

## Treating Hypotonia

Many patients with low muscle tone go undiagnosed and untreated for months or years, leaving parents feeling lost in a system with no real answers.

In 8th grade, Meredith Zanelotti came down with a bad case of the flu, so bad that she had trouble walking in her Ellicott, Md., home. Her flu passed but from then on her parents noticed that she experienced severe pain in her legs after each soccer practice. Interestingly, the pain subsided after Meredith downed her usual post-practice snacks and Gatorade. Her Highland, Md., pediatrician, **Mel Stern**, puzzled by the strange symptoms and their response to the snacks, suspected they had genetic rather than skeletal origins. Indeed, at Johns Hopkins tests revealed that Meredith had Carnitine Palmitoyltransferase (CPT) II Deficiency, an extremely rare genetic disorder characterized by recurring episodes of muscle-fiber breakdown, which explained the girl's lower limb pain. Pediatrician/geneticist **Ronald Cohn**, an expert on hypotonia, quickly figured it out.

"Dr. Cohn was an angel who fell out of the sky," says Meredith's mother, Gail Zanelotti. "When I told him food seemed to make her muscle pain go away, he put two and two together."

Cohn explains that for CPT II Deficiency patients like Meredith, multiple triggers – from exercise to a virus – can set off the painful breakdown of muscle tissue. Loading up on carbohydrates has the effect of normalizing muscle metabolism and suppressing any muscle aches. But too often, Cohn says, such symptoms can mask as orthopedic or rheumatologic conditions, delaying diagnosis and treatment. He adds that community pediatricians are generally good at detecting signs of hypotonia and appropriately referring patients to pediatric neurologists or developmental pediatricians (see story page 6). But there is no one place where these patients can receive a comprehensive workup with an eye on both physical and genetic causes in diagnosing patients, which explains why Cohn led the development of the Johns Hopkins Hypotonia Center, the only such center in the world.

"Through my residency and clinical experience," Cohn says, "I realized a whole lot of patients out there have low muscle tone and not necessarily a skeletal-muscle disorder."

In fact, hypotonia is associated with over 600 known genetic conditions, and potentially many more yet unnamed conditions. Center staff like genetic counselor **Emily Lisi**,



**Outgoing teen Meredith Zanelotti has been able to remain active through management of her low muscle tone and underlying genetic disorder at the Johns Hopkins Hypotonia Center.**

Cohn explains, have the ability to look beneath the surface of hypotonia and identify these often more serious underlying conditions, which otherwise go undetected and untreated with dire results. CPT II Deficiency, for example, can lead to life-threatening kidney failure, though many people with the disorder are completely unaware of its existence until they undergo genetic testing. Similarly, genetic testing of hypotonia patients has led to the identification of chromosomal abnormalities like Williams Syndrome and related structural problems in the brain, heart and kidney, among other organs. Such clinical information, Lisi notes, is also helpful for parents who are thinking about having more children.

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**George Dover, M.D.**  
 Director,  
 Johns Hopkins  
 Children's Center  
 Given Professor of  
 Pediatrics

## Healthy Resolutions

**W**ith New Year's comes resolutions, and our friends at the American Academy of Pediatrics have come up with some healthy ones for our patients. They range from "I will brush my teeth twice a day, and wash my hands after going to the bathroom and before eating" for preschoolers to "I will eat at least one fruit and one vegetable every day" for 13-year-olds and up (see <http://www.aap.org/advocacy/releases/jankidstips.cfm>). Indeed, so much about good pediatric medicine is encouraging prevention and wellness—but even more is about continuing to study and understand childhood diseases and develop new and more effective ways to detect and treat them. And that, we know, works best through a collaborative practice of pediatric medicine with you the community pediatrician.

So, on our end this new year, we resolve to continue to partner with you and with your patients and their families. As this first issue of *Pediatrician* in 2009 illustrates, we'll continue to explore new ways to detect and treat rare genetic disorders and their symptoms, as well as more common conditions like food allergy. Our patients are greatly challenged by complex chronic conditions like cystic fibrosis, and we'll carry on our research efforts with groups like the Cystic Fibrosis Foundation to prolong survival and improve the quality of life for those patients. We'll share with you what experts around the country tell us at our Grand Rounds about understanding diseases like sickle cell, but we'll also continue to look to your insights in managing both common and complex disorders. So, please do share your experiences with us this year via e-mail to our editor Gary Logan at [glogan@jhmi.edu](mailto:glogan@jhmi.edu), to help us provide an even higher level of care for all of our patients.

Thank you, enjoy this issue and have a Happy and Healthy New Year!



**Christoph Lehmann, M.D.**

## Neonatal Online

**L**ooking for the latest on ECMO in neonates? Intravenous Ibuprofen? Oxygenating neonates? Sure, there're lots of neonatology journal articles out there on such topics but not so much that actually organizes, condenses and translates such critically important subjects into daily patient care.

"It's hard to aggregate all the information that's being published in a way that makes sense at the bedside," says neonatologist **Christoph Lehmann**. "Our online newsletter provides something that is really applicable. At the end of an article, hopefully you've learned something that changes the way you practice medicine."

That was the aim, Lehmann explains, in launching *eNeonatal Review* in 2003 to some 1,200 subscribers, mainly neonatologists, respiratory therapists and NICU nurses. Each monthly e-letter includes summaries of half a dozen neonatal topics and commentary by Hopkins Children's neonatologists

Lehmann, **Edward Lawson** and **Lawrence Noguee**. The articles, which are supplemented by podcasts, are fully accredited and provide CME credits online.

"This is not the esoteric stuff," says Lehmann. "Occasionally we'll throw something in that's more theory but mostly we're practicality oriented."

Apparently the formula is working as *eNeonatal Review's* online list has grown to over 10,000 subscribers, including an increasing number of community- and hospital-based pediatricians. Breastfeeding of pre-terms, CPAP in the delivery room, among other topics, are of interest to general pediatricians, says Lehmann.

"Most of these topics are everyday clinical issues," says Lehmann, "and oriented for those who want to know the latest evidence, the latest approaches, and what has been proven to work." ■

For more information, visit <http://www.hopkinscme.edu/ofp/eNeonatalReview/>

### At CME

## Continuing Education Schedule 2009

**March 30-April 1 The Spectrum of Developmental Disabilities: A Pragmatic View of the Social Brain** Topics include gene-environment effects on social development, development of peer relations, and Asperger Syndrome diagnosis.

**April 20-24 37th Annual Pediatric Trends** Topics include ambiguous genitalia, anxiety disorders, childhood obesity, and pediatric stem cell transplant.

**September 24-25 24th Annual Pediatrics for the Practitioner: Update 2009**

Unless otherwise noted, all courses are at Johns Hopkins University School of Medicine, Turner Bldg. For more information, call 410-502-9634 or email [cmenet@jhmi.edu](mailto:cmenet@jhmi.edu).

## From the **Bedside to the Bench** and Back

In the traditional evidence-based approach of academic medicine research, investigators begin with a basic science observation and end, hopefully, with a clinical treatment. Countless times and over many years this bread-and-butter method has moved scientific discoveries into meaningful clinical outcomes. But hematologist **Michael DeBaun** of Washington University School of Medicine revealed at a recent Grand Rounds at Hopkins Children's that a reverse translational research model – in which investigators first make a patient observation, conduct retrospective and prospective cohort studies, study the disease mechanism and then pursue a targeted intervention trial – may also serve patients well.

“This is just the reverse,” says DeBaun. “We go from an observation at the bedside to working with our colleagues in basic science, a bedside-to-bench approach. Hopefully, we come back to the patient with a target therapy.”

To make the case, DeBaun began Grand Rounds with his observation of an 11-year-old child with sickle cell disease with diffuse pain for three weeks, despite a prescription for pain medicine. There was no wheezing on examination, but after conducting pulmonary function tests, DeBaun and his colleagues noted that the patient had significant airway obstruction

—asthma. That, and a series of clinical observations, prompted DeBaun and his team to conduct a retrospective cohort study that found asthma increases the risk of acute chest syndrome and the rate of painful crises in sickle cell children (*Pediatric Pulmonology* 2004; 38(3):229-232). Then, in his two prospective cohort studies, he found that asthma is an independent risk factor for pain and acute chest syndrome (*Blood* 2006; 108(9):2923-7), and for premature death (*Haematologica* 2007) in sickle cell patients.

“Sickle cell children with asthma had a two-times greater risk of being hospitalized for pain than sickle cell patients without asthma,” DeBaun reported. “And the children who were admitted to the hospital with pain and asthma had a four times greater risk of developing acute chest syndrome.”

The take-home message, he said, is that given the high rate of asthma among children with sickle cell disease – about 20 percent – coupled with the increased rate of pain associated with asthma, every child with sickle cell disease should be evaluated for asthma and, if diagnosed, appropriately treated. Often times the respiratory symptoms can be a complication of sickle cell disease, such as acute chest syndrome. “But,” DeBaun added, “in our experience the respiratory complications are most



“The patient’s symptoms and complications go beyond any one discipline.” —MICHAEL DEBAUN, M.D.

often related to asthma and should be treated as asthma.”

DeBaun added, however, that while studies have shown that steroids, a cornerstone of asthma exacerbation treatment, reduce the painful episodes in sickle cell patients, they also tend to hasten those patients’ recovery to baseline. The result has been a 25 percent increase in hospital re-admissions for those patients.

“The care of the child with sickle cell should be multidisciplinary and include hematologists, neurologists, cardiologists and pulmonologists,” DeBaun concluded. “The patient’s symptoms and complications go beyond any one discipline.” ■

## Preventing Pediatric Injuries: What Works?

“If a disease were killing our children in the proportions that injuries are, there would be a huge public outcry and we would be told to spare no expense to find the cure.”

Citing the above quote from former Surgeon General C. Everett Koop, **Andrea Gielen**, director of the Johns Hopkins Center for Injury Research and Policy in the Bloomberg School of Public Health, provided a recent Grand Rounds overview on the latest in pediatric injuries. The bad news? In 2000, according to the Centers for

Disease Control and Prevention, the incidence for injuries among children 0-14 years old was 3.4 million, of which 7,273 were fatal and 135,635 were hospitalized injuries. Total lifetime costs? \$50.5 billion, including \$11.9 billion for medical costs alone. The good news? The number of unintentional injury deaths for leading causes among children under 14 years of age has declined from 1987 to 2004. Motor vehicle fatalities decreased from 3,587 to 2,431, bicycle injury fatalities from 389 to 132, and burn fatalities

from 1,233 to 512. Much of the credit goes to interventions like bicycle helmets, car seat laws, and smoke alarms, but also to an epidemiologic approach to studying injury, the development of evidence-based interventions, and to increasing collaborations between public health professionals and pediatricians. Citing Hopkins’ experience, Gielen noted that increasing and improving physician counseling, disseminating safety products at reduced cost, and training students and professionals in injury control has

resulted in greater engagement with parents and improved safety behaviors among families. Two Hopkins Children’s safety centers, Gielen added, are models for how partnerships between public health and pediatrics can reduce injury risk. “Despite great progress,” she concluded, “injury remains the number one health threat to children. Effective interventions exist but challenges remain, especially for low income families.” For more information, visit <http://www.jhsph.edu/injurycenter/index.html> ■

# Targeting CFTR

**A**t the annual North American Cystic Fibrosis Conference in Orlando, Fla., last October, **Preston Campbell**, the CF Foundation's vice president for medical affairs, reported on a diverse pack of new and ongoing therapies designed to improve quality of life, extend survival and find a cure for CF patients. Leading the charge, he noted, are drugs targeting the defective CF protein itself, Cystic Fibrosis Transmembrane Regulator, or CFTR.

"Our hope is that through these new therapies and improved care CF patients will live with the disease and die from other causes," he said, noting that CF patients' survival is now in the 37-year plus range and going up each year.

Regarding the CFTR focus, Campbell explains that while proteins produced from normal cells create channels in their membranes that, like gates, enable ions to come and go, the gate in the defective CF protein is either missing or impaired, preventing chloride from moving out. The result is the characteristic thick mucus produced in CF patients' lungs. Restoring the CF protein function, Campbell notes, may produce benefits ranging from improved airway clearance to reduced infections in the lungs.

Among the therapies targeting CFTR is VX-770, developed by Vertex Pharmaceuticals, which has been shown to open up chlo-

ride channels and lower sweat chloride values, a diagnostic measure of CF. The results from a Phase I trial of 16 patients over two weeks in March 2008, Campbell explains, show for the first time that a drug could actually fix the biochemical flaw in some CF patients.

"There was a significant reduction in the concentration of salt in the sweat, reflecting restoration of CF protein function," says Campbell. "Lung function went up 10 percent, too," he

**"We have so many programs in the pipeline because they increase our success by increasing our shots on goal."**

— PRESTON CAMPBELL, M.D.

adds, noting that results of a Phase II dosing trial of the drug will be coming soon.

While VX-770 appears to be safe, Campbell says, it benefited only a small number of CF patients because the majority of patients have a mutation that prevents CFTR from getting to the membrane where it's supposed to operate. These patients are predicted to benefit from another compound in the pipeline, a corrector known as VX-809. Campbell sees promise in combining the use of both Vertex therapies.



**Preston Campbell, M.D.**

"You get the protein to the working part of the CF cell with 809 and then boost the effect with 770," says Campbell.

Another "very promising" CFTR-targeted therapy, says Campbell, is PTC-124, a compound that also allows the protein to be made. This will help patients with premature stop mutations, which result in only part of the protein being made. A small trial of the drug in Israel and Europe has shown through nasal potential difference tests an increase in transport of chloride across cell membranes, as well as some improvement in lung function. A larger international trial is being organized.

Other therapies in the pipeline, Campbell noted, are designed to hydrate thick CF mucus in the lungs, fight infections and the inflammatory

response of CF, and supplement patients' nutritional needs. A diversity of therapeutic approaches is key, he explains, because failure is expected in any drug discovery program. Only 20 percent of Phase I clinical trials are successful, 50 percent of Phase II, and 80 percent of Phase III trials.

"We have so many programs in the pipeline," says Campbell, "because they increase our success by increasing our shots on goal." ■

For more on the CF therapeutic pipeline, visit <http://www.cff.org/research/DrugDevelopment/Pipeline/>

For information about trials at the Johns Hopkins CF Center, visit <http://www.hopkinscf.org/>

## Research Briefs

### CF and Vitamin D

**Existing recommendations** for treating vitamin D deficiency in children with cystic fibrosis are too low to cover the need, leaving most at high risk for bone loss and rickets, according to Hopkins Children's researchers. In their study in the October 2008 issue of *The Journal of Pediatrics*, they found nearly half of the 262 children with

CF in the study were vitamin D deficient, and the majority of these remained persistently so, despite restorative doses equal to or higher than the recommendations set by the Cystic Fibrosis Foundation. "Clearly we haven't established an optimal dose for treating vitamin D deficiency and more research is needed to do so," says pulmonologist

**Peter Mogayzel**, director of Hopkins CF Center. "But what we do know for sure is that the current recommendations are too low, and doctors should treat their patients with vitamin D deficiencies more aggressively." For more information, go to [www.hopkinschildrens.org](http://www.hopkinschildrens.org) and click "Newsroom/News Releases." ■

# Drinking Milk Decreases Milk Allergy Reactions

**B**y the time her daughter Reagan was a few months old, Lissa Roberts suspected the extreme eczema she was experiencing had something to do with foods. Indeed, a RAST (radioallergosorbent) test ordered by Reagan's pediatrician identified allergies to eggs, milk and peanuts. And, like most parents of children with food allergies, Roberts was told to avoid the culprits – especially milk – treat reactions when they occur, and wait for the child to outgrow the allergy. That scenario seemed extremely stressful, considering that Reagan's reactions could be severe and even life-threatening. Also, avoidance would be no easy chore given the prevalence of milk products in everything from crackers to spaghetti sauce.

"From then on we moved forward very cautiously," Roberts says. "No pizza, no ice cream socials, and we took our own food and hand wipes to every birthday party."

The Roberts' experience is one that Hopkins Children's immunologist **Robert Wood** has seen countless times. Noting that "the quality of life of a child with food allergy is comparable to the quality of life of a child with diabetes," he has been determined to develop therapies that go beyond strict food avoidance or waiting for the child to outgrow the allergy. And he took a significant step in that direction in a recent study that showed giving children with milk allergies increasingly higher doses of milk over time may ease



**Immunotherapy, notes immunologist Robert Wood, with a young milk-allergy patient and immunology fellow Pamela Guerrerio, is designed for patients who will likely not outgrow their food allergy.**

and even help them completely overcome their allergic reactions (*Journal of Allergy & Clinical Immunology*, Oct. 28, 2008).

"Our findings suggest that oral immunotherapy gradually retrains the immune system to completely disregard or to better tolerate the allergens in milk that previously causes allergic reactions," says Wood.

In the study, Wood explains, he and fellow researchers followed over four months allergic reactions among 19 children – ages 6 to 17 – with severe and persistent milk allergy. Of the 19 patients, 12 received progressively higher doses of milk protein, and seven received placebo. At the onset of the study, the children were able to tolerate on average only 40 mg, or about a quarter of a teaspoon, of milk. But at the study's end, the children who had been receiving increasingly higher doses of milk protein were able to tolerate a median dose of over 5 ounces of milk, without any allergic reaction or with mild symptoms like mouth itching or minor abdominal discomfort. Those who had been getting the placebo were unable to tolerate

doses higher than 40 mg without having an allergic reaction.

"Albeit preliminary and requiring further study," Wood says, "these results suggest that oral immunotherapy may be the closest thing yet to a true treatment for food allergy."

Wood notes that the tolerance in children treated with milk continued to build over time, and recommends that these children, with close monitoring by their parents and doctors, continue to consume milk daily to maintain their tolerance. He adds that future studies, like this one, must be pursued with extreme caution as patients are at risk of serious reactions. Immunotherapy is designed for patients who, based on family history and testing, will likely not outgrow their food allergies – about 20 percent of all kids with milk allergy, including Reagan Roberts, who participated in the study.

"It was stressful, but looking back it was well worth it," says Lissa Roberts. "We're not scared of milk anymore." ■

For more information, call 410-955-5883.

## Hypotonia

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"In addition to providing recurrence risk information, diagnosing the underlying genetic condition is important for giving parents a clearer picture of what may be in store for them in the future," says Lisi.

Drawing more patients through the Center has also allowed Cohn and Lisi to classify patients, improving diagnostic and therapeutic options. Some patients, like 4-year-old Laneah Whiddon of Bowie, Md., suffer severe hypotonia with breathing and swallowing problems, and with no clear underlying dis-

order or cause of the hypotonia. The Center's approach, Cohn says, is to empathize with parents and take the burden of diagnosis off their shoulders.

"I tell parents that while I continue to chase the diagnosis, at the same time we'll continue to focus on the management of the child," Cohn says. "The majority of parents appreciate not having to worry too much about what it is. Whether or not you have a diagnosis, together we will manage the child the best we can."

His patients' parents agree. "He's been

there to guide me on what to do and what not to do," says Laneah's mother, Dana Whiddon. "Without him, I'd feel pretty lost."

"He's been our go-to guy," says Gail Zanelotti. "He's allowed us to see the whole picture." ■

For more information, call 410-955-3071 or visit the Johns Hopkins Hypotonia Center Web site at [http://www.hopkinsmedicine.org/geneticmedicine/Clinical\\_Resources/Hypotonia/](http://www.hopkinsmedicine.org/geneticmedicine/Clinical_Resources/Hypotonia/)

# Managing a Complex Muscle Disorder

**L**utherville, Md., pediatrician **Jason Goldstein** says he instantly thinks “genetics consult” when he sees a child with signs of hypotonia, or low muscle tone. But that hasn’t always been the case in his clinical experience, he adds, because genetic services with a focus on hypotonia are “really rare, a very specialized niche.”

“If you’re not at a center that has a geneticist, and not every center has one, you’re talking about a big commitment of time and travel to get your patient to the right person,” says Goldstein. “Here, you have all that you need at your fingertips.”

Goldstein was referring to the Johns Hopkins Hypotonia Center (see page 1). General pediatricians can identify low muscle tone in tracking their patients’ milestones, Goldstein says, but making a diagnosis is a whole other matter. Because hypotonia, a symptom and not a condition, is associated with some 600 genetic disorders, having a combined genetics-hypotonia service nearby is a rare opportunity.

But that, he stresses, doesn’t mean community docs simply

drop off and drive off. Coordination of care with the geneticist, as well as subspecialists like neurologists and pulmonologists, is crucial. The hypotonia center will likely direct care but the primary care will continue through the community pediatrician’s office.

“You try to stay current on the disease and on top of the management,” says Goldstein. “I always talk to the subspecialists to make sure we’re on the same page and that I understand the plan.”

Hypotonia may be caused by trauma, genetic, muscle, or developmental disorders, such as

**“There are few things in life more difficult than having a seriously sick child, especially when you’re a first-time parent of a critically ill newborn.”**

— JASON GOLDSTEIN, M.D.

Down syndrome and muscular dystrophy. Infants with hypotonia tend to have a floppy “rag doll” appearance with arms and



Jason Goldstein, M.D.

legs hanging by their sides and little or no head control. Patients may also have problems with mobility and posture, breathing and speech. Hypotonia does not affect intellect, though an underlying condition may result in delays in social, speech and reasoning skills.

Treatment begins with a thorough diagnostic evaluation, including an assessment of motor and sensory skills, balance and coordination, mental status, reflexes, and functioning of the nerves. Diagnostic tests such as a CT scan of the brain, an EMG to evaluate nerve and muscle function, or an EEG to measure electrical activity in the brain may

also be necessary.

Because low muscle tone may affect multiple organ systems and patients may face risks of recurrent aspirations and infections, protecting the airways and ensuring that patients grow and develop are two of the highest priorities for pediatricians. Not unique to hypotonia but certainly prominent, adds Goldstein, is the challenge pediatricians face in helping parents come to grips with the diagnosis. “There are few things in life more difficult than having a seriously sick child,” Goldstein says, “especially when you’re a first-time parent of a critically ill newborn.” ■



## Pediatrician

**Pediatrician** is produced quarterly by the Johns Hopkins Children's Center Office of Communications and Public Affairs.

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Designer: Abby Ferretti

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Distribution: Naomi Ball

Web site: [www.hopkinschildrens.org](http://www.hopkinschildrens.org)

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