Identifying Factors that Impact Development and Lung Health

It is critical to identify potentially modifiable risk factors that contribute to early programming of asthma risk and lung function, especially as levels of pulmonary function “set” in the first years of life have health implications across the life course.

While the origins of chronic lung diseases are multifactorial, the underlying mechanisms leading to reduced lung function involve chronic airway inflammation associated with a cycle of injury, repair, and remodeling. Notably, airway inflammation and remodeling begin even before birth, and a fundamental cause is abnormal immune responses to various environmental factors.

Exposure to environmental toxins during prenatal and/or early childhood development alters the normal course of lung growth, resulting in changes that affect both structure and function of the respiratory system. Optimizing respiratory health in children before they reach school age is a major determinant of their future susceptibility not only to chronic lung disease but also heart disease, cognitive disorders, and even longevity.

Rosalind J. Wright, MD, MPH, Dean of Translational Biomedical Research, Director of the Clinical and Translational Science Award, and the Horace W. Goldsmith Professor in Children’s Health Research, Icahn School of Medicine at Mount Sinai, leads an innovative research program to identify lifestyle and environmental factors that influence child development and lung health over the life span.

Researchers now know that during these early developmental stages, rapidly changing cells are susceptible to the adverse effects of a range of environmental factors. These include air pollution, tobacco smoke, diet, chemicals in everyday consumer items, as well as psychological stressors.

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Early Success in Reducing Asthma ER Visits and Hospitalizations Through In-Home Program

The Pediatric Visiting Doctors program at Mount Sinai provides in-home multidisciplinary care to children with special health care needs in Central and East Harlem, New York. For children with poorly controlled asthma, a pediatrician, social worker, and care coordinator manage the patient’s asthma together, along with the primary care doctor, subspecialists, and community organizations. Through a unique combination of environmental remediation, medication management, education, psychosocial support, and enhanced care coordination, the program helps families improve their children’s health. Early study data suggest good outcomes (see graph). The program is led by Maureen Braun, MD, and Elaine Lin, MD, both Assistant Professors of Pediatrics; and Joseph Truglio, MD, MPH, Assistant Professor of Medicine, Pediatrics, and Medical Education, Icahn School of Medicine at Mount Sinai.

Graph shows 32 patients enrolled in the program for at least 3 months and receiving at least 1 home visit. Analysis of equal pre/post-enrollment periods up to 1 year revealed reductions in both ER visits and hospitalizations.* Patients were enrolled during inpatient hospitalizations at Kravis Children's Hospital at Mount Sinai, or through referrals from outpatient clinics and community-based groups.

*Data from July 2013-March 2015
Reducing Seizures With a Responsive Neurostimulator

Colin is 14 and lives with his family in New Jersey. He was born via normal delivery after a pregnancy complicated by maternal Lyme disease. Development was normal until he developed infantile spasms.

He has tried and failed more than 15 antiepileptic medications, and continued seizures have impacted his development. Colin is unable to walk and has behavioral abnormalities, including episodes of screaming and self-injurious behavior. He is wheelchair-dependent and experiences four to six seizures per day.

Colin has undergone five epilepsy surgeries, placement of a vagus nerve stimulator, and placement of a ventriculoperitoneal shunt for hydrocephalus.

His seizures were initially thought to arise from the right frontal lobe, and his first surgery, a right frontal resection, was performed at an out-of-state hospital. He subsequently developed atonic seizures, and a corpus callosotomy was performed. Two years later, Colin underwent an anterior commissurotomy and placement of bilateral strip electrodes by Saadi Ghatan, MD, at Mount Sinai Beth Israel after the seizures recurred.

After the commissurotomy, it was hoped that there would be clear lateralization of the seizure onset, but, unfortunately, electrographic seizures arose from the right temporal lobe, while clinical seizures arose from the left temporal lobe and occipital lobes. The left temporal lobectomy and occipital disconnect failed to halt the seizure activity, and the family was offered the option for Colin to receive the RNS® System, a responsive neurostimulation device by NeuroPace.

On September 15, 2015, he became the youngest person to be treated with the RNS System, approved for treatment of refractory complex partial seizures in patients ages 18 and older.

During the surgery, two cortical electrode strips were placed in the right temporal and left frontal lobes, and an additional two electrodes were inserted in the bilateral thalami in anticipation of possible use in the future. The device is programmed every three weeks to detect abnormal epileptiform discharges that may result in a seizure and to stimulate those areas of the brain to prevent the abnormal discharges from resulting in a seizure.

Two months after the procedure, Colin has experienced a significant decrease in seizure activity, from about three to four seizures every morning to only one per morning.

Mount Sinai’s epilepsy team is headed by Steven M. Wolf, MD, Director of Pediatric Epilepsy and of the Comprehensive Pediatric Epilepsy Center, in partnership with co-director Patricia Engel McGoldrick, NP, MPA; and Saadi Ghatan, MD, Chair of Neurosurgery, Mount Sinai West and Mount Sinai St. Luke’s, and Director of Pediatric Neurosurgery, Mount Sinai Health System. To learn more about the epilepsy program, visit www.nycepilepsyteam.org.

As founding director of the Physiological Assessment of Children’s Environmental Risk (PACER) laboratory at Mount Sinai, Dr. Wright, in collaboration with Alfin G. Vicencio, MD, Chief of Pediatric Pulmonology at Kravis Children’s Hospital at Mount Sinai, is examining these multifactorial relationships in a series of population-based studies within the diverse communities served by the Mount Sinai Health System.

The effort is supported by funding from the National Institutes of Health (NIH) through the National Heart, Lung, and Blood Institute, the National Institute of Child Health and Human Development, the National Institute of Minority Health and Health Disparities, and the National Institute of Environmental Health Sciences, along with the recently established NIH-funded Children’s Health Exposure Analysis Resource (CHEAR) Laboratory Hub at Mount Sinai.

It is expected that these resources, coupled with the close collaboration within Mount Sinai that exists between the most basic mechanistic research on programming lung health and clinical care delivery, can facilitate the translation of cutting-edge findings to new prevention, diagnostic, and treatment plans for childhood asthma that may have lifelong implications for patients.

Identifying Factors that Impact Development and Lung Health continued from page 1
**Significant Growth for Pediatric Programs**

During 2015, the Department of Pediatrics had significant growth and success in our academic missions of clinical care, research, and education, marked by:

- the launching of a dedicated pediatric transport service for interfacility transports to and within the seven hospital campuses of the Mount Sinai Health System for critically ill and injured infants and children.

- the opening of the Blau Center for Children's Cancer and Blood Disease at Kravis Children's Hospital, the Comprehensive Children's Growth Center at Mount Sinai, and a pediatric program in the integrated Susan and Leonard Feinstein Inflammatory Bowel Disease (IBD) Clinical Center.

- the announcement of a Mount Sinai—Children's Hospital of Philadelphia (CHOP) alliance in pediatric cancer. Development of programs in cardiac care and fetal medicine is under way. Additionally, U.S. News & World Report recognized our outstanding pediatric clinical services in its 2015-16 “America's Best Children's Hospitals” guidebook with rankings in seven specialties: Cancer; Diabetes & Endocrinology; Gastroenterology & GI Surgery; Nephrology; Neurology & Neurosurgery; Pulmonology; and Urology.

Critical to our ability to deliver exceptional care is a commitment to transformative biomedical research and discovery and extensive collaboration between investigators and clinicians throughout the Health System. In 2015, the Department’s robust extramural grant portfolio placed us among the top 15 pediatric departments nationwide in National Institutes of Health funding. With new initiatives planned for 2016, we expect to continue our long and distinguished tradition of excellence.

**HEMATOLOGY/ONCOLOGY**

**Leading International Studies of GVHD Biomarkers**

The most deadly complication of bone marrow transplantation (BMT) is acute graft-versus-host disease (GVHD), which can result in organ damage and lead to death in up to 20 percent of bone marrow transplants. Although GVHD is associated with lower rates of leukemia relapse, that is of no benefit for the large numbers of patients, mostly children, who receive a bone marrow transplant to cure nonmalignant conditions, such as sickle cell disease or immunodeficiency. GVHD-related morbidity and mortality must be reduced to make curative transplants a more widely used therapeutic option for these diseases.

To accomplish this goal, John E. Levine, MD, MS, a member of the Department of Pediatrics, and Medicine, at the Icahn School of Medicine at Mount Sinai, teamed with James L. M. Ferrara, MD, DSc, Ward-Coleman Chair in Cancer Medicine, and Professor and Director, Hematologic Malignancies Translational Research Center at The Tisch Cancer Institute at Mount Sinai. Together, they formed the Mount Sinai Acute GVHD International Consortium (MAGIC) to develop new blood tests to guide GVHD treatment according to risk and to predict its occurrence before clinical symptoms appear.

The test to guide GVHD treatment has been developed and will determine eligibility for multicenter high- and standard-risk GVHD clinical trials that will open to enrollment in early 2016. The test to predict GVHD occurrence is under development and expected to be available for use in clinical trials by the end of 2016. Both tests will be validated for use in children by analyzing plasma samples from 900 pediatric patients transplanted at Mount Sinai; the University of Michigan; Vanderbilt University; Children’s Hospital Los Angeles; Emory University; The Hospital for Sick Children in Toronto; Bambino Gesù Hospital in Rome; and the University Hospital of Würzburg, Germany.

Dr. Levine, who is also the newly appointed Director of BMT Clinical Research and Director of Pediatric Hematology/Oncology Research, has secured a commitment from the Pediatric Blood and Marrow Transplant Consortium to fund this international effort to bring GVHD biomarkers into clinical use for children.

**COMPREHENSIVE EVALUATIONS FOR GROWTH DISORDERS**

Growth is an important window to the health of a child. Poor growth may reflect poor nutrition or systemic disorders, such as rheumatoid arthritis, or gastrointestinal, kidney, and cardiac disease. It may also reflect genetic and/or hormonal abnormalities. The Comprehensive Children’s Growth Center at Mount Sinai treats disorders such as growth hormone deficiency, Small for Gestational Age (SGA), and other hormonal and genetic disorders leading to growth delay/failure. Physicians currently treat 1,300 patients with growth disorders, accounting for nearly 4,000 annual visits. The Center provides comprehensive evaluations utilizing the expertise of Mount Sinai subspecialists. To learn more, or for patient referrals, call 212-241-6936 or visit www.kravischildrenshospital.org.
Kidney Transplant Program Drives Excellent Outcomes and Care

The Pediatric Kidney Transplant Program at Kravis Children's Hospital at Mount Sinai historically has been one of the 15 busiest programs in the country and the largest pediatric kidney transplant program in New York State, and has become renowned for excellence in care that has been maintained by a core group of pediatric nephrologists, including Division Chief Jeffrey Saland, MD.

Outcomes, publically available on the websites of the United Network for Organ Sharing and the Scientific Registry of Transplant Recipients, have been routinely excellent: one- and three-year graft survival rates are in excess of 95 percent. For the past three years, avoidance of chronic steroids has been the routine, with very low rates of rejection and viral complications.

Fully integrated with the Pediatric Urology team, led by Jeffrey A. Stock, MD, the program is able to achieve these same outstanding results for children with complex bladder or other urological conditions. In part due to excellence in kidney transplants for children, Pediatric Nephrology and Pediatric Urology are highly ranked in U.S. News & World Report's 2015-2016 “Best Children's Hospitals” guidebook, joining multiple other ranked teams at Kravis. This assures a broad swath of expertise for transplant patients who may have additional medical needs.

The transplant program recently welcomed Ron Shapiro, MD, a past president of the International Pediatric Transplantation Association, as its new Surgical Director. Dr. Shapiro did his surgical training at Mount Sinai, and then completed his transplant fellowship at the University of Pittsburgh, where he served on the faculty for more than 25 years before being recruited to return to New York, joining and augmenting Mount Sinai’s team of accomplished transplant surgeons, urologists, and nephrologists.

Advancing Genetic and Microbiome Research for IBD

Marla C. Dubinsky, MD, Chief of the Division of Pediatric Gastroenterology & Hepatology, and Co-Director of the Susan and Leonard Feinstein Inflammatory Bowel Disease Center, continues to build upon her previous pioneering research exploring the interplay between genetics and the microbiome in determining— and preventing— inflammatory bowel disease (IBD).

Dr. Dubinsky, along with her colleagues at UCLA and Cedars Sinai Medical Center in Los Angeles, were among the first to conduct an initial and pivotal IBD family study of the microbiome, which sequenced and analyzed fecal and genetic samples from 21 pediatric IBD patients and their first-degree relatives to examine microbial composition and metabolites of genetically similar individuals both affected and unaffected by IBD. Analysis demonstrated that fecal bacterial patterns were the most important predictors of disease, insight that represented a breakthrough in the understanding of IBD and how to potentially prevent it in high-risk populations, such as siblings or offspring.

Subsequent research conducted at Mount Sinai with world-renowned scientist Jeremiah Faith, PhD, centered on the next level of microbial analysis using animal models and involving implanted human stool samples from both affected and unaffected members of the first family study in genetically engineered humanized mice to observe the impact on the development of IBD. Findings suggest that stool elicits the onset of disease. Ongoing animal studies aim to identify the protective and disease-causing bacteria, an effort to develop targeted fecal transplant interventions.

In the next two years, the researchers will partner with communities where IBD is very common within families, and analyze stool, genetics, and immune markers from affected and unaffected family members to yield further insights into at-risk and perhaps more importantly, the protective patterns that keep certain family members from developing IBD.

Investigators will also follow participants long-term to monitor which initially unaffected members eventually develop disease. Understanding the pre-clinical state of IBD can perhaps one day lead to preventive strategies.