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The driving force behind research — be it basic, applied, or translational — is the quest for new knowledge, for answers, if you will, to the question, “Why?”

Here at SUNY Downstate Medical Center, our research faculty is making great progress in understanding the “Why?” of a number of disease states, among them epilepsy, HIV/AIDS, diabetes, substance abuse, multiple sclerosis, and certain forms of mental illness. Ranking among the world’s elite, our researchers are expanding the scientific understanding of these diseases, and in some cases, finding sophisticated applications to improve treatment.

That’s not surprising. SUNY Downstate researchers have a rich history of making significant scientific and treatment discoveries — from the development of MRI and Diffuse Optical Tomography technology, to the Nobel Prize-winning discovery of the critical role nitric oxide plays in the body; and more recently, the synthesis of materials for tissue engineering and targeted drug delivery.

Included in the enclosed series of articles is a sampling of innovative research SUNY Downstate scientists are conducting to enrich knowledge on a whole host of diseases.

For example, we are investigating compounds for a drug that would prevent the development of epilepsy; advancing the best possible care to HIV-infected children, adolescents, and their families; exploring pancreatic precursor cells as a potential treatment for type 1 diabetes; teasing out the ways narcotics act on the central nervous system; and learning more about how viruses infect cells.

We have also, in this issue of Profiles in Innovation, included a list of recent publications from Downstate faculty that underscores the considerable breadth of research conducted on this campus.

I hope the articles in this issue will pique your interest in following our significant scientific and treatment discoveries. Perhaps, sometime in the future, when you hear of a major breakthrough in medicine at Downstate, you’ll remember reading about it here first.

Very truly yours,

Ian Taylor, MD, PhD
Dean, College of Medicine
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According to the U.S. Department of Health and Human Services, 9.1 percent of all Americans 12 and up — more than 22 million people nationwide — abuse illicit drugs and/or alcohol. Globally, the numbers are even more staggering: About 2 billion of the world’s 6.5 billion inhabitants suffer health problems related to alcoholism and/or drug abuse, says the World Health Organization.

While many are users and innocent bystanders caught in the intractable problems of alcoholism and drug addiction, SUNY Downstate Medical Center researchers are starting to unlock the causes of these diseases. In fact, SUNY Downstate scientists revolutionized the field of alcoholism research. They discovered that many neurological deficits found in the brains of alcoholics are not caused by excessive drinking. Rather, they are inherited, potentially predisposing individuals to alcohol abuse in the first place.

Other SUNY Downstate researchers have traced the effects of prenatal drug exposure on children; teased out the ways narcotics act on the central nervous system; and proposed the existence of neurochemical receptor malfunctions that may increase the risk for alcoholism.

These contributions could bring about a new day in the way our medical community treats substance abuse. A day when the world’s most difficult health problems prove not so intractable after all.
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Sometimes, someone comes along who changes everything. In the field of alcoholism research, that someone was Henri Begleiter, PhD, a distinguished professor of psychiatry and neuroscience at SUNY Downstate Medical Center.

Dr. Begleiter, who died in April 2006, at age 70, was internationally revered as an innovator who redefined medical science’s view of alcoholism.

“Before Henri came along,” says his longtime collaborator Bernice Porjesz, PhD, professor of psychiatry and behavioral sciences, and director of SUNY Downstate’s renamed Henri Begleiter Neurodynamics Laboratory, “the dominant view in the field was that anomalies and dysfunctions found in the brains of alcoholics were the result of drinking.”

Dr. Begleiter was the first to conceptualize the important role genetics plays in the development of alcoholism and related disorders. One of his major accomplishments, Dr. Porjesz says, was in thinking, “Maybe the dysfunctions we see in alcoholics’ brains are something that these alcoholics had prior to becoming alcoholics. Maybe these dysfunctions put them at risk for alcoholism.”

Throughout his celebrated career, Dr. Begleiter dug deep into the complex relationship between genetics and behavior, laying groundwork that continues to provide insights into alcoholism’s genetic links.

As a young scientist, Dr. Begleiter explored the workings of the healthy brain — how humans hear, see, and think. To conduct such research, he needed to compare healthy and abnormal brains, and thus chose to study the brainwave activity of alcoholics.

“We wanted to know what functions are affected by alcoholism, what functions recover with abstinence, and so on,” Dr. Porjesz explains. “We studied this by comparing the brainwave activity of alcoholics with that of non-alcoholics.”

Together, Drs. Begleiter and Porjesz identified a type of neural hyperexcitability that didn’t exist in the brains of non-alcoholics. That piqued their scientific curiosity and their research interest shifted, from normal brain function to alcoholism.

Drs. Begleiter and Porjesz found that one measure of a certain type of brainwave activity, called P3, “was very low in alcoholics,” Dr. Porjesz says. When they began to look into this phenomenon, “We thought, of course, it was the function of drinking alcohol for so many years,” she adds.

Drs. Begleiter and Porjesz next tested recovering alcoholics who had been sober for significant lengths of time. They found the same activity — a very low P3 response.

Concurrently, studies coming out of Scandinavia indicated that boys whose biological fathers were alcoholics were four times more likely to develop alcoholism than boys whose fathers weren’t alcoholics. This was true even for the sons of alcoholics adopted as newborns by non-alcoholic families.

This startling finding led Dr. Begleiter to wonder whether the irreversible brainwave deficits he and Dr. Porjesz saw in alcoholics — the low P3 — existed before these individuals developed alcohol dependence.

“So we looked at the sons of alcoholic fathers,” Dr. Porjesz recalls. The pair specifically chose sons of alcoholic fathers, rather than alcoholic mothers, to ensure that any anomalous brain wave activity hadn’t resulted from prenatal alcohol exposure. The boys were between 7 and 13 and had never been exposed to alcohol or drugs.

“Lo and behold,” Dr. Porjesz recalls, “they too had this low amplitude P3, which, given everything that was known about alcoholism at that point, was astonishing.” Using this data, Dr. Begleiter proposed that these brain-
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The data, published in 1984 in the prestigious journal *Science*, changed the way many researchers and professionals think about alcoholism. “Until then,” says Dr. Porjesz, “we believed alcoholism ran in families solely because children would see their parents drinking and, basically, alcoholism is what they learned.”

These results spurred Drs. Begleiter and Porjesz to study the relationships between genetics and alcoholism. In 1989, Dr. Begleiter founded and led, until his death, the nine-site Collaborative Study on the Genetics of Alcoholism (COGA), examining families heavily affected by alcoholism. In its 18th year, the study, which Dr. Porjesz now leads, includes almost 25,000 individuals and remains the world’s largest study of genetics and alcoholism.

A major focus for the COGA project is the underlying genetic causes of brainwave patterns that distinguish individuals at risk for alcoholism and other so-called externalizing disorders, such as drug abuse, conduct disorder, and anti-social personality disorder. This approach, which COGA adopted many years ago, has been instrumental in identifying several genes involved in alcohol dependence and related disorders in the COGA families.

“When with these ‘risk genes’ in hand,” says Dr. Porjesz, “we’re now running prospective studies in the next generation of children in these families. We’re comparing children with and without these genetic variants as they go through the age of risk. That way, we can study the interaction of these genes and the development of alcoholism and other related disorders.”

Today, the Henri Begleiter Neurodynamics Lab is at the forefront of alcoholism research. Says Dr. Porjesz, “We’re learning new things from our studies all the time.” The multidisciplinary staff continues to discuss their research and new ideas weekly, much as they did, at Dr. Begleiter’s initiation, while the distinguished professor was still alive.

Dr. Porjesz recalls, “Lots of times, everyone would be on one track and Henri would come up with something, some great idea, out of left field. It would be something no one else would have thought of. And that’s something about Henri — an incredible creativity and ability to think outside of prescribed categories — that I particularly miss.

“Even though we have to move ahead without Henri’s vision, ground-breaking ideas, enthusiasm, and charisma, we’re moving forward. We are dedicated to continuing his innovative approach.”

Bottom right: Bernice Porjesz, PhD, and her team. From left to right: Arthur Stimus, project coordinator; Dr. Porjesz; David Chorlian, senior scientific programmer; Madhavi Rangaswamy, PhD, assistant professor; and Kamarajan Chellappan, PhD, assistant professor, during a weekly lab meeting.
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In 1984, SUNY Downstate Medical Center researchers Henri Begleiter, PhD, and Bernice Porjesz, PhD, found that individuals with the highest risk for alcoholism have what researchers call acute alcohol tolerance. Or, what the general public knows as a hollow leg, an ability to consume large amounts of alcohol with little apparent effect.

Now, more than 20 years later, Dr. Sheryl Smith, PhD, a neuroscientist in the SUNY Downstate department of physiology and pharmacology, believes her research is uncovering an explanation: Acute alcohol tolerance most likely results from a neurological disorder that involves GABA receptors.

These receptors respond to the neurotransmitter GABA (gamma-aminobutyric acid), believed to be the brain’s chief inhibitory chemical. “It’s the calming force that we all need to control our thoughts, to relax,” Dr. Smith explains.

But GABA receptors also respond to alcohol. In healthy people, the more alcohol consumed the more relaxed they become. “There’s not a lot of incentive to keep drinking because the person will just fall asleep,” Dr. Smith explains.

This isn’t the case for people with acute alcohol tolerance. They experience alcohol’s calming effect at very low doses. The effect abates quickly; and higher doses don’t lead to increased relaxation, unless a large amount of alcohol is consumed fast. “Slamming down a big dose quickly has a big effect,” Dr. Smith observes. “Of course, that’s very dangerous.”

Dr. Smith’s data show that in certain rodent models of anxiety, when alcohol wears off, GABA receptor changes occur: The more alcohol consumed the more GABA receptors transformed, which in turn leads to more anxiety. “There’s a very good chance a normal person has very low levels of alpha 4 subunits,” Dr. Smith says. “But disorders of GABA receptors that elevate levels of alpha 4 subunits produce anxiety, which encourages individuals to self-medicate with alcohol.”

These alpha 4 GABA receptors respond differently to alcohol than normal GABA receptors. In fact, when tested in vitro, they respond only to low doses of alcohol. For example, low doses of alcohol calm laboratory rodents that express high levels of alpha 4 GABA receptors and exhibit acute alcohol tolerance. But higher doses offer no additional soothing benefit, unless the animals are given high doses over a short period of time.

Moreover, Dr. Smith notes, when the alcohol wears off, the animals show increased levels of alpha 4 subunits and increased anxiety. Extrapolating this observation to humans, Dr. Smith believes that individuals with acute alcohol tolerance have GABA receptor disorders. They drink more because a low dose of alcohol calms them, but higher doses don’t put them to sleep. “When the alcohol wears off,” Dr. Smith says, “these alpha 4 subunits can make a person anxious and craving more alcohol for its perceived calming effects. In that way,” she says, “drinking can become a vicious cycle.”

Dr. Smith’s research may lead to the identification of the human brain’s alcohol receptor — the altered GABA receptor — something researchers have long pursued. “In our experiments with animals and with human DNA in vitro, we think we’ve found one likely candidate,” she says. “What remains to be done is confirm this finding in alcoholics in vivo.”

“Theoretically, that discovery may open the way,” Dr. Smith notes, “to the development of drugs that would decrease the levels of alpha 4 subunits, decrease the jitters and transform an alcoholic into someone who could drink socially.

“A person who can fall asleep after two glasses of wine,” she continues, “will not be wanting more.”
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What does prenatal cocaine exposure do to a child’s development? That’s a difficult question for medical researchers, healthcare providers, and educators. Reports in professional journals are contradictory, some highlighting drug-related developmental problems, such as lower IQ and increased language difficulties, and others downplaying them.

Further complicating the study of prenatal cocaine exposure are a host of additional impediments that may impact the intellectual and psychological development of these children: low socio-economic status, erratic or neglectful parenting, family instability, and poor nutrition, to name just a few.

Now, SUNY Downstate Medical Center Professor Diana Dow-Edwards, PhD, has some answers. Since the mid-1980s, when crack first appeared on America’s streets, Dow-Edwards is able to document the drug’s effects. “Cocaine’s impact depends on when it’s administered,” she explains.

In the first trimester, when the fetal brain’s basic structures are beginning to grow, cocaine exposure affects primary functions such as breathing and heart rate, as well as the ability to withstand stress. “We see that the neuroendocrine system suffers considerably,” Dr. Dow-Edwards says.

Cocaine exposure in the second trimester affects memory and emotions, and third-trimester exposure takes its toll on the cerebral cortex, which makes sense of sensory input and coordinates both thinking and planning.

“We’ve done a variety of different tests on these cocaine-exposed animals and they often do not perform as well as normals,” Dr. Dow-Edwards says. This fact is mirrored in the clinical literature; prenatal exposure to cocaine causes many children to suffer significant decreases in IQ and language development compared to their non-exposed peers.

Dr. Dow-Edwards also discovered through her rat tests that early cocaine exposure tampers with the brain’s so-called “reward circuitry,” the ability to experience pleasure. The neurotransmitter dopamine “is very critical to the functioning of the reward circuit,” Dr. Dow-Edwards notes. But prenatal cocaine exposure disrupts that circuit by “uncoupling certain proteins from certain dopamine receptors, as Wang and Friedman discovered,” Dr. Dow-Edwards says. Left with difficulty experiencing pleasure, “these rats show an abnormal interest in the drug later in life.”

Such ill effects are not all that interests Dr. Dow-Edwards. She wants to find out how to counteract them, to learn whether enriched environments, replete with companions, cognitive stimulation, and a healthier diet, can create improved developmental outcomes.

“Right now, as control subjects, we’re testing normal rats in different environments — in an enriched environment and an impoverished environment, with toys or no toys, with friends or no friends.”

Already, Dr. Dow-Edwards is finding that rats raised in enriched environments “do better on radial arm mazes” than rats raised in impoverished environments. “They’re smarter and more sociable.” And, in a finding that is likely to alter the service provided to children whose mothers used cocaine while pregnant, “we’ve found they didn’t like cocaine as much as those rats that were socially isolated.”

Dr. Dow-Edwards has submitted a grant proposal to the National Institute on Drug Abuse so that she can test these interventions in rats with perinatal cocaine exposure.

Dr. Dow-Edwards hopes her studies will have what scientists call a “translational effect,” that will improve clinical care and social services for children who are exposed to cocaine in utero. “My goal,” she says, “is to advance the understanding of drugs’ effects on children’s development and on their functioning in school and in life.”
Prenatal Cocaine Exposure – What Happens?

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“What are the purely biological effects of this drug? That’s something we can uncover in the lab,” explains Dr. Dow-Edwards, who has appointments in the Department of Physiology and Pharmacology, and Department of Anatomy and Cell Biology.

Her research confirms cocaine’s pernicious influence on growing brains. Her results not only enrich scientific knowledge, but, more importantly, may improve the lives of an estimated 1 million American children who suffer the consequences of prenatal cocaine exposure.

By controlling cocaine exposure in the rat tests, Dr. Dow-Edwards is able to document the drug’s effects. “Cocaine’s impact depends on when it’s administered,” she explains.

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More than 1.5 million Americans are addicted to narcotics. Heroin claims an estimated 1 million regular users, while hundreds of thousands more abuse morphine, codeine, Oxycontin®, and Vicodin®.

Alan Gintzler, PhD, chair of the Department of Biochemistry at SUNY Downstate Medical Center, is trying to understand why. Funded by the National Institute on Drug Abuse, Dr. Gintzler and his colleagues are exploring how cells in the central nervous system respond to the ongoing presence of opium-derived drugs. “If you really understood the adaptations that chronic morphine use elicits,” says Dr. Gintzler, “you would be able to understand the dependence on narcotics that people develop, and what happens when you take the drug away.”

It could also help medical professionals intervene in the process of narcotic addiction itself; both by preventing addiction to pain-relieving narcotics, and blocking drug cravings in users. His research, Dr. Gintzler believes, “could be used to detox. It could also be used as an adjunct for pain therapy to prevent patients from becoming addicted.”

Specifically, Dr. Gintzler has focused his attention on one mechanism of the addiction process—the fact that animals and humans develop a well-documented tolerance for narcotics. In cancer patients, “if you give them morphine, initially it controls their pain very well,” Dr. Gintzler explains. Over time, however, the patient needs higher doses to achieve the same relief. “After a couple of months, you can give as much as several grams of morphine and it’s barely enough,” Dr. Gintzler notes. “Several grams are enough to kill someone who is just starting to use morphine.” A similar phenomenon occurs with drug addicts.

Dr. Gintzler’s research shows how this adaptation occurs. “Cells in the central nervous system communicate by releasing chemicals called neurotransmitters that are then received by receptors on the surfaces of other cells,” he says. Many cells in the brain transduce their signals once the receptor is activated by using G proteins. Dogma in Dr. Gintzler’s field dictates that after habitual exposure to opioids, communication between the opiate receptor and the G proteins becomes interrupted. When the opioid activates the opiate receptor, the signal that is generated can no longer get through.

Dr. Gintzler’s work challenges this view. “The conversation between opioid receptors and G proteins “is still going on, but it changes,” he explains.

During initial opioid exposure, one part of the G protein, called the alpha subunit, communicates with the receptor. After chronic exposure, another part, the betagamma subunit, takes over. The previously silent betagamma subunit now is suddenly heard and signals opioid exposure.

Adaptations to the habitual presence of opioids don’t stop there. During initial exposure, Dr. Gintzler discovered, opioid receptors communicate with one type of G protein, an inhibitory type. After long-term exposure, they switch to another, excitatory type.

These adaptations may save cells. But they don’t help people who take opioids for either pain relief or pleasure. “From the cell’s point of view, tolerance is protective and adaptive,” Dr. Gintzler notes. After all, the drug’s presence disrupts the cell’s equilibrium. But once the drug is present on a regular basis, a new equilibrium develops. Should these drug levels drop, the adaptations become unbalanced and withdrawal ensues.

While much of Dr. Gintzler’s work examines this process on a cellular level, he hopes his research will help prevent and treat narcotic addiction in living, breathing human beings. “The understanding of adaptations that are elicited by the chronic use of morphine,” he says, “will enable us to identify the pivotal changes that underlie the craving phenomenon, and then target them to weaken their effect.”

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Schematic representation of the discovery by Dr. Alan Gintzler and colleagues of changes in signaling molecules and their associations in response to chronic morphine.

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Seizing control: Expanding medical science’s knowledge and treatment of epilepsy

Since the time of the ancient Greeks, medical science has endeavored to make sense of epilepsy. Nevertheless, the illness, which affects 50 million people worldwide, remains highly resistant to treatment. In fact, 30 to 40 percent of epileptics suffer from severe seizures despite significant medical intervention. Epileptics have a death rate that is two to three times higher than the population as a whole. And, each year in the United States, 25,000 to 50,000 of the nation’s 2.5 million epileptics die of seizures and related causes, such as drowning, falls, and traffic accidents.

But with neuroscience’s rapid advancement, great progress is being made in understanding the causes of epilepsy and in developing possible treatments. SUNY Downstate Medical Center is on the forefront of this progress, with one of the country’s largest groups of basic-science and physician researchers focused on the disease.

Supported by funding from the National Institutes of Health, SUNY Downstate scientists are exploring the causes of sudden unexpected death in epilepsy; the process by which brain cells become permanently epileptic; and the connections between epilepsy and an often severe, chromosomally related developmental disorder called Fragile X syndrome. They are also researching the role a neurotransmitter called gamma-aminobutyric acid plays in the development of epilepsy and designing computer models that both predict and target for therapy the immediate causes of seizures.

The answers these researchers find may usher in a new era, one in which epilepsy finally yields to treatment.
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Though there are different types of epilepsy, many who suffer from the disorder were first put at risk by a head injury, stroke, meningitis, or other damage to the brain. Using techniques pioneered by her mentor and colleague, Robert Wong, PhD, Dr. Merlin has found the basic pathway that turns a relatively normal brain into an epileptic one. She is testing compounds that may block that pathway, and thus block the development of the disease in high-risk individuals. “The hope is that someday, these interventions will be clinically applicable,” Dr. Merlin explains.

On the surface of human brain cells are three groups of receptors known as mGluRs, metabotropic glutamate receptors. “The hyperactivity” of one of those groups, Dr. Merlin has discovered, “seems to have a particular ability to persistently enhance the excitability of the brain.” In other words, epilepsy in brain-injured and other high-risk people may be caused by the over stimulation of a certain set of receptors by a neurotransmitter called glutamate. This process sets off a cascade of events within networks of brain cells, resulting in long-lasting changes in channels within the cells, “opening them, closing them, and modifying them in a permanent way,” Dr. Merlin explains. Such changes make the brain cells, in essence, epileptic.

To block that process, and thus prevent the disease in high-risk people, Dr. Merlin and her colleagues are testing the efficacy of certain chemical compounds. In experiments using guinea pig brain tissue, an amino acid called L-cysteine sulfinic acid (CSA) appears to do the trick. So does a blocker of a particular kind of mGluR. “It’s very preliminary,” says Dr. Merlin, but it seems these compounds may “interfere with the pathway that produces the epilepsy.” That’s particularly exciting to Dr. Merlin, who works not only as a researcher but also as a clinician at Brooklyn’s Kings County Hospital, across the street from SUNY Downstate. “Currently, all the available drugs only suppress seizures once the person already has epilepsy,” Dr. Merlin explains. “But a drug that would prevent the development of epilepsy could decrease the population of epileptics worldwide.”
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Robert Wong, PhD, distinguished professor and chair of physiology and pharmacology at SUNY Downstate Medical Center, is motivated as much by a keen intellectual interest in the basic workings of the brain as by a desire to help those who suffer from seizure disorders. “My habit of studying the brain is more like observing the brain,” says Dr. Wong. “I don’t start with theories. I try to test. I don’t try to predict things. I’m just interested in observing various brain activities and figuring out what they are.” That approach has led to one of the most highly acclaimed careers in modern epilepsy research. And with good reason: Dr. Wong’s findings have shaped the field since the late 1970s, when, working with colleague Roger Traub, MD [see page, 26], he first identified the mechanism that causes seizures. Dr. Wong also developed many of the techniques that underlie epilepsy research worldwide.

Now, using his observational approach, Dr. Wong is pursuing a new facet of his research interest: why 30 percent of children with the genetic developmental disorder known as Fragile X syndrome also suffer from epilepsy. “In Fragile X,” says Dr. Wong, “there’s just one genetic defect,” one protein that’s missing. By studying how this mutation leads to epilepsy, Dr. Wong may once again spur major breakthroughs in epilepsy research.

As a postdoctoral fellow, Dr. Wong wanted to learn how brain cells worked together to cause seizures.

So, in collaboration with Dr. Traub, he applied his observational method. Dr. Wong explains that they discovered that when a brain cell, a neuron, gets excited “it sends a signal out to a few other neurons. Those communications are very strong and have a high probability of exciting many other neurons.”

Excited neurons can then excite their neighbors, which, in turn, excite the neurons that surround them. As the process mushrooms, a kind of neuronal “hyper-synchronization” ensues, Dr. Wong says. The excited neurons “discharge in unison,” generating the abnormal electrical activity that results in seizures.

Building on this important finding, Dr. Wong went on to discover that in the normal brain, the excitatory process described is usually inhibited by a neurotransmitter called GABA, gamma-aminobutyric acid. But GABA production can be curtailed by the repeated excitation of the cells that produce it. “So one way that epilepsy occurs is when the excitation becomes too strong or when inhibition is not strong enough,” he explains.

Dr. Wong’s collaboration with Lisa Merlin, MD (see page 18) and Greg Taylor, a SUNY Downstate MD/PhD student, resulted in the discovery of how interictal spikes, synchronized electrical discharges shorter than one second, evolve into discharges of longer duration and more clinical significance, termed ictal discharges. This process occurs when a neurotransmitter called glutamate stimulates a group of receptors on the surfaces of brain cells, known as metabotropic glutamate receptors. The glutamate transforms the cells in a way that allows for long-lasting excitatory activity. “Changing the communication between cells is fundamental to the process by which normal brain cells become prone to epilepsy,” Dr. Wong says.

Now, using these findings, Dr. Wong is examining the causes of epilepsy and developmental disorders in children with Fragile X syndrome. Says Dr. Wong, “Fragile X is a very well-defined disorder. Only one gene and one protein are involved, and these produce huge changes in the brain.”

Not only are children with Fragile X mental retardation syndrome prone to epilepsy, but more than 30 percent suffer from autism. Dr. Wong believes that by exploring the alterations that result from these genetic changes, he and his collaborators may learn to better understand epilepsy and the profound, often devastating developmental disorders that Fragile X can cause. Says Dr. Wong, “Fragile X is a great key to the puzzle of how the brain works.”

That’s a puzzle Dr. Wong continues to piece together through his ongoing and careful observation of the brain. “If you concentrate on selective details,” Dr. Wong says about his method, “those small details might become applicable to a very big picture.” The very big picture that is epilepsy.
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Generalized or focal seizure activity frequently involves the limbic system, a group of brain areas that are critically important for making memories and expressing emotions, but are also prone to seizure activity. The limbic system can strongly influence a much more basic set of brain structures: the autonomic nervous system. These “low-level” brain areas regulate heart rate, blood pressure, and respiration.

SUDEP is thought to result when seizure activity spreads from the cortex and limbic system into the autonomic nervous system (ANS) in a peculiar way. “All seizures have some impact on the ANS, but life-threatening changes in heart rate or blood pressure are uncommon,” Dr. Stewart explains. “Death is likely to be caused by some very peculiar involvement of the ANS as seizure activity spreads through the brain.”

Until recently, it’s been difficult to study precisely how this happens, because researchers were unable to control where seizures occur or follow the paths of seizures from cortex or limbic areas into lower parts of the brain. But about a year ago, Dr. Stewart’s lab developed a technique that for the first time allows them to cause seizure activity in the limbic area of a laboratory animal’s brain without involving the cortex, and to follow this activity through the ANS and into the periphery.

“With this tool for studying animals and our ability to study seizure activity in patients in the hospital epilepsy unit, we can essentially define the patterns of brain activity that cause specific changes in the autonomic nervous system,” Dr. Stewart says.

Dr. Stewart believes his lab will soon identify the type of brain activity associated with SUDEP and how it may vary from patient to patient. By so doing, they may eventually enable epileptics who sense a seizure coming on to treat themselves with medications that control heart rhythms and/or blood pressure. “In those cases,” Dr. Stewart says, “they could administer something which would dramatically lower the chances they would suffer an abnormal heart rhythm, a spike in blood pressure, or respiratory distress that could result in sudden death.”

“These are real therapeutic targets,” Dr. Stewart notes, explaining that many existing medicines have the potential to protect patients “once we establish what they need to be protected from.” In the meantime, he and his colleagues are making much progress toward their goal of identifying the brain patterns that foretell SUDEP. “The tools to predict seizures and their impact on the body for an individual patient are coming,” he says. “And with them, a chance to save many lives.”

sudden unexplained death in epilepsy (SUDEP)

SUDEP is a term used to describe the sudden and unexpected death of an individual with epilepsy, usually during a seizure or in the immediate postictal period. It is a serious and under-recognized cause of death in epilepsy patients. SUDEP is a complex phenomenon that involves the interplay of various factors, including seizure duration, seizure severity, and individual factors such as age, gender, and comorbid conditions.

SUDEP is often not the result of a single factor but rather a combination of factors acting together. Research is ongoing to better understand the underlying mechanisms and to develop strategies to prevent SUDEP. This includes identifying potential risk factors, improving seizure control, and developing new therapies that can help prevent SUDEP.

Mark Stewart, MD, PhD, is reviewing seizure activity recorded during experiments on rats with Kiyomi Koizumi, MD, PhD, distinguished professor of physiology & pharmacology, and Rena Orman, PhD, a postdoctoral fellow.

A section of rat brain tissue showing the paraventricular nucleus, a part of the hypothalamus. Darkly stained cells are evidence of elevated levels of c-fos, a protein marker used to indicate activity. The increase in c-fos expression in the paraventricular nucleus after seizures indicates that these cells were strongly activated by the seizures.

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Dr. Perkins is interested in the mechanisms of neuron-to-neuron communication. To study how brain cells communicate — how they excite or calm each other down — she and her colleagues record electrical activity in slices of hippocampus taken from the brains of healthy laboratory guinea pigs. These brain slices are treated with a chemical that makes them fire in ways similar to the ways human brain cells fire during epileptic seizures. “In fact, electrical recordings from the brain tissue of people with epilepsy look an awful lot like the guinea pig recordings we do in the lab,” Dr. Perkins says.

Through this recording process, Dr. Perkins learned that “under certain conditions, when an interneuron releases GABA onto a principal neuron, it excites that neuron and can trigger an epileptiform seizure.”

These discoveries in guinea pig brain slices were confirmed recently by other labs that conducted studies on the brain tissue of human beings with severe epilepsy: GABA can play an excitatory role in the generation of epileptic seizures. “Seeing the data from the human brain tissue studies has made me excited about what I could do to help people with the disease,” she says.

In her studies, Dr. Perkins has seen that “the same cell can receive both calming, inhibitory GABA-mediated input and excitatory GABA-mediated input.” Now, with funding from the National Institutes of Health, she and her colleagues hope to discover which kinds of interneurons are responsible for the excitatory and the inhibitory types of GABA responses. “Right now, it’s not clear whether these different types of GABA responses are produced by different types of interneurons,” Dr. Perkins explains. “Our early data suggest that they are.”

Such a discovery could help unravel the mystery of GABA’s role in causing epileptic seizures, and may elucidate the role the neurotransmitter plays in other important brain functions such as learning and memory. Discovering the source of GABA’s excitatory action could also help in developing treatments for the difficult-to-control disease of epilepsy.

“We might be able to enhance GABA’s calming effect without also enhancing the excitatory effect,” Dr. Perkins explains. “That,” she says, “would be especially good news for patients with epilepsy.”
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is GABA a culprit?

Katherine Perkins, PhD, is on the trail of a mystery. That mystery? The role the neurotransmitter GABA, gamma-aminobutyric acid, plays in causing epileptic seizures.

What makes this a mystery is that for a very long time, neuroscientists have believed that GABA’s major role in the adult brain was as the chief inhibitory neurotransmitter, calming brain cells down and thereby decreasing the electrical activity that can result in seizures.

But in 1991, Robert Wong, PhD, and fellow SUNY Downstate researcher Hillary Michelson, PhD, made what was then a startling discovery: GABA could be used by the brain cells that release it, called interneurons, to excite other interneurons. In so doing, GABA can cause a large group of interneurons to become active simultaneously.

“The finding that interneurons could use GABA among themselves as an excitatory transmitter was very controversial and very exciting,” says Dr. Perkins, who was a graduate student in Dr. Wong’s lab at the time and is now an associate professor of physiology and pharmacology at Downstate. “And I’ve been interested in the excitatory action of GABA ever since.”
In fact, “these models are like teenagers,” says Mark Stewart, MD, PhD (see page 22). “They can actually talk back and say things we didn’t program them to say.” They also, Dr. Stewart observes, are “teaching us some things about brains that we didn’t anticipate.”

In particular, Dr. Traub’s models are educating neuroscientists about how the epileptic brain works, and what parts of the seizure process to explore and target in an effort to prevent and/or treat epilepsy.

Roger Traub isn’t your average neurologist. While an undergrad at Princeton University, he won a prestigious senior mathematics prize. Then he did graduate training in math at Massachusetts Institute of Technology for a year, before attending medical school at the University of Pennsylvania. After a stint as a National Institutes of Health research fellow studying the degenerative brain disorder known as Creutzfeldt-Jakob—mad cow disease—he joined the research faculty at IBM, where he began his pioneering work on mathematical models of brain-cell activity.

His research at IBM put him in touch with other scientists who were using animal brain tissue slices to study the brain’s electrical activity. Using their data, he began piecing together mathematical descriptions of neural activity. Dr. Traub emphasizes that the collaborative nature of this work is what has made his computer models so successful. “Modeling by itself gets you nowhere,” he states. “We understand what’s happening in these EEGs because,” by using recordings of brain activity in conjunction with computer models, “we can see the whole picture.”

Before Dr. Traub’s models, neurologists didn’t understand the relationship of fast oscillations to the seizure process. Fast oscillations “happen because of an electrical coupling between cells in the axons of brain cells, something we didn’t expect,” Dr. Traub says. Using the information Dr. Traub uncovered, neurology researchers may one day be able to predict and even avert seizures.

Pointing to the EEG, Dr. Traub explains, “If you can target these fast oscillations, a predictor of the onset of seizures, with a drug, rather than the bursts of the actual seizure, which is what neurologists usually go after, you’ll prevent seizures.”

The neurologist/mathematician cautions that this is not yet a done deal. First, researchers must identify the protein that controls the electric coupling his computer models predicted. Then, they must develop a drug that can alter the process. “Still,” he says “it’s really astonishing how much we’ve already learned from these computer-generated models of brain cells’ electrical activities.”
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This is how seizures start, says Roger Traub, MD, professor of physiology and pharmacology and of neurology, as he points to a wavering line on what looks like a brain wave recording called an electroencephalograph (EEG). In fact, this image doesn’t come from a human brain at all. Rather, it’s computer-generated, based on mathematical models of brain cells’ electrical activity that Dr. Traub has spent years developing. “Thirty thousand lines of Fortran!” he says, referring to the computer language in which his program is written.

In particular, Dr. Traub is tracing a low-amplitude oscillation that precedes the spikey, quick-succession bursts that seem to indicate a seizure. He then compares it to an actual EEG recording of a seizure. The two are almost identical. What’s so important about Dr. Traub’s work, why it has received so much national and international attention, is that it doesn’t simply approximate the brain’s activity; it predicts it.

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Working in one of the HIV epicenters, the talented and dedicated staff at SUNY Downstate are national and international leaders in basic and clinical HIV research, care, service, and education. “We published one of the first papers on AIDS in 1984,” Dr. Landesman recalls. “By then, we had accumulated 10 cases.”

Today, SUNY Downstate is home to a number of world-class HIV-related facilities and programs. The Special Treatment and Research (STAR) Health Center integrates state-of-the-art medical care with pioneering research in HIV/AIDS and treatments. The HEAT Program—Health & Education Alternatives for Teens—offers medical care and empowerment to HIV-positive and high-risk youth. The International AIDS Vaccine Initiative (IAVI) established a lab at SUNY Downstate where scientists work on potential vaccines that may one day stop the infection before it starts.

In the last 25 years, significant scientific and treatment discoveries developed at SUNY Downstate have given HIV patients a world filled with promise. But SUNY Downstate faculty researchers are not stopping there. Their goal is to see HIV eliminated entirely.
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One group of trainers — Nicholas A. Rango HIV Clinical Scholars — receives two years of specialized instruction as part of a program created and funded by the New York State Department of Health’s AIDS Institute. To date, SUNY Downstate has trained 19 HIV Clinical Scholars.

Nurse practitioners Amanda Swan and Katherine Marx are the newest HIV Clinical Scholars. Until their fellowships end in June 2008, they’ll treat patients, deepen their knowledge of HIV medicine, attend weekly seminars on public health and AIDS policy issues, and explore research methods. “For me, as a new nurse practitioner,” says Ms. Swan, “having a preceptor — a clinician who serves as my mentor — has really helped.”

Ms. Marx agrees. “I’m able to meet with my preceptors weekly to go over patient questions and issues. If I need someone to look at something — a rash I’m not sure about — the preceptors are right there. That kind of support is a really important part of my training.”

But not the only important part. The Clinical Scholars from SUNY Downstate meet weekly with fellow HIV Clinical Scholars from around New York to discuss policy issues and public health. “We have seminars on international AIDS issues, on epidemiology, on youth work — a whole variety of topics,” says Ms. Marx. “These seminars have allowed me to put my clinical work in context and to think about how to become more active in public health issues.”

Still, these Clinical Scholars say the most important part of their training is the relationships they develop with patients at Downstate’s HIV clinics for adults and adolescents. Says Ms. Swan, “Especially in HIV work, patients tell you things about themselves that a lot of other people don’t know. You play a big part in their life. When I finish this program, that will be what I remember most — my relationships with the patients here.”

Of course, those relationships may continue if Ms. Swan, like a number of the HIV Center’s trainees, remains at SUNY Downstate after her fellowship is complete. That’s what Tracey Wilson, PhD, a cognitive psychologist, did after finishing two years of post-doctoral training at SUNY Downstate in 1997.

Sponsored by the Association of Teachers of Preventive Medicine and the Centers for Disease Control and Prevention (CDC), Dr. Wilson was able to apply her training to researchers and healthcare professionals from Central and Eastern Europe as part of the Fogarty AIDS International Training & Research Program started in the 1990s. Funded by the National Institutes of Health, the program is named after a former member of Congress.

“It was a means of linking up academic medical centers to centers in the developing world that were gearing up to fight HIV,” Dr. DeHovitz explains. To date, the Fogarty program at SUNY Downstate has provided short-term training to more than 5,300 professionals in HIV-related fields and long-term training to more than 70 others.

A number of the first Fogarty researchers trained by SUNY Downstate faculty came from the Czech Republic, Hungary, and Poland. “Some of them were basic science researchers; some were public health researchers,” Dr. DeHovitz explains. “And some did clinical research with a health outcomes focus.”

Now, as the AIDS epidemic has spread to the former Soviet Union, so has the Fogarty program, creating educational partnerships with researchers and healthcare providers in Russia, Estonia, Georgia, and Armenia. “We bring people over here for training,” says Dr. DeHovitz, who directs the project, “and help create relationships and partnerships with — in a cadre of individuals who can work together and who continue once they return to their countries.”

In that way, SUNY Downstate offers its considerable HIV expertise to Brooklyn, N.Y., and beyond.
It happens mostly behind the scenes. But "one of the most important things we do at the HIV Center," says Director Jack DeHovitz, MD, MPH, professor of medicine and of preventive medicine and community health, "is to train new researchers, healthcare practitioners, and leaders."

In fact, health professionals come to SUNY Downstate from throughout the world to receive specialized training in HIV medicine, prevention, and research. "Because of our expertise in these areas," Dr. DeHovitz says, "we can offer instruction and mentorship that would be hard to replicate elsewhere."

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But not the only important part. The Clinical Scholars from SUNY Downstate meet weekly with fellow HIV Clinical Scholars from around New York to discuss policy issues and public health. “We have seminars on international AIDS issues, on epidemiology, on youth work — a whole variety of topics,” says Ms. Marx. “These seminars have allowed me to put my clinical work in context and to think about how to become more active in public health issues.”

Still, these Clinical Scholars say the most important part of their training is the relationships they develop with patients at Downstate’s HIV clinics for adults and adolescents. Says Ms. Swan, “Especially in HIV work, patients tell you things about themselves that a lot of other people don’t know. You play a big part in their life. When I finish this program, that will be what I remember most — my relationships with the patients here.”

Of course, those relationships may continue if Ms. Swan, like a number of the HIV Center’s trainees, remains at SUNY Downstate after her fellowship is complete. That’s what Tracey Wilson, PhD, a cognitive psychologist, did after finishing two years of post-doctoral training at SUNY Downstate in 1997.

Sponsored by the Association of Teachers of Preventive Medicine and the Centers for Disease Control and Prevention (CDC), Dr. Wilson was able to apply her interest in individual behavior change to the field of HIV prevention. “A large part of my post-doc training was in different areas of public health — basic epidemiology, infectious disease epidemiology, and the design and evaluation of prevention programs,” she says.

That training enabled her to design and implement programs to help stop the spread of HIV and other sexually transmittable diseases — programs she continues to develop today as an associate professor in SUNY Downstate’s Department of Preventive Medicine and Community Health.

The HIV Center provides similarly intensive training to researchers and healthcare professionals from Central and Eastern Europe as part of the Fogarty AIDS International Training & Research Program started in the 1990s. Funded by the National Institutes of Health, the program is named after a former member of Congress.

“It was a means of linking up academic medical centers to centers in the developing world that were gearing up to fight HIV,” Dr. DeHovitz explains. To date, the Fogarty program at SUNY Downstate has provided short-term training to more than 5,300 professionals in HIV-related fields and long-term training to more than 70 others.

A number of the first Fogarty researchers trained by SUNY Downstate faculty came from the Czech Republic, Hungary, and Poland. “Some of them were basic science researchers; some were public health researchers,” Dr. DeHovitz explains. “And some did clinical research with an interest in individual behavior change to the field of HIV prevention.”

Now, as the AIDS epidemic has spread to the former Soviet Union, so has the Fogarty program, creating educational partnerships with researchers and healthcare providers in Russia, Estonia, Georgia, and Armenia. “We bring people over here for training,” says Dr. DeHovitz, who directs the project, “and help create relationships and partnerships within a cadre of individuals who can work together and who continue once they return to their countries.”

In that way, SUNY Downstate offers its considerable HIV expertise to Brooklyn, N.Y., and beyond.
Despite making up almost 30 percent of all HIV/AIDS cases in the United States, women and children are the disease’s least recognized faces. In most places, that is.

“Women and Infants Transmission Study (WITS) team (left to right): Magalie Joseph, RN, Dr. Sheldon Landsman, Ava Denove, RN, Anna O’Neal, Gail Joseph

In fact, since the pandemic began in the early 1980s, “our major research accomplishments have come in the area of HIV disease in women, and the impact on children born with the virus. In fact, this research is changing the standard of care in many areas, and with it, the course of the HIV epidemic as a whole.

In some ways, SUNY Downstate’s Brooklyn location made this research a natural fit. “Very early in the epidemic,” recalls Sheldon Landsman, MD, professor of medicine and assistant dean for clinical education, “we started seeing babies with the disease.”

Realizing that those on the front lines needed to understand how this new and rapidly spreading disease impacted HIV-positive women and their children, Dr. Landsman teamed with Howard Minkoff, MD, distinguished service professor of obstetrics and gynecology, Joan Hittelman, PhD, clinical associate professor of psychiatry and pediatrics, and Hermann Mendez, MD, professor of pediatrics, to design and implement the nation’s first study of perinatal HIV transmission, the Maternal and Infant Transmission Study (MITS) that ran from 1985 through 1993.

Contrary to earlier reports, the study showed that only about 25 percent of babies born to HIV-positive mothers developed the disease, and that “prematurity and low birth weight seemed to enhance the risk of infection,” says Dr. Landsman. The research also suggested that cesarean section and/or the time between a woman’s water breaking and her infant’s delivery had significant bearing on whether the child would become HIV positive; the more quickly the child was delivered, the lower the risk.

MITS led to important policy recommendations as well. At the time MITS began, doctors only tested women for HIV who had self-identified risk factors, such as injection drug use or a drug-using partner. But “something like 30 percent of the women in the study had risk factors for acquiring HIV that they didn’t identify,” Dr. Landsman says. “So, Howard Minkoff and I published a paper saying you shouldn’t offer HIV testing to pregnant women based on the HIV risk factors they identify. You should offer it to all pregnant women.”

Later studies confirmed that using risk factors alone would fail to identify many HIV-positive pregnant women. The American College of Obstetricians and Gynecologists adopted Dr. Landsman and Minkoff’s position; routine HIV screening for all pregnant women is now the standard of care in the United States.

To find answers to the questions raised by their initial research in MITS, the SUNY Downstate team developed and implemented a next-generation study called the Women and Infants Transmission Study (WITS), which ran from 1989 through 2006. The study examined a number of issues that have had great bearing on the lives of women and infants with HIV, including: how does HIV disease progress in pregnant women? Are there specific factors that increase the risk of perinatal HIV transmission? What course does HIV infection take in infants?

Dr. Minkoff explains, “One of the things that WITS showed is the relationship between viral load [the amount of HIV in the blood] and fetal transmission. A high viral load increases the risk of maternal-infant transmission. But if the viral load is undetectable as a result of medication, there’s a very low risk of transmission.” Dr. Landsman and other WITS investigators demonstrated that a shortened time between a woman’s water breaking and her child’s delivery reduced by 50 percent the risk of perinatal HIV transmission. Because elective cesarean section cuts the time between membrane rupture and delivery to zero, the practice of elective cesarean section, too, is now the standard of care.

The result of these and related research: Maternal-infant HIV transmission has been virtually wiped out in the developed world. Says Dr. Landsman, “That’s a very real and substantive accomplishment. Antiretroviral therapy is important, but it’s no cure for people with HIV. This stopping of maternal-infant transmission represents a powerful means of HIV prevention.” Twenty years ago, that was almost unimaginable.

The Women’s Interagency HIV Study, based at SUNY Downstate Medical Center and other locations throughout the country, is one of the world’s most comprehensive studies of HIV disease. “This study tries to look at the effect of the disease on all aspects of women’s health,” says renowned HIV researcher and co-principal investigator Howard Minkoff. The study examines not only the immune functioning of the women enrolled, but their cardiovascular health, their cognitive abilities, and their gynecological problems.

Since 1993, when the study began, Dr. Minkoff and his staff at SUNY Downstate have explored these ques-
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and regression in HIV-positive infants and children. Understanding how important it was to track and treat HIV in young children, she and pediatrics professor Hermann Mendez, MD, pioneered studies into the disease’s impact on that age group. “Before the medications were developed, HIV was devastating to these children’s brains,” Dr. Hittelman recalls. “Their muscles would become tight. They couldn’t move. And they lost the ability to speak.”

Many children born to HIV-positive mothers were also drug-exposed. The Maternal and Infant Transmission Study (MITS) and the Women and Infants Transmission Study (WITS) separated out the effects of prenatal drug exposure from those of HIV. “The drug-exposed infants,” Dr. Hittelman says, “manifested some neurological insult, but it was mild compared to that of HIV. And often they outgrew its effects. The HIV-positive infants looked perfectly normal at birth, but they became progressively worse. It was terrible to watch.”

As the AIDS epidemic advanced, Dr. Hittelman’s studies focused on the impact that HIV and HIV medications had on children’s development. Surprisingly, many children who were HIV-positive and undergoing treatment progressed as well as their uninfected peers, Dr. Hittelman and her colleagues found. Only those with what are called AIDS-defining illnesses (illnesses the Centers for Disease Control and Prevention uses to validate an AIDS diagnosis) experienced developmental problems. “That’s when the virus goes to the brain and we start seeing developmental delays,” Dr. Hittelman says. Such delays were also linked with increased mortality, she and her colleagues found.

“Now the women in our study are getting older,” Dr. Minkoff says, “so in a way, our next funding cycle is really about HIV and aging.” Many of the women in the observational study are undergoing perimenopause, which triggers hormonal changes that may have an effect on the virus. Many have been HIV-positive for more than a decade, and have taken potent medications for long periods of time. “There may be long-term toxicities associated with chronic exposure to these medications,” Dr. Minkoff explains.

Conclusions drawn from the study alerted medical professionals to the special health issues women with HIV face. But Dr. Minkoff is equally proud of the policy changes the study prompted. “I remember being at a meeting where one of the Army’s chief physicians said to me, ‘Thanks for your article,’” Dr. Minkoff recalls. Before the article came out, the U.S. Army wouldn’t allow pregnant women enrolled in its health services access to anti-retroviral therapies. Says Dr. Minkoff, “It’s nice to know that a single article based on our research and the ethical issues it raised can make such a difference in the lives of women with HIV.”

“Early on in the epidemic,” says Joan Hittelman, PhD, clinical associate professor of psychiatry and pediatrics, “we realized that in children there was a serious neurodevelopmental component of HIV infection. “The children we saw then were spastic. It was terrible to watch them lose their motor abilities and slip backwards on cognitive milestones. And then, of course, many of them died.”

It was a bleak situation that many turned away from. But not Dr. Hittelman, who, as director of Downstate’s Infant Behavior Laboratory, had created Downstate’s Infant and Child Learning Center early in the epidemic expressly to address developmental delay and regression in HIV-positive infants and children. Many children who were HIV-positive and undergoing treatment progressed as well as their uninfected peers, Dr. Hittelman and her colleagues found. Only those with what are called AIDS-defining illnesses (illnesses the Centers for Disease Control and Prevention uses to validate an AIDS diagnosis) experienced developmental problems. “That’s when the virus goes to the brain and we start seeing developmental delays,” Dr. Hittelman says. Such delays were also linked with increased mortality, she and her colleagues found.

Today, with the exception of a study looking into the long-term consequences that perinatal antiretroviral therapy may have on children born to HIV-positive women, there’s little research going on at SUNY Downstate into HIV’s impacts on children. That’s because, thanks in part to the earlier research conducted by SUNY Downstate faculty, almost no cases of perinatal HIV transmission exist any more in Brooklyn, or, for that matter, in the developed world.

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If ever there was a disease in need of a vaccine, it’s AIDS. The illness, caused by the human immunodeficiency virus (HIV), has killed more than 25 million people worldwide since 1981; almost 3 million died in 2006 alone. Globally, an estimated 40 million people are living with HIV infection.

Other viruses — polio, smallpox, hepatitis A and B — have yielded to vaccines that build immunity to specific viral agents. But HIV remains elusive, due in large part to the nature of the virus. HIV is a retrovirus, and like other retroviruses, it inserts copies of its genetic material into cells in a way that makes them less visible to the body’s immune system. In addition, HIV mutates rapidly. And, there’s no single HIV — various subtypes thrive in different parts of the world.

Nevertheless, scientists believe an AIDS vaccine is not only possible, but necessary. A vaccine is the best way, they believe, to eradicate a disease that is spreading rapidly in areas with minimal healthcare infrastructure, such as Sub-Saharan Africa, India, and the former Soviet Union.

“Even though there are a lot of challenges,” says Adrian McDermott, MSc, PhD, an assistant professor of immunology at the Downstate Medical Center in Brooklyn, “the potential benefits are so great that it’s worth the effort.”

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Preclinical assessment of a prototype vaccine using a technique known as 4-color flow cytometry. The panels displayed represent the analysis of data generated by a flow cytometer, which uses lasers to accurately count immune cells from vaccine recipients that have been tagged with a number of fluorescently labeled antibodies. This information enables researchers to determine the quality of the immune response generated in test subjects and ultimately the potential success of a particular vaccine.

Preclinical assessment of a prototype vaccine using a screening technique called IFNg ELISPOT. Data in each square represents the immune responses of vaccinated test subjects and aids in the evaluation of potential vaccine candidates. The number of spots correlates to the ability of the subject’s immune cells to recognize HIV vaccine proteins.
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IAVI has the only applied research and development lab dedicated solely to AIDS vaccine development. Scientists at IAVI are aggressively working to produce the next generation of novel and improved vaccine candidates and to rapidly translate these advances into new vaccines for human testing. Developing safe, effective, and accessible HIV vaccines is not just IAVI’s mission; it is Dr. McDermott’s calling in life.

In pursuit of that calling, Dr. McDermott leads IAVI’s Preclinical Core Immunobiology Lab, which evaluates the efficacy of emerging vaccine candidates. He also heads up IAVI’s Live Attenuated Consortium (LAC), which is researching so-called immune correlates — biological indicators of immunity to HIV.

Immunity to HIV? Is such a thing possible? There are individuals who, though repeatedly exposed to the virus, remain uninfected. Similarly, a group termed “elite non-progressors” tests positive for the virus but never develops immune deficiencies. One group of non-progressors, an Australian cohort identified in the 1990s, is missing a type of HIV gene called nef. To investigate this phenomenon, scientists developed a mutant simian immunodeficiency virus (SIV) that is also missing the nef gene. After initial exposure to this mutant virus, the SIV delta nef vaccine elicits a protective response in 95 percent of the animals tested.

At present, the mechanism that offers this protection is unknown. “Something’s protecting them, though,” Dr. McDermott says, “so we’re trying to find out what that is.” Toward that end, Dr. McDermott is examining these animals’ immune responses and their genetics.

Finally, he and his colleagues work closely with IAVI’s Vector Design group that researches biological agents, such as benign viruses that might deliver an HIV vaccine to the area of the immune system that can best use it to provide immunity. One possible vector is the reovirus that would carry the vaccine to the gut, to which HIV migrates soon after entering the body.

“The immune correlates and the vectors program are very closely linked,” Dr. McDermott explains. With 4 million people annually infected with HIV, Dr. McDermott feels these programs can’t come to fruition soon enough.
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Dr. McDermott’s research hasn’t stopped there. His lab has helped standardize assays — scientific tests — that researchers in the LAC Consortium use to judge “different experiments in the context of the same assays,” he says. “It’s about standardization across many different investigators.”

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“Once the individual becomes infected,” says Dr. McDermott, “you would have immunity in the spot where the depletion of [immune] cells takes place.”

“So the immune correlates and the vectors program are very closely linked,” Dr. McDermott explains.

With 4 million people annually infected with HIV, Dr. McDermott feels these programs can’t come to fruition soon enough.
When you look at all the HIV statistics, 50 percent of all the newly infected cases are in people below the age of 25,” says Jeffrey Birnbaum, MD, MPH, assistant professor in the Department of Preventive Medicine and Community Health at SUNY Downstate Medical Center. “To meet their special needs, Health & Education Alternatives for Teens -- HEAT -- is there.”

HEAT provides HIV-positive and high-risk youth with medical and mental health services, case management, support groups, and outreach and education. Its staff of 12 offers a variety of support groups for teenagers and off-site HIV counseling and testing, in addition to other services. “We also constitute a network of other adolescent service providers who are concerned about HIV prevention,” Dr. Birnbaum says. Among the HEAT staff, he notes, are two young people who “do direct street outreach and speak to other youth at schools and youth programs.”

Funded by the New York State AIDS Institute and the federal Ryan White Program, HEAT is unique in Brooklyn. It is the only program in the borough specifically designed to meet the medical, mental health, and social service needs of HIV-positive and high-risk youth. But a program that offers world-class medical expertise to a community in need is hardly unique at SUNY Downstate.

Among SUNY Downstate’s HIV-related projects that directly benefit the community are the Infant and Child Learning Center, once New York State’s only preschool and early intervention program providing services to HIV-positive children. And, the FACES clinic (Families, Adolescents and Children’s Experiences at SUNY) offers tailored services to HIV-positive children, parents, and their families.

HEAT’s emphasis on specialized services for HIV-positive teens is unusual. “There are a lot of people in the pediatric AIDS world and in the adult field, too, who think they can just squeeze teenagers into their programs,” Dr. Birnbaum says. “But unless you’re set up to work with teens, you’re not going to be that successful.”

Adolescents have special needs related to the developmental stages of the teenage years, Dr. Birnbaum says. It’s those needs, and the lifestyle issues they create, that HEAT was designed to meet. “Ostracized gay youth. Ostracized transgender youth. Teenage moms,” Dr. Birnbaum says. “They each come with different sets of issues. We’re equipped to deal with those issues in ways that pediatric providers or adult providers probably are not.”

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So Dr. Hittelman started her own program: the Infant and Child Learning Center (ICLC). Begun in 1987, the ICLC was, says Dr. Hittelman, “a special education preschool,” then serving 24 HIV-positive children. In those days, when treatments were few and most children with HIV died before finishing...
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In the 1980s, Joan Hittelman, PhD, clinical associate professor of psychiatry and pediatrics, had a problem. The HIV-positive children she saw in her clinic had nowhere to receive the early-intervention services they desperately needed to ameliorate their HIV-related developmental delays and obstacles. In her capacity as director of Downstate’s Infant Behavior Laboratory, Dr. Hittelman worked with early-intervention providers. But with the inception of the AIDS epidemic, “Nobody wanted to accept a referral from us,” she says. “With the intense AIDS phobia at that time, all the early intervention providers could think was that they were going to get an HIV baby.”

So Dr. Hittelman started her own program: the Infant and Child Learning Center (ICLC). Begun in 1987, the ICLC was, says Dr. Hittelman, “a special education pre-school,” then serving 24 HIV-positive children. In those days, when treatments were few and most children with HIV died before finishing...
Hermann Mendez, MD, was a resident in pediatrics when babies with an unknown immune deficiency started being born at SUNY Downstate in the early 1980s. “I think we had one in 1981, and one in 1982,” says Dr. Mendez, now a professor of pediatrics at SUNY Downstate. Soon the problem snowballed. By the end of 1984, he says, “we had 70 or 80 cases in children.”

As part of SUNY Downstate’s pioneering work in HIV, Dr. Mendez collaborated with SUNY Downstate faculty, including Sheldon Landesman, MD, Howard Minkoff, MD, and Joan Hittelman, PhD, to establish the FACES (Families, Adolescents and Children’s Experiences at SUNY) clinic for HIV-positive children and their families. “The clinic’s mission was then, as it is now,” Dr. Mendez says, “to provide the best possible care to HIV-infected children, adolescents, and their families, and to conduct clinical research to advance that care.”

Toward those ends, the FACES clinic offers medical and mental health services, case management, and nutritional advice; it runs clinical and observational trials that detail the impact on children of HIV exposure, infection, and medication. Because antiretroviral drugs can be difficult and complicated to take, “We also have a mental health worker who deals with medication compliance,” Dr. Mendez explains.

The FACES clinic involves the community it serves in all aspects of its work. “We have the largest community advisory board in the country,” Dr. Mendez proudly states. The group numbers more than 60.

One of the staff’s most important jobs is to work with HIV-positive pregnant women. “Many of these women don’t have an indication for treatment,” Dr. Mendez says, explaining that their HIV-infection has not progressed to a point where they need medication. “When they get pregnant, we put them on antiretrovirals. They have planned cesarean sections, which, we’ve learned, significantly reduce the risk of perinatal HIV transmission. And these women are having babies who are healthy.” The FACES clinic follows these infants and offers them medical services as well.

The FACES staff also provides care to long-term survivors of HIV, young people who, years ago, were perinatally infected. “But we’re losing our business...” Dr. Mendez says with a smile. “The rate of HIV infection among children has declined at an amazing rate. In a few years, I’m looking forward to closing up shop.”
elementary school, “we taught sign language so the kids would be able to communicate with us after they lost their ability to speak,” Dr. Hittelman recalls. “And we spent a lot of time talking with them about death and dying.” The Infant and Child Learning Center offered special education, physical, occupational and speech therapies, counseling, and nursing services. “We tried to get the children back to normal, or at least to become their best-functioning selves,” Dr. Hittelman says.

Within a couple of years of its founding, the ICLC began serving children and premature infants with other medical problems. The ICLC also provided a program for school-aged children who had been temporarily forced out of the public school system because of their HIV status.

By the mid-1990s, as a result of scientific breakthroughs that helped prevent perinatal HIV transmission, relatively few HIV-positive babies were being born in Brooklyn. The stigma around HIV began to abate and antiretroviral therapy started to improve the well-being and extend the lives of HIV-positive children. So the program expanded its mission to include an early intervention and preschool program for medically involved children with developmental delays, with a special emphasis on premature infants. The program has grown to a point where it is building its own facility.

“We now serve over 500 families in their homes and another 100 in our center,” Dr. Hittelman explains. “And I’m very happy to say that only a few of those kids have HIV.”

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Dr. Joan Hittelman, Director, Infant and Child Learning Center.
Diabetes can be devastating. Caused by the body’s inability to produce insulin or to use insulin properly, diabetes can result in blindness, limb amputation, kidney failure, cardiovascular disease, and death.

At present, 180 million people globally suffer from diabetes symptoms. Here in the United States, 7 percent of the population is diabetic.

Diabetes isn’t just a terrible illness, though. It’s one of the world’s fastest growing health problems. The World Health Organization estimates that unless urgent action is taken, by 2015 the number of people with diabetes will increase by 50 percent. American cases are expected to double by 2030.

Can diabetes be stopped? Researchers at SUNY Downstate Medical Center believe the answer is yes. They have pioneered clinical treatments that can put diabetes into remission, or prevent it altogether. They are exploring the public health issues that contribute to diabetes’ rise. And they have made progress toward an elusive research goal: regenerating the insulin-producing beta cells of the pancreas.

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In the mid-1990s, Mary Ann Banerji, MD, professor of medicine, helped pioneer a novel approach to the treatment of patients with newly diagnosed type 2 diabetes—the kind that occurs when the body is unable to use the insulin it produces, or to meet the increased demand for insulin that can result from obesity.

Instead of prescribing what was then the standard treatment—drugs such as metformin and sulfonylureas—Dr. Banerji, with colleagues Samy McFarlane, MD, MPH [see page 48], Rochelle Chaiken, MD, and Harold Lebovitz, MD, offered patients a short course of injectable insulin.

The result? Amazing. “About 40 percent of our patients had their blood sugar return to normal,” recalls Dr. Banerji. “They were able to stop taking insulin. In fact, they didn’t need any diabetes medications at all.”

By contrast, none of the patients who received standard care had their blood sugar return to normal. And only one third were able to meet “target” blood sugar levels. Moreover, Dr. Banerji’s insulin treatment put patients with type 2 diabetes into remission for an average of three years. “Normalizing blood sugar levels allowed the pancreas’ insulin-producing beta cells to recover and start producing insulin again,” she explains.

Dr. Banerji and her team have been on the forefront of other medical breakthroughs. In 1994, they identified a previously unreported form of diabetes in people of African descent. Termed “Flatbush diabetes” after SUNY Downstate’s Brooklyn neighborhood, the illness has an unusual presentation. It primarily affects adults and presents with ketoacidosis, a state of insulin deficiency characterized by high levels of acids and sugar in the blood.

Since ketoacidosis was involved, clinicians believed that patients “needed to be treated with insulin forever,” Dr. Banerji recalls. Her research helped prove “this type of diabetes usually needs insulin only for a short while and then can be treated with pills for years thereafter.”

As director of the SUNY Downstate Endocrinology Clinic and Diabetes Center, Dr. Banerji is an advocate of research into scientific questions that have a direct impact on clinical care. She uses her clinical experience to pose basic research questions that advance care for the growing population of people with diabetes.

To understand the causes of diabetes, Dr. Banerji studies the connection between diabetes and fat storage in the body. “People’s bodies store fat in different places,” she explains. Fat can be stored in the abdominal cavity, or in the liver; it can be marbled in muscle. Storing fat on the hips, being “pear-shaped,” appears to have little bearing on the development of diabetes, Dr. Banerji says. But “from our early work using CT (computed tomography) scans, we’ve learned that storing fat in the abdomen or the viscera is a central component of type 2 diabetes.”

Dr. Banerji and her colleagues also demonstrated that South Asians who have the same body-mass index as whites—body mass index is a ratio of weight to height—often have more fat and less lean muscle mass, leading to higher rates of diabetes and cardiovascular disease.

Dr. Banerji and her team of nurse practitioners and diabetes educators are participating in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, the National Institutes of Health’s largest clinical trial involving people with type 2 diabetes. The trial is designed to determine whether cardiovascular events (heart attack, stroke, or cardiovascular death) can be prevented in individuals with type 2 diabetes through intensive control of blood sugar, blood pressure, and lipid levels.

The medical realities of diabetes aren’t Dr. Banerji’s only concern. She believes lifestyle interventions can address many of the underlying causes. “The diabetes epidemic will require public health measures and lifestyle changes to combat our current state of excessive food intake and physical inactivity,” Dr. Banerji observes.

With funding from the Centers for Disease Control and the State of New York, Dr. Banerji is investigating novel approaches to treatment and prevention. “Our mission,” she says, “is to educate people—both those at risk and those with diabetes—out in the community.”

Toward this end, she works with Downstate’s Center for Health Promotion and Wellness and the non-profit Brooklyn Diabetes Task Force, a coalition of hospitals and healthcare organizations, on educating people at health fairs and houses of worship. The Task Force also sponsors an annual diabetes fitness walk.

Dr. Banerji chooses to see diabetes in a broad context, hoping to understand both its physical and its social causes. “To me, that’s critical,” she says. “You have to understand diabetes’ various presentations and its social context in order to know where to focus research efforts.”
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If I have a patient who’s at risk,” Dr. McFarlane says, “my first recommendation will be diet and exercise.” But such lifestyle interventions are notoriously difficult to maintain. Even highly motivated patients have trouble keeping weight off and exercising on a regular basis. Moreover, the risk of diabetes increases with age, with the dying off of the pancreas’ insulin-secreting beta cells [see page 50]; many older adults aren’t able to exercise with the intensity necessary to prevent diabetes. “Because of that,” Dr. McFarlane says, “we want to investigate other ways to prevent not just the disease but the complications arising from it, such as strokes and heart attacks.”

Dr. McFarlane is doing just that, spearheading SUNY Downstate’s participation in several large-scale, multisite international clinical trials to test drugs that might prevent diabetes-related complications in people at high risk. Among these is the ORIGIN (Outcome Reduction with Initial Glargine Intervention) trial, which is looking at whether giving the drug glargine, a long-acting insulin, early in the course of diabetes will help prevent heart attacks and strokes.

He is also looking at the relationship of diabetes to metabolic syndrome (characterized by a collection of symptoms that include obesity, impaired glucose tolerance, hypertension, elevated triglycerides, and low HDL) and their interplay with cardiovascular disease. “Diabetes is considered a cardiovascular disease equivalent,” he notes, “so the effects of treatment on both illnesses can not be overlooked.” For example, recent studies have shown that diuretics and beta blockers, which are used to treat cardiac disease, decrease glycemic control and increase the risk of developing diabetes. Because of this, “the risk profile for both diseases has to be evaluated in totality,” Dr. McFarlane cautions.

Dr. McFarlane has been extremely successful in attracting and enrolling large numbers of African-Americans and Caribbean-Americans to take part in his studies, despite a longstanding distrust of clinical trials by many in these communities. On the walls of his office hang certificates of appreciation from several churches that worked with him to recruit trial participants. How did he manage this where other researchers failed?

Dr. McFarlane sees clinical trials as a service to the surrounding community, which has a high prevalence of diabetes, hypertension, hypercholesterolemia and other chronic illnesses at disproportionately high rates. “Of the 1,000 supposedly healthy people we screened for one trial, 23 percent had diabetes and didn’t know it,” he says. “A lot of these individuals didn’t have doctors. We enrolled them in our clinic and provided them with care much, much earlier than we would have if they had waited until symptoms were evident.”

“Quality of care and treatment outcomes are closely linked,” continues Dr. McFarlane. “A short or sporadic patient encounter doesn’t provide the time needed to address patient motivation or to have an impact on complex behaviors. Enrolling patients in clinical trials is one way to help address this.”

Dr. McFarlane hopes his research and the advances he pioneered in clinical care will help stem the tide of the diabetes epidemic, a tide that is rising all around him. “One thing that clinical research has taught me,” he says, “is that in dealing with this disease, we can find methods that work.”

His questions aren’t merely academic, but fundamental to overall health, not only for individuals but also for the nation as a whole. Right now, more than 21 million Americans — a full 7 percent of the population — have the disease. Another 41 million between the ages of 40 and 74 are at risk. Public health experts anticipate those numbers will double by 2030, with an attendant increase in personal, social, and financial costs.

“This is quite serious,” says Dr. McFarlane, professor of medicine and chief of SUNY Downstate’s Division of Endocrinology, Diabetes and Hypertension, and editor-in-chief of Therapy, published by Future Medicine Inc. “The epidemic is claiming the lives of myriads of people and leaving others blind and amputated. I hope my research will help do something about this.”

Ninety five percent of people with diabetes in the United States suffer from type 2 diabetes. The illness, formerly known as adult-onset diabetes, is highly preventable, related, in large part, to obesity and inactivity.
Can diabetes be prevented? Or, what about the heart attacks and strokes that prematurely take the lives of about 65 percent of all diabetics? Samy McFarlane, MD, MPH, wants to know.

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Might the pancreas, under the correct conditions, be coaxed into producing new, insulin-producing islets from existing, undifferentiated precursor cells that are similar to embryonic stem cells?

“That’s the question we’ve been working on for about the last 10 years,” says Dr. Teitelman. Though her data are not yet published, it seems that, at least in mice, such new growth is possible. “We’ve found what looks like precursor cells that we can identify,” she says. “And these cells appear to be able to regenerate the islet.”

Endocrinology’s gain was neuroscience’s loss: Gladys Teitelman began her career “analyzing the precursors to neurons,” one of the brain’s cell types, she explains. Then she came across an organ that had many of the same markers of development that neurons had. That organ was the pancreas, and it, says Dr. Teitelman, “has become the focus of my whole career.”

For years, Dr. Teitelman studied biological markers that indicated stages of pancreatic development. When Dr. Miriam Vincent, then already chair of Downstate’s Family Practice Department, went back to graduate school to study cell biology and joined Dr. Teitelman’s lab, the two made a major finding in their field: That beta cells, which produce insulin, “have beta receptors that respond to insulin,” Dr. Teitelman explains.

In other words, beta cells can read their environment and discover how much insulin is needed to control blood sugar. 

Dr. Teitelman and her former student and clinical collaborator, Miriam Vincent, MD, PhD, professor and chair of family practice, have pioneered the concept that a feedback mechanism helps control the proliferation of insulin-producing beta cells in the pancreas, and that this is key to the body’s ability to control blood sugar.

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“It’s good to go into a field where very little is known.” So says Gladys Teitelman, PhD, professor of anatomy and cell biology at SUNY Downstate Medical Center.

The field to which she refers is endocrinology and, in particular, the study of the endocrine cells of the pancreas that are grouped in the islets of Langerhans. These cell clusters secrete the body’s two most important blood-sugar-regulating hormones, insulin and glucagon — hormones that have a huge impact on the lives of people with diabetes.

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Dr. Teitelman is pursuing a new scientific question, the answer to which may have a tremendous impact on the lives of people with insulin-dependent, type 1 diabetes. These individuals, who often develop diabetes in childhood or young adulthood, have had their beta cells destroyed by their own immune systems.

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This finding explains how islets often increase in size and strength in response to the body’s increased demand for insulin during pregnancy or sustained weight gain. In fact, 85 percent of obese people do not develop diabetes, despite their increased insulin requirements.

Later, Drs. Teitelman and Vincent explored similar feedback systems in the islets’ alpha cells, which control the liver’s release of glucose. "We believe the hormone that alpha cells produce—glucagon—affects the development of the endocrine cells,” says Dr. Teitelman, “and there are other hormones that are active in the absence of glucagon, but they are not as efficient.”

Widely known in their respective fields, the two researchers differ about the impact their work has on the lives of people with diabetes. “Our research has enhanced our understanding of diabetes but it hasn’t yet changed the treatment,” Dr. Teitelman says. But Dr. Vincent, the clinician, is more sanguine: “We have a better understanding of the disease and we have more treatments,” she says, citing the development of drugs such as Januvia™ and Byetta®, so-called incretin drugs that use hormones in the gut to help maintain appropriate blood sugar levels.

Dr. Teitelman is unsure where her newest discovery about the ability of precursor cells to regenerate the islets will lead. “Nobody knows how it’s going to pan out with respect to treatment,” she says. “I think— I hope—this will be applicable to people with type 1 diabetes. But there’s still a lot more to learn.”

“These cells, if present in humans, may help circumvent the effect of diabetes.”
blood sugar. Functioning normally, beta cells can then produce that amount of insulin, sometimes by increasing their numbers through cell division. Says Dr. Vincent, “The idea that islet cell hormones themselves would feed back to the pancreas and help control their own growth — that that was the way they functioned — was very exciting.”

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Later, Drs. Teitelman and Vincent explored similar feedback systems in the islets’ alpha cells, which control the liver’s release of glucose. “We believe the hormone that alpha cells produce—glucagon—affects the development of the endocrine cells,” says Dr. Teitelman, “and there are other hormones that are active in the absence of glucagon, but they are not as efficient.”

Widely known in their respective fields, the two researchers differ about the impact their work has on the lives of people with diabetes. “Our research has enhanced our understanding of diabetes but it hasn’t yet changed the treatment,” Dr. Teitelman says. But Dr. Vincent, the clinician, is more sanguine: “We have a better understanding of the disease and we have more treatments,” she says, citing the development of drugs such as Januvia™ and Byetta®, so-called incretin drugs that use hormones in the gut to help maintain appropriate blood sugar levels.

Dr. Teitelman is unsure where her newest discovery about the ability of precursor cells to regenerate the islets will lead. “Nobody knows how it’s going to pan out with respect to treatment,” she says. “I think— I hope—this will be applicable to people with type 1 diabetes. But there’s still a lot more to learn.”

“These cells, if present in humans, may help circumvent the effect of diabetes.”
Viruses are among the world’s most dangerous and debilitating agents.

Often comprised of little more than genetic material with a protein coating, viruses have produced a huge number of scourges—AIDS, polio, influenza, smallpox. Viruses cause a host of cancers and may even be implicated in diseases such as multiple sclerosis and certain forms of mental illness.

Until recently, however, the process by which viruses infect cells has been inadequately understood. Enter Christopher Hellen, DPhil, and Tatyana Pestova, PhD, DSc, Downstate researchers who have revolutionized the study of viral infection.

By teasing apart the process by which viruses hijack a cellular apparatus known as a ribosome, Drs. Hellen and Pestova, along with colleagues such as Henri Tiedge, PhD, have made significant inroads in the fight against dangerous viruses.

Today, their research undergirds efforts to combat a number of viral illnesses. Someday, that research may transform the way modern medicine fights diseases as common as the common cold, as life-threatening as hepatitis C.
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A war story? A science fiction novel? Far from it. This scenario is exactly what happens when viruses invade the cells of humans, animals, and plants. “Viruses take over some fundamental cell structures and use them for their own harmful purposes,” explains Christopher Hellen, DPhil, associate professor of microbiology and immunology at SUNY Downstate Medical Center.

Dr. Hellen and his collaborator, Tatyana Pestova, PhD, DSc, an assistant professor of microbiology and immunology, received international acclaim for exploring this hijacking process and studying basic cellular mechanisms.

“They’re pioneers in this field,” says Henri Tiedge, PhD, a professor in Downstate’s departments of neurology, and physiology and pharmacology. In particular, the pair focuses on how a cellular apparatus called a ribosome translates genetic information into the proteins that perform functions inside and among cells. In collaboration with Dr. Tiedge, they also explore the mechanism of translation in neurons.

“The process of protein synthesis underlies some of the most basic cellular functions,” says Dr. Hellen. Drs. Hellen and Pestova’s research may transform the way medical science understands the role of the ribosome and the multitude of activities in which it is involved.

How does the small structure that is a ribosome use a cell’s genetic code to create proteins? A type of RNA, called messenger RNA (mRNA), contains a copy of the DNA’s genetic information and ferries it to the ribosome. The ribosome then reads the mRNA like tickertape. The information the mRNA contains tells the ribosome which amino acids to put together in which order. This process of decoding mRNA to make proteins is known as translation.

“Researchers have been studying how human ribosomes engage and translate mRNA for at least 40 years,” Dr. Hellen says. “But in many aspects of this research, there hasn’t been any real progress.”

Drs. Hellen and Pestova, however, are making great advances. They are the only team in the world to replicate the process of mRNA translation in the lab. “We’ve been able to purify all the necessary components and reconstitute this entire process in vitro,” Dr. Pestova explains.

Dr. Pestova and Hellen used their method to explore mRNA translation in normal cells. This is how they began to collaborate with neuroscientist Dr. Tiedge, whose interest is in communication among neurons. “Our areas of research are quite different,” Dr. Tiedge says about their work together. “But we share...
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Thus, the annoying common cold may one day be defeated by an antiviral drug based on their research. This work also may favorably improve the battle against life-threatening viruses. Already, a number of biotech and pharmaceutical companies are using Drs. Hellen and Pestova’s research to develop drugs to fight the Hepatitis C virus, which has infected 3 percent of the world population - 170 million people. Hepatitis C can result in chronic, often fatal health problems such as cirrhosis and liver cancer. At present, there’s only one treatment for the disease — injectible interferon. But interferon’s efficacy is limited and its side effects can be debilitating. Several of these new antiviral drugs, based on Drs. Hellen and Pestova’s research, are now in clinical trials.

Understanding how ribosomes work may lead to new treatments for other grave diseases. In diseases such as muscular dystrophy and cystic fibrosis, that process is defective. In muscular dystrophy in particular, the ribosome stops reading the mRNA too early in the translation process. “We would like for the ribosome to be able to overcome that stop,” Dr. Pestova notes.

Here, too, progress is being made. Says Dr. Hellen, “There are biotech companies that are looking for small molecules that will be able to trick the ribosome so that it doesn’t recognize the premature stop sign and simply continues its work.”

Using cells’ basic mechanisms to foil disease may one day revolutionize treatment for a whole host of illnesses, from the common to the calamitous. “Our research is fundamentally important to understanding the workings of cells,” says Dr. Hellen, “and to everything that happens inside of them.”

Inside of them, and by extension, inside of us.
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