

# CLINIC FOR SPECIAL CHILDREN NEWSLETTER

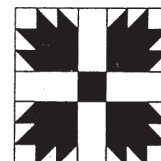
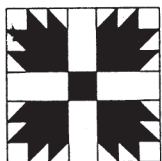
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\* LANCASTER COUNTY, PENNSYLVANIA \*

SUMMER 2004

*The traditional quilt pattern used in this issue of the newsletter is called "Bear Paw" for its resemblance to a paw or foot print. The tracks pointing outward in four directions bring to mind how the Clinic has forged a path from its foundation over the last fifteen years. In this issue of the newsletter you will read about advances in medical care for children with rare disorders. Treatment for some disorders has been a constant effort in progress since the clinic began, others are recent efforts. For some of these disorders the clinic offers the most advanced care for children anywhere in the world. In seeking to improve care for children we also have forged a path in clinical research, seeking state of the art methods, equipment and collaborations to learn as much as possible about rare diseases and to bring this new knowledge back to help the children who need it. From our time and effort in forging better medical care and advancing research, we find ourselves educating others by example. This path will grow even more in the next few years as we find ways to help others learn to care for children in other places with rare, difficult disorders. The fourth footprint has led to a path created by many generous people over the years who have supported the clinic and who have shown it is possible for a small independent non-profit clinic built on a farm in Pennsylvania to make a difference in the future of many children's lives. We will continue to make new tracks.*

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## AUCTION SEASON IS HERE !

**July 17 ~ Shippensburg**  
**September 11 ~ Blair County**  
**September 18 ~ Lancaster County**

Plans are cooking for all three auctions that support the clinic. Handmade quilts, furniture, crafts, farm items, baked goods, chicken barbeque and so much more are featured at all three sales. In each area, volunteers on the auction committees are busy with preparations and do an amazing job organizing these events. This support is very important to the clinic and provides approximately one-third of the operational funds needed each year to run the clinic. There are also other reasons we look forward to the auctions. They help build a network of support for children and families who need the clinic. The auction is a reunion of family and friends for many. The auction helps spread the word of services available at the clinic and of our work to improve care and promote research on rare inherited diseases.

**Shippensburg:** The first auction of the season takes place on July 17th at Leinbach's Produce Auction on Rt.#11 north of Shippensburg, PA. This will be the 6th year the community in Shippensburg has volunteered support for the clinic. Over 30 quilts, cedar chests, lawn furniture, plants and a two-seated spring wagon with lights were some of the items donated this year. Please call 717-532-9088 for more information.

**Blair County:** The 8th annual auction sponsored by families in the Blair County region will take place on September 11 at the Morrison Cove produce auction center on Rt.#36 south of Roaring Spring, PA. Many Amish families from Somerset County are



*Staff Meeting*

The Clinic Staff, from left, Donna Robinson, Dr. Kevin Strauss, Dr. Erik Puffenberger, Miriam Echternach, Dr. Holmes Morton, Caroline Morton, Christine Hendrickson. Not pictured, Rebecca Smoker, and Debbie LaBerge

helping with this auction as the clinic's services have been extended to help children with genetic conditions in that area. Call 814-793-3634; 814-793-3010 or 814-224-5442 for information or to donate items.

**Lancaster County:** It's hard to believe this will be the 14th annual auction in Lancaster County for the clinic. Last year



hurricane Isabel was bearing down on us and it was easy to believe that was auction #13! This year the event will take place as always on the third Saturday of September, September 18th, at the Leola Produce Auction facility on Brethren Church Road, north off Rt# 23 in Leola. Auctioneers will begin at 8:30 am, Dr. Morton and Dr. Strauss will give their brief remarks at 11:00 am before the quilts and major furniture pieces start at 11:15, gift certificates and lawn furniture will be sold at 1:00pm. Please call one of the following to arrange a donation for the sale: 717-626-4863, 717-354-5415, or 717-656-9694.

**Highlights from last year.....**Support was nearly blown away for last year's auction in Lancaster County, but Hurricane Isabel left town just as the tents were ready to be put up on Friday afternoon. Travel was difficult for many who had planned to attend from out of town and attendance was lower than the year before. But, in spite of everything we had a good auction. Some highlights from 2003 in Lancaster:

1428 registered bidders ~ 3228 items auctioned including 82 large quilts, an Amish school playhouse and many other sheds, new spring wagon, two complete bedroom furniture sets and many other furniture pieces, lawn furniture, swing sets, crafts, toys ~ food sold included 18,000 donuts, 7300 sandwiches with 500 Buffalo burgers & 2200 pork barbeque & 3800 subs donated by Sheetz ~ 3800 pieces of chicken ~ 520 pizzas ~ 6600 ice cream cones ~ 3500 soft pretzels ~ 4000 cups of lemonade ~ 168 strawberry pies ~ 400 milk shakes ~ 2048 bags of freshly made potato chips..... just to give you some of the flavors of the auction and what to look forward to again this year.

We express our thanks and appreciation for all members of the three auction committees who work so hard each year to make the auctions such fun and a great success and provide the clinic with very needed support to continue its work.



#### .....COMING AROUND

Eight years ago at the auction, three Morton children bid on a pony and "won" much to the surprise of their parents, Holmes and Caroline. They named their pony *Third Saturday of September*, after the auction's traditional date and she was always called "*Saturday*". At the time she joined the Morton family she was about 12 years old and well trained as a driving pony although at times she definitely had a mind of her own as ponies often do. Hitched to a specially made beautiful oak meadowbrook cart *Saturday* made the rounds on Strasburg's back roads. She and Mary even won a few blue ribbons in the local fair. Last year, ironically the day after the auction, *Saturday* passed away at the age of 20, a victim of West Nile virus. She gave the family much pleasure over the years. The hand made oak meadowbrook cart, slightly used but well cared for, will be for sale at this year's auction in Lancaster. It bears many happy memories for the Morton's and they hope another family and pony will enjoy it as much as they did.

#### A GENEROUS GIFT

The Clinic for Special Children received a major gift from a thoughtful, generous friend of the clinic which presented us with a wonderful challenge to think of the future that will mean so much to the clinic and the children it serves for many years to come. This gift came at a time when the clinic's board of directors was ready to begin the process of development of the next five- year strategic plan and the gift is a major influence on our planning which is in progress. We are excited about the future for the clinic and are very grateful to our friend for her gift of "great possibilities" which challenges the clinic to plan and offers others a challenge to match her gift.

The directors and other board members are in the process of defining the vision for the clinic for the next five years and detailing goals and objectives to realize this vision. It is our hope this plan will help bring a greater focus on care for children with complex medical conditions and help stimulate interest, research and better services within the region and in the larger medical community. This plan will help us develop the clinic's potential more fully and transfer what is learned here to ultimately benefit many other children.

We will present our strategic plan when it is finalized in the fall and hope others will plan to join our thoughtful friend to consider major gifts in support of the clinic's future.

#### CLINICAL RESEARCH SUPPORT FROM THE AJS FOUNDATION

The AJS Foundation for MSD has awarded the Clinic a grant to expand clinical studies regarding the effect metabolic disorders have on the development and function of the brain. A major focus of the work at the clinic is **detection, treatment, and prevention of central nervous system disease** that too often occur with many metabolic disorders and that are little understood. The grant will be used to purchase software, computer equipment and cover the cost of initial studies of eleven patients with maple syrup disease, PKU, and glutaric aciduria, type 1. Studies will focus on neurochemical disturbances in these three disorders using MR spectroscopy, correlating with structural changes in the brain observed by high-resolution MRI. The MRS technique will allow quantitation of a variety of chemicals in the living brain, providing insight into basic mechanisms of neurological dysfunction.

We are grateful to the Stamps family and the AJS Foundation for MSD which they founded for this support. We hope this new technology will deepen our understanding of metabolic brain injuries and improve our ability to prevent neurological disability.

#### THANKS TO THE HAMMER FAMILY

The Hammer family in Springfield, NJ, planned a Family Fun Day this spring to raise funds to support the clinic in its on-going research to improve care of children with maple syrup disease. Sounds like everyone who participated had a great time and we very much appreciate the support. Many thanks to all, especially the Hammer family!

*Newborn screening for genetic diseases is one of the most important mechanisms by which the recent advances in modern genetics can be translated into the care of a patient.* Holmes Morton, M.D.



## PROGRESS NOTES 2004

### SIDDT SYNDROME

Holmes Morton, M.D.

**THE SYNDROME:** Over two generations, nine families from an Old Order Amish Community have lost twenty infants to an autosomal recessive syndrome which we now call SIDDT. We first learned of the disorder from two general pediatricians from central Pennsylvania, Drs. Allen Ettenger and Bruce Lidston, who had cared for several of the infants. Infants with SIDDT syndrome typically die before 12 months of age of abrupt cardiac and respiratory arrest. Male infants with SIDDT have poorly developed testes. Females with SIDDT have normal external genitalia, and have normal female hormones in blood and urine. Despite these differences, male and female infants die at approximately the same age. Cardiac and respiratory monitoring shows periods without respiratory effort (apnea), slow heart rate (bradycardia), and low oxygen levels (hypoxia) during sleep, not unlike that seen in premature infants. Episodes of apnea, bradycardia, and hypoxia can also be provoked in SIDDT infants by loud noises or physical stimulation such as blowing on the face or bathing, as part of an exaggerated startle reflex. Over the past 20 years, many of the SIDDT infants underwent extensive biochemical, endocrinological, and genetic testing at university medical centers in Pennsylvania, but no abnormalities were found. Brain MRIs, EEGs, and even careful examination of two brains by neuropathologists, did not provide an explanation of the deaths.

**MAPPING THE GENE MUTATION:** Last year with the help of our friend Dr. Terry Sharrer at the Smithsonian Institution, we were able to recruit the help of Dr. Dietrich Stephan at the Translational Genomics Research Institute (TGen) in Phoenix Arizona. Terry Sharrer also convinced Robert Wells, Vice President, and Steve Fodor, CEO of Affymetrix, to support our work through the donation of SNP genotype chips valued at \$40,000. The Affymetrix 12,000 SNP array allowed Erik Puffenberger and Dietrich Stephan and his associates at TGen to use DNA from four infants and their parents to map the site of the abnormal gene to a small region of chromosome 6. The Human Genome Data Base listed 37 genes within this region, and indicated where in the body each gene was expressed. Our clinical understanding of the syndrome led us to think that the mutation would be found in the gene called TSPYL, which is expressed both in the brain and in testes. Erik Puffenberger sequenced the TSPYL gene in our lab at the Clinic for Special Children and found a "frame shift" mutation that introduced a pathologic stop codon and would thereby prevent synthesis of functional TSPYL protein. All affected infants were found to have two abnormal copies of the TSPYL gene, and all parents were carriers of the mutation.

**IMPLICATIONS:** Identification of the TSPYL mutation provides a simple, inexpensive diagnostic test for SIDDT that will eliminate much unnecessary and expensive testing for the Amish families in Pennsylvania. The Amish variant of SIDDT will almost certainly be found in the central European populations from which the Amish people derive, and in the general population of the United States. As is always true for such disorders, other variants of SIDDT syndrome that arise from other mutations in the TSPYL gene will be found throughout the world. Most important, discovery of the genetic cause of this syndrome will allow us to ask questions about how the gene mutation causes disturbances in

the regulation of breathing and heart rate that lead to the sudden deaths of these infants.

**SIDS (SUDDEN INFANT DEATH SYNDROME) AND MUTATIONS IN THE TSPYL GENE:** We suspect that a subgroup of infants with Sudden Infant Death Syndrome (SIDS) will be found to have mutations in the TSPYL gene. As is true for other common neurological syndromes in children - including cerebral palsy, dystonia, mental retardation, autism, and seizures - SIDS does not have a single cause. The OMIM entry for Sudden Infant Death Syndrome (#272120) lists a number of genetic disorders that have been found to cause sudden cardiac deaths in SIDS victims. Approximately 5-10% of SIDS deaths are caused by undiagnosed disorders of fatty acid oxidation and other metabolic disorders. Exposure to opiates during pregnancy increases the risk of SIDS from 1.39 to 5.83 deaths per 1000 infants.

SIDDT and mutations in TSPYL may be relevant to the subgroup of SIDS patients whose deaths are caused by disturbances in the development and function of brain stem centers that regulate breathing and heart rate. Drs. Hannah Kinney, Jim Filiano (currently at Dartmouth Medical School), and their colleagues at Children's Hospital of Boston have described abnormalities of the arcuate nucleus and its associated structures in a large number of SIDS cases. The abnormalities of the arcuate nucleus apparently arise from injuries caused by fetal infections, drug exposures, focal vascular accidents, and prematurity as well as from heritable cerebral malformations and from several different abnormalities in the network of neurochemical receptors within the brain stem. The mutation in the gene for TSPYL described in our paper causes profound disturbances of neurological control of the heart and respiratory system, and results in the death of 100% of infants who are homozygous for the mutation. We expect that less severe mutations in the gene for TSPYL will give rise to more subtle, but at times fatal, disturbances of brain stem function. It is reasonable to suggest that pathological SIDS registries contain cases with mutations in TSPYL gene that result in reduced activity of TSPYL protein. Such cases may be less recognizable than our patients either because they are female or have more subtle dysgenesis of the testes.

**FURTHER RESEARCH:** Dietrich Stephan and his colleagues at The Translational Genomics Research Institute have begun the next phase of study of SIDDT, which will include more detailed mapping of the expression of TSPYL in the developing brain of laboratory animals. DNA specimens from SIDS infants can also be sequenced to determine if a portion of SIDS cases have mutations in the gene for TSPYL. We also hope to recruit the help of Dr. Hannah Kinney to do more detailed anatomical studies of the brain stems of SIDDT infants, including using antibodies to TSPYL protein to compare the expression of this protein in the brain stems of SIDDT and SIDS patients.

*This collaboration between physicians and scientists at the Clinic for Special Children, Translational Genome Research Institute (TGEN), Affymetrix, and our use of information from the Human Genome Project represents an example of how modern genetics can, and should be, used to gain insight into difficult medical problems. From such work, hope and help for these children will come.*



## PROPERDIN DEFICIENCY .....

.... *tragedy, an auction, a wedding, and hope*

Holmes Morton, M.D.

At the Shippensburg Auction last year I was approached by the grandmother of two boys who had died of an overwhelming infection called Meningococcal bacteremia. She said her grandsons appeared to be healthy until they suddenly became ill with this unusual infection. Within a few hours after the onset of symptoms they died, despite emergency care and antibiotics. Not long after her grandsons died, her brother and a nephew had also had a similar infection. She asked if some "genetic factor" could have been somehow responsible for these infections. I suggested that she and other family members come to the Clinic to discuss the problem.

The family history indicated an x-linked disorder, which means that a woman who is a carrier, and is married to a non-carrier, will pass the deficiency on to 50% of her sons, and 50% of her daughters will be carriers. Men who have properdin deficiency, and are married to non-carriers, will not have affected sons, but 50% of his daughters will be carriers. In large families, over several generations, x-linked disorders can become very common.

Kevin Strauss knew that there is only one immune disorder that puts people at high risk for Meningococcal bacteremia and is an x-linked genetic trait and that is *Properdin deficiency*. We asked Dr. Patricia Giclas, an expert in disorders of complement, at the National Jewish Medical Center in Denver Colorado to measure the properdin level in the nephew who had survived. The protein properdin was absent in his blood. Once we knew Properdin deficiency was the risk factor, Erik Puffenberger in our lab sequenced the gene for properdin and found a severe mutation which not only provided us with a final explanation of the deficiency but could then be used to identify affected males who are at high risk for deadly infection and female carriers.

When we asked how best to obtain samples on the extended family to determine who is at risk, the family decided the best way to accomplish this was to meet the extended family at a wedding. Kevin, Christine, and I talked with family members and drew blood samples for three hours on a Saturday night at the wedding reception. That would only happen in Lancaster County! Out of 63 people tested, we found 12 males who were at risk for overwhelming infection, and 14 female carriers.

As we reviewed medical literature about Meningococcal infections to develop a plan to help prevent infections in those at risk, we came across a particularly interesting and thorough review of the subject written by Dr. Marcel van Deuren in Holland. We sent him information about this Mennonite form of properdin deficiency and a long discussion about how we thought the problem should be managed. He sent a long, helpful letter which opened with the following remarks.

*"... first, it is always nice to notice that somewhere in the world people/colleagues are interested in my scientific output and knowledge on meningococcal infections, which indeed (was formed) more than 15 years in my special field of interest. ....Second, it is interesting to read – as a Dutchman – how a group of originally Dutch people, after spreading out via Poland, Germany and Russia, is now in the United States under your medical care and scientific interest. Recently, I became more aware of this group (and the Amish), after seeing a young adult man in my outpatient clinic with Cartilage Hair Hypoplasia (who by the way is also IgA and MBL-deficient). I do thank you and of course Dr. McKusick for your*

*excellent descriptions of these and other types of inherited diseases. Especially your recent publication in the Am. J. Medical Genetics (2003;121C:5-17) was very informative to me.*

We expect to continue to work with Dr. van Deuren to study the contribution of mannose binding lectin as a risk factor for severe infection not only in individuals with properdin deficiency but also in people with cartilage hair hypoplasia, a common form of dwarfism found in the Amish of Lancaster and in Finland.

**MENINGOCOCCUS and PROPERDIN** At any time 2-10% of people have meningococcus in the nose and throat. Meningococcus is a small bacterium that lives only in humans. Nasopharyngeal colonies of meningococcus are unusual in children under age 4 years, but are found in 30% of young adults between ages 15 and 24 years. The bacteria is passed from one individual to the next from hand to mouth, by kissing, on shared drinking glasses, eating utensils, or toothbrushes, or by exposure to droplets from a sneeze or cough. Meningococcus only causes illnesses if it breaks through the mucus membranes of the nose, throat, or lungs and gets into the bloodstream. This invasion occurs when injury, infection, or malnutrition weaken the normal barriers of the mucus membranes. Once in the bloodstream, meningococcal bacteria multiply rapidly, injure blood vessels throughout the body and weaken the heart, leading to shock. The bacteria also collect within small blood vessels in the membranes that cover the brain, causing the condition called meningitis.

Properdin is an important part of the body's immune response against meningococcus and several other similar bacteria. Properdin deficiency greatly increases both the risk of meningococcal bacteremia and the likelihood that such infections will cause death or permanent disability. A properdin-deficient individual's risk of invasive meningococcal disease is 70,000-fold higher than that in the general population. Over a lifetime, properdin-deficient men have a 50-80% risk of becoming infected with meningococcus and a 75% chance of dying from the first infection.

**PREVENTION AND TREATMENT** Properdin-deficient individuals can be protected from invasive infections by a combination of measures. These include 1) vaccination against meningococcus and other bacteria, 2) use of oral antibiotics, both to clear the bacteria from the mucus membranes and suppress growth on bacteria that get into the bloodstream, and 3) rapid treatment of meningococcal bacteremia. We have reviewed the current medical literature, and have spoken with specialists in infectious diseases and immunology to develop detailed guidelines for prevention and early treatment of infection.

### NEWBORN SCREENING FOR PROPERDIN DEFICIENCY

We are currently working with the Pediatrix Newborn Screening Laboratory in Pittsburgh, PA to develop a rapid screening test for properdin deficiency that could be done on all high-risk newborns. This test would be done using a standard newborn filter paper test for PKU and other genetic disorders, and would detect both properdin-deficient males and female carriers. Currently, any infants born to a female carrier can be tested through our clinic; female carriers who are pregnant should have a midwife or doctor contact us about the testing procedure.

## DEFINING REASONABLE MEDICAL CARE FOR PATIENTS WITH GLUTARIC ACIDURIA

Holmes Morton, M.D. and Kevin Strauss, M.D.

An international debate is taking place about the treatment of Glutaric aciduria, Type1 (GA1). Dr. Georg Hoffman's group in Germany plans to issue guidelines for treatment of GA1 which have been developed through a series of consensus meetings in Europe. These meetings were sponsored by the Milupa formula company, which is the European counterpart of Mead Johnson. Kevin Strauss attended one of the meetings in Heidelberg, Germany last fall.

The Clinic's 16 year experience with the treatment of GA1 was described in two papers published in the American journal of Medical Genetics in August 2003. Our approach differs significantly from that suggested by Dr. Hoffman's group. For example, the European Guidelines remain vague about the need for Newborn Screening for GA1, while we think that detection of asymptomatic infants is essential to any successful treatment plan. They advocate the use of Milupa formula which is lysine deficient to treat GA1, while we think this and other metabolic formulas, sold to treat GA1 contain amino acid mixtures that have not been shown to favorably change the biochemical abnormalities in GA1 patients, and contain amino acids that may make brain injury more severe when used as part of the emergency treatment of GA1 patients.

The following overview outlines what we consider to be reasonable medical care for patients with GA1 based on the Clinic's 16 year experience with the treatment of patients.

### Reasonable care for GA1 given current evidence:

**1) Newborn screening for GA1 is a prerequisite to any rational approach to treatment.** Treatments can only be developed, and will only be effective, when started in presymptomatic infants.

**2) Most, if not all, injuries to the basal ganglia in patients with GA1 occur during acute, usually infectious, illnesses.** Once a neonate is diagnosed with GA1, an explicit plan should be written, and parents should understand where acute medical care will be provided and what physicians will be available to deliver that care on an emergency basis.

**3) The most difficult phase of GA1 management is the transition period between onset of illness and hospitalization.** During such illnesses, infants should be managed by a physician who is scientifically knowledgeable about GA1, and has direct experience treating the disorder during acute illness. This physician should make all major decisions about treatment in and out of the hospital. Emergency room physicians, pediatric intensive care physicians, and general pediatricians should have specific training in the care of a GA1 patient before assuming responsibility for these patients. Genetic consultants in the US and Europe are usually not available to be acute care providers. Unfortunately, infants who are at the highest risk for brain injury are cared for by physicians who have no knowledge or experience with GA1, and they are asked to follow treatment guidelines written by specialists who are research scientists who also have no direct experience caring for an infant with the disorder.

**4) The role of diet, metabolic formulas, specific cofactors, anticonvulsants, fluid and electrolyte management in the daily management of GA1 appears to be less critical to neurological outcome than the timing and design of emergency care.** The purpose of outpatient management including dietary protein restriction, metabolic formulas, cofactors and pharmacologic agents, such as anticonvulsants, is to attenuate or slow the development of pathophysiologic conditions that lead to acute brain injury. Collectively such treatments improve outcomes, however, the relative importance of individual interventions are largely unknown. At minimum, each element of treatment should be part of a "rational" care plan.

**5) Dietary management of GA1, including the prescription of metabolic formulas, should not cause essential amino acid deficiencies or other forms of malnutrition, systemically or in the brain.** Lysine, tryptophan, and serotonin deficiencies are life-threatening disorders. Metabolic formulas when misused have caused disability and death in some patients with GA1, PKU, MSUD, and other metabolic disorders. Presently, the metabolic formulas used to treat GA1 contain excessive concentrations of non-essential "excitatory" amino acids which in the setting of acute brain intoxication may be harmful. These formulas are also deficient in omega-3 fatty acids, which are essential nutrients in the developing brain and the formulas provide insufficient trace minerals and vitamins when used chronically as the major source of nutritional support.

Regardless of our differences, we think the efforts by Dr. Hoffman and others to improve the medical care of patients with GA1 is important.

### AN UP-DATE IN SOMERSET COUNTY

Kevin Strauss, M.D. and Christine Hendrickson, R.N.

Beginning in autumn of 2002 we identified a rare genetic disease called 5,10-methylene tetrahydrofolate reductase deficiency (MTHFR) in four Amish children from Somerset County, Pennsylvania. In collaboration with the *Pediatrics* newborn screening laboratory in Pittsburgh, we developed a quick, accurate, and inexpensive molecular test for the disease. Cooperation among the Somerset Amish community, Clinic staff, and *Pediatrics* allowed us to screen approximately 240 Amish children and adults within the last year. We found that 1 in 4 healthy adults are "carriers" of the abnormal gene. This means that about 1 in 60 Amish babies born in Somerset County will have MTHFR disease. From these numbers, we expect that 1 or 2 newborn Amish babies with MTHFR deficiency will be identified each year.

MTHFR disease arises from both the toxic effects of high homocysteine on blood vessels and a low supply of methionine to the brain. Methionine deficiency results in poor brain growth and development, especially during the first 3 years of life. High homocysteine levels damage blood vessels throughout the body. A major risk for patients with MTHFR is narrowing or clotting in blood vessels that can reduce blood flow to the heart, brain, or lungs. Without specific therapy, this could result in death or permanent disability. Therapy for MTHFR reduces blood homocysteine to a safer level while increasing the brain's supply of methionine. The most important therapy is a nutrient called *Cystadane* (betaine), which allows the liver and kidneys to convert homocysteine to methionine.



Dietary therapy for MTHFR deficiency is effective. All three MTHFR patients identified during early childhood (ages 10 months to 4 years) responded well to treatment with *Cystadane*. The two younger infants in this group had significant increases in head growth in the months after starting therapy; all three children are making progressive gains in muscle strength, motor skills, language comprehension, and social interactions. *Cystadane* therapy reduces the total homocysteine value by about 50%, but does not bring this value down to normal. Consequently, all patients with MTHFR deficiency are treated with medications that reduce the tendency of blood to clot. Studies are in progress to investigate if another nutrient, 5-methyltetrahydrofolate (metabolin), can further lower the ratio of homocysteine to methionine in blood.

Starting treatment for MTHFR early in life is key to its overall effectiveness. To prevent neurological impairment from the disease, it is necessary to identify asymptomatic infants in the first weeks of life. Young parents can now be tested to see if they are carriers of the abnormal MTHFR gene and thus at risk of having an affected child, and the molecular screening test done by Pediatrix is now routinely done on all Amish babies born in Somerset County. With the parents written consent, the molecular test is added on to the standard filter paper screen for PKU and other disorders. The newborn MTHFR test requires no extra blood samples and can detect affected babies within the first week of life, before there is significant damage to the brain and blood vessels. In the Autumn of 2003, the first asymptomatic Amish newborn was detected by this test. She was started on therapy by 2 weeks of age. She is now 9 months old, and her growth and neurological development are normal.

In June of 2004, Dr. Strauss, Christine and Shawn Hendrickson, Dr. Laura Hollar-Wilt and Dr. Richard Horenstein from the University of Maryland traveled to Somerset County to visit children being treated for MTHFR deficiency, do follow-up carrier testing for selected families, and educate local practicing midwives, nurses, and physicians about MTHFR screening and the medical care of affected newborn infants. Dr. Horenstein is considering a research project to uncover any long term health consequences for MTHFR carriers. He enjoyed meeting members of the Somerset community and was a great help in our work. We are grateful to all of the families and professional care providers in Somerset County that have made this important work possible. We appreciate donated laboratory studies by collaborators from the National Institutes of Health, University of North Carolina, University of Colorado, and University of Medicine and Dentistry, New Jersey. We owe special thanks to Bennie C. Yoder for his help organizing our efforts in Somerset County, and Dr. Michelle Sredy, who has coordinated laboratory services and provided outstanding local pediatric care for children with MTHFR disease.

## LABORATORY RESEARCH UPDATE

Erik G. Puffenberger, PhD, Laboratory Director

As outlined in the last newsletter, the clinic laboratory is working to identify the specific disease mutations which are found in the Amish and Mennonite populations. Blood samples from clinic patients have been used to perform DNA sequencing of candidate genes. If there is strong clinical or biochemical evidence to suggest a particular candidate gene, we will sequence that gene first. This simple strategy has allowed us to identify the molecular basis of genetic disease (i.e. the mutation) in many patients. Over the past year, this has included single mutations for Bardet-Biedel

syndrome (BBS1), severe combined immune deficiency (SCID), and properdin deficiency, as well as two mutations causing osteoporosis-pseudoglioma syndrome (OPPG).

When there is no strong biochemical evidence linking a disease to a particular gene, it is necessary to map the general location of the disease gene among the 22 human chromosomes. For seventeen disorders found in clinic patients, the gene location is unknown. Unfortunately, without knowledge of the gene location, efforts to identify the disease gene are nearly impossible.

In order to localize and identify additional disease mutations, we have initiated mapping studies of several diseases. Previously we reported that Affymetrix, Inc., had donated 100 DNA microchip arrays (a \$40,000 gift) to the clinic. 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 are collaborating with Dr. Dietrich Stephan of the Translational Genomics Research Institute in Phoenix, AZ, to genotype our patient samples using the donated chips. They began the DNA chip analyses last summer. Several previously mapped disorders were sent for validation purposes, including maple syrup urine disease and Crigler-Najjar syndrome. We were able to map all validation diseases to their correct chromosomal region using the Affymetrix chips. This suggested that we would be able to map the unknown genes accurately and efficiently.

The first successful mapping study using these chips has been completed. This study involved a condition known locally as Swarey syndrome (which we have formally called sudden infant death with dysgenesis of the testes (SIDDT) see related article on SIDDT. Using the donated DNA chip arrays, Dr. Stephan's lab generated roughly 12,000 genotypes per individual. By analyzing the genotypes of all the affected individuals, we were able to identify a region on chromosome 6 where all four patients were homozygous for the same piece of DNA. This strongly suggested that the disease gene was present in this region. After sequencing two candidate genes in this region, we found a frameshift mutation in one of them which caused loss of function of the gene. The results of this study will be published in July in the Proceedings of the National Academy of Sciences (PNAS).

In addition, we have preliminary data mapping the genes for three other disorders; specifically, 1) a form of seizures and mental retardation, 2) posterior column ataxia and retinitis pigmentosa, and 3) a form of congenital/progressive hypomyelination. The disease genes map to chromosomes 7, 1, and 6, respectively. We are actively working to sequence candidate genes for each disorder. For the third disorder named above, we identified the causative mutation in two of our patients. Hopefully, in the next few months, we will identify the causative genes for the other two disorders.

**NEWS NOTE:** As of June, 2004, hospitals and midwives in Pennsylvania can send a single filter sample to Pediatrix (formerly NeoGen) in Pittsburgh for the required and supplemental newborn screening. This ends the controversial decision in January by the PA Department of Health to send newborn samples to the New England Screening Lab at the University of Massachusetts.



## Newborn Screening & Genetic Medicine in Pennsylvania

The clinic sponsored a Genetic Medicine Symposium on December 11th and 12th, 2003 in Strasburg in collaboration with the Pennsylvania Chapter of the American Academy of Pediatrics. The meeting offered a forum to discuss the current science and future directions of newborn screening for genetic disorders in Pennsylvania. Lectures and discussions at this first meeting addressed newborn screening follow-up topics. Material presented will help form the basis of a curriculum for other collaborative educational activities related to newborn screening and the practice of genetic medicine in Pennsylvania.

This first symposium included most of the major pediatric medical centers in Pennsylvania in addition to interested leading pediatricians and neonatologists. In addition to Dr. Morton, Dr. Strauss, and Dr. Puffenberger on the clinic staff other participants included Dr. Robert Cicco, President of the Pennsylvania Chapter of the American Academy of Pediatrics, Dr. Richard Kelley, Kennedy-Krieger Institute; Dr. Craig Hillemeier, Chairman of Pediatrics at Penn State-Hershey Medical Center; Dr. Cheston Berlin, Penn State- Hershey Medical Center; Dr. Gerald Berry, Jefferson Medical College; Dr. Marc Yudkoff, Children's Hospital of Philadelphia; Dr. Michael Ryan, Chairman of Pediatrics at Geisinger Medical Center; Dr. Lakshmanan Krishnamurti, Dr. David Finegold, Pittsburgh Children's Hospital; Dr. Tom Foley, Dr. Edwin Naylor, Dr. Don Chace, Dr. Philip Vaughn and Rick Banas of Pediatrix (formerly NeoGen) and Roger Eaton, PhD, Director of the New England Newborn Screening Program at UMASS. We hope the collaboration and information presented at this meeting will eventually contribute to additional medical seminars and a more effective network for the care of infants diagnosed through screening in Pennsylvania for genetic disorders.

### CHARTING A COURSE FOR OTHERS

During the past year and especially this summer the clinic hosted students and pediatric residents who asked to spend time here as part of their training or course work. Each year it seems more and more requests are coming from students who seek to learn in the unique environment of the clinic. In the next few years we hope to develop several courses on genetic medicine for college and medical school students as well as courses for pediatric residents and practicing pediatricians who wish to learn more about diagnosis and medical care for children with genetic conditions. We asked students to give us their thoughts on why they asked to come to the clinic and what they learned through their experience. The following are some of their comments.

*The Clinic for Special Children is a unique and inspiring facility that melds both a patient care setting and a state of the art genetic research lab. I have been working on elucidating the genetic basis of diseases as part of a collaboration between TGEN (in Phoenix) and the clinic for the past year. Through my research we have uncovered a number of genes responsible for genetic disorders. I have also had a lifelong goal of becoming a pediatric physician. My visit to the clinic allowed me the opportunity to see first and foremost how genetics and medicine can work together. I was able to interact with the very people that we have been working to help...and I was able to see what possibilities there are for me after medical school. My trip to the Clinic for Special Children has completely inspired me as to the new exciting world of genetics and medicine and has reinforced my love and passion for patient care. I can not thank the Clinic staff enough for allowing me to spend time*

*with them, for sharing goals and concerns, for answering all of my questions and for teaching me more about their unique environment than I ever thought possible. Jennifer Parod, Research Associate, TGEN. (worked with Dr. Dietrich Stephan and collaborated with Dr. Puffenberger in the search for the gene for SIDD Syndrome)*

*As a fourth-year medical student at the University of Heidelberg Medical School in Germany, working on a thesis at the Dept. of Human Genetics and interested in becoming a pediatrician one day, there is probably no better place in the world to go than the Clinic for Special Children. I have been doing some research in the Section for Metabolic Diseases at our institute for more than a year. That often gave me the chance to deal with DNA of young patients suffering from diseases hard to spell and rarely seen on a general pediatric ward. After my supervisor told me about this very special place in Pennsylvania embedded within the Amish community I was eager to learn more about the way of treatment here compared to treatment strategies in Heidelberg. What I have seen here so far is just amazing to me: the Clinic for Special Children is a peaceful and unique place where latest findings in research and molecular genetic diagnostics are combined with a very simple and practical approach of how to treat children affected by all different kinds of genetic metabolic diseases. Physicians here... made me keep in mind whatever research is done it should be done for the patients. I especially want to thank the patients and their families who would tell me about their experiences and worries and by doing so teach me in a very special way. I hope I will be able to take back as much experience as possible and keep the spirit of this clinic in my mind!... Carolin Hartmann*

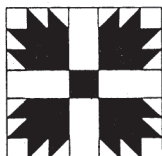
*This rotation was the best one I have done and probably ever will do. The Clinic offers a truly unique vision of medicine...at the same time a glimpse into the past and future of medicine. Of the past is that they spend as much time as necessary with each patient. They know them as people and make housecalls when needed. Of the future.. is patient centered care. Each patient has a care plan designed especially for them. They fuse research and clinical experience to create extraordinary medicine. I have worked with many doctors and many scientists and all I can say about Drs. Morton and Strauss is that I am in awe. The Amish people are as lucky to have this clinic as the clinic is to have the Amish people. I am honored to have been a part of it. Laura Hollar-Wilt, M.D., Pediatric resident, 2nd year, Hershey Medical Center*

*The project I have chosen of developing a new method of organic acid analysis should prove to be very challenging and exciting. I am looking forward to adding to the existing knowledge of this method to allow for quicker and more accurate diagnosis of many genetic disorders. I am very excited to be working at such a highly respected facility with many intelligent researchers / doctors. Zachary Ichter, Millersville, PA, Junior biology major, Ursinus College.*

*I am working with Dr. Puffenberger on a project that entails sequencing much of the UGT1A1 gene for parents of children who have Crigler-Najjar. We are checking for polymorphisms and creating haplotypes to see which haplotypes have the largest effects on bilirubin levels. This is a very exciting and hopefully very helpful project. It is an honor and a privilege to be able to do my internship in such an extraordinary place. Colleen Hall, senior biotechnology major, Elizabethtown College.*

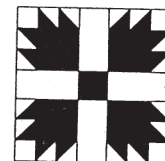
*In addition to the residents and students whose comments are included above we also have a rising senior from Pequea Valley High School, Devon Brackbill, who is volunteering this summer at the clinic in research activities. Devon, a top honors student, has interest in medicine and biology and we hope his experience here will encourage and challenge him.*

THE CLINIC FOR SPECIAL CHILDREN  
P.O. BOX 128  
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**2004 Annual Benefit Auctions**  
to support  
**THE CLINIC FOR SPECIAL CHILDREN**

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



**Shippensburg, PA ~ July 17**  
**Blair County / Morrison Cove ~ September 11**  
**Lancaster County / Leola ~ September 18**

*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.

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

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