



# CLINIC FOR SPECIAL CHILDREN NEWSLETTER

VOLUME I NUMBER 20

\* LANCASTER COUNTY, PENNSYLVANIA \*

SUMMER 2003

*In this issue of the Newsletter we write of Possibilities : from Kevin Strauss' remarks at last September's auction , to the work in progress on many different genetic disorders, to the information the field of genetics brings to bear on research to understand diseases, to education and training of students and future physicians, and to the role of the Clinic for Special Children to help these possibilities continue to grow in the future.*

## POSSIBILITIES

by Kevin Strauss, M.D.

One hundred years ago Dr. William Osler remarked that the sharpest contrast in medicine was that between possibility and reality. This is true now as it was then. If one looks up the word *possibility*, they find several words which can be used in its place: **"hope, within reach, and practicable"**.

Wallace Stegner summarizes these various meanings of the word when he outlines the elements that allow the possible to become real. First *optimism*, then *pragmatism*, and finally *strenuous work*. For him, these are the foundations of charity. I am certain that Holmes and Caroline Morton, Richard Kelley, and members of the clinic's board with the courage to start this special project understand all these meanings of the word possible. The community that comes together each year to raise money and support especially understands its first and last meaning: *Hope* is centered on the belief that no child should suffer. *Practicable* means that lives can be improved with means at hand.

Fourteen years ago one could only imagine a reality that would grow from the hope to have a place where special children could seek care. The reality is still unfolding ---every day there are more children with new and difficult problems. They drive us on to new possibilities, but the core elements remain the same:

*We are optimistic.* Optimism is a gift from children. By paying attention, taking time to listen and think, by seeking ways to relieve suffering, we learn that many metabolic diseases are treatable with means currently at hand.

*We seek solutions that are practical.* One of the largest challenges of modern medical science is to make new discoveries available to people who need them. There is much hope in new medical therapies, but they are meaningless if we cannot bring them to bear on people's lives.

*We continue to work strenuously.* When I began work here last year, some hoped Dr. Morton may finally get some rest. He does not seem better rested to me, and I understand why. Children don't get sick in "day-tight" compartments. Worry and sadness don't stop when the sun sets at the end of the day. There is always pressing work - the children are not all well, they are not all safe from harm. **Much more is possible.**

## AUCTION DATES FOR 2003:

JULY 19 - SHIPPENSBURG  
SEPTEMBER 6 - BLAIR COUNTY  
SEPTEMBER 20 - LANCASTER COUNTY



Log Cabin Quilt featuring the clinic made and quilted by families of children with glutaric aciduria for the Lancaster auction

## 2003 AUCTIONS

Summer always brings anticipation of benefit auctions now in three locations. The auction sponsored in **SHIPPENSBURG** took place on July 19th with beautiful weather and good attendance. A spring wagon made especially for the event brought a good price and there were 22 quilts donated for the sale in addition to furniture, lawn furniture, plants and a variety of other items.

The 7th **BLAIR COUNTY** auction will take place on Saturday, September 6 at Morrison Cove on Rt 36 south of Roaring Spring, PA. The auction will begin at 9:00 am and will feature quilts, furniture, crafts and delicious food. Please contact 814-793-3634 or 814-793-3010 or 814-224-5442 for more information or to arrange a donation for the sale.



The 13th auction in **LANCASTER COUNTY** will be held Saturday, September 20th at the Leola Produce Auction facility on Brethren Church Road, north of Rt# 23 in Leola starting at 8:30 am. This year Dr. Morton and Dr. Strauss will give their brief remarks earlier at 11:00 am before the major furniture pieces start at 11:15 and quilts go up for sale starting at 11:30. Gift certificates and lawn furniture will start at 1:00. Please call one of the following to arrange a donation for the sale: 717-626-4863, 717-354-5415, or 717-656-9694. We know of many beautiful quilts already sent in and more on the way. A new Amish carriage, a spring wagon with two seats, new furniture, lawn furniture and another Amish school playhouse will also go up for sale with many other items. We look forward to the delicious chicken barbecue, pork roast, soft pretzels, ice cream, pizza and all the other food items that will be prepared. We are told some people come just for the donuts!

*Please join us for one of the auctions and help support the clinic. The Clinic depends on the auctions each year as a major source of revenue to support the annual operating expenses of the clinic. Due to the support each year from the community through the auctions, the clinic is able to provide comprehensive medical services at a low cost for families, many of whom care for children with chronic conditions without benefits such as health insurance.*



"Buggy Jam" at the 2002 Lancaster County Auction  
photo by R.I. Kelley

#### HIGHLIGHTS FROM LAST YEAR.....

A record number of quilts and furniture were donated for the 2002 auctions and a record crowd bought an amazing amount of food. We are very grateful to the three auction committees in Lancaster, Blair County and Shippensburg for their energy and effort to bring the clinic outstanding community support. In a year which saw many non-profit organizations struggle financially to survive, we especially counted our blessings and offer our thanks to all who generously supported us.

#### Some highlights from the Lancaster auction last year:

94 full size quilts (including tops & comforters);  
1644 registered bidders;  
approximately 4000 items donated and sold including 16 sheds,  
an Amish School playhouse, a buggy, pony & wagon.  
Nineteen auctioneers volunteered their services.  
And, the food: 3500 soft pretzels; 1500 pizza slices;

4000 subs; 2500 ham & cheese sandwiches; 2500 pork barbecue sandwiches; 2520 pounds of chicken (60 cases); 175 fresh strawberry pies; 6000 cones of ice cream; 1620 servings of french fries; 600 pounds of potato chips; 2500 cups of lemonade; 768 cups of rhubarb fruit drink and 20,000 donuts!

\*\*\*\*\*

#### A NEW HPLC

The clinic recently received a new HPLC (amino acid analyzer) as a gift through the AJS Foundation for MSD. Our old amino acid analyzer has been the work horse in our lab since 1990 and has yielded 17,634 amino acid profiles over thirteen years to monitor children with maple syrup disease and other disorders. Five years ago Hewlett Packard granted us an updated chemstation unit for the analyzer, however we were recently informed by Agilent Technologies (formerly part of Hewlett Packard) that service and parts for our old unit was limited. We are very grateful to the AJS Foundation, the Stamps family and friends for this much needed gift. We will put it to good use and continue to offer this essential lab service at a very reasonable cost to our patients.

#### NEW ROOMS, NEW STUDIES FOR THE AMISH RESEARCH CLINIC

Over the winter the lower floor office space was renovated to create two additional exam rooms to accommodate the increased needs of the Amish Research Clinic under the direction of Dr. Alan Shuldiner of the University of Maryland School of Medicine. The research clinic recently began an extensive new study of causes of heart disease in Amish families. Studies of the adult Amish population related to diabetes, hypertension, longevity, osteoporosis, and cardiac calcification continue. Dr. Dwight Stambolian, University of Pennsylvania, also continues his studies of myopia and other vision problems in the adult Amish population. For more information about these genetic studies and clinics call 717-687-8371.

#### GRANT FOR PKU STUDIES

The Mid-Atlantic Connection for PKU and Allied Disorders, (MACPAD) provided a grant to the clinic to study PKU in Amish and Mennonite patients to determine the distribution of various PKU gene mutations within this population. One goal of the study is to determine if the cofactor bipterin can improve amino acid tolerance and alleviate neurological symptoms. Another goal is to assess the general nutritional status of older patients with PKU. Funds for the grant were raised by a walkathon in New Jersey sponsored by parents/members of MACPAD.

#### HELP FROM FRIENDS

We thank the Paul I. Sheaffer Insurance Agency and staff, especially Misty Wintsch, Senior Account Executive, for their recent fund raiser sponsored to benefit the clinic and to help "make special children healthier". The event raised \$2331.00 with support and donations from many area businesses including Sheaffer Insurance and Garden Spot Bowling. Your help is much appreciated by all of us at the clinic.



## PROGRESS NOTES

### Methylene tetrahydrofolate reductase deficiency in Somerset County, Pennsylvania

Kevin A. Strauss, M.D.

This year we identified a rare genetic disease called 5,10-methylene tetrahydrofolate reductase deficiency (MTHFR) in three Amish children from Somerset County, Pennsylvania. As a result of an enzyme deficiency, the liver cannot convert a chemical called **homocysteine** to the essential amino acid **methionine**. The liver tries to compensate by using another molecule, **betaine**, to produce methionine from homocysteine. Betaine is derived from **choline** and its precursor, **phosphatidylcholine (PC)**. These natural dietary constituents normally present with high levels in the blood. MTHFR disease arises from both the toxic effects of high homocysteine and deficient supplies of methionine and phosphatidylcholine (PC). High homocysteine levels injure blood vessels throughout the body, placing children and adults at risk for early-onset heart attack, stroke, or blood clots in the lungs. Methionine and PC are vital nutrients for the brain and other body tissues. Low supplies result in abnormal brain growth, function, and development.

Children with the disease may have slow brain and head growth during the first year of life, low muscle tone, and poor social interaction. They are unlikely to sit up, stand, or walk on time, and may never do so. Children who initially learn to walk may lose this ability later in life, as their limbs become increasingly stiff. Most affected people will not learn how to understand or speak language, and may make poor eye contact despite the ability to see normally. As they get older, they may be severely retarded. A few individuals with the disease have initially developed normally, only to have a decline in thought and language during young adult years. Some of these patients were diagnosed with early onset schizophrenia or dementia. Patients with MTHFR rarely have seizures.

A major risk for affected patients is clotting in the arteries and veins that can block off blood flow to the heart, brain, or lungs. Without specific therapy, many patients will die or suffer permanent injury due to a sudden clotting event. This risk may extend to parents of affected children. These parents are *carriers* of the abnormal gene, meaning they have one normal and one abnormal gene copy. As carriers, liver enzyme activity is sufficient to maintain blood methionine levels and prevent brain disease. However, carriers can develop mild or moderate elevations of blood homocysteine if their dietary intake of methylfolate and/or choline-PC is low. This puts them at risk for early heart attack or stroke.

Therapy for MTHFR is directed at reducing blood homocysteine to a safe level, while increasing the brain's supply of methionine, choline, and PC. This is first accomplished with diet. Infant formula is a good source of protein and certain formulas, such as Pediasure, are high in both methionine and choline. Eggs are an **excellent** source of both methionine and PC. Affected children are encouraged to

eat 1-2 eggs per day. The major form of therapy is a nutrient called **Cystadane (betaine)**. This natural compound allows the liver to convert homocysteine to methionine, lowering the homocysteine while simultaneously supplying the brain and other organs with an adequate supply of methionine. Cystadane works very well, but typically *does not* bring the homocysteine level down to normal. It can be mixed in with milk, formula, or solid food and has no side effects. While the homocysteine remains even mildly elevated, it remains important to use low doses of medicines such as **aspirin** to reduce the tendency for the blood to clot. Because the use of aspirin can be dangerous in children, this medication should **never** be given to a child unless under the strict guidance of a medical doctor.

At the Clinic for Special Children we are interested in learning more about MTHFR so we can design approaches to early diagnosis, treatment, and disease prevention. Many problems associated with MTHFR can be eliminated by a safe and well-tolerated nutrient therapy. Starting the treatment early in life is key to its overall benefit. This requires that we identify people with the disease and young parents who may be carriers. We are working with the NeoGen newborn screening laboratory in Pennsylvania to set up a simple test to be done on all babies born in Somerset County. This test would be part of the standard filter paper screen of all newborns, would require no extra blood samples, and could detect affected babies within the first weeks of life before the disease causes significant injury to the brain and blood vessels. We made significant progress on July 9, 2003. Dr. Strauss and Christine Hendrickson traveled to the workplace of Bennie C. Yoder in Springs, PA, and collected blood samples on seventy willing individuals from the community. These samples will be used for carrier testing and the development of a newborn screening test. The testing will allow us to start affected infants on therapy as early as possible, before they have any signs of brain disease. We appreciate help from the community as we learn more about the extent of MTHFR disease in the Somerset County Amish and the various ways it impacts the health of children and adults.

### Swarey Syndrome in the Belleville Amish Community

Holmes Morton, M.D.

Over the past two generations nine families from the Belleville Amish community collectively have lost twenty infants to what is locally known as Swarey Syndrome. The clinic has cared for the last three of the infants who died from this lethal, genetic syndrome. Other infants were cared for by local physicians and major medical centers in PA. Several infants were studied extensively at a cost of hundreds of thousands of dollars which yielded little helpful information. The syndrome is unexplained, no diagnostic tests are available and recognition is difficult, particularly in affected females. Despite the initial healthy appearance of the infants, modern medical care has had little help to offer these infants.

Infants with Swarey syndrome die of apnea or an unexplained respiratory arrest usually before six months of age. Affected newborns, who otherwise appear to be normal, have a peculiar cry and are usually difficult to feed. Amish women who cared for many of the infants say they can recognize affected infants at birth by the unusual sound of their cry. Parents report infants have seizures, but EEG's are normal. Male infants with Swarey syndrome have ambiguous genitalia. Both males and females have had the same degree of neurological dysfunction and die at approximately the same age.

Over the past 10 years searches for the genetic basis of the disorder have been extensive. Endocrinologic and biochemical tests included normal steroid and organic analysis by gas chromatography mass spectrometry in our lab and elsewhere. Neo Gen Supplementary Screening laboratory in Pittsburgh has tested several of the infants using tandem mass spectrometry and RIAs for congenital adrenal hyperplasia. Plasma and cerebral spinal fluid amino acids and neurotransmitter metabolites were normal. Chromosomes have been done repeatedly over the years both to determine sex of the infant and as an effort to find any aberration in a chromosome. PCR and gene sequencing has been done in our laboratory to rule out a variant of spinal muscular atrophy and a laboratory in Boston searched for other known mutations, but neither of these studies of candidate genes were informative.

The staff at the Clinic for Special Children have devoted much time to discussing case histories with families, studying genealogies, reviewing medical records, extensive biochemical and genetic tests that were done by our laboratory and elsewhere to help understand this unexplained deadly disorder. We think the only way to find the genetic basis of the syndrome is to do homozygosity mapping to find candidate genes. DNA from recent and past cases of Swarey syndrome families were collected for mapping studies using the latest SNP mapping technology available. Once the gene is identified it will give us early and accurate diagnostic capability and hopefully lead to more information about the cause and possible treatment for this disease. The gift from Affymetrix of DNA microchip arrays (see laoratory news) has been extremely useful in this search and after months of effort with two different labs, we now have preliminary data to localize the gene. We hope to make progress and to have possibilities for infants in the future born with this disorder.

### CRIGLER - NAJJAR CONFERENCE '03

The Clinic hosted a national conference on Crigler - Najjar Disease in June for families affected by the disorder. The conference was held at the request of parents after an earlier scheduled conference was cancelled and focused on topics of interest including advances in phototherapy to help control high bilirubin, current practices in liver transplant, and research in cell transplants.

The meeting was attended by 17 families with 21 children/adults with C-N. Dr. and Mrs. John Crigler also

attended the meeting as special guests. The following speakers and topics were presented:

Dr. Holmes Morton presented a clinical summary about the rationale for the *Clinic for Special Children Crigler-Najjar Treatment Protocol*. Dr. Kevin Strauss discussed *Bilirubin toxicity: Case studies and neuropathology*. Dr. Erik Puffenberger described *Genetics and Molecular Biology of Crigler-Najjar Syndrome*.

Dr. George Mazariegos and Lynn Seward, RN, of the liver transplant team from the University of Pittsburgh Transplantation Institute, presented information related to *liver transplant* - what is involved in the decision to be listed for transplant, transplant procedures, recent data on immune modulation and transplant outcomes.

Dr. Bryon Petersen, University of Florida and Dr. Steve Strom, Pittsburgh Children's Hospital, presented new developments in hepatic *stem cell transplants*. Dr. Hank Vreman, Stanford University, discussed current technology of *phototherapy* approaches including the use of LED lights and data on a recently tested new phototherapy unit. Graham Hart, PhD, Medical Physicist from Bradford, England discussed what effect phototherapy or high bilirubin may have on color vision. He and his wife, Maria, conducted vision studies with volunteers at the meeting. Alex Carmichael, an engineer from Australia and a grandfather of a child with C-N, presented his design of an innovative phototherapy "box".

David Strayer, MD, PhD, Department of Pathology and Cell Biology at Jefferson Medical College, Philadelphia, presented *gene therapy* research using the SV40 viral vector and immune suppression. Michael Blaese, MD, reviewed other current efforts in gene therapy and discussed what has happened since the last C-N meeting regarding the approach called "chimeraplasty".



Dr. Morton and Dr. and Mrs. Crigler with C-N Conference participants



## DISCUSSION OF LIVER TRANSPLANT & GENE THERAPY:

None of the patients with Crigler-Najjar disease at the Clinic has undergone liver transplant. Parents and patients were discouraged by high costs, the many clinical and social difficulties of liver transplant, and by the significant risks of chronic immune suppression. Liver cell transplant, a promising new technique in 1996, did not control serum bilirubin adequately, required aggressive immune suppression, and now appears unlikely to become a viable alternative to whole or partial liver transplant.

In the past ten years decisions about liver transplant have also been delayed because of improvements in non-surgical management of the disorder and more recently, by encouraging developments in gene therapy. In September 1999 Clifford Steer and his colleagues reported successful repair of the gene mutation of the Gunn rat using a new approach to gene therapy called *site-directed mutagenesis by a chimeric oligonucleotide*. Gene repair by *site-directed mutagenesis* appeared to be ideal for patients with point mutations of the gene as in the case of Crigler-Najjar syndrome. However, this experiment has not been replicated. The biotech firm that was formed to develop the technology has gone into bankruptcy.

Successful hepatic stem cell transplants and gene replacement studies using viral and non-viral vectors appear to offer new possibilities, however, the techniques discussed at our June conference will undergo many refinements and years of additional laboratory studies to show efficacy and safety before the first human studies can be started. Once human studies begin and treatment protocols are established, it will be 5-10 years before significant comparisons can be made between these new therapies and liver transplant. The transplant center at Children's of Pittsburgh has done more than 5000 liver transplants for children over a 20 year period and currently does approximately 50 whole liver transplants per year. Over the past five years the perioperative mortality has decreased - over three years 150 transplants have been done without a perioperative death. Immunosuppressive therapy has also improved to both prevent rejection and limit side effects of chronic immune suppression. Liver transplant will remain the therapy for Crigler-Najjar to which experimental gene therapies will be compared for many years to come.

**CONCLUSIONS:** The 10 year experience at the clinic indicates that Crigler-Najjar syndrome can usually be managed to prevent severe or lethal neurological injuries. Infants must be recognized and treated before brain injury occurs. Phototherapy remains an essential part of therapy, however, especially during illnesses, treatment involves management of many different aspects of bilirubin metabolism and toxicity. Prolonged fever, dehydration, fasts, vomiting, signs of liver dysfunction, cholecystitis, or neurological signs of bilirubin intoxication should be evaluated carefully. Current medical management of Crigler-Najjar syndrome allows prevention of acute bilirubin intoxication in infancy and early childhood; nonetheless, the risks of irreversible brain injury and the costs of care over 10-20 year periods are high. Liver transplant is likely to remain the only definitive treatment of the disorder for the next decade.

## LABORATORY NEWS

For the past four years, the clinic laboratory has been identifying the specific disease mutations which are found in the Old Order Amish and Old Order Mennonite populations. This work contributes to more specific diagnostic capability and often leads to improved medical care for patients. Blood samples from clinic patients have been used to perform DNA sequencing of candidate genes. This strategy has allowed us to identify the molecular basis of genetic disease (i.e. the mutation) in many patients. In the absence of strong evidence linking a disease to a particular candidate gene, it is necessary to know the general location of the disease gene among the 22 human chromosomes. Unfortunately, not all known genetic disorders have been localized to specific chromosomal regions. For seventeen of the disorders found in clinic patients, the chromosomal localization is unknown; thus, efforts to identify the disease gene are nearly impossible.

In an effort to develop techniques to localize and identify additional disease mutations, we have solicited help from several biotechnology companies. One company, Affymetrix, Inc., sent representatives to visit the clinic and to determine our needs. After that visit, the company donated 100 DNA microchip arrays (a \$40,000 gift). These chips can provide genotype information used in mapping (or localizing) disease genes to specific chromosomal regions. Once the disease gene is localized, we can search through the list of genes found in that same chromosomal region for an appropriate candidate gene to sequence. The chips require special (and expensive) instrumentation and training. We have arranged for the donated chips to be sent to the lab of Dr. Dietrich Stephan, who will actually perform the analyses using DNA samples collected at the clinic. They began the analysis several weeks ago and the preliminary data is now being studied. Several previously mapped disorders were sent for validation purposes. If the technique works properly, we should be able to verify the mapping of these genes, thus demonstrating the utility of the method. DNA samples from patients and families with unmapped disorders are being run to identify the genomic localization of their genetic disease. One such unmapped disorder, Swarey syndrome, is the first disorder we are testing with these chips. Currently, we have preliminary data localizing the Swarey disease gene. In the coming weeks, we will be searching this region for suitable candidate genes to sequence.

### **The clinic uses a DNA sequencer to perform diagnostic tests for specific mutations in the following disorders :**

Aldosterone deficiency  
Amish microcephaly  
Byler disease  
Cartilage- hair hypoplasia  
Congenital nephrotic syndrome  
Crigler Najjar disease (Amish & Mennonite)  
Cystinuria  
Ellis-van Creveld syndrome  
Familial hypercholelanemia

Fragile X syndrome  
 Galactosemia  
 Glutaric aciduria type1 GA 1 (Amish variant)  
 Glycogen storage disease, type 6 (Mennonite)  
 Hirschprung disease  
 Homocystinuria  
 Maple syrup disease MSD ( Mennonite)  
 McKusick-Kauffman syndrome  
 Medium chain dehydrogenase deficiency (MCADD)  
 Mevalonate kinase deficiency  
 Nemaline rod myopathy  
 Osteogenesis imperfecta  
 Phenylketonuria (PKU)  
 Propionic acidemia  
 Pyruvate kinase deficiency  
 Sitosterolemia  
 Spinal muscular atrophy, type 1  
 Tyrosinemia, type 3  
 3-B-OH-steroid dehydrogenase deficiency  
 3-methylcrotonylglycinuria

#### RECENT JOURNAL PUBLICATIONS:

A special issue of the American Journal of Medical Genetics Part C (Seminars in Medical Genetics), August 2003, published four articles from the Clinic for Special Children: **Pediatric Medicine and the Genetic Disorders of the Amish and Mennonite People of Pennsylvania** by D. Holmes Morton, et. al.;

**Genetic Heritage of the Old Order Mennonites of Southeastern Pennsylvania** by E. G. Puffenberger;

**Type I Glutaric Aciduria, Part 1: Natural History of 77 Patients** and

**Type I Glutaric aciduria, Part 2: A Model of Acute Striatal Necrosis** by K. Strauss and D. H. Morton.

Other publications:

**Branched-chain Ketoacid Dehydrogenase Deficiency: Maple Syrup Disease** by Kevin Strauss, MD and D. Holmes Morton, MD was published in Current Treatment Options in Neurology, 2003.

Recent research related to our patients with Nemaline Myopathy (Chicken Breast Disease) was published by J.P. Jin of Case Western Reserve University School of Medicine in The Journal of Biological Chemistry, July 11, 2003 issue. The article titled **Truncation by Glu180 Nonsense Mutation Results in Complete Loss of Slow Skeletal Muscle Troponin T in a Lethal Nemaline Myopathy** will contribute to the on-going work at the Clinic to understand and treat this deadly disease.

#### OUR WEB SITE:

[www.clinicforspecialchildren.org](http://www.clinicforspecialchildren.org)

The clinic recently updated our web site to include listings of recent publications in addition to information regarding laboratory tests available.

#### MEETINGS AND LECTURES:

In addition to recent publications, the Clinic staff has also presented papers and lectures at a number of professional meetings.

\* Four posters were presented at the Annual American Society of Human Genetics Meetings last fall in Baltimore.

\* Dr. Morton presented the Joe Ireland Lecture sponsored by SHS International at the Royal College of Physicians in London on the *Management of Maple Syrup Disease*.

\* Dr. Strauss traveled to Brazil at the invitation of physicians in that country who wish to establish facilities to improve treatment for metabolic disorders, specifically maple syrup disease.

\* Dr. Morton also presented a plenary lecture titled *From Genome to Disease Prevention* at the American Diabetes Association annual meeting in New Orleans and lectured for the 17th year at the National Youth Science Camp in West Virginia.

\* Dr. Strauss presented senior rounds at Boston Children's Hospital and grand rounds at Boston Medical Center.

\* Dr. Morton presented grand rounds at St. Christopher's Hospital, Philadelphia, and is scheduled at Children's Hospital at Hershey Medical Center, and Doylestown Hospital.

\* In October, Dr. Strauss will participate in the 3rd International Workshop on GA I in Heidelberg, Germany.

\* Drs. Morton, Strauss and Puffenberger also lectured at the Temple University/LGH Family Practice Review Courses in Lancaster.

\* Donna Robinson will give a series of lectures to update the pediatric staff at Lancaster General Hospital on current trends in the care of patients with metabolic disease.

#### CLINIC OPENS IN OHIO

Das Deutsch Center for Special Needs Children in Middlefield, Ohio, celebrated its official opening in its new location in July. The clinic is modeled after the Clinic for Special Children to care for children with chronic conditions related to genetic diseases, to provide diagnostic services and contribute to research on rare disorders that affect families in this region of Ohio. The clinic is under the direction of Dr. Heng Wang

*We need your support each year to continue our work. Please consider a donation to the clinic. We also invite you to attend one of our auctions this year and enjoy the spirit of community support evident at these events. Your help is very much appreciated and we thank you.*

Clinic for Special Children  
 PO BOX 128  
 Strasburg, Pennsylvania 17579



## JOHN RIEHL

As a father, John Riehl knew the needs of special children and how the challenges of caring for them can teach all of us how to be better, compassionate people. He also taught us and contributed his insight and wisdom to the clinic for nearly ten years on the clinic's Board of Directors. His example and his gifts to the clinic will always be a part of us. He died last winter. We miss him.

## GIFTS IN MEMORY

Memorial donations were designated for the clinic from the family of Seth Hand, a special and courageous young boy whose doctor was Dr. Richard Kelley. Friends and family of Mr. Lawrence Winans, a long time friend of the clinic, donated funds in his memory to the clinic. We very much appreciate these thoughtful gifts.

## LEARNING AT THE CLINIC: PLANTING SEEDS OF POSSIBILITIES

An MD /PhD student at Hershey Medical Center who studied at the Clinic is pursuing a doctoral thesis inspired by his experience and observations while at the clinic. Bill Zinnanti writes of his experience.... *The week that I worked with Dr. Morton and Dr. Strauss we started each morning with a visit to the Pediatric Intensive Care Unit (PICU) to see a four-year old boy in the coma stage of maple syrup disease. I watched carefully as Dr. Morton and Dr. Strauss reviewed all the information collected during the night on this child. I will not forget the words of one of my attending physicians to Dr. Morton about whether this child would wake up again, let alone walk or speak. Dr. Morton maintained that a phenomenon of this kind of brain swelling was that the patient had the ability to recover completely and two weeks later he did. One of the great success stories of a child in coma from maple syrup disease has inspired my thesis research for the next three years ...at least.*

Bill Zinnanti is now conducting his thesis research in the neuroscience lab of Dr. James Connor at Hershey Medical Center. Bill will use a special culture system based on animal models to study the effects of metabolic disorders such as glutaric aciduria and maple syrup disease on the blood brain barrier.

*Footnote: The boy in coma was recently seen rollerblading at his home and is fully recovered.*

Over the past year a number of students and medical residents in training have come to the clinic to learn about genetic disorders and how the clinic functions to care for children with complicated diseases. We hosted residents from Children's Hospital of Philadelphia, Crozer Pediatric Services and Lancaster General among others. Next month a senior at Dartmouth Medical school will spend several weeks at the clinic to learn how we approach care for children with complex chronic medical needs. During the next year we will assess how the clinic might develop further opportunities for medical students, residents and fellows to learn at the clinic through more defined courses of study.

*Two students contributed insight into the genetic history of the Amish and Mennonite populations. Both students worked under the direction of Dr. Erik Puffenberger in our lab and both gave us interesting, unexpected but similar information.*

## ANCIENT FAMILY HISTORY

Last year, the lab hosted a student from Elizabethtown College, Kym Helwig, who performed a study of Crigler-Najjar syndrome in Amish and Mennonite families. This disease is found in both plain populations and we know that the same mutation causes the disease in both groups. Since the mutation was identical, it was believed that a common ancestor for both Amish and Mennonite cases could be found. However, no clear genealogical connection could be made. We analyzed many genetic markers around the mutation in order to estimate the age of the mutation. The estimate of mutation age is calculated based on the amount of shared DNA surrounding the mutation. The more recent the common ancestor, the larger the shared portion of DNA around the mutation. As the common ancestor becomes more and more remote, the shared piece of DNA becomes smaller and smaller. As an example, the average shared fragment of DNA around the maple syrup urine disease (MSUD) mutation in Mennonite patients is roughly 8 centimorgans, which corresponds to about 8 million bases of DNA surrounding the mutation. If the Amish and Mennonite Crigler-Najjar patients shared a common ancestor at or around the time of emigration to the U.S. (as in MSUD patients), then the shared fragment of DNA should be about the same size. However, the data clearly show a shared fragment of DNA which is significantly smaller than expected (< 1 centimorgan or 1 million bases of DNA). This places the common ancestor back approximately 65 generations or roughly 1500 years. This indicates that the mutation was carried into each population independently and that the common ancestor for this mutation in Amish and Mennonite patients lived around 500 A.D.

## UNDERSTANDING POSSIBILITIES BY ANALYZING THE PAST

Mary Caperton Morton, a biology major at Franklin & Marshall College, performed analysis of mitochondrial DNA at the clinic to study genetic history and diversity in the Old Order Amish and Mennonites of Lancaster County. She analyzed over 200 samples under the direction of Dr. Erik Puffenberger in the lab to discover a total of 43 different sequences or haplotypes tracing back to 80 founding women of the Lancaster Old Order populations. A finding of interest is the striking dissimilarity between the two groups in that only *four* of the 43 haplotypes were shared by both the Amish and Mennonites suggesting that the two groups were not a genetically homogeneous population at the time of the Amish split in 1693. This finding indicates that the founding populations of Amish and Mennonites were not closely related genetically, even though they share similar social histories. Her study helps us understand the factor known as the "founder effect" that contributes to the relatively high incidence of genetic disorders in isolated populations. We know that many of the genetic diseases we treat today actually came into the population by chance centuries ago. *(Mary is the daughter of Dr. and Mrs. Morton and spent much of her time growing up with the clinic.)*

THE CLINIC FOR SPECIAL CHILDREN  
P.O. BOX 128  
STRASBURG, PENNSYLVANIA 17579



2003 Annual Benefit Auctions  
to support  
**THE CLINIC FOR SPECIAL CHILDREN**

*Quilts Handmade Toys Furniture Crafts Baked Goods Chicken Barbeque  
Donations Appreciated*

**Shippensburg, PA ~ July 19**  
**Blair County / Morrison Cove ~ September 6**  
**Lancaster County / Leola ~ September 20**



*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.*

**Clinic for Special Children**  
P.O. Box 128 Strasburg, PA 17579  
(717) 687-9407

**WEB SITE:** [www.clinicforspecialchildren.org](http://www.clinicforspecialchildren.org)

**Clinic for Special Children Board of Directors:**

Holmes Morton, MD President  
Richard I. Kelley, MD, PhD Secretary  
Caroline S. Morton, Treasurer  
Enos Hoover  
Leonard Hurst

**Staff:**

Holmes Morton, MD, Director  
Caroline S. Morton, EdM, Executive Director  
Kevin A. Strauss, MD, Pediatrician/Genetics Fellow  
Erik G. Puffenberger, PhD, Laboratory Director/ Geneticist  
Donna Robinson, RN, CPN, Nurse Practitioner  
Deborah LaBerge, RN, MSN, Immunization Program  
Christine Hendrickson, RN, Office Nurse  
Rebecca Smoker, Office Manager, part-time  
Miriam Echternach, Assistant Office Manager, part-time  
Richard I. Kelley, M.D., PhD, Consulting Geneticist

The Clinic for Special Children is a registered charitable organization. In accordance with Pennsylvania law, we are required to advise you that a copy of our official registration and financial information may be obtained from the PA Dept. of State by calling toll free 1-800-732-0999. Registration does not imply endorsement.