CLINIC FOR SPECIAL CHILDREN
NEWSLETTER

VOLUME I NUMBER 30 * LANCASTER COUNTY, PENNSYLVANIA * SUMMER 2010

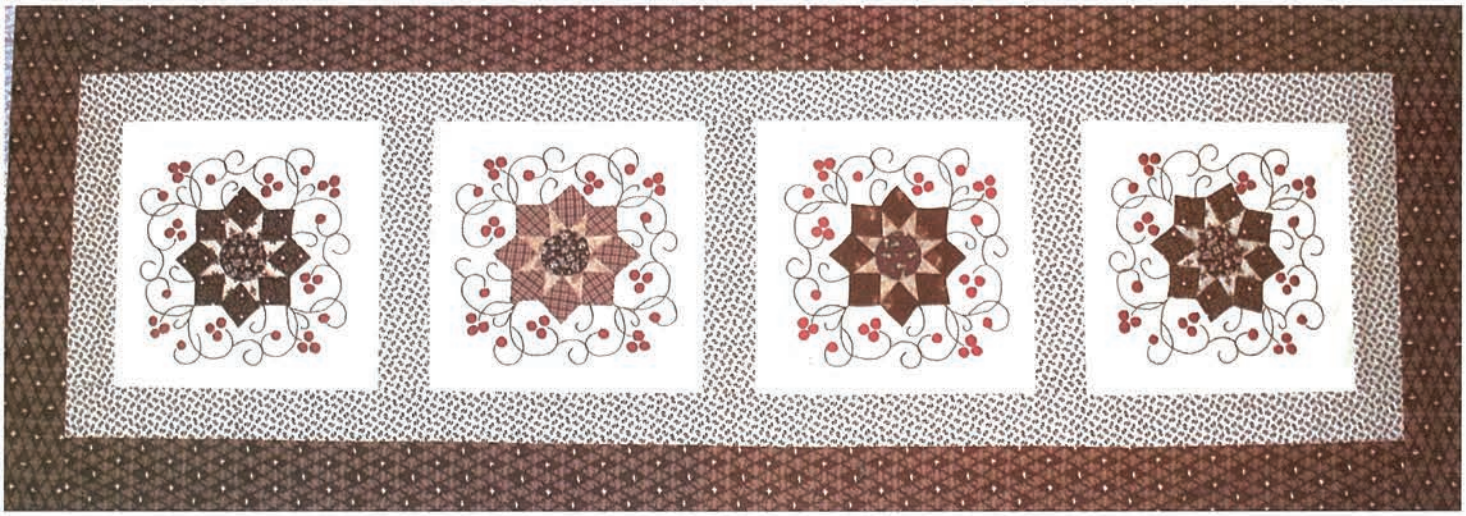
2010 BENEFIT AUCTIONS

JULY 10 ~ SHILOH, OHIO

JULY 17 ~ SHIPPENSBURG, PA

SEPTEMBER 11 ~ BLAIR COUNTY, PA

SEPTEMBER 18 ~ LANCASTER COUNTY, PA



MARKING MILESTONES

In celebration of the Clinic for Special Children's 20th year we sponsored a meeting last November to reflect on twenty years of progress in genetic medicine. Dr. Joseph Martin, Dean Emeritus of Harvard Medical School, and his wife Rachel were our special guests along with many other physicians, patients and community members who had various roles in the formation of the Clinic in 1989. It was a meaningful day for all who attended.

In September of this year, as we cap our 20th year and on the eve of our 20th Benefit Auction in Lancaster County, we are sponsoring another conference to look forward to how the Clinic should continue to develop its services and also assist other clinics modeled after ours to provide needed medical services to other communities throughout the United States and Canada.

Medical Caring for Special Children in the Time of Genomic Medicine: A Conference in Recognition of the 20th Clinic For Special Children Benefit Auction September 18, 2010.

On September 17th the Clinic will host a meeting about the diagnosis and treatment of the *Medical Genetic Conditions of the Plain Communities of North America.* This will be a working conference to update our catalogue of known disease phenotypes and gene mutations within the Amish, Mennonite, and Hutterite Populations found in hundreds of communities across the United States, Central America, and Canada. Many laboratories throughout North America are involved in basic research to uncover the genetic causes of inherited illnesses, develop rapid molecular diagnostics and expand methods for newborn screening, but after a diagnosis is made physicians and local health care services are needed to provide medical care. The application of knowledge of genetics in the everyday practice of medicine is called *Genomic Medicine*. Those invited to the September 17 Conference will be asked to discuss how information about genetic disorders is being used within specific subpopulations to provide more accessible and effective medical care.

The Clinic For Special Children was founded as a non-profit organization in 1989 to provide a place where children with MSUD, Glutaric Aciduria, MCADD, and several other inherited troubles could find medical care. The Clinic has grown over the 20-year period because such care is needed, and the Clinic has grown through the support of the Amish & Mennonite Communities of Pennsylvania and Ohio. Today we are a medical home for more than 1700 children and adults with 105 different inherited conditions. Is *The Clinic For Special Children* a model of health care that can be used within other Plain Communities? *Das Deutsch Center for Special Needs Children* was established in Geauga County Ohio in 2001 and has grown steadily. A

Committee from Western Indiana will attend our September 17 Conference and discuss their plans to expand an existing community-supported birthing center and a clinic for the management of hemophilia to include a new *Clinic for Special Children.* What are the medical and economic incentives for Plain Communities in Ohio, Kentucky, Indiana, Wisconsin, and elsewhere to establish and support non-profit Clinics that specifically serve the special medical needs of children and adults with inherited disorders? How can we help find and train physicians and nurse practitioners to help staff such Clinics?

These topics will be explored at the conference on September 17th and will be part of our challenge as we begin the Clinic for Special Children's third decade.

AUCTION SEASON

Two benefit auctions were held in July and we look forward to two more in September. All four events help fund about 28% of the Clinic's annual operating costs. **Please join us at an auction. We need your support.**

Shiloh, Ohio ~ July 10 Families in Shiloh, Ohio, sponsored the sixth auction in that region. We are very grateful for the support growing for the Clinic from this community. Thank you to all who helped.

Shippensburg, PA ~ July 17 In addition to quilts, tops and wall hangings, a new carriage and furniture, this auction had many beautiful plants donated for sale from local nurseries. As a special feature at this auction, children lined up all day for the "train" ride around the auction property. The fresh donuts, ice cream, pork barbecue and chicken were big sellers.

Blair County, PA ~ September 11 Beautiful quilts, hand crafted benches and chairs, chicken barbecue, soft pretzels, mums and other plants invite bidders to Morrison's Cove Produce Auction in Central Pennsylvania for the 14th Annual Auction for the clinic. Breakfast will be served starting at 7:00 a.m. Contact Amos at 814-793-3926, Eli at 814-793-3010 or Paul Ray at 814-224-5442 for information or donations for the auction.

Lancaster County, PA ~ September 18

The 20th annual auction for the Clinic in Lancaster County will start at 8:30 on September 18th at the Leola Produce Auction. Plan to arrive early for breakfast fare including omelets and fresh donuts. Dr. Morton, Dr. Strauss and Dr. Rider will offer a few remarks around 11:00AM. followed by the quilt sale and furniture auction blocks. Lawn furniture and Gift Certificates will be sold around 1:00 PM.

This year the sale will feature two new carriages. One is an Amish carriage or buggy and the other a two seater Mennonite family carriage. For those interested in a smaller ride or are looking to use less gas, there will be a miniature pony with harness and cart for sale and also two more miniature ponies.

Quilts will include a Postage Stamp, Jacobs Ladder, various patchwork, applique and Center Diamond designs. Locally made cherry and oak bedroom sets, a cherry hope chest, martin houses, play houses and sheds, swing sets, garden and farm items, crafts, baked goods and as always, fresh subs, chicken and pork barbecue will be sold.

Call one of the following if you have items to donate or for more information: 717-626-4863; 717-354-5415; or 717-656-9694. The Leola Produce Auction is located on Brethren Church Road, north off Rt. #23 in Leola (between Lancaster and New Holland).

Thank you to all who volunteer; all who donate, all who come; and all who bid and buy. We especially thank the children who inspire all of us to work harder and to keep the Clinic growing and thriving.

FIND YOUR WAY TO HELP THE CLINIC IN A CORN MAZE

The Clinic was selected this year as one of the featured nonprofit organizations to benefit from activities at the CORN MAZE at Oregon Dairy. This year's maze, located next to Oregon Dairy on Oregon Pike in Lititz, features the shape of a cow with its intricate multiple stomachs. The Clinic will be the featured organization during the weekend of September 10th - 12th. The other organizations to benefit this September include Neffsville Volunteer Fire Company, Water Street Ministries and Hospice of Lancaster County. Thank you to joint sponsors, Oregon Dairy and WIOV-I105 for this great community support.

A CHALLENGE TO MATCH

We have another call for a matching gift challenge. A family foundation will donate **$50,000** to the Clinic **IF** we can match this amount with other donations before December 1, 2010. Last year we were able to meet and double the goal. This year it was suggested that our challenge is to TRIPLE the goal. Please help us meet this challenge.

We are very thankful for this generous gift and for the commitment of support for the Clinic.

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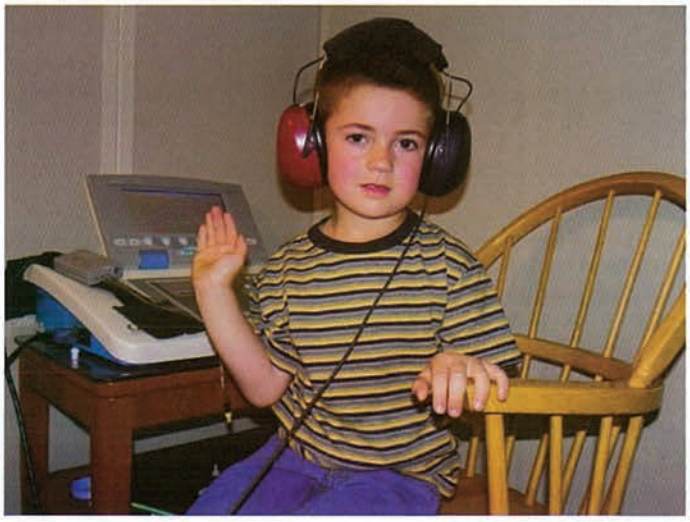


Hearing Lab Up and Testing, Testing, Testing.....

With thanks from several donors including the Strasburg Area Sertoma Club, Dr. Morton's MacArthur grant, the Neuber Charitable Trust, the Genetics of Hearing Lab is complete and we are now scheduling hearing exams on a regular basis. **Dr. Kamal Elliot** of A&E Audiology has agreed to come one or two days monthly to evaluate patients for hearing loss. Working with Dr. Elliot is **Lynda E. Steelman,** Au.D, who recently completed her doctorate at Bloomsburg University and is a pediatric audiologist on staff with A & E Audiology. **Andrew Elliot** is

also a member of the audiology team working at the clinic. He is a hearing aid technician and IT manager for A & E Audiology and is working on his degree in computer science. **Donna Robinson**, CSC's Nurse Practitioner, helps coordinate the hearing testing program for the clinic.

AUDIOLOGY: GENETICS AND DEAFNESS

The start-up of the hearing lab has reminded us how common hearing problems are and that the causes of hearing loss are varied and complex. Recurrent middle ear infections in early childhood can cause prolonged hearing loss that prevents normal language development. Middle ear infections and poor drainage is especially a problem for children and adults with Down syndrome. About 15-20% of all hearing loss in infants is caused by cytomegalovirus (CMV) infections before birth. Recent studies suggest that treatment of the mother with an anti-viral called ganciclovir during the pregnancy may help protect the fetus. Also, detection of CMV in the newborn, using the newborn screening blood spots, may allow treatment of CMV, thereby preventing hearing loss and other problems of congenital CMV infection. We recently found profound hearing loss in an infant who had high bilirubin levels as a newborn, which is a preventable form of deafness and is often associated with injuries to other regions of the brain. Noise related hearing loss is very common but is especially severe and sudden in people who carry a mutation in the gene COL1A2, which causes a form of brittle bone disease.

Erik Puffenberger has recently shown that the most common recessive form of early hearing loss in people of European descent, a mutation in the gene called Connexin 26 or GJB2 35delG, is found within the Amish and Mennonite populations. A severe form of Usher Disease has been known for many years in the Lancaster County Amish. The disorder causes severe hearing loss before age 5 and progressive blindness in the teenage years. The molecular cause of this disorder has been uncovered through the exome sequencing studies being done at Broad Institute, however, we have also learned that hearing can be restored in patients with this form of Usher Disease through a cochlear implant, which may help limit the terrible isolation these patients experience when both vision and hearing are gone.

One of the most common causes of hearing loss in the Mennonite population arise from mutations in a gene called EDNRB, which is the first gene studied in Lancaster County by Erik Puffenberger as the cause of Hirschsprung's disease. Many people who have two abnormal copies of the mutated EDNRB do not have abnormal innervation of the colon, but do develop severe hearing loss. Little is known about the natural history of this disorder. We have also learned of several recessively inherited disorders in families in Lancaster County, Somerset and Big Valley that are caused by as yet unknown mutations. We are also aware of an autosomal dominant form of otosclerosis in a Mennonite family. We think this form of hearing loss will be very common.

Our studies of the genetics of hearing loss have just started at the Clinic. Our hope is that early recognition of childhood hearing loss of all forms will lead to more effective care, allow normal language learning, prevent problems in school and, ultimately, prevent the isolation of deafness.

CLINIC PROGRESS NOTES..... Dr. Kevin Strauss

Matt O'Connor, a cardiology fellow at Children's Hospital of Philadelphia, continues his important work studying the treatment and outcome of congenital heart disease in Amish children with Ellis-van Creveld syndrome. Matt has shown remarkable commitment to his patients, and made multiple home visits at no charge to families. He periodically visits the Clinic to see patients and assist with the interpretation of complicated echocardiograms.

Clinic staff, in collaboration with **Bridget Wardley** from **Applied Nutrtion**, recently published a comprehensive paper in **Molecular Genetics and Metabolism** about the principles of management and formula design for maple syrup urine disease. The new formula discussed in the paper, Complex Junior, is now available for commercial sale.

Two clinical studies of MSUD are reaching completion. The first, a comprehensive review of metabolic control and health outcomes following liver transplant, is ready to be submitted for publication. Clinic staff and the transplant team of Children's Hospital of Pittsburgh worked together in this 7-year effort. The study reports on 38 patients followed for an average of 4 years (maximum 13 years) after transplant. The major findings are as follows: 1) All 37 patients are alive and well and no re-transplants have been necessary; 2) Liver transplant allows for stable metabolic control on unrestricted protein intake and protects patients from metabolic toxicity and brain damage during illnesses; 3) Although frequent blood tests and daily medication are necessary after transplant, overall quality of life is excellent and the rate of serious side effects is low; 4) Transplant protects the brain from further injury, but does not reverse brain damage that is already present prior to the procedure; 5) The liver from an MSUD patient (adult or child) can be successfully grafted into another individual who does not have MSUD (called a "domino" transplant) without causing significant metabolic disturbances in the recipient; 6) Over the same time period, there have been 21 successful MSUD transplants done elsewhere, at centers in the U.S., Argentina, Brazil, and India. Dr. Strauss presented these data to a group of metabolic physicians in Europe, many of whom are counseling MSUD patients.

The second collaborative study is aimed at determining the chronic structural and chemical changes of the brain caused by MSUD. We are working with **Dr. Gregory Moore** at the **Hershey Neuroimaging Research Center**. Many patients have volunteered to participate and the study has been a success. Thus far, we have imaged 15 MSUD patients and 13 age-matched sibling control subjects. Six additional patients will be studied in the near future. Preliminary results show the following: MSUD patients have significantly lower cerebral levels of chemical messengers (called neurotransmitters), lower energy production, and less stable cell membranes. These changes are only partially corrected by liver transplantation. **Emilie Muelly**, a medical student at Hershey, is analyzing the data; this will form the basis of her PhD thesis. **Pavlina Todorova**, a senior at **Franklin & Marshall**, is participating as part of her year-long honors thesis in biology and will pursue a PhD in neuroscience at University of Texas Southwestern in September. We will continue collaboration with Dr. Moore to better understand and treat diseases like MTHFR deficiency, propionic acidemia, Salla disease, and glutaric aciduria type 1 (GA1).

Over the course of the next year, **Dr. Rider** hopes to critically examine the challenges faced by adolescents and adults with MSUD. He will use interviews and structured questionnaires to identify the specific problems faced by MSUD adults so that we can better serve that population. **Diana Shellmer**, a clinical psychologist at Children's Hospital of Pittsburgh, will assist in this effort. Dr. Rider also continues his important work defining the problems experienced by the growing number of adults who have other genetic disorders, including cartilage hair hypoplasia, pyruvate kinase deficiency, cystinuria, and immune defects. He recently drafted a detailed and pragmatic manuscript about the care of patients with pyruvate kinase deficiency. It summarizes a large volume of clinical and molecular data, representing a collaborative effort among students, nurses, and doctors over the last two years. It will be the most detailed and useful report about PKD published to date, and describes the special problems patients encounter across the lifespan: severe anemia and hyperbilirubinemia as newborns, recurrent transfusions as infants, and risks of blood infection and chronic iron toxicity following surgical removal of the spleen.

This information was the subject of Dr. Rider's Pediatric Grand Rounds presentation at Boston Children's Hospital in May.

Dr. Rider also continues to advance our approach to young patients with congenital immune disorders. Through his efforts, our youngest Amish patient with severe combined immune deficiency (now age 2 months) receives all of her immune-protective medications free of charge and is enrolled in a gene therapy trial at the National Institutes of Health in Maryland. Gene therapy will restore her immune function. A recent study showed this approach to be effective in 90% of patients with ADA deficiency. In the future, we may be able to use this strategy to treat other disorders that affect cells bone-marrow derived cells, such as cartilage hair hypoplasia, pyruvate kinase deficiency, and two other types of SCID (RAG1 and IL7R deficiencies). Because the effective treatment of SCID depends critically on early diagnosis, Dr. Rider is working closely with Mei Baker, a researcher at the University of Wisconsin, to add confirmatory molecular testing for Plain variants of ADA, RAG1, and IL7R deficiency to state newborn screening. Since 1978, 45 children from the Plain community have been diagnosed with SCID. Two-thirds of these children died because of late or inadequate treatment. Their families have formed a large and active support group dedicated to improving the lives of future children. Dr. Rider plans to host the SCID Family Support Group for a June 2011 meeting in Lancaster.

A NEW FORMULA FOR GA1

A new formula, developed at the Clinic in collaboration with **Applied Nutrition**, has improved our ability to manage children with GA1. Five children treated with this formula from birth have reached their second birthday free of brain injury. All have grown and developed normally. We expect the main benefits of the formula stem from 1) a high-quality blend of essential amino acids that may partially restrict lysine entry into the brain while also improving the cells' capacity to produce energy (through a process called anaplerosis), and 2) a higher content of carbohydrate, which appears to afford protection for unknown reasons. These are speculations, and need to be studied further. Drs. Morton and Strauss are preparing a research publication about these five children. They will use it as an opportunity to summarize the Clinic's current approach to GA1 care and more clearly define priorities for future research. We hope this information will be a useful resource for families and health care professionals. Like the MSUD infant product, the new GA1 formula (Glutarade) is attracting considerable interest beyond the local community. It will likely be commercially available in the autumn of 2010.

NEPHROTIC SYNDROME MEETING

On April 14th, 2010, we hosted a family conference about nephrotic syndrome. About 40 people attended; most of them were parents of children with nephrotic syndrome or affected adults. We treat four different genetic disorders that cause nephrotic syndrome: NPHS1, NPHS2, Pierson syndrome, and Yoder Dystonia. In each of these conditions, a defective renal filtering mechanism results in excessive protein loss in the urine (proteinuria). Low protein levels in the blood creates risks for swelling, infections, abnormal blood clotting, poor growth, and hypothyroidism. Over time, proteinuria damages kidney cells and eventually leads to kidney failure. Management of chronic kidney disease is complicated, and kidney failure can only be effectively treated by transplantation. We were fortunate to have speakers Drs. Steven Wassner and Jorge Baluarte, who direct the pediatric kidney programs at Hershey and CHOP, respectively, talk to families in clear, practical language about the treatment of chronic kidney disease and the process of transplantation. Dr. Rider gave a nice summary about the medicines used to protect transplanted kidneys and Lisa Brown, the director of the Financial Assistance Program, reviewed the types of financial help available for families who are cared for at Hershey. Historically, untimely death and unnecessary suffering have been high in this group of patients; we hope this meeting was an important step forward.

COLLABORATION WITH BROAD INSTITUTE

Our collaboration with the **Broad Institute** in Boston allowed us to identify the genetic cause of congenital microcephaly and chorioretinopathy in Mennonites, a disease described by Victor McKusick more than 40 years ago. This collaboration has expanded to include mapping for 12 different disorders. In the meantime, Dr. Puffenberger has studied the whole-exome sequencing technology employed by Broad, and believes it could be a great asset to our lab. Like the Affymetrix system, this technique will allow us to connect advanced molecular technology directly to patient care. It should improve our ability to map genetic causes of disease within the population and also provide valuable ancillary data, such as the HLA sequences used to identify donors for stem cell transplant. Erik asked Ion Torrent, a company that makes exome analyzers, to donate a system valued at $50,000. The request was declined, but we are committed to acquiring a system by other means. On this front, the Clinic was recently awarded a $38,000 grant from the Crown Foundation in Lancaster. This money will be primarily used to purchase new high-density genotype arrays. Over the next year, we will use these arrays to genotype every new patient evaluated at the Clinic. Christian Casteneda, a student at F&M, has written computer software that will allow us to efficiently search and compare these data across our entire genotype bank, which now includes 1000 individuals.

Dr. Morton remains involved in educating professionals about genetic disorders that can be mistaken for child abuse. Among Plain sects, these include disorders such as TJP2 and BAAT deficiencies, GA1, rickets, and osteogenesis imperfecta. This topic was covered in more detail at our CME course in May, 2010.

Seated l. to r.: Dr. Kevin Strauss, Dr. Erik Puffenberger, Dr. Holmes Morton; standing, l. to r. Dr. Nick Rider, Adam Heaps and Nikolas Muenke review data with the Broad Institute.

LABORATORY NOTES

from Erik Puffenberger, PhD., Lab Director

Disease Gene Research Update:

In past newsletters, we have enumerated our successful disease mapping studies. To date, we have identified the causative gene for 14 separate genetic diseases using genetic mapping studies. Many of the diseases, such as LYK5 deficiency ("Pretzel" syndrome) and CDFE (cortical dysplasia and focal epilepsy), were previously undescribed in the medical literature. We have preliminary mapping data for more than a dozen other disorders, but we have yet to identify the causative gene. To facilitate rapid identification of the causative genes for these

disorders, we embarked on a collaboration last summer with the Broad Institute in Cambridge, MA. As we previously reported, we organized a joint project to perform "exome" sequencing on selected clinic patients. The "exome" is the part of the human genome that codes for proteins and comprises about 1% of our DNA. While it is a tiny fraction of our total DNA, it contains the overwhelming majority of disease mutations.

We originally sent 30 DNA samples representing 9 different genetic diseases. Seven of the nine disorders were previously mapped. This mapping information allowed us to focus on a subset of genes that were found in the specific mapped region for each disorder. This was a significant benefit to the analyses. After the first full exome was completed, we immediately recognized the utility of this approach. The first data set was generated from a Mennonite individual with microcephaly and chorioretinopathy. The unfiltered data was daunting. There were 17,270 DNA sequence variants in this patient; 3,512 variants were novel (i.e. unique to the patient) and, of these, 2645 were potentially disease-causing changes. Our mapping of the microcephaly disease gene to chromosome 22q13 provided a necessary filter to constrain this large data set. When the analysis excluded all gene variants which did not reside on chromosome 22q13, only one variant remained. This same technique has allowed us to identify the putative mutation for 4 of the 9 disorders sent to the Broad Institute. In addition to the microcephaly gene, we have also found the gene mutation for posterior column ataxia with retinitis pigmentosa (AXPC1), Amish lethal seizure syndrome, a form of non-syndromic mental retardation, and a new form of Usher syndrome. We eagerly await the data for the final 5 disorders.

"Exome" sequencing is very expensive and time consuming. The Broad Institute is currently providing this service to the clinic for free. This saves the clinic much-needed resources and will lead to development of diagnostic testing and potential treatments for these disorders. Unfortunately, this work will not remain forever free. However, as prices drop for the hardware and reagents and new technologies arise, we expect that an affordable "exome" sequencer will be available in the near future. When that occurs, we plan to add "exome" sequencing to our list of laboratory services. We will keep you abreast of our progress in future newsletters.

Vaccine Program at the Clinic for Special Children: Nicholas L. Rider, D.O.

Childhood vaccination has dramatically reduced infant mortality and improved the overall health of children worldwide. At the Clinic, we recommend routine childhood, adolescent and adult vaccination according to the Centers for Disease Control schedule (www.cdc.gov/vaccines/recs/acip). Starting early in life with safe, effective vaccines provides an infant with infection fighting protection while their own immune system develops. Vaccines do not 'weaken' immunity; rather, they strengthen specific immune responses against dangerous infections. It is important to begin early as babies/young children are the most susceptible to sickness.

We recommend giving the full series of shots to all children unless there is a clear contraindication to avoid vaccination. Reasons to discuss modifying the vaccine schedule for your child include – family history of severe immune deficiency, mitochondrial disorder or metabolic disorder. Many children with these conditions can still safely receive vaccines; however, you should discuss this with your pediatrician. It is important to check growth and development and reassess family history prior to giving vaccines to a child. This allows children to receive the benefit of vaccination in a safe manner.

At the Clinic, we provide vaccines for our patients at routine visits. For other children within the community, we offer a vaccine clinic. Our vaccine clinic is held every other Wednesday, with appointment slots every 15 mins from 9am – 4:30pm; the charge is $20/child/visit. Please call (717-687-9407) to schedule an appointment for your child or utilize another pediatric practice/county resource to have your children immunized. We remain available to answer your questions about vaccination.

Matt O'Connor, M.D., cardiology fellow at Children's Hospital of Philadelphia, shares insights about his experience studying children with Ellis-van Creveld syndrome:

As a pediatric cardiologist at The Children's Hospital of Philadelphia, I have been studying Ellis - van Creveld syndrome (EvC) and its relationship to congenital heart malformations, in conjunction with the medical staff at the Clinic for Special Children. EvC is a common cause of dwarfism among the Plain community, with an incidence of approximately 1 case out of every 5000 births among the Lancaster County Amish. Congenital heart malformations are observed in approximately 60 - 70% of individuals with EvC. Many of these defects are complex and require surgery.

It is generally known that patients with EvC have poor outcomes following surgery to repair heart defects. The reasons for these poor outcomes are not exactly known, but some evidence points to small lungs playing a significant role. Small lungs in EvC are a consequence of a small rib cage; due to the dwarfism seen in EvC, many of the bones in patients with EvC are short. In my experience caring for children with EvC and heart disease, it became clear that physicians did not have enough information to provide families with realistic counseling about survival and complications in children with EvC undergoing surgery for heart defects. Recently, we reviewed the records of 15 children with EvC born over the past six years and identified 11 children with heart defects. Many of these children had heart surgery, and we reviewed the outcomes of these children with regard to survival and complications. Through this study, we found that lung problems appear to be responsible for most of the deaths, as well as the complications in those who survive surgery. Moving forward, we hope to find better ways to assess the size and function of the lungs in patients with EvC before subjecting them to heart surgery.

HOW MSUD AND LIVER TRANSPLANT THERAPY AFFECT THE BRAIN

Research at Hershey by Emilie Muelly, Graduate Student at Penn State Hershey Medical Center

Maple Syrup Urine Disease (MSUD) is a condition in which molecules build up and cause damage to the brain, resulting in a variety of symptoms. Some of these symptoms are acute with a risk of rapid brain swelling. Other symptoms, such as depression and anxiety, may occur chronically and their mechanism is not well understood. In collaboration with the Clinic for Special Children, we are taking a closer look at how MSUD chronically affects the brain, and how these effects might be modified by liver transplantation. Using Magnetic Resonance Imaging (MRI), we can capture different types of information about the brain, including size and structure of different regions, connectivity pathways between different areas, and the concentration of specific neurochemicals. We are comparing MSUD patients to their siblings and also correlating results from the MRI with blood amino acid levels, patient history, and chronic symptoms. This will allow us to better understand how chemical disturbances in MSUD chronically damage the brain. The ability of liver transplantation to eliminate the risk of acute crisis and the need for protein restriction is now well established. In our study, we will try to determine if liver transplantation can alter brain structure and function in ways that reduce the risk for chronic symptoms. We thank those

who have volunteered for the study thus far, and are still enrolling new participants. Once we have analyzed the data, we hope to have a picnic with all the participants to share the results. If you are interested in finding out more about the study, ask one of the doctors at the Clinic for more information.

CME COURSE

A CME course about nutritional therapy and complementary medicine was sponsored by the Clinic on March 26th.

ANNUAL TRANSPLANT SYMPOSIUM ~

Children's Hospital of Pittsburgh UPMC and the Clinic for Special Children sponsored the ***Annual Children's Symposium on Transplantation for Maple Syrup Urine Disease and Crigler - Najjar Syndrome*** on June 10, 2010 in Strasburg. The meeting provided a forum for discussion of topics related to long term outcomes of transplant, neurodevelopmental effects of transplant, research updates and questions for discussion from parents and patients. To date, 42 patients with MSUD and 9 with Crigler Najjar Disease have received liver transplants at Children's Hospital of Pittsburgh.

LOOKING AHEAD

September 17 - Conference on Genetic Conditions found in the Plain Populations - held as part of the celebration of the Clinic's 20th Anniversary.

October 15 - CME Course, Transplantation as Novel Gene Therapy;

November 10 - EVC dwarfism - Management of the Newborn with Heart Disease with Dr. Matt O'Connor;

Other Conferences planned with dates to be announced:

Bile Salt Disease family Conference;

Endocrine Disease Complications: Adrenal Hypoplasia, Cartilage Hair Hypoplasia (CHH)

Please call the Clinic for information or to register (717) 687-9407.

TRANSLATIONAL GENETICS: What does it mean?

The Clinic for Special Children was founded as a place where the knowledge from the fields of biochemistry and molecular genetics would be translated into new principles of medical care to help patients with inherited disorders. Although much of the knowledge of the human genome project was produced in laboratories far from the bedside, the translation of this information into medical practice ultimately requires a commitment to care for the patient. The every day practice of medicine is the next frontier of Translational Genetics. An understanding, an acceptance of the fact that many common illnesses arise in all people from genetic predispositions, but are nonetheless treatable, may ultimately be the most important contribution the Plain Communities and our Clinic for Special Children will make to the practice of medicine.

CONTINUING COLLABORATION WITH F & M

We continue to enjoy vibrant academic contributions from F&M students. Krysta Brown is writing up nearly two years of work on iron toxicity in pyruvate kinase deficiency, Pavlina Todorova is helping Dr. Strauss with the MSUD MRI study at Hershey Medical Center, and Christian Castenada is designing intuitive computer software that will allow Clinic doctors to seamlessly analyze a patient's genetic information during the course of a regular office visit. Each student of the Biology 338 class (taught at F&M by Drs. Puffenberger, Morton, and Strauss) created a clinically useful written summary of a disease managed at the Clinic. Essays of sufficient quality will be edited by Clinic staff and posted on the Clinic website as a resource for clinicians and families throughout the world. Several Biology 338 students are helping Erik with genetic testing. Steve Chorney, an alumnus of Bio 338 and current first year student at Scranton Medical College, returned this summer to study congenital adrenal hyperplasia.

SUMMERTIME AT THE CLINIC

This spring and summer the Clinic has engaged many students in research projects and clinical studies. Dr. Morton, Dr. Strauss and Dr. Puffenberger taught a seminar class in medical genetics at Franklin & Marshall College for the spring semester.

Andrew Staffaroni, F&M Eyler Fellow for 2010

From Andrew:

My interests in the Clinic and its work first began when I was a sophomore at Franklin & Marshall, where I attended a lecture given by Drs. Puffenberger and Strauss. I was blown away by their work and it quickly sparked a personal interest in genetic medicine. Over the next two years, these interests led me to molecular genetics research at F&M and I eventually enrolled in the "Plain People and Modern Medicine" class as a senior. It was, without a doubt, the most interesting and thought-provoking course I have taken during my time at F&M. One of the greatest aspects of the course was the opportunity to visit the Clinic. After finishing classes on most Friday afternoons, I made my way out to Strasburg where I worked on a gene sequencing project and had the opportunity to shadow some of the physicians. When it came to my attention that they were offering a summer fellowship program at the Clinic for graduating students, my decision to apply had already been made.

From the beginning of my summer research, I became interested in a specific case presented to me by Dr. Rider. The project caught my attention because it gave me the opportunity to combine diagnostic research with patient interaction, an aspect of the Clinic's work which I find so appealing. Within the first few weeks, we found a novel mutation in a gene coding for a dopamine transporter (SLC6A3), a protein important for proper neurotransmitter function in the central nervous system. The mutation is responsible for a rare disorder known as Infantile-Parkinsonism Dystonia. My current and future work with this

case involves monitoring the results of amino acid therapy, as well as assessing the carrier frequency of this mutation within the Old Order Amish population. Additionally, I helped to uncover a novel mutation in another gene, NTRK1, which codes for a receptor protein important in nerve cell growth. This mutation is linked to a rare condition known as Congenital Insensitivity to Pain with Anhidrosis.

When I am not busy with laboratory work, I spend my time researching to better understand the underlying biology and treatment options associated with each disorder. While the molecular work I am involved in is truly fascinating to me, it is the unique opportunity to interact with the patients and families of whom my work is directly benefiting, that makes this experience so gratifying. My involvement at the Clinic has shaped my attitude towards clinical medicine and research and has provided me with a unique knowledge and experience base that I am sure will serve me well in my future education. My work here has been inspiring in so many ways, and I give my thanks to both the Clinic staff and communities I am so fortunate to work with.

Why I chose The Clinic for Special Children:
from: LouAnn Fromuth

As a Pediatric Nurse Practitioner student, my goal is to experience as many pediatric illnesses as possible; so when I am in practice, I can pull from these past experiences to provide optimal care. Knowing that the Clinic for Special Children focuses on unique Pediatric metabolic and genetic disorders, what better place to gain knowledge of these unique illnesses that might rarely be seen in a private office setting. I had the great fortune to see it every day and become familiar with the up to date treatment of these disorders. Although most of the patients were Plain (which is a unique cultural group in itself), there were some English patients that came to the clinic as well. This opened my eyes to the fact that these illnesses are within all pediatric cultural groups.

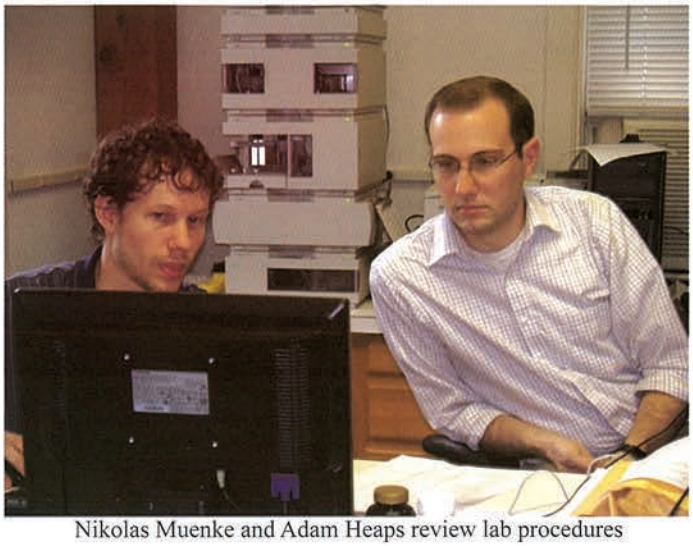
The Staff of the Clinic are open and welcoming to teach all about these disorders. I've witnessed how their eyes light up when describing the complexity of the illness, how they were able to map the gene sequences that genetically predisposed the children to these illnesses, and how they have developed treatment guidelines so others who come after will benefit from their knowledge. In this day of Healthcare reform and insurance constraints, this practice does not allow that to dictate their care. They provide care to ALL persons, insurance or not. They allow as much time as needed for parents to understand and become familiar with the complexities of their child's illness. They are truly passionate about their practice to better understand and provide care to the children of Lancaster County and the world that seek their expertise.
It was a wonderful experience and I would not have changed it in any way. I do know now that if I should ever come across a newborn screening that is abnormal, or a metabolic disorder I am not familiar with in my practice, the Clinic for Special Children will be my first phone call to make for direction and collaboration in the care of that pediatric patient.

Eric Sherman has returned to the clinic this summer after his freshman year at Swarthmore College. One of his current projects involves optimizing a bisulfite DNA sequencing protocol for the gene UBE3A. Bisulfite sequencing detects abnormal methylation patterns within this gene. These abnormal methylation patterns lead to Angelman syndrome, a severe neurological disorder found in 1/12,000 children. When the assay is optimized, the clinic will be able to perform inexpensive diagnostic testing for this disorder. Eric is also developing assays to rapidly detect polymorphisms and mutations using the Roche LightCycler and a technique called high resolution melting analysis. These assays are being used to assess the frequency of different DNA variants in the Amish and Mennonite populations. This work will be critical to determining the relevance of putative mutations that have been identified in clinic patients through our collaboration with the Broad Institute.

We hosted another Swarthmore College student this summer. **Ernesto Manzo** is a rising senior who heard about the clinic through a lecture on campus by Dr. Puffenberger. Ernesto worked here for 8 weeks and learned to perform polymerase chain reaction (PCR), DNA sequencing, and microarray analysis. He worked on several projects including gene sequencing of PTPN11, LMNA, TJP2, and FLVCR1 in clinic patients. He used SNP microarrays to perform a mapping study on a rare disorder called retinal dystrophy-aplasia cutis congenita. He and **Andrew Staffaroni** worked together to identify the specific mutation in the gene NTRK1 which causes congenital insensitivity to pain with anhidrosis (inability to sweat). The clinic benefited immensely from his hard work and we wished he could have stayed longer; hopefully, we can lure him back next summer to continue his studies.

NEW STAFF AT THE CLINIC

Adam Heaps joins the Clinic staff in August to assist Dr. Puffenberger in the laboratory. Adam is from the New Holland area and graduated from Franklin & Marshall College in 2008 with a degree in Biology. He is currently working on his masters degree in Biology at Millersville University. Since his graduation at F&M Adam has worked for the college as a laboratory technical assistant and as an intern in media services. As a student he taught science to elementary students through the Spalding Leadership Program. Adam is also an Eagle Scout and recent recipient of the Boy Scouts of America National Order of the Arrow Distinguished Service Award for his leadership activities.
We are so pleased to welcome Adam to our staff and look forward to including Adam and his wife Kristen in Clinic family events.


Nikolas Muenke and Adam Heaps review lab procedures

..... and Farewell

We regret we have to say good bye to **Cris Mitchel**l who has worked part time in our lab for the past two years. Cris has assumed a full time job at a hospital lab near her home in Phoenixville. Cris has made a very effective contribution to the efficiency of our lab and has helped maintain information necessary for monitoring requirements. We will miss her as part of our staff.

Nikolas Muenke will be leaving the Clinic at the end of August to pursue his medical studies in Germany. However he will not be leaving the clinic "family" entirely as he will stay in touch through his new relatives, the Morton's. Nikolas will marry Sarah Morton, daughter of Holmes and Caroline Morton, in August.

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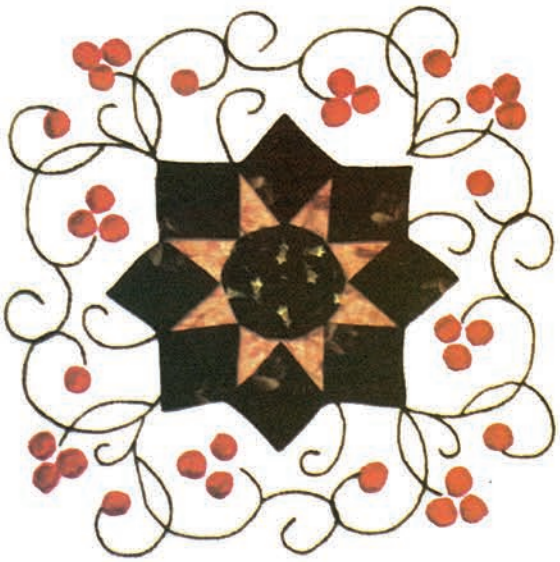

MISSION

The Clinic for Special Children was established in 1989 as a non-profit medical service for Amish and Mennonite children with genetic disorders. The Clinic serves children by translating advances in genetics into timely diagnoses, and accessible, comprehensive medical care, and by developing better understanding of heritable diseases.

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Thank you