Celedón has been wrestling with this question for his entire career: Why does asthma affect so many Hispanics? In a study of families in Puerto Rico, he recently discovered some surprising possibilities.
TOUGH ON TOTS

PUERTO RICAN CHILDREN
MORE LIKELY TO HAVE ASTHMA
IF PARENTS ARE STRESSED
BY MELINDA WENNER MOYER

When Juan Celedón began his medical internship at Lincoln Hospital in the Bronx in 1989, one thing struck him more than anything else. “I was impressed with how much asthma there was,” he recalls. In the Bronx, hospitalization rates for the respiratory disease are five times higher than the national average, and death rates from it are three times higher. Asthma predominantly affects Hispanics, both in the United States and abroad—in particular, Costa Ricans and Puerto Ricans, the latter of whom have the highest lifetime asthma prevalence in the world. So Celedón, who hails from Colombia, recognized a research opportunity. Now, as the Niels K. Jerne Professor in the Department of Pediatrics in the University of Pittsburgh School of Medicine, chief of service in the Division of Pediatric Pulmonology, Allergy, and Immunology at Children’s Hospital of Pittsburgh of UPMC, and director of Children’s Center for Environmental Health, he is teasing out the potential causes of asthma in Hispanic populations. Among possible risk factors, he recently discovered that Puerto Rican children whose mothers or fathers suffer from stress-related conditions like depression are at a greater risk of developing the disease.

Celedón knew that some Puerto Ricans experience high levels of stress because of poverty and exposure to violence. Given their high asthma burden, he wondered whether the two factors might be related. In a study he published in 2010 with researchers at Harvard University, Virginia Commonwealth University, and the Behavioral Sciences Research Institute in San Juan, Celedón interviewed the parents of 339 pairs of Puerto Rican twins. The researchers interviewed the parents to see whether they had experienced symptoms of post-traumatic stress disorder, depression, or antisocial behavior, and the team also inquired about their children’s respiratory health. Celedón and his colleagues found that 1-year-olds had more asthma symptoms if their dads suffered from PTSD, depression, or antisocial behavior. After controlling for a number of potential intervening factors—such as whether or not their parents had asthma—he found that kids aged 1 and 3 were also more likely to be diagnosed with and hospitalized for asthma if their mothers were depressed, and they were more likely to use oral steroids if their fathers were depressed.

No one yet knows why and how, exactly, parental stress influences asthma severity.

“It’s unclear what’s happening,” Celedón says. It could be that stressed-out parents don’t monitor or treat their children’s symptoms as well as healthy parents do, ultimately leading to complications. But Celedón wonders whether parental stress could also be affecting certain genes in the kids, switching them on or off through the addition of methyl groups in an epigenetic process—a change in gene expression resulting from environmental influences—known as DNA methylation. Earlier this year, Swiss researchers reported that male mice separated from their mothers early in life—an intervention that causes them stress—give birth to offspring with abnormal DNA methylation patterns. It’s possible, Celedón says, that such epigenetic changes could contribute to children’s respiratory problems, and he plans to conduct more research to find out.

Also, obesity has long been known to increase asthma risk, and Celedón is striving to understand why. Earlier this year, he and colleagues at Harvard and Washington University in St. Louis found that inhaled steroids do not ease asthma symptoms as effectively in overweight and obese children as they do in normal-weight kids. Obesity could affect asthma risk for many reasons, but work Celedón published in 2009 suggests that genetics might be a common link: He and colleagues identified, based on a genome-wide linkage analysis, the very first gene associated with both body mass index (BMI) and asthma. The gene, called PRKCA, codes for a protein called protein kinase C alpha, which earlier research by other investigators suggests affects airway inflammation, mucus production, and the smooth-muscle contraction that causes wheezing.

Although Celedón is focused primarily on understanding asthma’s causes, “there is a lot of interest in trying to find predictors of asthma attacks, or who’s at high risk,” he explains. In a 2010 study published in CHEST, he and his colleagues developed a clinical score that predicts a child’s risk of suffering an asthma attack based on answers to 17 yes/no questions about symptoms, medication use, and medical history. The team developed the score using data from a cohort of Costa Rican children and then tested how well it predicted symptoms in a group of American kids. “Much to our surprise, in spite of major differences in the type of health care and access to care between the two environments, we found that it performed relatively well,” Celedón says. With this approach, “you don’t need to obtain any lab data to try to assess who’s at risk, so it could be used for primary care in developing countries”—and here, as well.
Studying adolescence in the lab is like trying to hit a moving target, says David Sturman (PhD ’11), a Medical Scientist Training Program student at the University of Pittsburgh School of Medicine. Although adolescence in humans lasts through most of the second decade of life, it spans from the fourth to the sixth week in rats. But in spite of these challenges, Sturman and his advisor—Bita Moghaddam, a PhD and University of Pittsburgh professor of neuroscience, psychiatry, and pharmaceutical science—have, for the first time, recorded and compared neuronal activity in awake adolescent and adult rats. Their study, which was published in the Journal of Neuroscience in January, provides new insight into the curious way adolescents weigh risks against rewards during this period of development. It also may offer insight into their vulnerability to developing disorders that could affect them throughout their lives.

The study of adolescent cognition and emotion is both challenging and rich with possibility. The symptoms of many psychiatric disorders—such as schizophrenia, anxiety, bipolar disorder, and drug addiction—often first appear during adolescence. Although these disorders cause great disruption to an individual’s life and strain relationships with family and friends, the physical impact of these disorders on the brain is largely invisible. The brain’s shift into a neurobiological disorder is subtle; the processes and interactions of the neurons change, while the number of neurons remains the same.

Previous studies have observed regional neuronal activity in adolescents using brain imaging, such as functional magnetic resonance imaging (fMRI) or electroencephalography (EEG). In contrast, Moghaddam and Sturman’s study compares the activity of individual neurons in the orbitofrontal cortex—a part of the brain that calculates payoff and punishment when an individual is making decisions—in both adolescent and adult rat brains. They did this by surgically wiring electrodes into the rats, which had been trained to poke their noses through an illuminated hole for food, a basic reward-driven task. Logistically, Sturman says, all of the above was tricky, as was timing the surgery and recovery, in order to take advantage of the brief window of rodent teenhood.

Each rodent was placed into a box with three nose-poke holes. The team found that, overall, the brain activity in the adolescents was similar to that of the adults; but when the adolescents successfully stuck their snouts through the illuminated holes and received sugar pellets as a reward, the excitatory levels of their orbitofrontal-cortex neurons were two to four times higher than those of adult brains. The young rats’ inhibitory levels, in contrast, were markedly reduced—a critical finding since neuronal inhibition is key to controlling the precise timing of neuronal activity.

These differences might help answer fundamental questions about adolescence: the thrill-seeking, the overreacting to upsetting or pleasurable experiences. Even when behavior may appear similar between the two groups, says Sturman, “the adolescent prefrontal cortex is in a different state than [that of an] adult.”

Give an adolescent rat a treat, and you feed him for a day. Teach him to find it himself, and you can learn a lot about the neurobiology of teenage reward-seeking.

Inhibitory processes are essential for efficient communication between groups of neurons. The variable, frenzied neuronal activity detected in the young rats does not necessarily indicate that adolescents are more excited by rewards, says Sturman. Rather, there is something fundamentally different in how the neuronal networks compute, exchange, and store information regarding salient events. He and Moghaddam hypothesize that these processes are less efficient in adolescents than in adults, thus requiring more resources to process rewards—and their consequences. A better understanding of these differences in the exchange of informational currency might further illuminate normal teenage development as well as the various vulnerabilities that come with the territory, from addiction to mood disorders.

“This is really a magical period in which we can step in and prevent these diseases,” says Moghaddam. Imbalances in the excitatory and inhibitory processes of neurons—which impair the exchange of information from neuron to neuron—have also been implicated in the onset of schizophrenia and other psychiatric disorders. Moghaddam says, “If we understand mechanistically what neurons, what receptors, what neuro-chemicals are involved, or are undergoing major changes during adolescence, then we can understand what the trigger point is. And if we can understand that, then we are much better-equipped to control the disease and prevent the transition [into psychiatric disorders].”