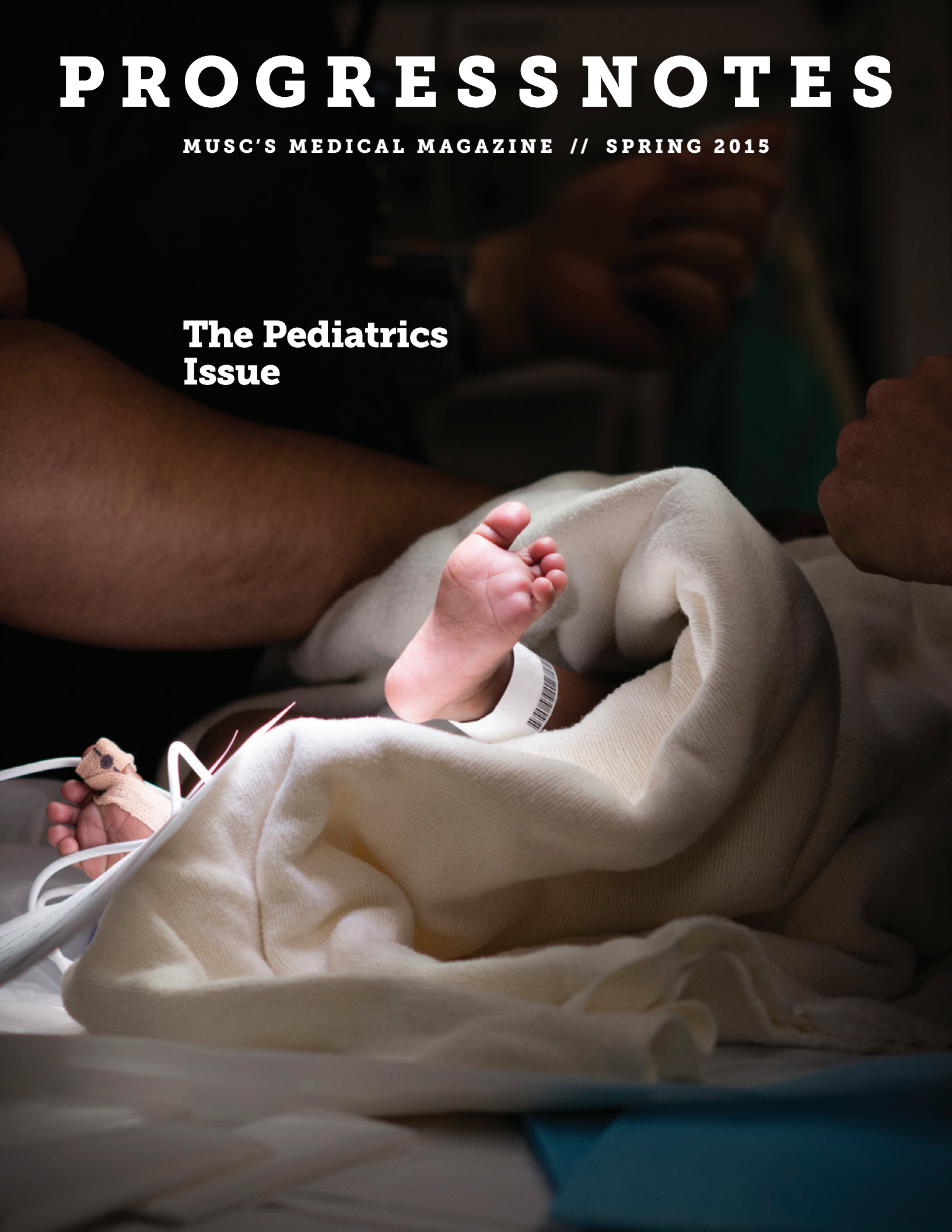
PROGRESSNOTES

MUSC'S MEDICAL MAGAZINE // SPRING 2015

The Pediatrics Issue



Measles Outbreak Highlights Need for Immunization

In a recent interview with the MUSC News Center, **Sandra L. Fowler, M.D., MSc,** a pediatric infectious disease expert at MUSC Children's Hospital, answered some common questions about the Winter 2015 measles outbreak and the threats posed by an underimmunized population.

Q: How likely is it that someone here [in South Carolina] will get the measles?

A: South Carolina has a 90% overall measles immunization rate, leaving it vulnerable to an outbreak. Measles is probably one of the most infectious agents we know of. You're infectious for up to four days before you break out into the rash. So it's really hard to contain except for being immune. The vaccine is highly effective. It's really the only method we have of preventing the spread.

Q: What should people do if they aren't sure if they were immunized as children?

A: If you were born in 1957 or before, you can consider yourself immune because the virus basically infected the entire birth cohort. If you were born after 1957, you should have had two immunizations to give you the best protection during an outbreak. If you don't know if you had the second one, the safest thing is to get a second dose.

Q: Do you know of any fellow physicians who are vaccine skeptics?

A: Nobody I work with, nobody in my professional societies, is a vaccine skeptic. In my profession as a pediatrician and my specialty, infectious disease, we've been dealing with these issues for about 15 years. We're seeing increasing movement toward personal belief exemptions. My colleagues and I don't feel that these so-called personal belief exemptions are appropriate. When people insist on those exemptions, they should be educated about the consequences and asked to sign a piece of paper saying they understand that their child will be excluded from school and group activities if there's an outbreak. Unfortunately, or fortunately, this outbreak is giving us a bigger voice to the public than we have had before and is bringing to light the dangers of an underimmunized population.

*Abridged from an interview by Helen Adams for the MUSC News Center (*MUSC.edu/pr/newscenter*). Photograph by Sarah Pack. Read full interview at http://tinyurl.com/q8ldxwz.*

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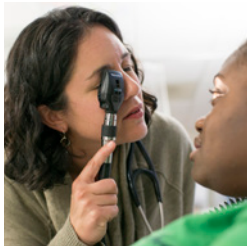

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On the cover: An infant being cared for in MUSC Children's Hospital's Pediatric Cardiac Intensive Care Unit. Photograph by Brennan Wesley.

Digital Exclusive

Coming Full Circle: Mother returns to the fragile world of the NICU

MUSC
MEDICAL UNIVERSITY of SOUTH CAROLINA

A NEW BANK JUST FOR BABIES

Bringing donated human milk to South Carolina's tiniest babies

BY KATHARINE H. HENDRIX

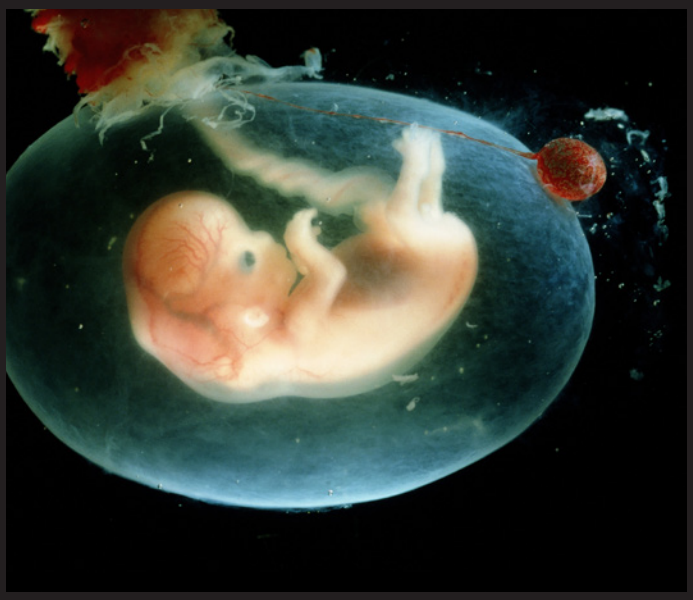
An idea that was planted three years ago will soon bear fruit with the establishment of South Carolina's first human milk bank. **Sarah N. Taylor, M.D., MSCR**, a neonatologist at MUSC Children's Hospital and Medical Director of the Mother's Milk Bank of South Carolina, first raised the issue of providing donor milk as the standard of care for infants with breast-feeding difficulties at a 2012 meeting of the South Carolina Neonatal Consortium—a group that includes all of the state's tertiary- and many secondary-care centers. "There is a decreased risk of death for babies who are born preterm if they receive breast milk. Mom's milk is better than any medicine we give," says Taylor. Preterm infants receiving mother's milk at discharge are less likely to be re-hospitalized and have fewer upper respiratory and gastrointestinal symptoms. "Also, they get all the significant long-term health benefits full-term babies do, such as decreased (risks for) leukemia and diabetes," says Taylor.

Neonatologists have long known that mother's milk is the best infant nutrition and research now shows that, when the mother's milk is not available, feeding with donor milk is superior to formula. Taylor illustrates these findings with the example of necrotizing enterocolitis—a serious disease of the digestive tract in which the intestines become inflamed and begin to die. "About 10% of very low birth weight babies get this disease, and a third of those who do die. Another third suffer long-term problems," says Taylor. "For every 15 babies who receive mother's milk, you will prevent one case of necrotizing enterocolitis. For every 33 babies who receive donor milk, you will prevent one case of (the disease). So, donor milk is not nearly as good as mother's milk, but it's much better than formula."

Since 2003, MUSC Children's Hospital has purchased donor milk from milk banks in North Carolina and Texas. However, the administrative burden of shipping the milk over long distances as well as frequent supply shortages make this an expensive and time-consuming process. "We need more moms to donate and South Carolina moms don't want to send their milk to Texas and then have it shipped all the way back—plus there's a huge cost savings if we can keep the milk local," says Taylor.

With support from the South Carolina Birth Outcomes Initiative, a collaborative formed by the South Carolina Hospital Association and the United States Department of Health and Human Services, South Carolina's first milk bank will be fully operational within the next six months. "We are months away from pasteurizing the milk. Just like cow's milk, (it will be) sterile when it leaves the milk bank and will be available to very preterm babies throughout the state." Furthermore, the Consortium has made it a standard of care that all babies with a birth weight of less than 1500 grams who are hospitalized will receive mother's milk or donor milk until they are at least 34 weeks of gestational age. "It's great that there is now this standard across the state for protecting these babies," says Taylor.

Mother's Milk Bank of SOUTH CAROLINA



Left: Human embryo at 7-8 weeks old. Image by Dr. G. Moscoso. Licensed from sciencesource.com.

GETTING AT THE HEART OF PRE-ECLAMPSIA

Heart development genes implicated in hypertension in pregnancy

BY KIMBERLY MCGHEE

Downton Abbey fans were shocked when, shortly after giving birth, beloved Lady Sybil suddenly fell into violent seizures and died. Few fans had heard of eclampsia, the most severe form of pre-eclampsia (PE), which can lead to liver and kidney failure, stroke and seizure, bleeding disorders, and death. Although PE is usually successfully treated before progression to eclampsia in the U.S., it remains the leading cause of preterm birth and can increase a woman's lifetime risk for cardiovascular disease. The hallmark symptoms of PE—aggressive hypertension and protein in the urine—are likely due to leaky or stunted blood vessels.

A surprise finding by **Kyu-Ho Lee, M.D., Ph.D.**, of MUSC's Department of Pediatrics may shed light on the chain of events that sets this potentially deadly disease in motion. That finding, and the exciting line of research that has grown from it, would not have been possible without close collaboration between researchers and clinicians at MUSC Children's Hospital.

Lee, who studies the role of the gene *Nkx2-5* in embryonic heart development, knew that abnormal placentae and amniotic blood vessels were also seen in *Nkx2-5* mutant mice. When he learned of a study of women with early-onset or severe PE by neonatologist **Carol L. Wagner, M.D.**, and Obstetrics & Gynecology Chair **Donna D. Johnson, M.D.**, curiosity led him to test the placental samples they had collected for *Nkx2-5* expression.

To his amazement, he found a correlation between very high levels of *Nkx2-5* expression in specialized placental cells known as trophoblasts and high levels of sFlt1, an emerging PE biomarker, in some PE patients.

"We were very excited by this completely unexpected link between fetal heart development and a highly significant disease of pregnancy," says Lee. This excitement led to a fruitful collaboration with Johnson and maternal fetal medicine specialists **Eugene Y. Chang, M.D.**, and **Roger B. Newman, M.D.**, Vice Chair of Women's Health Research.

sFlt1 is produced by alternative messenger RNA splicing of the vascular endothelial growth factor (VEGF) type 1 receptor (VEGFR1), which relays signals promoting blood vessel growth. Like VEGFR1, sFlt1 can bind VEGF in the circulation, but because it thus competes with VEGFR1 signaling, it antagonizes blood vessel growth as a part of a normal balancing mechanism. Disproportionately high sFlt1 levels during pregnancy are associated with abnormal blood vessel development and the onset of PE symptoms.

Recalling from his cardiac research that Sam68, an RNA splicing factor, was activated downstream of *Nkx2-5* expression in heart development, Lee also found elevated Sam68 levels in the PE samples that correlated with *Nkx2-5* and sFlt1 expression levels. When Sam68 expression was depleted in cell models using RNA interference, alternative splicing of VEGFR1 produced less sFlt1 RNA.[1]

"We think that Sam68 is the lever regulating sFlt1 production and that *Nkx2-5* is pressing on that lever in some PE patients," says Lee.

To prove this hypothesis, Lee is monitoring sFlt1 and Sam68 levels in an animal model overexpressing *Nkx2-5* in the placenta and is looking for other harbingers of PE, with the hope that the *Nkx2-5* pathway could be targeted to find future treatments for PE.

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A KNOCKOUT PUNCH FOR PEDIATRIC BRAIN TUMORS?

Targeting DIPG with nanotechnology

Figure left: Chemotherapy drug encapsulated in a micelle is targeted to the interior of cells. Image courtesy of Dr. Ann-Marie Broome.

BY KATHARINE H. HENDRIX

Despite decades of clinical trials to find effective therapies, the prognosis for children with diffuse intrinsic pontine glioma (DIPG), a common pediatric brain tumor, remains grim. Generally diagnosed before age ten, most DIPG patients survive less than one year. "Diffuse intrinsic pontine glioma is the worst of the worst pediatric brain tumors," says **Amy-Lee Bredlau, M.D., MSCI**, a pediatric neuro-oncologist and Director of the Pediatric Brain Tumor Program at MUSC Children's Hospital. "There is absolutely no therapy to cure DIPG. It is uniformly lethal," she explains.

The dearth of treatment options is due in part to the location of DIPG in the pons, which rules out surgery and greatly limits the efficacy of chemotherapy.[1] "The agents don't cross the blood-brain barrier and get into the tumor tissue," says Bredlau.

Hoping to improve the prognosis for these children, Bredlau formed a multidisciplinary team of clinicians and basic scientists focused on developing DIPG therapies. **Ann-Marie Broome, Ph.D., MBA**, Associate Professor in the Department of Radiology and Director of Molecular Imaging in MUSC's Center for Biomedical Imaging, who has published widely on the design of nanoparticles for targeted therapies, most recently on the use of gold nanoparticles for that purpose,[2] is one of Bredlau's primary collaborators. Together, the group has developed new platform technologies for DIPG treatment using both organic and inorganic nanoparticles.

"We are first trying to eliminate systemic toxicity by delivering currently approved drugs where they need to be and prevent them from going where they don't," explains Broome. "The second problem is that tumors often develop resistance to the chemotherapy. If you don't hit a cancer hard and fast with the correct chemotherapeutic, you run the risk of creating a new, more aggressive cancer."

By encapsulating existing chemotherapeutic agents in organic nanoparticles such as micelles or on solid-state nanoparticles such as gold, the team can deliver higher doses directly to the tumor, with the hopes of delivering a knockout punch to the cancer.

"The doses we are delivering with these targeted therapies are a hundred times what we could give systemically. These would be fatal doses if not targeted," adds Bredlau.

"We can target cells that will most benefit from the treatment and deliver high doses in a short window of time, which improves the likelihood that the cancer won't be able to recover," Broome explains.

So far, the team has produced dramatic results using targeted nanoparticles in animal models—results that were achieved much more quickly than with standard therapies (i.e., those using neither targeting nor nanoparticles). Leveraging these delivery platforms, they have increased chemotherapy doses by 10 to 1,000 fold and produced rapid tumor cell death—in some cases shortening the therapeutic window from 30 days to three.

Currently, the team has patented these platforms and is conducting *in vivo* studies with an eye to starting clinical trials as soon as possible.

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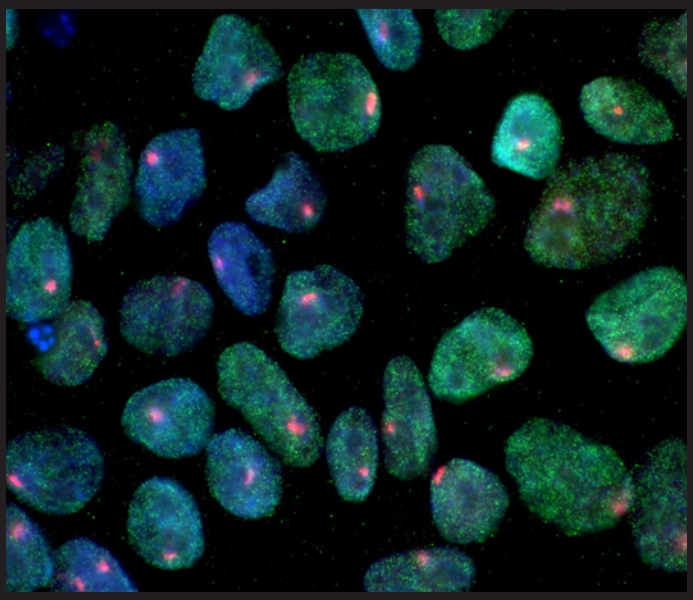

Left: Induced pluripotent stems cells (iPSC) derived from skin. Licensed from sciencesource.com.

DIVIDE AND CONQUER

Using iPSC stem cells to model two distinct phenotypes of X-ALD

BY KATHARINE H. HENDRIX

There is a saying that there are two ways to spend one's life—digging a lot of shallow wells in many areas, or digging a single deep well in one place. It can safely be said that **Inderjit Singh, Ph.D.**, a scientist specializing in neurodevelopmental and neurodegenerative disorders who serves as Scientific Director of the Charles P. Darby Research Institute at MUSC Children's Hospital, falls into the latter category. He has devoted over three decades to the study of X-adrenoleukodystrophy (X-ALD)—a genetically determined metabolic disorder depicted in the 1992 film *Lorenzo's Oil*. His persistence has paid off in the application of a novel research technique developed elsewhere[1] to the creation of much-needed diagnostic and therapeutic tools for this deadly disease.

X-ALD is a progressive, inherited disorder that primarily affects the adrenal cortex and nervous system white matter by promoting the accumulation of saturated, very-long-chain fatty acids in these tissues. Although the two primary ALD phenotypes are characterized by the same mutations in the *ABCD1* gene, their clinical course is quite distinct. The most common and aggressive type—fatal inflammatory childhood disorder (cALD)—presents in children younger than eight and leads to death by the age of twelve. A second, less aggressive variant—adrenomyeloneuropathy (AMN)—progresses more slowly, enabling many patients with this phenotype to survive into their fifties or sixties.

Thirty years ago, Singh was part of the team at Johns Hopkins that first described how peroxisome dysfunction—not mitochondrial dysfunction, which had been the prevailing theory—drives the impaired fatty acid metabolism seen in X-ALD.[2] Despite this leap forward, there was still no way to study each phenotype separately because there was no mouse or other model that could reproduce the two phenotypes.

Singh and his team, which includes **Mauhmad Baarine, Ph.D.**, and **Navjot Shah, Ph.D.**, recently overcame this barrier by harvesting skin cells from patients with the two disease types, reverse-engineering them to induce pluripotent stem cells (iPSC), and then re-differentiating those into neuronal cells. Using this method, Singh and his team identified differences in the two disease types not only by directly comparing neuronal cells but also by studying the differing epigenetic mechanisms triggered by excessive very-long-chain fatty acid accumulation.

Early results suggest that the load of very-long-chain fatty acids is higher in cALD and leads to an often lethal inflammatory response, whereas in AMN the lower load of very-long-chain fatty acids causes only oxidative insult.

"This is the first time we have been able to see the differences between two phenotypes of X-ALD," says Singh. "This could facilitate diagnosis early in childhood. We can predict which children will require more aggressive treatment."

Most exciting, this technique will allow researchers to develop and test potential mechanism-based agents to reduce fatty acid accumulation in human cells with the phenotype of interest, as they recently did for suberoylanilide hydroxamic acid.[3]

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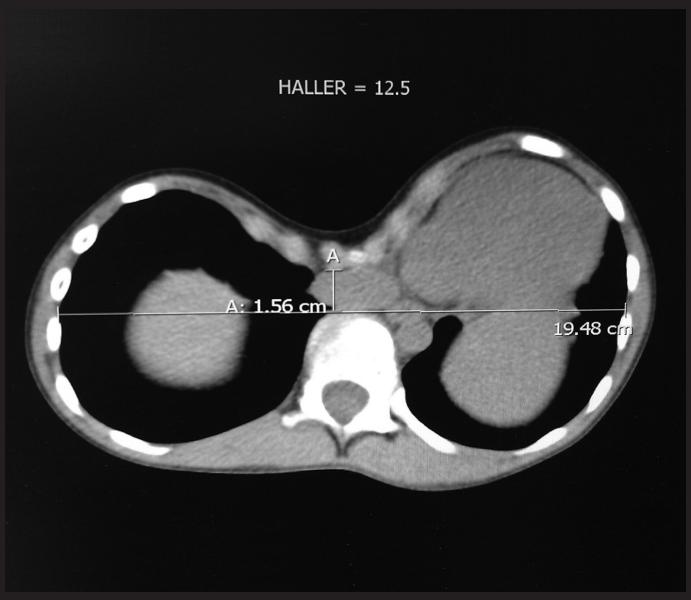

Figure left: CT scan demonstrates compression of the lungs and complete shift of the heart into the left side of the chest. The sternum is almost touching the spine.

HELPING FAMILIES DECIDE

Study gives pediatric surgeons objective guidelines for advising parents on *pectus* surgery

BY LINDY KEANE CARTER

The surgery to correct *pectus excavatum* (a congenital chest wall deformity in which abnormal growth of the ribs and the sternum produces a "caved-in" chest in children and adolescents) has undergone a revolution since 1996 when the minimally invasive approach was introduced. **André V. Hebra, M.D.**, Chief of the Division of Pediatric Surgery at MUSC Health, began offering this procedure in 1998. Several years later, Hebra and Donald Nuss, M.D., the Virginia surgeon who pioneered the approach that now bears his name, began evaluating and reporting on its outcomes and addressing some of its risks and complications. They introduced the routine use of thoracoscopy to guide the insertion of the corrective bar between the sternum and the heart, developed ways to better stabilize the bar to minimize migration and flipping, and recognized that the surgery should not be done on pre-pubescent children because of the risk of *pectus* recurrence.

As the operation became safer and outcomes improved, demand grew. The number of cases worldwide increased from about 200 per year in 1998 to more than 2,000 per year in 2002. Still, controversy simmered over the true benefits of the operation. Surgeons sought an objective measure of the deformity that would help them advise parents who were wavering about what could be viewed as elective surgery and that would persuade insurance companies that were increasingly refusing to cover it.

In 2001, Hebra and Robert E. Kelly Jr., M.D., from Children's Hospital of The King's Daughters in Virginia developed a ten-year study of 327 *pectus* surgery patients at 11 medical centers. All were evaluated pre-operatively and one year post-operatively with computed tomography (CT), pulmonary function tests, and body image survey. The CT scans provided the patient's Haller index, the objective measure of the severity of the deformity; a score greater than 3.2 is considered significant.

The final report, published in the December 2013 *Journal of the American College of Surgeons*, showed that surgical correction on those patients with a Haller index of 4 or greater improved pulmonary function and total lung capacity. In a smaller subset of patients who underwent testing during exercise (stress test), the investigators were able to demonstrate significant improvement in oxygen delivery by the heart and improved exercise tolerance.

"This study is the first conducted on a large number of children with *pectus excavatum* that validates the fact that correction of the deformity is not just cosmetic improvement," says Hebra. "Now, we can give parents the objective assessment in support of surgical intervention and we can predict the impact the operation will have on improving cardiopulmonary function. If the *pectus* is mild but the parents still want corrective surgery, we can delineate realistic outcomes and manage expectations."

Hebra has lectured extensively in the U.S. and abroad on the treatment options, risks, benefits, and outcomes of *pectus* surgery. These findings provide important guidelines for the management of *pectus* to physicians throughout the world.

MUSC Children's Hospital is a destination center for *pectus excavatum* and *pectus carinatum* (another common chest wall deformity). For more information, go to http://www.MUSCkids.org/pectus.

OWNING THEIR OWN CARE

Adolescent Medicine physician helps teens with chronic illness get ready for health care as an adult

BY LINDY KEANE CARTER

Adolescence is, by definition, a time of risky behavior, hormonal upheaval, conflict with authority, and bad choices. For young people with a chronic illness, one can add anxiety about changing from their pediatrician to a new provider and assuming responsibility for the care upon which their life depends. Not surprisingly, teens with a chronic condition are more likely to smoke cigarettes and marijuana and to have performed violent or antisocial acts.[1]

Medical transition planning is critically important for these youth, yet most pediatric practices neither initiate transition planning early in adolescence nor offer transition-support services.[2]

Adolescent Medicine has developed transition services for the pre-teens and teens who are being seen by specialists at MUSC Children's Hospital. **Lynn Manfred, M.D., EdD**, Clinical Director of Adolescent Medicine, helps young people with renal transplants, sickle cell disease (SCD), arthritis, lupus, and other chronic conditions prepare for self-care.

"I try to identify the kids as early as possible, at 11, 12 years old, before rebellion sets in," she says. Manfred involves them in projects designed to make sure they understand their medical problems. She also finds that at this age they are developmentally ready and willing to learn how to take their medications. Parents, too, receive her assistance in helping their children take on more responsibility for their own care.

SCD patients make up the largest group receiving Manfred's services. She reports that these young adults often have good pediatric care but, when they get beyond 18 years old, they have trouble finding a hematologist who will take care of them. With the arrival of a new hematologist at MUSC Health, their needs are being met, but South Carolina still needs more primary care physicians who are willing to work with hematologists, she says.

These transition services are based on the national program, "Got Transition," which was developed by the Maternal and Child Health Bureau and The National Alliance to Advance Adolescent Health (gottransition.org). Got Transition offers resources for pediatric and adult providers, such as a recommended timeline, a Quality Improvement approach outline, and three sets of customizable tools for different practice settings. Manfred feels that this information would be a good resource for an internist or family physician who is the new provider for a teen with a chronic illness as well as the pediatrician who is handing them off. Another helpful resource for primary care physicians, nurse practitioners, and physician assistants is a set of clinical guidelines on transitioning from adolescent to adult care developed by the American Academy of Pediatrics.[2]

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Great EXPECTATIONS

The new Advanced Fetal Care Center will provide integrated care to children with congenital anomalies

BY KIMBERLY MCGHEE
PHOTOGRAPHY BY BRENNAN WESLEY

MUSC Children's Hospital has a long history of treating congenital heart anomalies, serving as the anchor hospital for the Children's Heart Program of South Carolina and providing all procedures and catheterizations for children with cardiac issues throughout the state. It offers the only pediatric cardiac intensive care unit in the state staffed by pediatric cardiologists and nurses specializing in the care of children with congenital heart disease.

As impressive as these achievements are, plans to open a new Children's Hospital and Women's Pavilion in 2019 have inspired clinicians who diagnose and treat congenital heart and other anomalies to think even bigger and envision a fully integrated model of care that bridges prenatal and postnatal life and provides a life plan for children once counted lucky if they survived the first few weeks after birth.

The Advanced Fetal Care Center

The Advanced Fetal Care Center, which will be located in the new hospital, will provide a space where all MUSC Children's Hospital specialists involved in the prenatal and postnatal care of these children—the maternal fetal medicine (MFM) specialists who manage high-risk pregnancies, the neonatologists who stabilize the child after birth, the pediatric subspecialists who can definitively diagnose anomalies, and pediatric surgeons who can operate to correct abnormalities—will be able to meet with the family as a team to discuss the diagnosis, its implications for the child's life, and possible treatment options. A coordinator will help organize subspecialty care and act as a patient liaison. Ultrasound and fetal magnetic resonance imaging (MRI) will be available on the same floor.

According to **Sinai C. Zyblewski, M.D.**, Director of Fetal Cardiology and one of the champions of the new center, it "will serve as a portal of entry into a lifetime continuum of specialized care at MUSC Health for children born with congenital anomalies."

The Importance of Prenatal Diagnosis

Most of us cannot—or do not wish to—imagine the brutal shock a mother feels when she is told that her baby has a congenital anomaly. Each year, 2% to 3% of expectant or new mothers receive this news. How well they cope with it and how poised they are for the fight ahead depends in part on how and when the news is delivered.

Dr. Sinai Zyblewski is one of the pediatric cardiologists working with MFM specialists to improve prenatal detection of heart defects.

VIDEO: Dr. Sinai Zyblewski and Dr. Jill Mauldin discuss the new Advanced Fetal Care Center in the online edition.

If there is concern for a congenital anomaly, an MFM specialist such as Dr. Jill Mauldin (right) is consulted to interpret level 2 ultrasound results.

Jill G. Mauldin, M.D., an MFM specialist and Medical Director of MUSC Health Women's Care, and Zyblewski are both firm believers that prenatal diagnosis of these anomalies provides the families time to come to terms with the news and to understand the treatment plan for their child. They also believe that the close collaboration between MFM specialists throughout the state and pediatric subspecialists leads to both a higher rate of prenatal detection and better care for children as they transition from prenatal to postnatal life. Perhaps as a result of the seamless, integrated care, children with congenital anomalies who are diagnosed prenatally are healthier at the time of surgery than those diagnosed after birth. In February at the 18th Annual Update on Pediatric and Congenital Cardiovascular Disease, **Catherine W. Sechrist, M.D.**, a pediatrician at MUSC Children's Hospital, Zyblewski, and colleagues reported that significantly fewer infants with a prenatal diagnosis of single-ventricle cardiac defects required ventilator support before cardiac surgery than did those diagnosed after birth (46% vs 71%).

Consider two scenarios.

In the first, a congenital heart defect, among the most common of congenital anomalies, is not diagnosed until after birth, as is true of almost half (47%) of these cases in South Carolina. The orderly course of events the mother expected—the birth of a healthy infant, the time spent holding and bonding with her child, the joyous arrival home—shatters into almost incomprehensible fragments. The worried looks on the faces of the health care providers. The ache of separation when the child is airlifted to the nearest neonatal intensive care unit. Days spent wondering what could have gone wrong. The news that the child is being airlifted again for subspecialty care. The long drive to rejoin the baby. Finally, a diagnosis. The struggle to follow medical terms and understand the details of the procedures that will be needed. Wondering if the baby has a future.

"It is not uncommon to receive a baby who has already been on two flights in the first 48 hours of life and the mom is still in a different hospital recovering from having given birth," says Zyblewski.

South Carolina's MFM specialists and pediatric cardiologists are determined to offer patients a second scenario. They encourage community obstetricians who see a cause for concern on a routine 20-week ultrasound to refer the patient to a regional MFM specialist for diagnosis and management. The regional MFM specialist manages the pregnancy, usually in collaboration with a local pediatric cardiologist, enabling the mother to receive care close to home. Then, at the beginning of the third trimester, a prenatal consultation is requested at MUSC Children's Hospital, where the baby will be delivered.

Eighteen months ago, Zyblewski and other pediatric cardiologists began joining MFM specialists such as Mauldin for these prenatal consultations. Together, they obtain and interpret a focused ultrasound of the heart to confirm the diagnosis, and a genetic counselor, such as **Sally M. Shields, RN, CGC**, helps parents understand its implications and serves as a social support for the family. The team meets the mother and family to formulate a birth plan, choose an induction date, and discuss the subspecialty care that will be needed after birth. On the day of delivery, the appropriate team is in place to meet the needs of both mother and child, who are never separated.

The collaboration between MFM specialists and pediatric cardiologists at these prenatal consultations has proven so fruitful that plans are under way to open an intermediary Advanced Fetal Care Center in summer 2015 in the current MUSC Children's Hospital. There, families can meet with a team whose members include an MFM specialist such as Mauldin or **Eugene Y. Chang, M.D.**, a neonatologist, any needed pediatric subspecialist, a pediatric surgeon, a pediatric radiologist, and a nursing representative to discuss treatment options for their child. Although the space in the new Children's Hospital and Women's Pavilion will offer the ideal setting

for these team consultations, Mauldin and Zyblewski are already working to integrate currently available Women's Care and pediatric subspecialty services, to strengthen referral patterns and processes, and to improve the patient experience.

More Subspecialties to Come Aboard

The vision for the Advanced Fetal Care Center is that it will serve as a regional center for children with congenital anomalies and their families and that it will offer truly integrated prenatal and postnatal care through close collaboration between MFM specialists and the full spectrum of pediatric subspecialists. In addition to pediatric cardiology, a number of other subspecialties, including neonatology, urology, neurosurgery, general pediatric surgery, and otolaryngology, already offer prenatal consultations. According to **André V. Hebra, M.D.**, Chief of Pediatric Surgery, "the ideal consult enables the pediatric surgeon to educate parents about strategies related to the best delivery approach as well as the potential outcomes and treatment options for their infant while providing parents with the time to ask questions and express their values and concerns." In the opinion of pediatric neurosurgeon **Ramin Eskandari, M.D.**, "Families who receive a prenatal consultation do a better job of coping than those who learn about the anomaly after birth."

Currently, pediatric cardiology is the only subspecialty to conduct prenatal consultations jointly with an MFM specialist. That model will eventually expand to all other subspecialties in the new Advanced Fetal Care Center, where the family will meet with all providers at once. This is convenient for the family, but it also offers them the combined experience of all team members, a centralized treatment plan, and a consistency of message that avoids the miscommunication and confusion that can result from fragmented care.

"It's rewarding to me as a provider to do the multidisciplinary consults—the patients hear all the different perspectives at once and get their questions answered better," says Mauldin.

In addition to pediatric cardiology, the first subspecialties to begin participating in these multidisciplinary teams at the Advanced Fetal Care Center in its intermediary location will be pediatric urology, general pediatric surgery, and pediatric neurosurgery. Common anomalies evaluated and treated include hydronephrosis, posterior urethral valve, and renal anomalies (urology); abdominal wall defects (gastroschisis and omphalocele), diaphragmatic hernia, cystic lung lesions, and pulmonary sequestration (general pediatric surgery); and hydrocephalus and myelomeningocele (pediatric neurosurgery).

Improved Imaging Modalities

Among imaging technologies, ultrasound is the workhorse for prenatal diagnosis and, in recent years, the quality and resolution of imaging obtained with it have improved dramatically. However, when additional information is needed, the greater anatomic detail provided by fetal MRI can be useful in making, and sometimes changing, a diagnosis. According to **Meryle J. Eklund, M.D.**, a pediatric radiologist specializing in fetal MRI, **"**It is an amazing tool that really provides a window into the womb as the baby is developing. It takes out some of the guesswork with fetal diagnosis and it's an additional piece of information that helps fit the puzzle together."

At times, fetal MRI reveals that what was thought to be a potentially lethal anomaly is much less severe than expected. For example, in a recent case, fetal MRI revealed that a fetus who had been diagnosed earlier at an outside institution as having a large chest mass and who was thought to have a poor prognosis in fact had a much less severe and more treatable abnormality. In another recent case, a fetus diagnosed as having a potentially life-altering midline spinal tumor using ultrasound was found instead to have an easily correctable renal anomaly. "The fetal MRI changed the family's expectations, from thinking there was a diagnosis of cancer with all sorts of negative effects to understanding that there was only a kidney anomaly requiring a small overnight-stay surgery," says **Andrew A. Stec, M.D.**, Director of Pediatric Urology.

Even when fetal MRI reveals that the situation is worse than what was originally thought—for example, when a misdiagnosed case of hydronephrosis turns out to be a bladder outlet obstruction—the greater insight into the anomaly ensures that the appropriate treatment plan is in place and that the parents are not blindsided by an unexpected diagnosis after birth.

Setting Expectations High

Advances in imaging and surgical techniques and better integrated care mean that the bar has been set higher for those who treat congenital anomalies. These clinicians are no longer satisfied with survival of these infants. According to Zyblewski, "For a long time we have invested a lot of time and energy into survival but, in this day and age, it is about so much more than survival—it's about optimizing quality of life, giving these children the best chance for being able to complete school successfully, and optimizing their opportunity to grow into adults who are independent and can function." Ensuring prenatal detection of congenital anomalies and providing integrated, multidisciplinary care for both mother and child at the new Advanced Fetal Care Center are the first steps to meeting these great expectations.

VIDEO: Dr. David J. Annibale discusses South Carolina's professional collaboration in neonatal care in the online edition.

COMBINED EFFORT

MUSC Children's Hospital fosters professional collaboration, translational research, and advanced practice to enhance care for South Carolina's most critically ill newborns

For the developing human being, the journey from conception to first breath under bright lights is full of risk. Being born prematurely (i.e., before 37 weeks gestation) is one of those risks. In South Carolina the prematurity rate is 13.8%, as compared to the national rate of 11.4 % (2013). The state and the nation as a whole are striving to meet the March of Dimes' 2020 goal of 9.6%.

MUSC Health is dedicated to reducing premature births and caring for critically ill newborns. As a state-designated Regional Perinatal Center (RPC) and an academic medical center, it offers comprehensive maternal and neonatal medical and surgical subspecialties.

Prematurity is the most common reason for a baby's needing complex perinatal care, but any number of congenital problems, *in utero* injuries, or illnesses can deliver a baby to a neonatal intensive care unit (NICU). In South Carolina, NICU care is concentrated in seven level III centers, five of which are further designated as RPCs as regulated by the South Carolina Department of Health and Environmental Control (DHEC). Each RPC is responsible for managing the medical, transport, and educational needs of its region. MUSC Children's Hospital, with an average of 900 NICU patients a year, is one of the largest of the RPCs. Collaboration among these five RPCs is critical to achieving good outcomes for all South Carolina babies, says **David J. Annibale, M.D.**, Director of the Division of Neonatology and Director of the South Carolina Neonatal Medicine Consortium, an organization that works to improve the quality of neonatal care in the state. The partnerships are working. Infant mortality rates in South Carolina are improving more rapidly than in the rest of the country, says Annibale. South Carolina's mortality data put the state in the second best quartile as measured by the Vermont Oxford Network, an organization of more than 500 private and academic NICUs around the world that share quality and outcome data.

More than 190 nurses with highly specialized skills care for an average of 62 newborns a day in the NICUs at MUSC Children's Hospital

"Because of DHEC's strong regionalization system and the expertise that develops in large-volume perinatal centers, and because we can talk with one another and share approaches that work well or don't, South Carolina is definitely reducing infant mortality," says Annibale. Large-volume centers further reduce very low birth weight babies' (VLBW, <1500 grams or 3 1/3 pounds, at birth) mortality. A neonate's odds of dying can be as much as five times greater in a low-volume NICU.

Rita M. Ryan, M.D., Chair of the Department of Pediatrics, has been a clinical neonatologist for 25 years. "I am so proud of the officials who work for the state in Columbia who have supported perinatal regionalization, a concept strongly associated with improved

survival in VLBW babies. They are doing the right thing for babies for the right reasons," she says.

Successful practices shared

The South Carolina Neonatal Medicine Consortium began in 2003 through a collaborative effort between Greenville Health System (GHS) and MUSC Health. MUSC Health is represented by Annibale, (who leads the consortium), **Julie Ross, M.D.**, and **James Kiger, M.D.**, both Assistant Professors in the Division of Neonatology. Participants share information on quality improvement, data, and solutions. In this forum, MUSC Children's Hospital has shared its pioneering successes in the following approaches:

1. Nutrition for preterm babies. "It's critical to deliver nutrition within the first minutes of life," says Annibale. As a result of collaboration between MUSC Children's Hospital and other RPCs, all VLBW infants born at an RPC in South Carolina receive robust IV nutritional support within minutes of birth. When the baby transitions to nutrition by mouth, he or she receives breast milk, either the mother's or a donor's, even if it is only a drop every couple of hours. The point is to colonize the gastrointestinal tract with helpful bacteria and prevent it from regressing. Two neonatologists at MUSC Health, **Carol L. Wagner, M.D.**, and **Sarah N. Taylor, M.D.**, are internationally recognized for their research in neonatal nutrition (see article on page 19), and their work is the backbone of the units' emphasis on neonatal nutrition.

2. Care of the premature infant in the first hour of life — the "Golden Hour" — has been rolled out across the state and is based on the following practices:

- **Pulmonary support**. Immediate respiratory support to help the baby expand the lungs, delivered as gently as possible, is critical, followed by appropriate use of a ventilator and the rapid delivery of surfactant (a medication composed of substances deficient in preterm babies' lungs) when needed.
- **Antibiotics**. Because of the possibility of maternal infection in some babies, the neonatology team rapidly assesses that risk and starts antibiotics in those children within an hour of birth.
- **Temperature support and prevention of dehydration**. Low temperature and dehydration are life-threatening medical problems in VLBW infants that result from physiological immaturity and the inability of the baby's fragile skin to prevent heat and water loss.
- **Protection for the newborn brain**. MUSC Health has adopted several interventions aimed at preventing brain injury related to prematurity. This delivery room approach is a result of collaboration between nurses, physicians, and respiratory therapists.

3. Team development. The care of very sick, very small premature infants requires highly skilled teams.

Making new discoveries

Nutrition is a major area of research in the Division of Neonatology. Two physician investigators and one Ph.D. are demonstrating just how critical nutrition is to growth and long-term outcomes. **Bruce W. Hollis, Ph.D.**, Professor in the Department of Pediatrics, leads this team and focuses on the role of Vitamin D. Wagner conducts research on Vitamin D and breastfeeding.

Taylor is the lead researcher for preterm infant nutrition and growth. "The better you grow in the NICU the better your neurodevelopment at age two," she says. Growing tiny premature babies outside of Mom is notoriously hard, but Taylor's research has helped the NICU get to the point of being able to grow them efficiently. The goal is to enable the baby to leave the hospital at the same weight percentile as his birth weight percentile, which will keep him on his ideal growth curve. Otherwise, a gap in growth curves occurs, and the baby likely will not close it, leaving him at a later neurological disadvantage.

In the unit, therefore, the members of the clinical team—physicians, nurses, dieticians, pharmacists—recalibrate the nutrition every day. "Rather than saying a baby should get x number of calories per day to grow, we evaluate the baby's growth and then determine whether we need to change the calories, the protein, the ratio of nutrients," says Annibale.

"In the hospital, human milk is truly life-saving for premature infants," Taylor explains. Out of the hospital, mother's milk decreases re-hospitalizations, upper respiratory infections, and gastrointestinal illness in infants. Taylor is now studying how to help preterm babies breastfeed after discharge because other studies have shown that breastfeeding drops from 50% at discharge to 33% two to four weeks later to 8% six months later.

The consortium of NICUs began using early human milk nutrition several years ago. To meet the demand that resulted, Taylor suggested to the consortium that a South Carolina milk bank be established. By mid-2015, the state's first and only milk bank will be housed at MUSC Children's Hospital (see article on page 2).

Other research includes the first U.S. clinical trial using hypothermia to protect the neonatal brain from lack-of-oxygen injury related to perinatal events that might affect oxygenation or blood flow to the fetus before or after birth. In the area of laboratory research, neonatal lung development investigators are looking at the effects of oxygen on lung inflammation, the role of lymphocytes in the lungs of premature infants on the ventilator, and novel ways to use surfactant beyond the first 48 hours of life.

Multidisciplinary teams

The NICU at MUSC Children's Hospital admits approximately 900 babies a year. With large patient volume comes depth of expertise.

Annibale gives the following example from being at the bedside of a particularly sick baby. "I had three NICU pediatric respiratory therapists with me brainstorming on what would be the best next move. You can't do that in a center that takes care of five VLBW babies a year."

"You can't do that in a center that takes care of even 60 VLBW babies a year," says **John B. Cahill Jr., M.D.**, Associate Professor of Pediatrics and Medical Director of the MUSC Health Neonatal Intensive Care System. "You need to cross that 100-babies threshold to have the team skill set available to deliver the best care possible."

On that point, the literature is clear. "The science shows that large centers with more than 100 VLBW babies a year have significantly better survival statistics than centers with fewer than 100 VLBW babies per year," says Annibale. Adjusting for severity of illness, patients born at centers with low VLBW volumes (i.e., fewer than 50 annual admissions) have five-fold increased odds of death (Wehby et al. *Med Care* 2012;50:714-721).

More than 190 nurses work in the intensive care nurseries (66 beds) at MUSC Children's Hospital. They are joined by attending neonatologists, physician trainees (including seven Fellows in neonatal perinatal medicine), pharmacists, respiratory therapists, dieticians, occupational therapists, social workers, and case managers. In addition, there is the MEDUCARE pediatric transport team that brings babies by air and ground transport.

The MUSC Children's Hospital medical team is available to all of the state's perinatal centers for referrals for complex maternal-fetal and neonatal care. Neonatal surgical care includes complex general pediatric surgery, pediatric neurosurgery, pediatric ENT, pediatric ophthalmology, and pediatric cardiothoracic surgery, as well as pediatric anesthesiology.

But the team extends beyond the NICU, Annibale points out. A baby's outcome also depends on the care delivered by high-risk maternal fetal medicine obstetricians. To provide those high-risk mothers with comprehensive assessment and interventions, MUSC Health is creating an Advanced Fetal Care Center, which is scheduled to open in a temporary space in 2015 (see article on page 8). Also in the planning stages is a new hospital—the Children's Hospital and Women's Pavilion—which is projected to open in 2019.

The NICU team at MUSC Children's Hospital provides highly specialized care for 200 very low birth weight babies a year.

"South Carolina has a reason to be truly proud of its neonatal outcomes," says Annibale. The state's strong system of regionalized centers, the collaboration among those who staff them, and the team approach overall that includes maternal fetal medicine specialists is moving the needle toward the goal everyone seeks: getting babies off to the best start in life possible.

Pioneering New Therapies for Pediatric Patients

BY KIMBERLY MCGHEE

PHOTOGRAPHY BY BRENNAN WESLEY

Clinicians at MUSC Children's Hospital are not content with providing the best in current therapies for sick children but are pushing the frontiers of care through clinical trials. Profiled here are trials of some of the most innovative therapies—including a gene therapy for sickle cell disease and targeted therapies for pediatric brain tumors and cystic fibrosis—as well trials seeking to improve outcomes after pediatric heart surgery and to ensure healthier pregnancies through adequate vitamin D supplementation.

Gene Therapy Clinical Trial for Severe Sickle Cell Disease

A phase 1 clinical trial (NCT02140554) of a treatment for severe sickle cell disease (SCD) using gene therapy opened at MUSC in 2015 and is currently recruiting patients. The National Institutes of Health is also recruiting patients, and additional U.S. sites are planned to open later this year. According to **Julie Kanter, M.D.**, Director of Sickle Cell Research and principal investigator for the MUSC Children's Hospital site of the study, "This could be the first step toward a potentially curative treatment for patients with severe SCD."

In SCD, a mutation in the beta-globin gene causes the normally round and flexible red blood cells to take on a rigid sickle shape that makes it difficult for them to pass through small blood vessels. Blood vessels become blocked, depriving organs of oxygen and leading to painful vaso-occlusive crises and organ dysfunction. The sickled cells do not live as long as healthy red blood cells, cause blood vessel damage, and put affected patients at risk of stroke.

Currently, the only cure for a child with SCD is a hematopoietic stem cell bone marrow transplant (HSCT) from an HLA-matched donor, but less than 10% of affected patients have such a donor. Thus, although successful, HSCT remains only a rare option and poses the risk of graft-versus-host disease and graft failure.

The phase 1 gene therapy clinical trial to be conducted at MUSC, which is enrolling adult patients (18 years and older), adopts a different approach: the patient's own hematopoietic stem cells (HSCs) are harvested from the bone marrow, transduced with a lentivirus carrying a functional copy of the human beta-globin gene with anti-sickling properties (the LentiGlobin BB305 Drug Product; *bluebird bio, Inc.*), and then reinfused into the patient (after chemotherapy to clear existing marrow). These "genetically corrected" HSCs are designed to serve as a self-renewing source of healthy red blood cells, and so a single instance of gene therapy has the potential to cure the disease or drastically lessen its severity.

Dr. Julie Kanter

In a letter published in *Nature* (September 16, 2010), a group of French researchers conducting an early-phase clinical trial of a similar gene therapy in patients with ß-thalassemia major reported that a formerly transfusion-dependent patient remained transfusion-free two years after treatment. At the annual meeting of the American Society of Hematology in December 2014, clinical researchers reported that the first four patients with ß-thalassemia major enrolled in phase 1/2 studies using the same gene therapy are currently transfusion free. Although preliminary, these results point the way to a better future for patients with ß-thalassemia and severe SCD.

Novel Therapies for Cystic Fibrosis

The MUSC Health Cystic Fibrosis Center is among the top-enrolling sites for the Cystic Fibrosis Foundation's Therapeutics Development Network (TDN), the largest cystic fibrosis (CF) clinical trial network in the world. MUSC helped collect data that led to the approval in 2012 of ivacaftor (Kalydeco™; Vertex Pharmaceuticals), the first drug to target one of CF's underlying causes.

All CF patients have a problem with chloride channels, but, according to **Isabel Virella-Lowell, M.D.**, Director of Pediatric Clinical Trials at the center, the specific mutations that characterize a patient's CF subtype determine whether the chloride channel is missing, is made but does not reach the cell surface, or reaches the cell surface but does not open correctly. Ivacaftor was approved for the 4% to 5% of CF patients with a gating mutation after it was shown to dramatically increase lung function, decrease sweat chlorides by as much as 50 mmol/L, and reduce infections and exacerbations. In patients with a gating mutation, the chloride channel reaches the surface but does not open correctly; ivacaftor binds to the chloride channel and holds it open.

Studies are under way to assess whether combination therapies with ivacaftor can be used to help the 85% of CF patients with the F508del mutation. In these patients, the chloride channel is improperly folded and cannot bind to the cell surface. A successful combination therapy would include an agent(s) to refold the chloride channel and ivacaftor to open the channel once it reached the cell surface. Through the TDN, the MUSC Health Cystic Fibrosis Center has conducted trials of such combination therapies in adults and has opened enrollment for one in children.

Dr. Isabel Virella-Lowell

Targeted Therapies for Pediatric Brain Tumors

Amy-Lee Bredlau, M.D., MSCI, Director of the Pediatric Brain Tumor Program at MUSC Children's Hospital, is the principal MUSC site investigator for two trials, one led by St. Jude and one by Harvard, investigating whether targeting therapy based on the molecular subtype of brain tumors improves outcomes in pediatric patients. Both trials are currently recruiting patients.

The Molecular Risk-Directed Therapy for Newly Diagnosed Medulloblastoma Trial (NCT01878617)

Treatment for medulloblastoma is typically based on clinical risk, which is defined by the amount of tumor left after resection. However, recent studies suggest that prognosis varies widely among molecular subgroups of medulloblastoma (WNT, SHH, non-WNT non-SHH). More than 90% of patients with the WNT subtype and 75% of those with the SHH subtype survive on current therapy, whereas only 40% to 60% of those with non-WNT, non-SHH tumors do so. The St. Jude–led trial is assessing whether choosing the intensity of radiation therapy based upon a stratification of patient risk including molecular subtypes in addition to clinical risk prolongs progression-free survival compared with treatment stratification based upon clinical risk alone. An SHH inhibitor is used in patients with the SHH subtype.

Molecularly Determined Treatment of Diffuse Intrinsic Pontine Gliomas (NCT01182350)

Diffuse intrinsic pontine glioma (DIPG), an aggressive brain tumor located in the pons, typically occurs in children of elementary school age and is uniformly lethal. Radiation is the only treatment known to slow progression. Despite scores of clinical trials, no therapy has been found to improve on the progression-free survival (6.5 months) and overall survival (9 months) achieved with radiation. Biopsies have rarely been obtained for DIPG due to its position in the pons, hampering molecular profiling that could lead to the development of targeted therapies. Better imaging and surgical guidance technology have made biopsy of DIPG, once considered a dangerous surgery, much safer, opening the way for molecular analysis of these tumors.

Dr. Amy-Lee Bredlau

This Harvard-led trial tests whether basing treatment decisions on the molecular profile of a biopsied DIPG tumor leads to better overall survival than that seen in historical controls. Biopsy samples will be analyzed for overexpression of epidermal growth factor receptor (EGFR) and MGMT promoter methylation, both of which are thought to be prognostic in DIPGs. All patients will receive standard-of-care radiation and bevacizumab, which has been shown in preclinical studies of gliomas to enhance the effects of radiation. In addition, patients with $EGFR^+$ tumors will receive the tyrosine kinase inhibitor erlotinib, those with $MGMT^+$ tumors will receive temozolomide, and those with $EGFR^+$ $MGMT^+$ tumors will receive both agents.

"If these targeted therapies succeed in improving survival for children with medulloblastoma and DIPG, the results will likely be translated for treatment of other aggressive pediatric brain tumors, such as anaplastic astrocytomas and glioblastomas," says Bredlau.

For more information on these trials, contact study coordinator Kate McCormack at mccormk@musc.edu.

Corticosteroid Therapy in Neonates Undergoing Cardiopulmonary Bypass

In the United States, approximately 40,000 babies are born with a heart defect annually, and 10,000 of those undergo cardiac surgery requiring cardiopulmonary bypass (CPB). These complex surgeries would not be possible without CPB, which performs all of the functions of the heart and lungs, removing carbon dioxide and adding oxygen to the baby's blood and pumping it throughout his or her body.

However necessary, CPB is not without its drawbacks. Patients undergoing CPB develop a potent inflammatory response that may lead to poor heart, lung, and kidney function after the heart surgery. This in turn can lead to edema, longer times on the ventilator, the need for higher doses of heart medications, and a longer stay in the hospital. Children and especially neonates (<1 month old) are particularly vulnerable because of the immaturity of their organs and the disparity in size between them and the CPB machine.

Whether corticosteroids help mitigate the inflammatory response after CPB remains hotly debated. Most clinical trials to date have had limited patient enrollment and variations in clinical trial design (i.e., type, dose, and timing of corticosteroid) have undercut efforts to pool data in meta-analyses. Better efficacy data in neonates undergoing cardiac surgery are needed to determine whether the potential benefit of corticosteroids in controlling the inflammatory

Vitamin D and Maternal and Fetal Health

Vitamin D deficiency has been linked to lower birth weights and higher rates of preterm delivery. Recent clinical trials at MUSC Children's Hospital have explored how much vitamin D is required by pregnant women to ensure their own and their baby's health and how much is needed by nursing mothers to render their breast milk replete.

In a clinical trial (NCT00292591) led by **Bruce W. Hollis, Ph.D.**, and neonatologist **Carol L. Wagner, M.D.**, 502 pregnant women were randomized to receive 400, 2000, or 4000 IU/d of vitamin D. At study initiation, the daily reference intake (DRI) recommended by the Institute of Medicine (IOM) was 400 IU/d. More than half of all women and more than 80% of black women receiving 400 IU/d did not achieve sufficiency (*Journal of Bone and Mineral Research* 2011;26(10):2341–2357). The study also showed that maternal levels of 25(OH)D (25-hydroxyvitamin, a metabolite of vitamin D) of 80 nmol/L were needed to achieve IOM-defined sufficiency (50 nmol/L) in the cord blood that supplies the fetus. In stark contrast to current IOM recommendations (600 IU/d, 1-69 years), the study authors concluded that a DRI of 4000 IU best meets the needs of mothers and neonates. Those results were confirmed by a community-based trial supported by the Thrasher Research Fund, which also showed a strong correlation between vitamin D deficiency and preterm birth, even after controlling for race (*Am J Obstet Gynecol* 2013;208:137.e1-13).

Evidence suggesting a link between vitamin D deficiency and pregnancy complications led the W.K. Kellogg Foundation to fund a trial by Wagner and colleagues randomizing pregnant women to 400 or 4400 IU/d to study how 25(OH)D levels affect immune function and alter placenta architecture.

In May 2013 at the annual meeting of the Pediatric Academic Societies, Hollis and Wagner reported results of a lactation trial conducted jointly by MUSC and the University of Rochester to test whether supplementing the nursing mother could ensure sufficient levels of vitamin D in the exclusively breast-fed infants born at term (NCT00412074). The trial randomized 476 mother/infant dyads into three vitamin D treatment groups: 400 IU (mother)/400 IU (infant), 2400 IU/placebo, or 6400 IU/placebo. Infants receiving 400 IU daily and those whose only source was via breast milk of mothers receiving 6400 IU daily attained adequate 25(OH)D levels, suggesting that maternal supplementation with 6400 IU of vitamin D is at least as effective as infant supplementation in preventing deficiency.

Dr. Sarah Taylor (left) and Dr. Carol Wagner (right)

Preterm babies cannot grow exclusively on breast milk and require nutritional supplementation. Neonatologist **Sarah N. Taylor, M.D.**, studied 89 preterm babies weighing less than 1500 grams to see whether they were deficient in vitamin D and whether supplementation would help them grow better. More than 90% of infants in this NIH-supported trial were deficient in vitamin D at birth, with black infants showing the most dramatic deficiencies (unpublished results). All achieved sufficiency by term age when supplemented with an average of 600 IU/d of vitamin D. Improved bone mineralization and density were significantly associated with higher 25(OH)D levels. More studies are needed to determine the level of vitamin D supplementation required to achieve optimal bone density.

response outweigh side effects such as delays in wound healing and an increased likelihood of infection.

Hoping to address that gap in the literature, **Eric M. Graham, M.D.**, Director of the Pediatric Cardiac Intensive Care Unit (PCICU) at MUSC Children's Hospital, is leading a multicenter clinical trial (NCT01579513) that is randomizing neonates to either a single dose of methylprednisolone or placebo to be administered in the operating room just before cardiac surgery requiring CPB. The primary endpoint will be a composite mortality-morbidity outcome, but data will also be collected on the time spent on a ventilator, in the hospital, and in the PCICU. In addition, babies will undergo testing at one year to see if surgery and recovery caused any neurodevelopmental delays. "This trial's results will clearly define the clinical utility of steroids in pediatric cardiac surgery, improving the care we provide to these children," says Graham.

To learn more about this trial, contact Tricia Infinger at infingep@musc.edu.

Dr. Eric Graham

Putting the Pieces Together

A Primary Care Provider's Guide to Autism Spectrum Disorder

BY JANE M. CHARLES, M.D.; LAURA A. CARPENTER, PH.D.; AND KIMBERLY MCGHEE

"A Portrait of the Artist" by Emily L. Williams. Reprinted from *Drawing Autism* (Editor, Jill Mullin) with the permission of Akashic Books.

Part I: Screening and Diagnosis

On completion of this article, the reader should be able to:

- *Discuss the importance of using an appropriate tool such as the Modified Checklist for Autism in Toddlers to screen for autism spectrum disorder (ASD) in all children at 18 and 24 months and recognize the importance of early intervention.*
- *Recognize the importance of diagnosing and treating common comorbid psychiatric and medical conditions for ASD.*

The prevalence of autism spectrum disorder (ASD) spiked in the 1990s and has continued to skyrocket. Today, ASD is nine times more prevalent than in 1997 (147 vs 16 diagnosed cases per 10,000 children).[1,2] It remains a matter of debate whether this dramatic increase can be attributed to greater awareness, more sensitive screening tools, or an actual increase in the number of cases due to environmental or other factors. What is not debatable, however, is that—whatever the cause of the increase—the effect will be many more children and adults with a diagnosis of ASD. Developmental pediatricians alone cannot manage this population, and it will increasingly fall to pediatricians and adult primary care providers to do their part. And yet a 2011 study found that less than half of pediatricians routinely complete formal developmental screening as part of their well-child care.[3]

Since pediatricians and other primary care providers are undoubtedly already seeing patients with ASD and since that number is likely to grow, they should be familiar with the most recent guidelines on ASD management, including the 2007 policy statement by the American Academy of Pediatrics (AAP)[4] and the 2014 practice parameter from the American Academy of Child and Adolescent Psychiatry.[5] Both policy statements reiterate the importance of early diagnosis—made possible by screening all children for ASD at an early age—to provide children with ASD the early intervention they need to reach their full potential. They also emphasize that pediatricians should continue to treat the child with ASD throughout childhood and adolescence, serving as the child's medical home and coordinating all of the multidisciplinary services he or she will require.

The parents of a child with ASD may feel overwhelmed by the challenges they face in caring for their child, the ASD diagnosis itself, and the scope and variety of services their child needs. By serving

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Jane M. Charles, M.D.; Laura A. Carpenter, Ph.D.; and Kimberly McGhee have no relevant financial relationships to disclose.

Developmental pediatrician Dr. Jane Charles has devoted her career to caring for children with ASD.

as advocates for children with ASD and providing care that is in line with national recommendations, summarized here, pediatricians can help them "put the pieces together." They can assist parents in obtaining the support they will need to ensure their child lives as full and independent a life as possible.

Understanding ASD

Despite its growing prevalence, ASD remains poorly understood by the general public and many clinicians. People often fear what they do not know, and physicians may be reluctant to suggest that a child could have ASD, fearing parents' reactions. Removing some of the mystery around ASD could facilitate communication between physician and parent. Learning that some children can achieve excellent outcomes if intervention is begun early could convince parents of the value of early diagnosis and treatment.

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (*DSM-V*), published in 2013, recognizes delays in social communication and repetitive or "perseverative" behaviors as the two primary diagnostic criteria for ASD. The *DSM-V* also uses the umbrella term *autism spectrum disorder* to replace a number of related diagnoses in the *DSM-IV*, including autism, Asperger's syndrome, PDDNOS (pervasive developmental disorder not otherwise specified), Rett syndrome, and childhood disintegrative disorder.

Social Communication

Difficulty with social communication is the core feature of ASD. Children with ASD find it hard to interpret facial expressions, making it challenging for them to "read" social situations and develop social skills. Many children with ASD will have language delays. Those with cognitive skills above the range for intellectual disability may begin to speak on time but will have issues with the practical social use of language (i.e., pragmatic language).

Repetitive/Stereotyped Patterns of Behavior

People with ASD often engage in repetitive "perseverative" behaviors—they do not like to vary from their routines, become preoccupied with a specific object or interest, and often engage in the same action time and again. Those with high-functioning autism focus on one or two favorite subjects to the virtual exclusion of all else and may develop astonishing proficiency in their narrow areas of interest.

Sensory Overload

We make sense of the world outside us through our senses. Our brain tells us which sensory data deserve our attention—a truck horn warning us it is not safe to cross the street—and which can be safely ignored.

In people on the autism spectrum, the brain's role as arbiter of sensory data may be compromised. According to **Jane M. Charles, M.D.**, a developmental pediatrician at MUSC Children's Hospital who specializes in autism, "In your brain you have a policeman that organizes all of the input and makes sense of it for you—that little policeman is not working very well in some people with ASD."

As a result, people with ASD can feel barraged by and have trouble making sense of excess sensory stimuli. For example, they can feel anxious in noisy crowds or under bright fluorescent lights or be repelled by the textures of certain foods or items of clothing.

Etiology and Risk Factors

Autism spectrum disorder is extremely heterogeneous, making it difficult to identify a single etiology. It is estimated that 20% to 25% of children with ASD will experience seizures,[5] suggesting a neurobiological basis for the disorder. Imaging studies have shown white tract abnormalities in these children and differences in the areas of the brain associated with sensory stimuli processing and social judgments.[5] A functional magnetic resonance imaging study published in late 2014 by **Jane E. Joseph, Ph.D.**, Professor in the Department of Neuroscience at MUSC, confirmed that children with ASD and their siblings process faces differently—using different areas of the brain—than typically developing children.[6]

Genetics are also known to be involved—ASD is heritable and siblings of children with ASD are ten times more likely to develop the disorder.[5] Hundreds of copy number variations—the most significant of which occur at chromosomes 16p11.2, 15q11.2-13.1, 17q12, and 7q11.23—have been identified in children with ASD, but these genetic alterations account for only a fraction of cases.[7] Variations in copy number increase with age, putting fathers of advanced age more at risk of having a child with ASD.[8] A number of *de novo* mutations with strong association for ASD—most notably in genes *SCN2A*, *KATNAL2* and *CHD8*—have also been identified,[9] and more studies using whole-genome sequencing in children with ASD and their siblings are under way to identify additional clinically relevant mutations. Babies born extremely preterm or at a very low weight are also at increased risk of ASD,[10] as are those who were exposed to infection prenatally, suggesting an immune component.

Despite some parents' beliefs that childhood vaccines, including the measles-mumps-rubella vaccine, increase risk for ASD—a concern fueled by social media—no such link has been established in the scientific literature.[11] Failing to vaccinate a child puts him or her at greater risk of infection and increases the likelihood that diseases once under control could make a comeback.

Clinical psychologist Dr. Laura Carpenter specializes in the diagnosis of ASD.

Screening

Early diagnosis and intervention can make dramatic differences in outcomes in children with ASD.[12] However, outcomes are best when appropriate therapies begin early, ideally by 18 months of age or even earlier.[5] Although physicians should remain vigilant for early signs of autism, relying solely on clinical impressions of behavior gleaned during a brief visit will lead to missed cases of ASD.[13] Physicians should be responsive to parents' concerns, realizing that they have seen a far larger sample of their child's behavior and are more likely to notice the subtle, early signs of autism. These include problems with "joint attention" (i.e., a shared focus with another person on an object or another person expressed through a point or gaze), a lack of "pretend play" (i.e., the use of one object or toy to represent another), and a failure to respond when the child's name is called. The delay in developing social skills that is one of the central characteristics of ASD is not typical of most neurodevelopmental disorders, and so parental concerns about social skills should prompt a referral to a developmental pediatrician for an autism assessment.

To help ensure that all children with ASD benefit from early intervention, the 2007 AAP policy statement recommends that all children be screened for ASD at 18 and 24 months using an appropriate screening tool, such as the Modified Checklist for Autism in Toddlers (available at https://www.m-chat.org).

According to **Laura A. Carpenter, Ph.D.**, a clinical psychologist at MUSC Children's Hospital who specializes in the diagnosis of ASD, "The nice thing about this screening instrument is that it is completely free for pediatricians. Parents just complete it in the waiting room, and then the pediatrician reviews it. In all but 10% of cases, it either gives you a screen positive or negative right away." The test will miss some children with milder symptoms of ASD, such as those formerly classified as having Asperger's syndrome. The second screen at 24 months is important because some children with ASD experience regression of their social and communication skills in the first year or two of life and could be missed with a single screen. Although applied behavioral analysis (ABA), the gold standard for early intervention, can be administered to children who are diagnosed at an older age, outcomes will likely not be as good because the opportunity to intervene during critical developmental years has been missed. (Read more about ABA therapy in Part II of this series, which will appear in the Summer 2015 issue of *Progressnotes*.)

Establishing a Definitive Diagnosis of ASD

A child who screens positive for ASD should be referred to a developmental pediatrician for a full assessment and a definitive diagnosis. If a child is thought to have ASD, he or she is typically assessed using the Autism Diagnostic Observation Schedule, Second Edition, which involves the child being asked to engage in a number of tasks involving social interaction between the child and the examiner. The examiner observes and categorizes the child's behavior, and those categories are used to establish quantitative scores that can determine whether the child has ASD and, if so, identify his or her particular strengths and weaknesses. Interventions can then be tailored to target areas of deficit.

Assembling the Multidisciplinary Care Team

It is the pediatrician's responsibility to coordinate the multidisciplinary consultations and services a child with ASD requires. Any child with a speech delay should be referred to an audiologist to rule out hearing loss as a cause for communication and social skill delays.[5] Genetic screening can be useful in identifying chromosomes known to be associated with ASD.[5] If the child is experiencing seizures, as approximately 20% to 25% of children with ASD do, a neurophysiological assessment is recommended.[5] The child should be assessed for common comorbid medical conditions, such as gastrointestinal issues (particularly constipation and gastroesophageal reflux disorder) and sleep disorders, as well as common comorbid psychiatric conditions (see "Common Comorbid Psychiatric Disorders"). Properly diagnosing and treating these comorbid disorders improves the child's receptivity to therapeutic interventions.

Many parents with autistic children turn to complementary/alternative therapies, and the pediatrician should ascertain which ones they are using to ensure that there are no contraindications with prescribed medications. There is no evidence base to support the benefits of these therapies in children with ASD, and some have been proven or suggested not to work, including intravenous infusion of secretin,[14] oral vitamin B6 and magnesium supplementation,[15] a

casein-free diet,[16] administration of oral human immunoglobulin,[17] and omega 3 fatty acid supplementation.[18] In a few cases, such as heavy metal chelation therapy,[19] complementary/alternative therapies can be dangerous.

Common Comorbid Psychiatric Disorders

In a 2008 study of 112 ten- to fourteen-year-old children from a population-derived cohort of patients with ASD, 70% had at least one comorbid disorder and 41% had at least two.[20] Social anxiety disorder (29.2%), attention-deficit/hyperactivity disorder (ADHD) (28.2%), and oppositional defiant disorder (28.1%) were the most commonly observed.[20] The odds of having a second psychiatric disorder were increased in those with epilepsy. A 2011 review by the Interactive Autism Network of a national online registry of more than 4,000 children with ASD for parent-reported comorbid psychiatric disorders revealed that 26.9% had one comorbid diagnosis, 14% had two, and 6.3% had three.[21]

Faced with managing a complex disorder such as ASD, physicians can miss comorbid psychiatric conditions by blaming psychiatric symptoms on the disorder itself—a phenomenon known as *diagnostic overshadowing*. Accurately diagnosing comorbid psychiatric conditions is essential, because effective medications are available to treat them, whereas there is currently no effective pharmacological treatment for the core symptoms of ASD. It should be noted, however, that some medications (i.e., stimulants) used to treat children with ADHD may not be as effective in children who also have ASD.

Additional Resources on Diagnosing ASD

The AAP offers a number of good resources for ASD, including a publication called "Understanding Autism Spectrum Disorders" and a 2007 resource toolkit "Caring for Children with Autism Spectrum Disorders: A Resource Toolkit for Clinicians." An innovative web-based tool—the ASD Video Glossary—is available at firstsigns.org to help parents and professionals recognize early red flags and diagnostic features of ASD.

Part II of this article will appear in the summer issue and will focus on management, including early interventions, techniques for addressing disruptive behavior, and resources for helping teens transition to adult care.

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Coming Full Circle

Mother returns to the fragile world of the NICU

BY DAWN BRAZELL

PHOTOGRAPHY BY SARAH PACK

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One number will always stand out for Charlotte Edwards.

It is 110.

That's the number of steps based on her stride that it takes her to get from the elevator door on the eighth floor of MUSC Children's Hospital to the double doors of the neonatal intensive care unit (NICU). She knows because that is where her son, Legaré, was taken after an emergency cesarean section.

Born extremely preterm at only 25 weeks, Legaré weighed only 1 pound, 11 ounces. He had a 1 in 5 chance of surviving.

That was a number Edwards tried to ignore. Instead she focused on the number of steps it would take to get to the world of the NICU, where she and her husband would be living off and on for almost four months.

"The NICU is pretty much its own little world. It is such a rollercoaster ride. You really don't know what you're in for until you're in the NICU. There are all the beeps and buzzes and highs and lows."

The lows included being called in twice in the middle of the night along with a minister for support because Legaré wasn't doing well. He was not expected to make it.

Edwards would end up living in the surreal world of the NICU for almost four months, steeling herself as she came down the hallway each day for the news she'd receive. One day he would be thriving. The next, close to dying.

"I really had a crash course in nursing for the next 118 days. He received such excellent care and compassion from all of the nurses. It really inspired me to want to go to nursing school. I truly believe my son wouldn't be alive today if it wasn't for the staff. He got sick a lot and they were able to watch his vitals and catch his sickness very quickly."

A former real estate agent, Edwards discovered she had a gift for offering peer support to other families. Nurses noticed her gift and encouraged her to follow her calling to become a nurse.

"I've come full circle," she said in a recent interview as she tended one of two twin girls. She's back on the eighth floor of MUSC Children's Hospital as a nurse now, helping other parents in their journeys. Edwards' son is an active second grader who plays soccer, and she's grateful they have made it this far.

Every year, about 450,000 babies are born too soon in the U.S. Even if a woman does everything "right" during her pregnancy, it can happen. Most women never see it coming. Edwards certainly didn't.

"As a child, I always thought when you grow up it would be easy to have a baby. Until something happens to you, you don't realize how many things can go wrong. Having a baby is a miracle in itself. There is a human being growing inside of you, but you can have a lot of complications."

She found that out on a cool, clear day with bright blue skies on February 17, 2007. Edwards had just entered her third trimester of

A memento of Legaré's growth during his almost four-month stay at MUSC Children's Hospital's NICU.

pregnancy and was celebrating a growth spurt that merited getting some new maternity clothing. She then went to dinner with her family but began experiencing stomach pains. Going to St. Francis Hospital to get it checked out, doctors found her son's heart rate was dropping. Edwards' vitals were unstable.

The next thing she knew she was having an emergency C-section. She later found out that she had severe HELLP syndrome, a life-threatening obstetric complication involving a condition thought to be a variant of pre-eclampsia. ('HELLP' stands for the three major elements of the syndrome: H—hemoloysis, EL—elevated liver enzymes and LP—low platelet count.)

"Two days later on my 30th birthday I remember waking up and not knowing what had happened. I just remember bleeding out in the OR. They were trying to let me see the baby before they transported him to MUSC because they weren't sure if he was going to make it or if I was going to make it. That was my last memory until a couple of days later. We're both pretty lucky."

Edwards was on a ventilator for several days while her son was fighting for his life. Her husband, Adam, was going back and forth between hospitals. When she was able, Edwards was at her son's side.

"I remember thinking he just had to grow, that he was just really tiny and had to be in this incubator. I didn't grasp just how sick he was and all the things that can go wrong. His life was very fragile at that point. It's a delicate balance realizing that and trying to remain positive and hopeful."

Legaré had pneumonia twice, several different blood infections, urinary tract infections, and respiratory issues. Getting him off the ventilator was important. Friends reassured her, telling her not to worry, but Edwards knew what hung in the balance.

She treasured his good days—days when she could do kangaroo care, which meant she got skin-to-skin with Legaré just to cuddle with him. It's a therapeutic practice with wonderful healing benefits for these babies, one she now as a nurse encourages her patient families to do. 'Kangarooing' gave her moments when she could just let the hospital monitors fade away and indulge in feeling like a mom.

"It raises awareness that the NICU just isn't a place to grow. These are sick babies. All of their organs are immature and a lot can happen in the NICU. We had a couple of good weeks and, when

everything looked great, I would kangaroo. Then he got pneumonia and he had IVs coming out of his head, his arms—all over the place. You can tell people it's going to be a rollercoaster ride, but you have no idea what that means until you're on it yourself. You just jump on and hold on. It's a complicated and long road to recovery."

It's a journey that doesn't end at discharge, either.

Legaré faced multiple appointments with health professionals, including occupational and physical therapists and a nutritionist to help him, especially since he was diagnosed as failing to thrive. Edwards sweated over trying to get her 6-month old son to eat a meager 3 ounces—just 100 ccs.

"I can remember at night trying to feed him and crying because I knew if I couldn't get him to eat we'd be going back to the hospital to get a feeding tube. Every week someone would be coming in to do some type of therapy. It was like a revolving door. It was a whirlwind of doctors' visits for the first year of his life."

While other parents were celebrating other types of milestones, Edwards was celebrating that her son at 9 months wouldn't have to get a feeding tube. He would have to have antibody infusions, though, to help fight infections to which he was more susceptible. The first several years were difficult seeing if he was going to have delays and if he was going to get a lot of infections.

After Legaré turned 18 months old, Edwards started a parent partner program to offer bedside support for NICU families and to help them navigate what can be a complicated medical labyrinth.

"You can feel very isolated. I just felt parents needed to meet other parents in the same situation. I started coming back and giving bedside support and just offering resources to them."

That outreach confirmed her calling to go to nursing school and she joined MUSC Health a year and a half ago. She's also on one of the design teams planning the new $350 million Children's Hospital and Women's Pavilion slated to open in 2019. The teams all have a doctor, nurse, and parent representative on them. (Click here to read more about the new hospital.) Edwards said she's been pleasantly surprised that the parent input is weighed so heavily.

"I think it's wonderful that the new hospital will be based on family-centered care. When your baby is in there, it's still your baby even though you don't feel you have the right to change a diaper or take a temperature. Sometimes you feel you have to ask permission to be part of their care. It's important for the parents to feel like they are part of the care team and to develop the skills they need for when they take their babies home."

Though nurses already practice family-centered care, the new hospital will allow more privacy and space for families to be with their babies. The design will facilitate practicing family-integrated care, a cause dear to her heart.

Charlotte Edwards and Legaré today. Legaré is now an active second grader who plays soccer.

"We're good at promoting for parents to be patient advocates. We want them to be the voice of their baby. I think that's something we do very well in the NICU. We encourage families to ask questions. They are at the bedside every day. Staff can come and go, but they are the ones who know their baby."

Edwards exudes a sense of calm in the NICU. Obviously, nursing suits her.

"I like being a part of the nursing staff and really enjoy the interactions with the family members. It helps that I can relate to their stories. For example, a mom crying because she has to leave her baby, or when there is a setback regarding their baby's health. The nursing staff really takes pride in the care we give."

Edwards recently spoke to physicians at grand rounds to tell them her story and remind them of the human element that drives all of their work. She shared with them just how long that walk down the eighth floor hallway was for her. And when she finds herself rushing down the eighth floor hallway going task to task, she slows herself down.

"I remind myself that for the people I am walking next to—this could also be the longest hallway of their life."

Interview

MUSC Children's Hospital Welcomes Pediatric Neuroscience Specialists

Dr. Thomas Koch (left) and Dr. Ramin Eskandari (right).

In the summer of 2014, two new specialists in pediatric neuroscience arrived at MUSC Children's Hospital. **Thomas K. Koch, M.D.** was appointed to the position of Division Chief for Pediatric Neurology. Previously, he was Division Chief of Pediatric Neurology at Oregon Health and Science University for 16 years. He has also held clinical faculty positions at the University of California, San Francisco and the University of Maryland in Baltimore. **Ramin Eskandari, M.D., MS**, was recruited to be the hospital's pediatric neurosurgeon following his Stanford University fellowship.

PN: What are the pediatric neurological needs in South Carolina?

RE: From a neurosurgery standpoint, hydrocephalus management is the most common need. There is a lot of low or no prenatal care in South Carolina. Babies are born early, have hemorrhages, infections, and undiagnosed anomalies. I'm managing those patients in a different way, using new endoscopic techniques to treat hydrocephalus.

Brain tumors are number two and we're building that program with pediatric oncology. The third highest need is trauma. I'd argue that pediatric head trauma (from concussions or abuse) and spine trauma are underdiagnosed and the ramifications of not catching them early are underappreciated.

TK: In terms of nonsurgical neurological disorders in children, one of the leading diagnoses nationally is primary headache disorder. This is a spectrum, with migraine as the major component. It accounts for missed days of school, parents missing work, and frequent doctor's office and emergency room visits. Another major area of need is epilepsy. The number of children with new-onset

seizures needing a neurological evaluation exceeds the supply of pediatric neurologists nationally. Many of these children have complex needs, and addressing all of them is crucial for the delivery of comprehensive care. Other major areas of need are cerebral palsy and movement disorders, such as tics and Tourette Syndrome.

PN: Dr. Koch, can you give us a sense of your plans for building the division?

TK: I would like to establish within the division areas of specific strength to serve as regional and national referral centers. An academic medical center needs to serve as a health, healing, and discovery resource for the community, including the medical community. My first order of business is to expand our already comprehensive epilepsy program with the recruitment of additional pediatric epileptologists and the expansion of pediatric neurosurgery.

PN: What are your research interests?

TK: My primary area of interest is headache disorders. I was involved in a study at Oregon Health and Science University looking at the Emergency Department (ED) management of severe headache in children. Some of the preliminary work has already been published. I have discussed this work with our pediatric ED staff here and we are looking into re-evaluating our approach and trying to adopt a standardized protocol.

RE: When I came here I was lucky to have a start-up lab funded, which I'm outfitting, in the Darby Children's Research Institute, and the basis for my lab research is neonatal hydrocephalus. I've been doing that for 12 years and have had some small grants from research institutions. We are looking at the brain and its damage from hydrocephalus. The goal is to predict the point of irreversible damage. At the moment there are few evidence-based and clinical guidelines to guide surgeons as to when to treat pediatric patients with hydrocephalus. In my view, a lot of the deficits that we incur by delaying treatment or not recognizing the failure of treatment occur because we don't know what the damage is and when it happens. My other research is in epilepsy. I'm working with a postdoctoral investigator who has a fellowship to look at the mapping of epilepsy in pediatric patients. We are using a math model to be able to predict seizures.

I'm also working with a Ph.D. scientist in the Department of Neuroscience to examine malignant brain tumors in children. We're working on a tissue bank so we have our own tissue to do our research. The goal is to find new targets for therapeutics for malignant brain tumors.

PN: What is it about MUSC Health that attracted you?

TK: MUSC Health's philosophy to imagine what is possible and to grow and deliver exceptional health care is very exciting. The commitment to build a new Children's Hospital and Women's Pavilion underscores that commitment. It makes a clear statement that health care for children and their families is a priority.

RE: The thing that grabbed my attention was the need for pediatric neurosurgery. I felt that I could come here and help many people. But on top of that I felt I would have the support to grow as a surgeon. It appealed to me that there would be a new head of pediatric neurology. As soon as I got here, I began interacting with clinical faculty and neonatology and meeting with intensive care unit physicians and anesthesiologists—it's all been very collegial and supportive.

TK: Pediatric neuroscience is a major area for an expansion that will enable us to address the health needs of the children of this state and region. I am very happy to have left the Northwest and to now be a part of MUSC Children's Hospital.

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