CLINIC FOR SPECIAL CHILDREN NEWSLETTER

VOLUME I NUMBER 19 * LANCASTER COUNTY, PENNSYLVANIA * SUMMER 2002

LISTENING AND LEARNING.....

Let the wise listen and add to their learning, and let the discerning get guidence. Proverbs 1:5

The advances in medical care achieved here at the Clinic for Special Children over the last twelve years were the result of listening and learning from children. We believe it is important to take time to listen, time to think, time to ask and seek answers to difficult questions, time to care for very sick children. The ***Time*** *is a gift from those who support us. There would be little progress without it. Time makes all the difference. The Clinic was established in rural Lancaster County to care for children nearby who have complex medical problems due to their genetic disease. Much of what we learn comes from caring for Amish and Mennonite children who depend on us for their care. In caring for them we learned to listen and seek answers to difficult problems. We ask and seek guidance from many - from Harvard in Boston, Johns Hopkins and Kennedy Krieger in Baltimore, Philadelphia, NIH, Hershey, Lancaster General, and many others noted for their field of work. Children from as many as twenty - seven states and fourteen other countries have sought answers at our clinic. In this issue we report on lessons learned here at the clinic, lectures given and articles published in the medical literature for others now to hear and learn. We hope others will also listen, learn, and seek guidance for the sake of children who need their care and their time.*

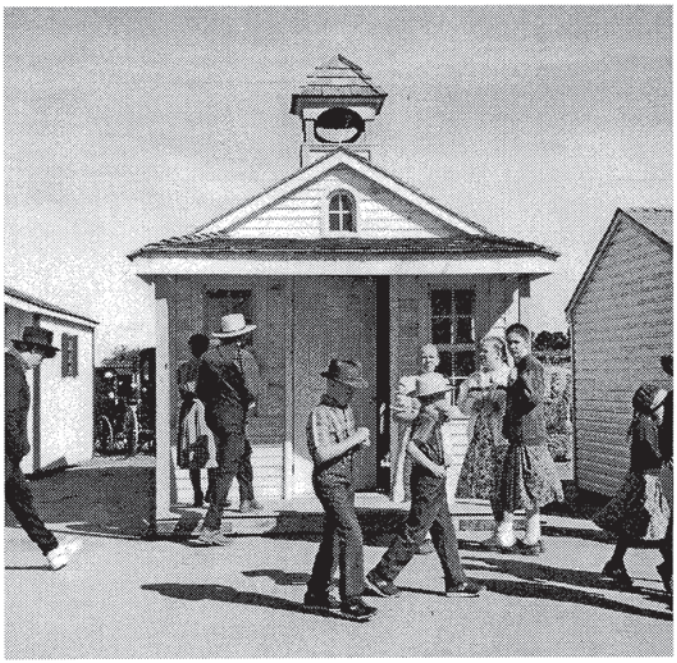
2002 AUCTION DATES

Shippensburg, PA ~ July 20
Blair County/Morrison Cove ~ September 7
Lancaster County/Leola ~ September 21

The Clinic is looking forward to the 2002 Benefit Auctions in three locations in July and September. These auctions provide much needed support for the Clinic each year and help us meet approximately one-third of our annual operating expenses.

BIDDING FOR SUPPORT.....
.....WHY DO WE NEED IT ?

Support from the auctions each year is necessary to help the clinic operate and provide comprehensive services to children with complicated genetic diseases at affordable rates. Funds received from the auction help the clinic purchase essential medical formulas and make them available at reduced rates to the families without insurance for their children's treatment. The clinic also needs funds to underwrite the cost of research to develop better diagnostic and treatment methods. For all of the children we care for with different diseases we are constantly working to improve treatment methods and to learn more about their disease. For some children, the clinic is the only place where their disease is studied. Children elsewhere also benefit from the work at the clinic as information developed here is shared with other physicians and parents through papers, letters, and lectures. We are very thankful we completed our expansion project last year without incurring any debt and we are grateful to all who continue to support the ongoing work of the clinic. We do need your help very much!



Amish School Playhouse at 2001 Auction

We thank all of the members of the auction committees and their volunteers for their time and hard work putting together these auctions. Without their help the clinic could not afford to provide comprehensive services for children with complex problems related to their genetic disease or to continue our research for better treatment . Thank you to all who work, attend the auction, contribute items and bid on them!

SHIPPENSBURG: **July 20** This will be the fourth year for the auction in Shippensburg, PA, at Leinbach's located one mile north of Shippensburg on Rt.#11. The auction committee reports there will be two new spring wagons, one Amish, one Mennonite and a Mennonite carriage for sale this year in addition to quilts, furniture and much good food. Quilts, lawn furniture, and buggies will be auctioned in the afternoon. Please call 717-532-5511 or 532-9088 for information about donating items for the sale.

BLAIR COUNTY: September 7 Mennonite families in Blair County, PA, look forward to the 6th annual benefit auction to support the Clinic. The event is held at Morrison Cove on Rt.36, six miles south of Roaring Spring, PA. This auction will feature beautiful hand made furniture, quilts, farm equipment, plants, many other items and great food. The auction will begin at 9:00am. Contact 814-793-3634, 814-793-3010 or 814-224-5442 for more information about the auction or to arrange donation of items for sale.

LANCASTER COUNTY: September 21 The 12th annual auction for the Clinic will be held at the Leola Produce Auction facility on the third Saturday in September. The event will begin at 8:30am, quilts will start selling at 11:00; large furniture at 11:30; lawn furniture at 1:00 and everything else in between and all day. Chicken barbecue, subs, pork roast, ice cream, fresh lemonade, soft pretzels, pizza, donuts and baked goods all will be available during the day. There will be new carriages for sale this year, beautifully made furniture, and many lovely hand made quilts. If you have items you wish to donate, please call one of the following: (717) 626-4863; (717) 354-5415; (717) 656-9694.

HIGHLIGHTS FROM LAST YEAR.....

Last year's auction in Lancaster was held as scheduled on September 15 only a few days after the shock of September 11. Many called to inquire if our plans had changed, but we kept our date. Many told us they needed to participate in something that was positive, uplifting in its purpose and life affirming. Families from as far away as Florida whose flights were cancelled, drove all the way to Lancaster. Although spirits were subdued, most welcomed the chance to be with other people in a friendly setting and a sense of community support prevailed.

A few highlights from the 2001 Lancaster auction:

1430 bidder numbers issued, attendance estimated at 6,000
3456 items were donated and auctioned including:
80 Quilts
2 Carriages and 1 Spring wagon
1 Pony with Cart and harness
1 Amish Schoolhouse Style Playshed
20 Auctioneers volunteered at 5 Auction Blocks
Food included:
3600 Subs, 2100 Pork Sandwiches, 3800 Pieces of Chicken, 6000 Soft Pretzels made with 600 lbs of flour
20,000 Donuts made and sold.....and probably eaten in 1 day!

***** COME SEE WHAT WE HAVE THIS YEAR! *****

OUR NEW WEB SITE NAME:
www.clinicforspecialchildren.org

CLINIC RECEIVES ROTARY CLUB GRANT

The clinic received an award of $1000 from the Rotary Club of Lancaster - South to help equip one of the clinic's new exam rooms. The grant was awarded through the Rotary Foundation's Community Assistance Program and was used to purchase a pediatric exam table with built in weights and measures for infant exams. The clinic is very grateful for this assistance and extends special thanks to all the Lancaster-South Rotary Club members, especially Dick Kramer and Bob Williams for their sponsorship and work for the award.

FARM SAFETY GAME UPDATE

Additional copies of the farm safety game , *Amos & Sadie's Farm ~ A Pathway to Safety* were produced and are available for purchase at Gordonville Book Store, Clay Bookstore, and Ken's Educational Joys in Ephrata. The newer games contain another set of question cards which are also available to those who purchased the first edition of the game. Please contact School Aid at (717) 445-4358 for information about the game or for the extra sets of question cards.

NEW BOOK: ***GOD'S GOLDEN CHILDREN***

Parents and children shared their thoughts and stories about their lives with Crigler-Najjar Disease in a new book titled *God's Golden Children.* Edited by Katie Martin, mother of two special C-N children, the book reflects the experiences and hopes of children born with this disorder which causes chronic jaundice and other complications due to the liver's inability to breakdown bilirubin. The clinic follows 22 children in the U.S. with Crigler-Najjar Disease Type I, one of the rarest disorders. The clinic's C-N caseload is the largest of any medical facility in the U.S. The book is available at the clinic or by order from: RD 1 Box 177-A, Swengel Rd., Mifflinburg, PA 17844.

CLINIC PROGRESS IN OHIO

Board members of the Das Deutsch Center for Special Needs Children in Ohio recently hired Dr. Heng Wang as the pediatrician to staff their new medical center. The center became the dream of several Amish families in the Geauga County region of Ohio and JoAnn and Don Leach as they were on their way home from clinical visits here at CSC several years ago. The new center was envisioned and created to serve the medical needs of children in northwestern Ohio and is patterned after the Clinic for Special Children. As preparation for his new work in Ohio, Dr. Wang spent several weeks at the CSC to learn how our clinic is organized and to observe Dr. Morton, Dr. Strauss and staff at work with patients, families and how we approach the study of difficult diseases. Expressing his thoughts on leaving the CSC to begin work in Ohio, Dr. Wang said *" The dream of Das Deutsch Center, of love and hope, humility and faith that I will be learning every day along with medicine, is waiting for me."* We wish Dr. Wang and the new Das Deutsch Center much success.

OTHER WORK AT THE CLINIC

The Clinic is also home to several other projects. Genetic studies of the Amish population continue in the Clinic's first floor office under the direction of Alan Shuldiner, M.D., Ph.D. of the University of Maryland, Baltimore. Dr Shuldiner's group studies the genetic basis of diabetes, hypertension, longevity, and cardiac calcification. Osteoporosis studies are also directed by Dr. Liz Streeten and myopia studies are directed by Dr. Dwight Stambolian, University of Pennsylvania. For information about these genetic studies and clinics, please call (717) 687-8371.

The Special Hearts Group enjoys activities in the new space in the lower level of the clinic's addition completed last year. The group includes severely disabled young adults from the local Amish and Mennonite communities and their helpers. Many of the participants are also patients of the Clinic. They are a joy to have around and always inspire our work.

PROGRESS NOTES

Problems in our patients remain the motivation for gaining new insights into inherited disorders. Two children with maple syrup disease who had critical brain edema led to hundreds of hours of work to better understand, treat, and prevent this problem. We have struggled to manage severe combined immune deficiencies in a neonate with maple syrup disease and in two infants with a form of dwarfism called cartilage hair hypoplasia. Bone marrow transplant was necessary in one patient and may be necessary in the other two. A two year old boy with EVC dwarfism presented with difficulty swallowing, recurring pneumonias, and an unsual neurological syndrome which finally proved to be due to spinal cord compression arising from malformations in the base of the skull and cervical vertebrae. The boy had a remarkable recovery following neurosurgery by Dr. Ben Carson at Johns Hopkins. Dr. Erik Puffenberger has now shown that three different "Old World" mutations cause the usual variants of PKU in the Amish and Mennonite populations of Pennsylvania. One of these mutations is likely to be responsive to the cofactor biopterin. Erik also recently found that one mutation causes propionic acidemia in the Amish and Mennonite people of Pennsylvania. When diagnosed in the asymptomatic infant by newborn screening this specific form of propionic acidemia is highly treatable. We have now found the mutation that caused the bile salt transport defect and vitamin K deficiency in the Amish baby mistakenly thought to have died of shaken baby syndrome. We have also started new efforts to find the genetic cause of three common disorders in the Pennsylvania Amish: an inherited form of seizures and mental retardation, a syndrome that causes respiratory failure and sudden infant death, and manic depressive illness.

Lectures and teaching seminars continue to be an important part of our work. Last fall Dr. Morton gave the 30th Annual Noone Lecture at Lankanau Hospital near Philadelphia: *A Road Less Traveled by: Genes, biology, and the practice of pediatrics.* He also gave the Margret A. Walsh Memorial Lecture at Boston Children's Hospital - *Genes, illnesses, and medical care. Individual variations in the natural history of genetic disorders* and he was visiting professor at Dartmouth Medical School. In March Drs. Morton, Strauss, and Puffenberger did our semi-annual workshop about Medical Genetics as part of the Temple University/Lancaster General Hospital Family Practice Review Course. In May, Dr. Strauss presented at the Children Hospital of Philadelphia Endocrinology Conference and described the similarities between the critical brain edema of maple syrup disease and diabetes mellitus. Dr. Rolf Pfannl, a fellow in neuropathology at Massachusetts General Hospital, and Dr. Strauss led two conferences in Boston about the embryology and neuropathogy of severe microcephaly. Dr. Morton gave the Chuck Reilly Lecture at York Hospital entitled *When do we learn to care?* In July Dr. Morton gave his 16th yearly lecture at the National Youth Science Camp. Dr. Puffenberger and Dr. Strauss presented topics to the MSUD Family Support Group Symposium held recently in Michigan.

PAPER PUBLISHED ON CLINIC'S WORK ON MAPLE SYRUP DISEASE

The paper, ***Diagnosis and Treatment of Maple Syrup Disease: A Study of 36 Patients*** published in PEDIATRICS Vol.109 No.6 June 2002, summarizes experiences at the Clinic for Special Children caring for 36 neonates with classical maple syrup disease over an 11 year period. We describe an approach to care that includes diagnosis and management of the at-risk and ill neonate, general pediatric care during common intercurrent illnesses, chronic nutritional care, and in-hospital management of severe metabolic intoxication and brain edema. The effects of maple syrup disease upon the growth, development, and health of the patient are related to many interacting variables which are listed as ***Determinants of outcome in patients with maple syrup disease***. The medical approach to management of this biochemical disorder must consider such variables throughout the lifetime of the patient. Prevention of malnutrition and intoxication of the brain is obviously just as important for the teenager and adult as for the infant and child.

The management of the disorder during intercurrent illnesses is particularly problematic for parents and physicians. Few follow-up programs have recognized the need to routinely monitor amino acid levels and change management protocols during common illnesses. Our experience clearly shows that episodes of metabolic intoxication requiring hospitalization resulted from the stress of intercurrent infections. Equally important, minor illnesses commonly cause increases in blood leucine concentrations and imbalances among the other essential neutral amino acids that compete with leucine for entry into the brain. Such imbalances persist for long periods of time if adjustments in therapy are not made to correct these abnormalities. Chronic deficiencies of valine and tyrosine are particularly common problems in patients with maple syrup disease.

Brain edema remains the most dangerous problem caused by maple syrup disease. It appears to us that there are three phases of brain edema in an ill patient with maple syrup disease. First, there is focal water accumulation in deep gray matter,which is readily seen by brain MRI. Dysfunction of these deep brain ganglia correlates with neurological findings and changes in behavior. Second, diffuse swelling of the brain develops and is seen clinically as somnolence, stupor or coma. This phase of general brain swelling is not well seen by MRI, as is true for early diffuse edema in patients with diabetic coma, hyperammonemia, and hypernatremic dehydration. Third, as the brain volume increases to more than 5-7% of its intial volume, the brain is pressed against the base of the skull, blood flow is interrupted in specific arteries causing focal ischemic strokes then rapid swelling due to injury and diffuse ischemia, venous congestion, generalized loss of blood flow and brain death.

We have known for several years that brain edema worsens rapidly in association with rapid decreases in serum sodium concentration and osmolarity. Since the submission of this manuscript we have learned that these decreases in serum osmolarity and generalized brain swelling itself may be the result of high levels of a brain hormone called *vasopressin.* Two effects of *vasopressin* are familiar to all of us - thirst and a concentrated urine. It is a hormone that normally protects against dehydration and shock. Vasopressin not only allows the kidney to hold onto water it also normally prevents excessive shrinkage of the brain by stimulating the uptake of sodium and water by a diffuse network of cells called *astrocytes*. Decreases in blood pressure, vomiting, dehydration, high serum sodium, glucose, or urea concentrations (all of which cause increases in serum osmolarity) provoke release of vasopressin by the brain. Risk factors for the excessive and abnormal uptake of sodium and water by the brain and the development of critical brain edema are increased blood and brain leucine, hyperosmolar dehydration and the associated prolonged increases in vasopressin. Patients at highest risk for brain edema are those who present with advanced signs of leucine intoxication

including recurrent vomiting in the setting of dehydration, high serum osmolarity, and who have intense thirst caused by high vasopressin levels. Studies are underway at the Clinic and Lancaster General Hospital using neuroimaging techniques and endocrinologic monitoring to better understand how to manage such patients to prevent progression to critical edema. We expect such studies will help explain and prevent acute brain swelling associated with maple syrup disease and several diffent biochemical disorders. Holmes Morton, M.D.

A limited supply of article reprints are available by request from the Clinic for Special Children.

PROGRESS IN UNDERSTANDING MICROCEPHALY

We are anticipating by the end of the summer the publication of two papers, one in the American Journal of Medical Genetics and a second in Nature Genetics, that describe a form of microcephaly that is known to occur only in Old Order Amish families whose roots are in Lancaster County. These papers are the culmination of more than 10 years of work by the Clinic staff on a disorder that, although well-known to the Old Order Amish and local physicians and midwives, has never been reported to the larger medical community nor had its cause explained. The two complementary papers not only describe in detail the characteristics of the disorder but also tell how an unusual biochemical abnormality ultimately led to the discovery of the genetic cause of the disease.

"Microcephaly" is the medical term for an abnormally small head. Although there are more than one hundred genetic disorders that include microcephaly as a principal characteristic, this particular type of microcephaly in the Amish is distinguished from most others by its extreme degree of microcephaly and the lack of other major physical abnormalities. It is a very common disorder among the Old Order Amish, occurring with an incidence of about 1 in every 500 births. At birth, most affected babies appear healthy and, except for a very small head, well-formed. The affected children have heads that measure only 10 to 11 inches in circumference, compared to the usual 13 to 14 inches for full-term infants. By cranial MRI of two patients, we found that their brains were severely underdeveloped, especially the forebrain, and resembled more the brain of a 5 or 6 month fetus. In the first few weeks after birth, most microcephalic babies nurse and grow well and respond to care and attention much as other babies do. However, before they are more than just a few months old, most of the babies develop extended periods of extreme irritability. Eventually, feeding becomes difficult and the babies weaken and die, almost always before their first birthdays. Sometimes the children develop rapid breathing and may die relatively quickly at the time of an otherwise simple cold or fever. Regardless of how long the babies live, they show none of the usual development of a young infant, nor do they ever seem to follow or regard faces.

Because extreme irritability and disproportionately severe illness at the time of otherwise simple colds are important characteristics of many of the metabolic diseases that we treat at the Clinic, in 1997 we undertook metabolic testing of an especially severely affected microcephalic baby. These tests disclosed an extremely high urinary level of 2-ketoglutarate, a compound that is closely tied to the metabolism of "mitochondria," where most energy in a cell is made. However, because there are hundreds of genes that are important in the mitochondrial metabolism of 2-ketoglutarate, we turned to our colleagues, Drs. Marjorie Rosenberg and Les Biesecker, at the National Institutes of Health in Bethesda, MD to help us determine which gene was involved. Using many samples of DNA that had been collected from the affected babies and their families, the team at NIH used "positional mapping" to determine that the critical gene was on chromosome number 17 of the 23 different human chromosomes. Then, by means of hundreds of additional tests taking more than a year, Drs. Rosenberg and Biesecker painstakingly narrowed the region of the chromosome bearing the disease gene down to a small section of the chromosomal segment designated "17q25." By this time Erik Puffenberger had joined the Clinic staff and added his expertise to the DNA detective work, and soon both a "candidate gene" and an apparently disease-causing mutation had been found by the research team. Amazingly, only a few months before this, the same gene had been discovered by a group of scientists in Italy and reported in the medical literature as the "deoxynucleotide carrier" gene, designated "*DNC*." Drs. Rosenberg and Biesecker were then able to show that, as expected, all Amish babies with this type of microcephaly had *DNC* mutations on both of their number 17 chromosomes, whereas each parent of an affected child carried only one mutation. As is usually the case in diseases involving a double dose of a mutant gene, the parents and some sibs who carry a single copy of the *DNC* mutation are completely normal

The next step was to prove that the *DNC* mutation was indeed the cause of the disease. The Italian scientists, headed by Dr. Fernando Palmieri, had earlier shown that the protein encoded by the *DNC* gene was essential for normal synthesis of the small circular chromosome found in mitochondria, the tiny but complicated "furnaces" in every cell that turn food into energy. Dr. Palmieri was therefore asked to study the specific mutation that had been found by the NIH team. He very gladly undertook this special project and, within a just few weeks, had inserted the abnormal gene into a bacterial "plasmid," a virus-like minichromosome. This allowed Dr. Palmieri and his colleagues to synthesize mutant DNC protein in the laboratory and then to show experimentally that the Amish *DNC* mutation completely abolished the function of the DNC protein. Because the urinary compound that first set off the search for the gene, 2-ketoglutarate, requires normally functioning mitochondria for its metabolism, we finally felt that we had indeed found the cause of the microcephaly.

We began our study of Amish microcephaly with the hope that the discovery of the mutant gene would lead us to a treatment, one that could be given to a mother during pregnancy in the same way that prenatal folic acid supplements are used to prevent neural tube defects (spina bifida). Although the nature of the *DNC* mutation now tells us that it will be very difficult to find a prenatal treatment for this severe form of microcephaly, what we have learned may yet be beneficial. Indeed, the discovery of the mutation causing a severe disease often makes possible the identification and treatment of children with milder forms of the same disease who are less impaired at birth. Moreover, *DNC* is one of the first genes linked to a specific biochemical process that is essential for normal brain growth. Understanding such brain-dominant biochemical pathways and how they function before and after birth is essential if we are to unravel the complex biochemistry of the brain and learn how to treat many other brain disorders that today have no effective therapies.

Richard I. Kelley, M.D. Ph.D.

REMEMBERING JOHN HOSTETLER

John was helpful to the Clinic for Special Children in many ways. I first met John at Elizabethtown College in the summer of 1988. He introduced me to Amish friends in Lancaster County who had been of help to Dr. Victor McKusick and him in the early years of genetic research. John came to the first meeting that Caroline and I had with Amish families to discuss the possibility of establishing a clinic in the winter of 1989. He arranged our first meeting with leaders of the Mennonite Church which was held in the home of his close friends, Amos and Nora Hoover, in the summer of 1989. John was a member of the original Board of Directors of the Clinic for Special Children and was actively involved on the board throughout the early critical years of development. After he moved to Indiana he remained an emeritus member of our board. In the last edition of ***Amish Society*** he wrote with interest about the clinic and our efforts to understand and treat genetic disorders. John always helped us, as he helped many people - quietly, thoughtfully, working through his friendships with people from many different places and many different walks of life. He will be remembered by all of us at the Clinic for Special Children. He helped make a difference in the lives of many children, many families. ....Holmes Morton, M.D.

CSC WELCOMES NEW STAFF MEMBER

Christine Hendrickson, R.N. joined the CSC staff in June. Christine worked at Lancaster General Hospital on the Pediatric Unit since 1994 and cared for many of our patients. She is already well acquainted with many families who come to the clinic. We are happy to have her join our medical staff.

CSC LABORATORY UPDATE

The laboratory has been quite busy the past several months. In a continuing effort to provide genetic diagnostic services, we have identified the specific mutations which cause genetic disease in the Amish and Mennonite populations. To date, we have identified 34 different mutations in 26 different genes which cause disease. In some cases, this involved verifying the presence of a mutation in our patients based on a previously published article. For diseases where the mutation had not been previously identified or published, we performed DNA sequencing to identify the causative mutations. We now offer carrier and diagnostic testing for all these population-specific mutations. (See next column.)

In our survey, 20 disorders were caused by a single mutation segregating in the population. However, 6 diseases exhibited mutation heterogeneity; that is, there was more than one mutation found in the respective population. Notably, DNA sequencing of the SLC3A1 and SLC7A9 genes in five conservative Mennonite cystinuria patients identified 4 separate mutations (2 for each gene). Other disorders caused by multiple mutations include congenital nephrotic syndrome (Mennonites), mevalonate kinase deficiency (Mennonites), phenylketonuria (both Amish and Mennonite), and familial hypercholanemia (Amish).

These findings are somewhat unexpected. It is a common belief that most rare genetic diseases in isolated populations (like the Amish and Mennonites) are caused by a single mutation carried into the population by a founder. Since these diseases are rare in the general population, it was believed that only one founder would be a carrier for any particular disease. As an example, all Mennonite patients with maple syrup urine disease (MSD) harbor the same mutation, namely c.1312T->A (a.k.a. Y393N) which they all inherited from a common ancestor. However, our results for the aforementioned diseases show that even in small, isolated populations, a significant proportion of genetic diseases are caused by more than one mutation.

Several diseases are found in both Amish and Mennonite patients from Lancaster County. This is not wholly unexpected as there are known (but distant) genealogical ties and they have a shared religious and geographical history. One disease found in both groups, Crigler-Najjar syndrome, is caused by the same mutation in the gene UGT1A1. We have confirmed that the mutation is identical by direct DNA sequencing and microsatellite marker analysis of the UGT1A1 gene region on chromosome 2. This research was performed this spring by a student from Elizabethtown College, Kym Helwig. She used DNA samples from Crigler-Najjar patients to verify that the mutant UGT1A1 gene in the Amish and Mennonites was identical and thus came from a common ancestor. In addition, she is currently performing additional analyses to ascertain the number of generations back to the common ancestor. In contrast to Crigler-Najjar syndrome, one other disease found in both groups, 3-methylcrotonylglycinuria, is caused by a different mutation in the MCCB gene in each group (c.295G->C in the Amish, c.518insT in Mennonites).

Erik G. Puffenberger, Ph.D., Lab Director

CSC Carrier and Diagnostic Testing

DISEASE	GENE	MUTATION	POPULATION
Aldosterone deficiency	CYP11B2	5 bp deletion	Amish
Bile salt transport defect	FHC1		Amish
	FHC2		Amish
Byler disease	ATP8B1	c.923G→T	Amish
Cartilage-hair hypoplasia	RMRP1	c.70A→G	Amish
Congenital nephrotic syndrome	NPHS1	c.1481delC	Mennonite
Cystinuria	SLC3A1	c.1354C→T	Mennonite
	SLC3A1	IVS6+2T→C	Mennonite
	SLC7A9	c.1166C→T	Mennonite
Crigler-Najjar syndrome	UGT1A1	c.222C→A	Amish and Mennonite
Ellis-van Creveld syndrome	EVC	IVS13+5G→T	Amish
Fragile X syndrome	FMR1	$(CGG)_n$ expansion	Mennonite
Glutaric aciduria	GCDH	c.1262C→T	Amish
Glycogen storage disease, type 6	PYGL	IVS13+1G→A	Mennonite
Hirschsprung disease	EDNRB	c.828G→T	Mennonite
Maple syrup urine disease	BCKDHA	c.1312T→A	Mennonite
McKusick-Kaufman syndrome	MKKS	c.250C->T/c.724G->T	Amish
Medium-chain acyl-CoA dehydrogenase deficiency	ACADM	c.985A→G	Mennonite
Mevalonate kinase deficiency	MVK	c.803T→A	Mennonite
Microcephaly with 2-ketoglutaric aciduria	MUP1		Amish
Nemaline rod myopathy	TNNT1	c.505G→T	Amish
Osteogenesis imperfecta	COL1A2	c.2098G→T	Amish
Periodic fever syndrome	TNFRS1A	c.362G→A	Mennonite
Phenylketonuria	PAH	c.782G→A	Amish and Mennonite
	PAH	c.280-282delATC	Amish
Propionic acidemia	PCCB	c.1606A→G	Amish and Mennonite
Pyruvate kinase deficiency	PKLR	c.1436G→A	Amish
Spinal muscular atrophy, type 1	SMN1	large deletion	Mennonite
Tyrosinemia, type 3	HPD	c.85G->A	Mennonite
3-B-hydroxysteroid dehydrogenase deficiency	HSD3B2	c.35G→A	Amish
3-methylcrotonylglycinuria	MCCB	c.295G→C	Amish
	MCCB	c.518insT	Mennonite

THE CLINIC FOR SPECIAL CHILDREN
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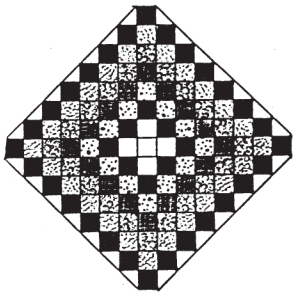
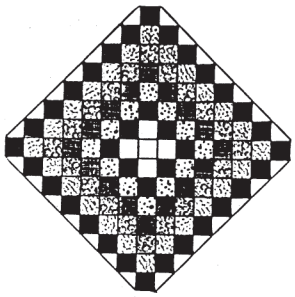


2002 Annual Benefit Auctions

to support

THE CLINIC FOR SPECIAL CHILDREN



Quilts HandmadeToys Furniture Crafts Baked Goods Chicken Barbeque
Donations Appreciated

Shippensburg, PA ~ July 20
Blair County / Morrison Cove ~ September 7
Lancaster County / Leola ~ September 21

Bring your checkbook, no credit cards accepted

Directions for Lancaster County auction: Time: 8:30 am Location: Leola Produce Auction, Brethren Church Road, Leola, PA
Directions: From PA Turnpike, exit 21 Rt. #222 south, exit to Rt. #772 south east, left on Peace Rd., 2nd right.
From Lancaster: Rt #30 east to Rt. #23 east, turn left (north) on Brethren Church Rd. past Leola.
From Rt. 30 (Gap): right to Rt.#772 (Newport Rd.) north west to Rt. #23, right on #23 (New Holland Pike), left on Brethren Church Rd. Auction is approximately 1 mile.

* *

The Clinic for Special Children is a non-profit diagnostic and primary pediatric medical service for children with inherited metabolic disorders in Lancaster County, Pennsylvania. The clinic serves Old Order Amish, Mennonite and other families with children who suffer from a high incidence of genetic diseases such as glutaric aciduria and maple syrup disease. Clinic services include diagnostic, genetic and metabolic laboratory testing, comprehensive pediatric medical care designed to prevent devastating effects of metabolic diseases, clinical research to improve treatment, and services to support the needs of parents. The Clinic is funded through a combination of fees for services, benefit auction proceeds and private contributions.
The Clinic is tax exempt under IRS 501 (c)(3), ID # 23-2555373.

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