

ADVANCES IN PEDIATRIC CARDIOLOGY

Affiliated with Columbia University College of Physicians and Surgeons and Weill Cornell Medical College

At Congenital Heart Center, Emphasis on Collaboration, Clinical Research, and Technological Expertise

The declining rates of morbidity and mortality in early childhood heart repair are driven by technological innovations, including recent progressive refinements in catheter-directed interventions, mechanical circulatory support, and hybrid procedures that incorporate catheter and surgical strategies. The NewYork-Presbyterian Congenital Heart Center supplies the volume of cases and the expertise essential for the trials that

bring these innovations forward. For the Congenital Heart Center, which is overseen by both the NewYork-Presbyterian Morgan Stanley Children's Hospital and the NewYork-Presbyterian Komansky Center for Children's Health, the collateral advantage is a clear understanding of the relative strengths of competing strategies.

"Every case of a congenital cardiac anomaly is unique, often with challenging complexities. Each week we hold 2 conferences lasting several hours where a panoply of subspecialists discuss the merits of one strategy over another," said Richard A. Friedman, MD, MBA, Chief of Pediatric Cardiology at both Morgan Stanley Children's Hospital and the Phyllis and David Komansky Center for Children's Health, and co-leader of the Congenital Heart Center. "Among our options, the best path is selected by a panel of experts that includes



cardiologists, interventionalists, anesthesiologists, and neonatologists, many of whom have participated in the studies that established the utility of the latest approaches."

The treatment of hypoplastic left heart syndrome serves as a ready example because there have been a series of recent incremental advances that can be employed in different combinations according to the demands of the case. One such advance is a better understanding of when to employ a hybrid rather than a fully open procedure in the first of the 3 phases of repair. The hybrid procedure circumvents the need for cardiopulmonary bypass, but the traditional Norwood approach often is still the best option. At the Congenital Heart Center, a hybrid procedure is employed only when the advantage is clear.

See **Heart Center**, page 3

UPCOMING CME

Hypertrophic & Restrictive Cardiomyopathy: Genetics, Imaging, and Emerging Treatments in Adult and Pediatric Patients

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NewYork-Presbyterian Hospital is one of the foremost academic medical centers in the world, with leading specialists in every field of medicine and a staff dedicated to the care of its patients. The Hospital enjoys a unique affiliation with two of the nation's leading Ivy League medical schools: Columbia University College of Physicians and Surgeons and Weill Cornell Medical College. With its academic partners, the Hospital shares a commitment to pursuing clinical excellence, engaging in groundbreaking biomedical research, offering outstanding medical education, and providing prevention and wellness services to the community. NewYork-Presbyterian Hospital ranks #1 in New York and among the top seven in the U.S. out of the nearly 5,000 hospitals evaluated by *U.S. News & World Report* for their 2012-13 Best Hospitals rankings. One of the largest and most comprehensive medical centers in the nation, NewYork-Presbyterian is also one of only 17 hospitals listed on *U.S. News'* prestigious Honor Roll.

Genetics Research Across Medical Specialties Now Yielding Secrets and Improving the Practice of Medicine

The decoding of the human genome and subsequent concerted efforts by physician-scientists to decipher the relationships between specific genes and the diseases they influence have already yielded tremendous advancements in medicine. This work is fostering important strides in understanding and caring for people with diseases affecting all health systems, and much of the laboratory and translational studies, as well as clinical research, are being done at Columbia University College of Physicians and Surgeons, Weill Cornell Medical College, and NewYork-Presbyterian Hospital.

Research abounds in every field. Within psychiatry, schizophrenia has long been known to be genetic in origin, but the networks of genes involved in this disability have not been well characterized. A recent paper found a link between schizophrenia and autism.¹ Columbia researchers examined a collection of mutations associated with schizophrenia and found occult interrelations among genes that had previously been thought to be unrelated. The researchers found that most of the mutated schizophrenia genes were related to 2 main gene networks, which together affect key processes, including axon guidance, synapse function, neuron mobility, and chromosomal modification.

The research, which was led by Dennis Vitkup, PhD, Associate Professor in the Department of Biomedical Informatics at Columbia's Center for Computational Biology and Bioinformatics, also looked at genes mutated in patients with autism and found the similarities were surprisingly robust. Noting that the genetic networks for autism and schizophrenia are closely intertwined, the researchers postulated that many other psychiatric disorders also might share the same genetic networks and interrelated molecular processes.

Significant research on the genetics behind psychological illness is being undertaken at Weill Cornell Medical College. As just one example, Francis S.Y. Lee, MD, PhD, Professor and Vice Chair for Research in the Department of Psychiatry and Professor in the Department of Pharmacology, who is also an Attending Psychiatrist at the Hospital, directs efforts focused on using genetic

models to define the role of growth factors, such as brain-derived neurotrophic factor, and their affect on the pathophysiology and treatment of affective disorders.²

Pulmonology has begun to explore the use of gene-based vaccines targeted against pulmonary infectious organisms. At Weill Cornell Medical College, a team led by Stefan Worgall, MD, PhD, Division Chief of the Pediatrics Pulmonology, Allergy and Immunology Division, has developed capsid-modified adenovirus vectors^{3,4} to heighten immune responses from genetic vaccines against both *Pseudomonas aeruginosa* and respiratory syncytial virus. In research on the pathogenesis of cystic fibrosis, Dr. Worgall is investigating the interaction of alveolar macrophages with *P. aeruginosa*.

Nephrologists and psychiatrists, meanwhile, were interested in the results of a large multinational study in which Columbia University played an important role.⁵ The study, led by Ali Gharavi, MD, Associate Director of the Division of Nephrology at NewYork-Presbyterian/Columbia, is the first to link congenital kidney disease, which together with urinary tract defects accounts for about one-fourth of all birth defects in the United States, with neurodevelopmental disorders. The study found that 10% of children born with kidney defects have genomic alterations that have been linked with neurodevelopmental delay and mental illness. The finding is important because it paves the way for identifying subgroups of patients with kidney defects whose treatment will be guided by specific genetic information. The

finding also alerts physicians who care for children with congenital kidney disorders that there may be a genetic basis for a neurodevelopmental delay or a mental illness that will occur later in life.

A co-author of this study was Wendy Chung, MD, PhD, Director of Clinical Genetics at NewYork-Presbyterian Morgan Stanley Children's Hospital. Her research interests span multiple areas, including the molecular genetics of obesity and diabetes; congenital heart disease; the genetic foundations of cardiomyopathies, arrhythmias, long QT syndrome, and pulmonary hypertension; congenital diaphragmatic hernias; mental retardation; inherited metabolic conditions; and susceptibility to breast and pancreatic cancers. She is Director of the Pediatric Heart Network Genetic Core, the Pediatric Neuromuscular Network Molecular Core, the New York Obesity Center Molecular Genetics Core, and the Diabetes and Endocrine Research Center Molecular Genetics Core. She also serves as Director of the Clinical Cancer Genetics Program and the Fellowship Program in Cytogenetics and Molecular Genetics.

Perhaps no area of medicine has been as affected by research into the genetic foundations of disease as much as oncology. Examples of genetic discoveries in oncology are plentiful. An important recent discovery is the revelation that certain cases of glioblastoma are caused by the fusion of 2 genes.⁶ Researchers, led by Antonio Iavarone, MD, Professor of Pathology and Neurology at Columbia's Institute for Cancer Genetics at the Herbert Irving Comprehensive Cancer Center at NewYork-Presbyterian/Columbia, conducted genetic analyses of patients with glioblastomas, searching for evidence of gene fusions. They found them, with the most common being fusions involving the fibroblast growth factor receptor (*FGFR1* or *FGFR3*) and transforming acidic coiled-coil (*TACC1* or *TACC3*) genes. The protein produced by the fusion of

FGFR-TACC disrupts the mitotic spindle, causing aneuploidy, and from there tumorigenesis. The finding is important because it provides researchers with a protein target for pharmaceutical research for a cancer that is especially difficult to treat.

Gastroenterologists have been interested in recent work performed by Manish Shah, MD, Director of Gastrointestinal Oncology at Weill Cornell Medical College, who with his colleagues elucidated the heterogeneity of gastric cancer, dividing it into 3 types.⁷ The first type, noncardia gastric cancer, is linked to environmental factors such as high dietary salt, tobacco use, and increasing age; clinical factors such as *Helicobacter pylori* infection and use of nonsteroidal anti-inflammatory drugs; and genetic factors including immune regulatory single-nucleotide polymorphisms. A second type, diffuse gastric cancer, is associated with *CDH1* mutation and family history and has no known environmental or clinical factors. The third type, proximal

gastric cancer, is caused by tobacco and alcohol use; has no known genetic link; and is associated with obesity, high body mass index, and gastroesophageal reflux disease. Dr. Shah's work has alerted those performing drug clinical trials that testing should be based on these subtypes and not on gastric cancer as a whole. Because of the genetic differences in subtypes, the effects of drug therapy may vary significantly between groups.

The field of clinical genetics is rapidly changing and improving the practice of medicine. As the field of genetics continues to grow so too will the physician-scientists at Columbia University College of Physicians and Surgeons, Weill Cornell Medical College, and NewYork-Presbyterian Hospital continue to be at the forefront of integrating genetics into all specialties.

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continued from [Heart Center](#), page 1

“In children who are not candidates for bypass, who are typically the children at highest risk, the hybrid procedure can be very effective,” explained Emile A. Bacha, MD, Chief of Congenital and Pediatric Cardiac Surgery, Morgan Stanley Children's Hospital and Komansky Center for Children's Health, and co-leader of the Congenital Heart Center. Although it was once thought that hybrid procedures would eventually become the standard in all hypoplastic left heart cases, Dr. Bacha said that experience demonstrates a place for both. The average national mortality rate for hypoplastic left heart repair in a recent survey was 17.4%, or about 70% higher than the 10% mortality rate at the Congenital Heart Center.¹

“About one-third of children are treated with the hybrid approach at our Center. So far all have survived,” said Dr. Bacha, providing in this statistic a

demonstration of the reward that comes from intensive planning and individualized care.

The selection of devices for addressing defects in aortic and pulmonary valves, septum, and cardiopulmonary circulation has been proliferating as manufacturers have begun to create more tools specific for addressing congenital heart defects in neonates and young children. Although this creates new opportunities for repair, effective deployment is case-specific. The trials conducted at the Congenital Heart Center are instrumental in providing subspecialists with an appreciation for what devices, sized optimally for the repair, are currently available.

“One of the strengths of our Center is that we participate in a large number of clinical trials. This provides us with experience with devices from a broad number of companies. Relative to a center that has worked closely with only 1 or 2 manufacturers, the

broader experience provides a versatility that can be useful for selecting among tools that may have relative strengths or weaknesses in any individual child,” said Jonathan Chen, MD, Surgical Director of Pediatric Cardiac Transplant at the Congenital Heart Center. Dr. Chen also noted that participation in a large number of clinical trials also has an advantage in very difficult cases for which an emerging device innovation can only be made available in the context of a clinical study.

Although the history of mechanical circulatory support in children was long dominated by the modification of devices developed for adults, Dr. Chen reported an increasing pace of innovation for devices specific for use in children. When adult devices were being modified, the challenge was not just size. The dynamics of blood circulation in children are much different, creating a variety

See [Heart Center](#), page 4

continued from **Heart Center**, page 3

of risks, including clot formation when blood flow is slow.

“The effort to create devices that are sized for children has been important for refining the effort to improve outcomes,” said Dr. Chen, who could have been speaking of a variety of devices but was referring specifically to ventricular assist devices (VADs). VADs, along with extracorporeal membrane oxygenation (ECMO) devices, are used in bridging children to transplant or recovery, or as so-called “destination” devices. In these cases, size selection can be particularly important in sustaining the growing child through a prolonged bridging period. Although any given VAD or ECMO may be effective, the size of the device may be an important factor in outcome for the individual child.

As a leading facility in cardiac transplantation in children, the Congenital Heart Center has accumulated a large volume of experience with both VAD and ECMO devices. In a recent publication that summarized 10 years of experience, much of it at NewYork-Presbyterian, both VAD and ECMO devices were found to increase significantly the likelihood of survival to transplant.² Yet the importance of matching the specific child to the best device cannot be overlooked.

“Maintaining a child on effective circulatory support until an organ becomes available, or for other considerations, has been a critical advance and one reason that transplant survival rates are improving,” said Dr. Chen, who noted that the first successful pediatric heart transplant was performed at NewYork-Presbyterian. With approximately 20 to 25 pediatric heart transplant cases annually, the Center continues to perform more of these procedures than almost any other program in the United States. Outcomes reflect the volume of experience. The average national discharge mortality rate for heart transplants is about 60% higher than that of the Congenital Heart Center (3.9% vs 2.4%).¹ Put another way,

the average survival rate of 96% is bettered at the Center.

Indeed, when compared with the national average, mortality rates for a broad number of procedures remain lower in absolute terms at the Congenital Heart Center. The term *absolute* signifies a percentage difference without any adjustment for the complexity of the cases. This includes arterial switch operations (2% vs 4%), procedures to correct tetralogy of Fallot (1.3% vs 1.7%), atrioventricular canal defect (0.7% vs 2.5%), and pulmonary autografts (0% vs 4.2%).¹ Yet, as a tertiary center at the forefront of research and innovation, the Center accepts some of the most challenging cases.

“We take all comers for a broad array of procedures. I think one explanation for our success is a deep bench. At case conferences, more than one approach may be proposed. We are put in the position of selecting the best of several options,” Dr. Bacha observed.

Often, the best option is collaboration. In hybrid procedures, interventional cardiologists work side by side with cardiac surgeons, both supplying their strengths to improve efficiency of the repair. According to Dr. Friedman, the Center has been aggressive in expanding imaging capabilities and recruiting innovative pediatric cardiac imaging specialists who are particularly critical to improving the results of catheter-based repairs. Three-dimensional imaging that allows myocardial movement to be monitored in real time promises to contribute to expanding capabilities.

“The progress that is being made with imaging and with catheter-based procedures is not only allowing us to perform established procedures more efficiently with the potential for reduced morbidity and mortality, but we are able to create whole new approaches that will possibly allow us to improve on traditional interventions,” Dr. Friedman said.

The broad advances in the acuity of 3-dimensional imaging will be critical to a planned expansion into fetal

cardiac repair interventions. The Congenital Heart Center already has created one of the most comprehensive facilities for in utero diagnosis of congenital heart abnormalities, but there are now plans to initiate fetal repairs.

“This is an extremely exciting area because there are a number of heart defects that are likely to be amenable to in utero intervention, such as opening up a stenotic aortic valve or, in special cases, addressing a septal defect, and this has great potential for allowing the baby to be born in a far more stable clinical state,” Dr. Friedman explained. These procedures are highly labor-intensive and particularly demanding of a multidisciplinary collaboration, but the Center is equipped to pursue a strategy that has the potential to substantially improve outcomes.

The capability of intervening in heart defects before birth will expand therapeutic options, but Dr. Friedman emphasized that each innovation is evaluated in the context of other options. At the Congenital Heart Center, the emphasis has been on a systematic collaboration of specialists with a broad array of expertise who can guide each case to the best solution. The case conferences provide the forum for developing a consensus on the best approach.

“Often there is a great deal of enthusiasm about a new device or a new approach, but the value of our detailed case conferences is that our focus never leaves the patient. We work together to decide what the best approach is given the specifics of the case. It helps us employ the right procedure for the right situation,” Dr. Friedman explained.

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