S. Berliner, ScD, professor and chair of the Department of Health Policy and Management at the School of Public Health; Dorothy Fyfe, MPA, assistant vice-president for planning; and Michael Gusmano, PhD, of the Hastings Institute.

“We hope,” says Dr. Stellman, “that our unique stakeholder collaboration can continue, in order to address the many pressing healthcare needs in our community.”

One of the project’s most powerful tools is GIS technology. Geographic information systems technology
captures, analyzes, and presents location-related data. BHIP will use it to create a sophisticated, block-by-block map that “will help us identify the factors that impact health among the study area’s one million residents,” Ms. Wong says. The map will also help assess the state of healthcare provision in the study area. Included will be healthcare providers’ hours of operation, languages spoken, and types of medical care offered. That information will be integrated with data on “health status, health service utilization, socio-economic, and housing indicators, as well as a variety of other variables affecting the community’s well-being,” Ms. Wong says.

Though the project is in its initial stages, its researchers have already identified many of the causes of acute care overutilization: Patients frequently come to the ER for non-emergencies because “there is a shortage of primary care in the area,” Ms. Wong says. In fact, 14 of the 15 zip codes under study have been deemed medically underserved areas by the federal government. Patients who do have primary care providers often don’t have access to them during evenings or on weekends. Other neighborhood-specific issues include substance abuse, mental illness, and patients’ inability to afford medication. Difficulty in navigating the fractured healthcare system plays a role as well: “Often, patients feel their medical issues can be dealt with more quickly by going to the ER than by being ping-ponging among specialists,” Ms. Wong explains.

After the BHIP has collected and analyzed all of its data, the project leaders will meet with organizations, including the Brooklyn Chamber of Commerce, the healthcare workers’ union 1199SEIU, eight health insurers, six hospitals, community groups, senior centers, and the Brooklyn Borough President’s office, to formulate solutions to the area’s healthcare problems.

“We envision new incentives for healthcare providers to make primary and specialty care more available in the neighborhoods under study,” Ms. Wong notes. Unnecessary use of acute care can also be reduced, she believes, by the creation of multispecialty ambulatory care centers that allow patients to have their complex medical problems addressed at one facility, rather than having to shuttle among medical offices. Insurers might well realize a financial benefit from paying doctors extra to see patients on weekends or evenings, so that they don’t incur the cost of expensive ER visits. The proper use of resources would improve the healthcare that area residents receive, and by extension, their health.

BHIP’s findings and recommendations may have much wider applications as well. One private insurer told Ms. Wong, “Your borough’s the toughest healthcare area in the country. If you can fix Brooklyn, you can fix the nation.”

Grace Wong, for her part, sees that the possibilities abound.
One doesn’t hear much about the crack-cocaine epidemic these days. The news articles about crack-exposed newborns, so common at the epidemic’s outset in the mid-1980s, have disappeared from the front pages of the nation’s newspapers. And the epidemic itself peaked in 1990.

Nevertheless, every year in the United States, an estimated 165,000 women smoke crack while pregnant, according to the federal Substance Abuse and Mental Health Services Administration. In the last decade, more than a million crack-exposed babies have been born.

Clinicians have studied the development of children exposed in utero to this purified, smoke-able form of cocaine since the epidemic began. They have documented problems with behavior and attention, deficits in language and cognition, lower academic achievement, and lower IQs. Neuroimaging has revealed anatomical differences in brain development between crack-exposed and otherwise healthy children. But, because many children exposed to crack in utero are raised in homes with drug-using and/or mentally unstable parents, separating the impacts of prenatal crack cocaine exposure from other influences on brain development, behavior, and cognitive function is difficult.

Studies with animal models can help answer questions about crack’s impact on exposed offspring. But to date, the only models available to researchers conducting studies in pregnant rats and their progeny have been ones that mimic maternal nasal cocaine use rather than crack binging, which gives users a faster and more intense “high.”

Diana Dow-Edwards, PhD, is attempting to rectify that problem. A professor of physiology and pharmacology and of cell biology, Dr. Dow-Edwards is using funding from the National Institute of Drug Abuse to develop a first-of-its-kind model of crack bingeing in pregnant rats. “If we can establish this model,” says Dr. Dow-Edwards, “we can set in motion a series of experiments that will inform our scientific understanding of the effects of in utero crack exposure on offspring.”

Dr. Dow-Edwards has been using rat models, albeit imperfect ones, to study crack’s impacts since the epidemic started more than 25 years ago. “Crack was a huge public problem then. As someone who had been researching the effects of in utero alcohol exposure, I had the tools to join other researchers in investigating this new problem,” she says about her early involvement in the field.

Crack bingeing is the most common form of cocaine use among pregnant women. Yet, to date, the evolution of a rat model of bingeing behavior has been slowed by difficulties in determining appropriate dosing levels and the complexity of certain surgical techniques. “A more accurate model can move the research in this field forward,” Dr. Dow-Edwards says.

Dow-Edwards explains. Crack users frequently binge for 12 hours or more. “In the fetus, these two phenomena may influence the development of those same brain areas that cause cravings in adults,” Dr. Dow-Edwards observes.

To better explore these effects, Dr. Dow-Edwards and her lab have devised a model that employs a difficult-to-implant jugular cannula in combination with frequent intravenous dosing. The cannula allows Dr. Dow-Edwards and her research group to inject cocaine directly into the rats’ bloodstream.

Now, they are working to achieve the kinds of crack-use sequelae that human mothers develop: severe weight loss, miscarriage, and premature birth. “If we can identify a sub-toxic but very robust dosing pattern, then we will be sure we have an accurate model of human in utero exposure,” Dr. Dow-Edwards says. Offspring from such a model could enable her lab to more accurately explore crack’s impacts. “We also want to examine whether enriched environments improve outcomes for offspring,” she says, “and to look at reward circuits and cognitive function.”

All this research is aimed at helping doctors and social service providers understand crack-exposed children’s specific needs and challenges. “Ultimately, the information we uncover,” Dr. Dow-Edwards says, “will end up helping kids.”

Teasing Influences Apart: A New Model for In-Utero Crack Exposure
The Repair Man: Brain-Machine Interfaces and the Quest for a New Kind of Prosthesis

It’s not often one hears scientists talk about their contracts with funders. But ask assistant professor of physiology and pharmacology and of biomedical engineering Joe Francis, PhD, if he has an idea about when the fully functioning, robotic prosthetic hand he’s been working on for the last several years might become an operating reality, and he says, with an impish smile, “it has to be done in four years, by definition of our contract.”

The contract with the U.S. military’s Defense Advanced Research Projects Agency (DARPA) calls for him to deliver a prosthetic hand that works like a real one — moving when its user thinks about moving it and feeling things almost the way a real hand does. But the hand is not all Dr. Francis is developing for DARPA. Dr. Francis is also at work on a computer-based, prosthetic brain.

That’s right. A computer-based, prosthetic brain.

“Basically, we’re trying to take what we’ve learned about the brain from animal experiments and reproduce in a computer model all the different parts of the brain that we’ve looked at. Then, we’ll put them together in a simulation, and, after that, have that computerized brain interact with a person’s real brain. If there’s anything missing — if part of the brain has been debilitated by a stroke, if there’s literally a part missing — we’ll be able to replace that damaged or missing part with an artificial component,” he explains, matter-of-factly.

The scientific questions involved in developing these prostheses are, obviously, incredibly complex. In the case of the prosthetic hand, there is the issue of communication between the user and the hand itself. At present, that communication is accomplished through electrodes implanted in the user’s brain that connect to the computerized prosthesis. But, to date, the electrodes scientists have implanted in animal and human brains have remained viable for a few years at most. After that, scars form around the electrodes, or, the electrodes shift their position, causing their malfunction.

To help solve this problem, one of Dr. Francis’s graduate students is designing nanotube-enhanced electrodes so thin they can’t trigger scarring. And, with Randall Barbour, PhD, a professor of pathology and biomedical engineering, Dr. Francis is investigating whether the electrodes can be eliminated altogether. Near-infrared spectroscopy — Dr. Barbour’s specialty — may enable the brain and the prosthesis to communicate wirelessly.

Dr. Francis is also studying force control, the ability to gauge and regulate the intensity of hand movements. For the last several years, Dr. Francis has been working with laboratory animals to better understand the many steps involved in this process. “We would like the person to be able to control how hard they’re squeezing another person’s hand, how softly they’re holding a pen,” Dr. Francis explains.

Moreover, a successful robotic hand, he says, will be able to “feel” things — the texture of a baby’s skin, for instance...
— not just hold them. “We’re working with developers of prosthetic skin and prosthetic bones to make it happen.”

The proposed brain prosthesis is, in some ways, an extension of Dr. Francis’s earlier research. Because both the hand and the brain must respond to novel environments and situations, computer models of the brain’s learning ability are central to both projects. “Really, this is about modeling learning, so that computer agents” — computer programs that perform tasks — “can help when there’s a steep transition of new learning required,” Dr. Francis explains.

In collaboration with William Lytton, MD, a professor of physiology and pharmacology, neurology, and biomedical engineering and an expert in the computer modeling of brain-cell activity, Dr. Francis’s group will “conduct some very detailed modeling of individual brain cell activity. We will also do some less detailed modeling of larger brain cell networks and see which ones are most effective,” he explains. Then, Dr. Francis’s group will try to apply these computerized models in the aid of animals with central nervous system injuries.

All of this work, of course, sounds like something out of an Arthur C. Clarke novel. But to Dr. Francis, this research is simply part of a lifetime’s interest in brain-machine interfaces, and a demonstration of compassion as well. “With these prostheses, we want to see if we can help people do 95 percent of what they were doing before,” Dr. Francis says. “More than that would be even better.”

### Midnight Oil:

**Sleep Disturbances’ Impact on Lipoprotein Production**

N ight-shift workers — everyone from nurses to police officers to researchers at the British Antarctic Survey Station — suffer from cardiovascular disease and metabolic syndrome at rates that are sometimes five times greater than their peers working the day shift. Metabolic syndrome is a cluster of medical conditions which includes high cholesterol and is linked to heart disease and stroke.

Though researchers have documented this phenomenon, to date, they have had trouble understanding its causes. But now, with funding from the National Institute of Diabetes and Digestive and Kidney Diseases, Mahmood Hussain, PhD, a professor of cell biology and pediatrics, appears to have brought its etiology to light. Using laboratory mice, Dr. Hussain has recently discovered that circadian rhythms — our 24-hour activity/sleep cycles — and the genetically controlled mechanisms that regulate them play a significant role in the production of lipoproteins. Lipoproteins are a group of soluble proteins that combine with and transport fats (lipids) in the bloodstream. Excess accumulation of these low-density lipoproteins in the plasma is a major contributor to heart disease. “When our circadian rhythms are disrupted,” Dr. Hussain explains, “we absorb more lipids and have more lipoproteins in the blood.”

Dr. Hussain, who has spent much of his career researching lipid formation, came to the question of how disruptions in circadian rhythms influence lipid production when Xiaoyue Pan, PhD, one of his post-doctoral fellows, approached him with the previously unexplored idea. She had studied circadian rhythms as part of her PhD thesis. “I said, ‘That’s fantastic! Let’s get started,’” Dr. Hussain recalls.

Drs. Hussain and Pan with members of their lab first experimented in normal mice, disturbing their natural sleep/wake cycles and measuring the resulting changes in lipid levels. Mice are naturally nocturnal. And “when we fed them during the day instead of during the night, they switched the timing of their activity and their lipid production from nighttime to daytime,” Dr. Hussain explains. “But when we kept them in constant light for five whole days, they lost this diurnal regulation of lipoprotein production,” and continued to produce lipoproteins around the clock.

To further explore the day/night cycles’ impact on lipid production, Dr. Hussain turned to mice that had mutations in the Clock gene. Clock is a member of a group of “genes found in every cell that regulate the body’s 24-hour cycle,” Dr. Hussain explains. Clock genes are themselves switched on and off within a part of the brain called the suprachiasmatic nucleus, which is sensitive to light. “Clock mutant mice cannot sense properly when daytime is and when nighttime is,” Dr. Hussain explains. Rather than having to keep his mice awake 24 hours a day, the Clock genetic mutation did the work for him. As a result, like many night-shift workers, the mutant mice were active and eating for many
more hours than their normal counterparts. The animals’ plasma lipid levels — especially their levels of so-called triglyceride-rich APOB-containing lipoproteins — increased “to very high levels and remained high throughout the day” when compared to their normal siblings.

Dr. Hussain’s research also led to the observation that “Clock mutant mice are prone to atherosclerosis” — hardening of the arteries — indicating that “disruptions in circadian rhythms may predispose individuals to this disease,” he says.

Dr. Hussain’s experiments have illuminated the pathways by which these APOB-containing lipoproteins are formed.

“We found that the Clock gene actually regulates another transcription factor called SHP [small heterodimeric partner], and SHP regulates MTP [microsomal triglyceride transfer protein],” a transfer protein that plays a pivotal part in the formation of APOB-containing lipoproteins. In earlier research, Dr. Hussain was the first to identify MTP as a key protein involved in the diurnal regulation of plasma triglyceride.

Having teased apart the mechanism by which sleep disruptions increase circulating lipid levels in laboratory mice, Dr. Hussain hopes to explore further the implications of those findings. How might sleep disruptions affect heart and kidney function? And, are there processes that can reduce lipid accumulation and lipoprotein formation in mice that are active almost 24 hours a day? He has another ongoing research project supported by the National Heart, Lung, and Blood Institute to look into ways to inhibit MTP as means to lower plasma lipids.

“Sleep disruption is a hallmark of our age,” Dr. Hussain notes. Social changes brought about by the television, the Internet, and frequent air travel, as well as the global marketplace, have increased the numbers of people with interrupted and insufficient sleep. For example, some traders wake up at 3 a.m. to watch the European markets, and there is a steadily increasing number of transcontinental business travelers, who frequently cross time zones. “It’s important to understand,” Dr. Hussain says, “how this lack of sleep is affecting our cardiovascular health.”

**Travel to the Junction: RNA’s Journey from Nucleus to Synapse**

How does the brain interact with its environment? What is the process through which internal and external stimuli influence brain cell activity, and with that activity, brain function?

For years, these questions have fascinated Henri Tiedge, PhD, a professor of physiology and pharmacology, who explores them at their most basic scientific level. In particular, Dr. Tiedge is enthralled by the subject of neuronal RNA translation. That’s the complex and largely mysterious process by which the genetic information stored in brain cells’ DNA is used to create ribonucleic acid (RNA) molecules that are the instructions for creating proteins. In neurons, the RNA itself can travel to remote parts of the cell where synapses are located, and build proteins on site.

“These proteins — neurotransmitter receptors, ion channels, protein kinases — are involved in synapse structure and function,” Dr. Tiedge explains. “They underlie the whole panoply of higher brain function.”

Dr. Tiedge wants to understand what enables the genetic information that is stored in a neuron’s DNA to find its way to the synapse. And, given that large amounts of this genetic information travel to synapses and are stored there until, often much later, the need arises for the information to be synthesized into protein: what controls how this genetic information gets to remote sites,
and what controls the use of this information to build proteins on site?

These are essential questions. “The process of reacting to stimuli by translating RNA into proteins is basically what allows the brain to interact with the outside world,” explains Dr. Tiedge. The localization of proteins at synapses enables communication among brain cells. This communication, in turn, is responsible for many of the basic processes in which the brain is involved — learning, memory, language, emotions, to name just a few. Deciphering the neuronal RNA translation process may explain much, not only about normal brain function, but also about abnormal brain function. Malfunctions in neuronal RNA translation appear to underlie autism, Alzheimer’s disease, and a form of mental retardation known as Fragile X syndrome, researchers say. Certain drugs of abuse may have long-term effects on consciousness and behavior by altering the ways brain cells make critical proteins. “Brain function,” Dr. Tiedge says, “depends on how these RNAs are localized and translated at synapses over time.”

Knowing that lay audiences may have trouble understanding molecular brain research, Dr. Tiedge is fond of analogizing the process of neuronal RNA transport to a New York City commute. How do straphangers know which subway to board in Manhattan in order to arrive at SUNY Downstate in Brooklyn? What information, in what form, allows them to catch the right train, get off at the right stop, and arrive at their desks at the beginning of the workday? Is there something that prevents the commuters from disembarking too soon and wandering aimlessly around downtown Brooklyn?

To learn the answers to these questions, Dr. Tiedge and his team perform experiments in cultures of rat brain cells, small pieces of brain tissue (“brain slices”), and postmortem human brain tissue. They have also developed mouse models. “We have found,” Dr. Tiedge explains, “that gene expression at the synapse is governed by a type of RNA called regulatory RNA.” Using knock-out mice that are missing certain of these regulatory RNAs, Dr. Tiedge has demonstrated that synaptic RNA translation into local proteins is instrumental in normal brain function; his knock-out mice have hypereexcitable brain cells, and the animals themselves are prone to seizures.

Much more research in this area remains to be done. The traveling instructions that RNAs receive come in the form of ensembles of nucleotides — molecules made up of nitrogenous bases, sugars and phosphates — called “codes.” “At the moment, we only understand some of the codes that get certain classes of RNA out of the cell’s nucleus where they’re made, to the synapses, where they function,” Dr. Tiedge says.

His new research in this area, funded by the National Institute on Drug Abuse, explores how drugs of abuse, such as opiates, impact neuronal RNA translation. “Once we understand all of the components in this process of neuronal RNA translation, we can think about how to address diseases such as autism and Alzheimer’s,” Dr. Tiedge says. His research on how drugs of abuse impact neuronal RNA translation may help explain mechanisms of action of these drugs and aid researchers in developing more effective treatments to reverse addiction. But his research has broad implications for all of neuroscience. “Basically,” Dr. Tiedge says, “this type of research has the ability to explain how brain cells function as a person interacts with his or her environment. This work may one day help explain a fundamental part of who we are.”

More than 1.25 million Americans suffer from heart attacks each year. Another 800,000 are affected by stroke. A rare form of blood-flow blockage in the intestines that affects about 35,000 people annually has a fatality rate of more than 70 percent. All these conditions have one thing in common: ischemia — inadequate or disrupted blood supply — followed by reperfusion injury.

Until recently, scientists believed that the tissue damage these ischemic events precipitate is mostly the result of blood-flow blockage. But, Ming Zhang, MD, PhD, a research assistant professor of anesthesiology and cell biology, has discovered there is another cause as well: inflammation that results from a post-ischemic autoimmune response that follows reperfusion. “When I came to Downstate in 2005, I began discussing this new concept with cardiologists and other clinicians,” Dr. Zhang recalls. “It was quite a novel idea for them. But now that we have more research to back up this concept, clinicians are becoming
interested in how the process works.” Indeed, Dr. Zhang’s research in humans and in laboratory animals may soon lead to the development of an agent that can help minimize the damage this autoimmune response generates.

Dr. Zhang’s interest in the causes of ischemic injury stems from research he conducted as a post-doctoral student at Harvard. “My mentor had a project on autoimmunity and inflammation,” he recalls. “As I became involved, I saw the many potential applications of this research.” In 2004, Dr. Zhang and colleagues were the first to publish on the subject, using laboratory animals to document the phenomenon in cases of intestinal ischemia.

“We discovered that with ischemia, cell membranes get damaged and intracellular components” — cell contents, in other words — “are suddenly exposed to the immune system,” Dr. Zhang explains. “When blood vessels are reperfused, the body’s innate immune system, which has never before encountered these ‘self’ components, goes on the attack. Certain antibodies dock onto the injured cells and destroy them.” These antibodies are a variant of the immunoglobulin, IgM. Since Dr. Zhang first discovered this process in intestinal ischemia, he and other researchers have documented it in animal models that include other types of ischemic injuries, such as heart attack, trauma, burns, and surgery.

With funding from the National Heart, Lung, and Blood Institute, Dr. Zhang is currently testing whether humans have similar responses. To conduct this research, he has enlisted several of Downstate’s cardiac surgeons. “In cardiac surgery, you have a kind of ischemia, too,” he explains. “The blood vessels are clamped off to allow the surgeon to operate on the heart.” When the clamps are removed, blood flow to the area is reestablished. “To help us ascertain whether IgM plays a role in postischemic injury, these surgeons are collecting samples of blood from patients’ hearts before surgery and after,” Dr. Zhang says. His lab then tests the IgM levels in those samples in an effort to ascertain whether this phenomenon is also a significant problem in humans.

Dr. Zhang believes his research has tremendous translational potential. “Imagine that a high-risk person — someone who had already had a heart attack or a stroke — could carry an injection ‘pen,’ like the EpiPens that people who have severe allergies carry,” he says. “If the person had another ischemic event, paramedics or emergency room personnel could inject this agent to block the autoimmune response.” Likewise, surgeons and anesthesiologists could administer such an agent during surgery, prior to reperfusion.

Dr. Zhang has already been working to make that possibility a reality. “While I was at Harvard, I developed a short peptide that can target the early reaction between the autoimmune antibody and the self-antigen,” Dr. Zhang says. [His mentor has started a biotech concern to further develop and market this treatment.] Now, Dr. Zhang is designing and testing potential chemical reagents to block this autoimmune response as well. “We have great hope,” he says, “that targeting this pathogenic IgM will help minimize injury in a whole host of ischemic events.”
High-density lipoprotein (HDL) cholesterol is known as the “good” cholesterol. Though its function in the human body isn’t entirely understood, HDL cholesterol likely removes from plaques on blood-vessel walls the excess low-density lipoprotein (LDL) cholesterol that is detrimental to heart health. In fact, the higher an individual’s HDL cholesterol level, the lower the risk of cardiovascular disease and of dying from coronary heart disease.

But much of what scientists know about HDL cholesterol is speculative, based on epidemiological data, rather than on hard science. In particular, the pathway that regulates the production and longevity of HDL in the bloodstream — “perhaps 70 percent of it” — remains largely unknown, says Weijun Jin, MD, an assistant professor of cell biology. Thus, explorations into ways to increase HDL cholesterol levels and realize the accompanying benefits, are, for the most part, in their infancy.

But, with funding from the National Heart, Lung, and Blood Institute, Dr. Jin is working to fill that information gap.

His interest in HDL cholesterol stems from his early work as a clinical neurologist in China. “A lot of my patients suffered from strokes and heart disease,” he explains.

Currently, there are no effective methods of boosting HDL cholesterol levels that do not pose significant side effect risks. “In the clinical setting,” Dr. Jin says, “you can use niacin [a B vitamin] to increase HDL levels by 15 to 30 percent. But the side effects are very uncomfortable.” These include hot flashes, itching, and gastrointestinal problems. Exercise can raise “good” cholesterol levels “maybe by 7 percent,” says Dr. Jin. And a daily alcoholic drink “maybe gives you another few percent. But, at best, these are all marginal.”

Impressed that statin drugs such as atorvastatin (Lipitor) have made great strides in lowering LDL cholesterol levels, reducing heart disease incidence, and decreasing cardiac deaths, Dr. Jin wondered whether it might be possible to untangle the HDL production pathway and thereby facilitate the development of an HDL-boosting drug that could offer similar cardiac benefits.

Working with human cell cultures and animal models, he and his laboratory colleagues began by studying an enzyme called endothelial lipase “that hydrolyzes” — breaks down — “the HDL cholesterol in your bloodstream,” explains Dr. Jin. “If you want to increase HDL, you have to inhibit lipase.” Soon, he discovered that endothelial lipase production and its persistence were controlled by enzymes called proprotein convertases (PC), which can reduce lipase levels. “This came as a surprise to us,” he notes. Earlier scientific research had shown that PCs play several roles in the human body. They activate viruses such as human papillomavirus and SARS and facilitate “cancer metastasis by activating proteins that allow cancer cells to spread,” Dr. Jin explains. But prior to Dr. Jin’s investigations, “PCs had not been associated with lipids at all.” These enzymes seem to play a pernicious role in the human body, but Dr. Jin believes their influence “may be dependent on the site of action. If we are right, targeting these particular PCs should effectively regulate HDL cholesterol in the bloodstream without impacting other systems.”

Building on this knowledge, Dr. Jin and his team experimented with boosting and blocking PC levels in mice. The results? In one experiment, using a gene transfer that increased PC levels, Dr. Jin’s team raised HDL levels by 50 percent. With another type of gene transfer, they lowered HDL cholesterol levels to zero. Along the way, Dr. Jin has also developed an assay that can test PC levels in the human bloodstream.

Now, Dr. Jin plans to investigate whether his PC-boosting method is effective in inhibiting as well as treating atherosclerosis in mice. “We’re hoping that we can get rid of the plaques, or, better yet, prevent their formation entirely,” he explains.

Dr. Jin’s research “is basic science,” he says. “But if our project is a success, it will likely point the way to additional therapies for heart disease.”

Plasma HDL-c was monitored over a two-week period after vector administration. Student t tests, were used to compare profurin with the control vector, AdNull. Both groups had four mice. The error bar represents a standard deviation and * p<0.05 and ** p<0.001 are confidence intervals.

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