

CLINIC FOR SPECIAL CHILDREN NEWSLETTER

VOLUME I NUMBER 29

* LANCASTER COUNTY, PENNSYLVANIA *

SUMMER 2009

Reflections on Twenty Years 1989 - 2009

1989

Patient Case Load: Approximately 100
Different genetic disorders treated in children: 12
Disorders diagnosed by the Clinic's lab: 4
Infants tested through Clinic's newborn screening for GAI: 400
Budget for Clinic's first year: \$163,000
Capital Investment for Equipment and Building: \$554,000
Staff: 3

"PROMISES TO KEEP"

From articles written for the first Newsletter in 1990:

In 1988 Dr. Holmes Morton first recognized that Glutaric Aciduria (GA1) was a common cause of cerebral palsy among Amish children in Lancaster County. The concept of the Clinic grew as he obtained evidence that brain damage from the disease was preventable, if infants could be diagnosed before complications developed.

First attempts to find support for research on GA1 and start the Clinic were frustrating. In the Spring of 1989 the Morton's laid the ground work and formed a voluntary board of directors with Dr. Richard Kelley, filed incorporation paperwork and met with local families and community leaders. The first meeting with the Mennonite community was hosted by Amos and Nora Hoover at their Lancaster County farm on July 29, 1989. The Morton's were advised that a clinic seemed like a good idea and if they could get it started, support would likely come from the Mennonite community.

The problem was HOW to get it started? Dr. Morton's grant application to NIH for GA1 research was not funded. In retrospect this disappointment was a blessing as it lead to other possibilities with more lasting promise for the future Clinic. As the Morton's prepared to sign for loans, an article by Frank Allen in the Wall Street Journal brought significant interest and support from readers around the country.

2009

Patient Case Load: 1,000 +
Genetic disorders treated in children: 109
Disorders diagnosed at the Clinic by molecular methods: 82
Infants screened for GAI - All infants in PA and in many other states through state wide screening
Genetic mutations originally identified by the Clinic: 48
Budget for 2009: \$1,450,000
Staff: 10



With the donations received from WSJ readers, Hewlett Packard's gift of GC Mass Spec diagnostic equipment and loan of temporary office space by Lancaster General at Willow Lakes Health Center, the Clinic for Special Children officially opened in January, 1990.

Most of Dr. Morton's efforts in 1989-90 were focused on identifying children who had glutaric aciduria and establishing the first newborn screening program anywhere in the world to diagnose Amish infants with GA1 before the onset of symptoms of brain injury. Among the patients he saw the first year were also Mennonite children diagnosed with maple syrup urine disease (MSUD) who previously relied on major medical centers in Philadelphia for their care, with distance and cost as major barriers to care. Dr. Morton's essential lab equipment in 1989 included a GC/mass spectrometer, donated by Hewlett Packard and an HP amino acid analyzer used to monitor

maple syrup urine disease which was purchased with funds raised by several Mennonite churches and an anonymous donor. Children with other genetic conditions and their families began to find their way to the small Clinic. As the need grew, land was found, the building was raised, staff gradually added over the years and the work continues to unfold and expand.

Today we provide medical care for 1029 children with complex medical problems related to 109 different genetic disorders that affect every organ system and range from highly treatable to invariably lethal.

AUCTION SEASON IS HERE

Shiloh, Ohio ~ July 11 Families in Shiloh, Ohio, sponsored the sixth auction in that region, and we are very grateful for the support growing for the Clinic from this community.

Shippensburg, PA ~ July 18 In addition to quilts, crafts and furniture, this auction always has many garden items and beautiful plants donated for sale. Homemade ice cream, lemonade, donuts, chicken barbecue and soft pretzels provided fuel for bidding.

Blair County, PA ~ September 12 Beautiful quilts, hand crafted furniture, chicken barbecue, soft pretzels and mums for fall, invite bidders to Morrison's Cove Produce Auction in Central Pennsylvania for the 13th annual auction to benefit the clinic. Contact Amos at 814-793-3634, Eli at 814-793-3010 or Paul Ray at 814-224-5442 for information or donations for the auction.

Lancaster County, PA ~ September 19

The 19th annual auction for the Clinic in Lancaster County will start at 8:30 on September 19 at the Leola Produce Auction. For those who arrive early, breakfast including fresh donuts and omelets will be available. Dr. Morton, Dr. Strauss and Dr. Rider will offer a few remarks around 11:00AM, followed by special items, the quilt sale and furniture. Lawn furniture and Gift Certificates will be sold around 1:00PM.

Among special items donated for auction is a wooden chain hand carved by the father of a patient from a solid block of wood and engraved with the notation of the Clinic's 20th anniversary. A gift from another father is a hand made, carved wood rocking horse glider. There may be a special birdhouse this year!

Quilts will include a Postage Stamp, Broken Star, various applique, Nine Patch and Center Diamond designs. Locally made cherry and oak furniture, garden and farm items, crafts, baked goods and as always, fresh subs, and the best chicken and pork barbecue.

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



Thank you to all who volunteer, all who donate, all who come, and all who bid and buy. We especially thank the children who inspire all of us to work harder and to keep the Clinic growing and thriving. Over the past 18 years the community sponsored benefit auctions have raised a cumulative grand total of over 4.5 million dollars to support the Clinic. That represents a lot of dedicated volunteers, handmade quilts, crafts, barbecued chicken, fresh donuts and twisted soft pretzels!! We are very grateful. The Clinic would not be here without this community support.

DOUBLE MATCH CHALLENGE

A Lancaster area family foundation has offered to donate \$50,000 to the Clinic IF we can match this amount with donations before December 1, 2009. As an added challenge this year we seek donations to DOUBLE match the challenge - to raise \$100,000 in matching contributions by December 1st. Please help us meet this goal and send a contribution to the Clinic for Special Children P.O. Box 128, Strasburg, PA 17579. We are thankful for this generous challenge gift and for the commitment of support.

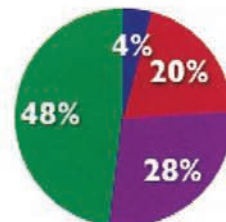
WE NEED YOUR SUPPORT !

We want to make every effort to keep services at the Clinic affordable for all families, especially those who do not have insurance. Unfortunately the Clinic has not been immune to the economic climate. In recent months donations have been less than in the past. The cost of running the Clinic and providing care has grown significantly in the last few years. This year we reduced our budget to be as lean as possible. Some clinical research projects are on hold and staff have not received any raises. As of last year, income received from patient fees covered only about 20% of our total cost. For the first time in over fifteen years we recently increased the amounts we charge for services to help make ends meet. Our fees are still significantly lower than charged elsewhere for comparable services. We regret we had to do this, but we must find income and support to keep the Clinic in operation. The community sponsored auctions generally raise another 28% of the funds needed to meet the actual cost of providing medical services. The balance needed each year to meet our expenses usually comes from donations from individuals and grants from foundations. Our long term goal is to increase the Endowment Fund through major gifts to cover a more significant percentage of our research, education and clinical studies costs through annual earnings. Unfortunately, in recent months the value of our endowment fund has decreased with the market trends. **We need major gifts to grow the Research & Endowment Fund to sustain the Clinic's work.**

Anyone want to match the 4.5 million raised by the community benefit auctions over the last 18 years????

SOURCES OF INCOME FOR THE CLINIC

- 4 % Research Endowment
- 20% Fees for Clinic Services
- 28% Auction Proceeds
- 48% Charitable Gifts



NEWS NOTES

Western Kentucky Holmes and Caroline Morton traveled to Western Kentucky in March to meet with healthcare providers, medical staff at Western Kentucky University and representatives of area Amish and Mennonite communities about the need to provide medical services to the communities in that region using the Clinic for Special Children as a model.

Dr. Morton was honored by the **Jeffrey Modell Foundation** with its annual **Dare to Dream Award** in New York on April 23.

Pretzel Syndrome Update and Family Picnic Families of children with Pretzel Syndrome met at the Clinic on June 29 for a picnic and to hear updates on research of this newly described genetic syndrome by Ksenia Orlova and Dr. Peter Crino from University of Pennsylvania School of Medicine.

PYRUVATE KINASE DISEASE MEETING JULY 25
Meeting with families in Belleville, PA

MSUD NUTRITION WORKSHOP JULY 29

Applied Nutrition and the Clinic sponsored a workshop on **July 29th** for patients and families in the region who have children with maple syrup urine disease. An afternoon nutrition workshop with team cook-off activities was followed by dinner program with presentations by Dr. Morton, Dr. Strauss, Dr. Rider and Applied Nutrition.

ANNUAL TRANSPLANT SYMPOSIUM AUGUST 20

Children's Hospital of Pittsburgh (UPMC) and the Clinic for Special Children jointly sponsored the **Fifth Annual Children's Symposium on Transplantation for Maple Syrup Urine Disease and Crigler-Najjar** on August 20 in Strasburg. The meeting included topics related to transplant procedures, research updates and questions for discussion from parents and patients. The transplant team from Pittsburgh and Clinic physicians presented the topics.

TWENTY YEARS OF PROGRESS

The Clinic's progress over the last twenty years and the support it receives is remarkable. Twenty years ago there were two genetic disorders in children that defined the need for the Clinic: Glutaric Aciduria, found in the Amish population and Maple Syrup Urine Disease, prevalent in the Old Order Mennonite population of Lancaster County. In this issue we reflect on efforts of twenty years to unravel the mysteries of Glutaric Aciduria to find successful treatment. The history of this effort in a way defines the Clinic's history.

DISCOVERY OF GLUTARIC ACIDURIA IN THE AMISH COMMUNITY OF LANCASTER COUNTY

Holmes Morton, M.D.

Answers would unfold slowly, after many later visits to Lancaster County.



How we came to be in Lancaster County, is a history of several *Roads Not Taken* and three disorders, medium chain acyl-dehydrogenase deficiency (MCADD), maple syrup urine disease, and glutaric aciduria. An interest in mitochondrial disorders of fatty acid oxidation, including the most common disorder MCADD, introduced me to Dr. Richard I. Kelley and brought me to Philadelphia Children's in 1986. The history of the Clinic for Special Children is often discussed by reference to glutaric aciduria and the Amish Community, but, the Clinic

would not exist were it not for a long struggle to care for children with MSUD and support for the Clinic by the Mennonite Community.

In the summer of 1986 I moved from Boston Children's Hospital to Children's of Philadelphia to work with Dr. Richard Kelley. As part of my fellowship research I was routinely using the GC/MS to study the fatty acids from patients with fatty acid oxidation defects, and whole blood filter paper specimens of infants and children with MCADD. Lab technician, Jim Coulter asked, "Holmes why don't you look at the mass spectra of this sample to see if this is a peak of glutaric acid; that is more than I usually see." Jim, an excellent technician, came to know how his friendly request that day ultimately changed my life. On days-off from CHOP in the early 1990s he came to the Clinic for Special Children and ran organic acids for me. The peak he asked about was glutaric acid, however, I could not find the pathologic metabolite 3-hydroxy-glutaric-acid by GC/MS in that first urine sample from an Amish child.

On June 19, 1988 I drove from Philadelphia to Leola to visit the Lapp family at their farm. I hoped to learn more about the disease, Glutaric Aciduria, re-examine their son, and collect samples from him while on a low protein diet and riboflavin. At that time GA1 was considered to be a very rare disorder; none of us at CHOP had seen the condition. On the first trip to see the child at Elizabethtown Hospital with my colleague at Children's Hospital of Philadelphia (CHOP), Dr. Michael Bennett, I had suggested that he possibly had a "benign biochemical phenotype" and that his dystonia might improve with treatment. The key to the diagnosis of the first case of the Amish form of GA1 was not the specimen, but a conversation with Dr. Charles Nictier, a developmental pediatrician at Elizabethtown Hospital for children with cerebral palsy. Dr. Nictier had sent the lab specimen on this Amish boy because of the history of normal early development that ended by the acute onset of dystonia during an intercurrent illness. Of course, I was wrong, both about the "benign phenotype" and the dystonia.

On that important visit, I learned the names of many more Amish families who had children similar to the Lapp's son; I began to make trips to Lancaster County to collect information on natural histories and urine samples. The disease followed a recessive pattern; many families had more than one disabled child. Most case histories were similar to the first patient. In 17 of 20 cases a period of normal development ended with the abrupt onset of generalized dystonia, usually during an illness, and always before 2 years of age. Urine specimens from these cases contained widely varying concentrations of glutaric

acid, and using better GC/MS methods in Dr. Kelley's new lab at Kennedy Institute, I soon found small amounts of 3-OH-GA in all specimens. Dr. Lorne Seargeant in Manitoba measured the glutaryl-CoA dehydrogenase activity on lymphocytes for the first case and showed the enzyme was absent. The diagnosis of GA1 was thus confirmed.

By September of 1988 it was apparent that GA1 was common in the Amish Community, all major family names were represented. I estimated a carrier rate of 1/10 and a disease prevalence of at least 1/400 newborns, which was similar to the prevalence of MSUD in the Mennonites of Lancaster County. The birth rate within the community was about 1000 babies per year, so, 2-3 new cases per year could be anticipated. I also learned that the brain injury was irreversible and that this brain injury was to be age dependent. All cases were injured before age 2, and, even the children with dystonia, appeared not to have further brain deterioration after age 2. The oldest patient I met that summer was an intelligent man in his 20s, who had developed dystonia at the age of 6 months, but had eventually learned to walk with canes and had stable neurological function. Regardless of being undiagnosed and untreated he had no further episodes of illness.

Most important, in August of 1988, I discovered the first asymptomatic case of GA1. She was a healthy 14 year old Amish girl, who had the same biochemical phenotype as her severely disabled sister, but she had escaped basal ganglial degeneration. Based on the study of this girl, by fall of 1988 I believed that GA1 would be treatable. However, it was also clear to Dr. Kelley and me that for any treatment to be effective it must be started in asymptomatic infants that were diagnosed by newborn testing, and, appropriate metabolic medical care would need to be offered during common illnesses. A newborn screening test for GA1 did not exist in 1988. Most of the children with GA1 that I saw in the Amish Community did not have access to pediatric care and could not be expected to travel to medical centers in Philadelphia or Baltimore for every common illness. These facts made the successful treatment of GA1 in 1988 unlikely, and defined the need for the Clinic For Special Children. GA1 families who did travel to CHOP for evaluations would find the same high costs for care that the families with MSUD faced. These facts made the successful treatment of GA1 in 1988 unlikely, and began to define the need for the Clinic For Special Children.

The need for the Clinic was also defined by the death from cerebral edema of two more children with MSUD in 1988. Both had developed fatal brain swelling unexpectedly during common illnesses – one child died at Community Hospital in Lancaster and the other died at CHOP. To me there were similarities between GA1 and MSUD. In both disorders acute brain injuries were being provoked by a poorly understood interaction between common illnesses and the underlying biochemical disorder. **My sense was that if we were going to be successful at treating either disorder, general pediatric care must be combined with early management of the underlying biochemical disorder.** The knowledge needed would only come from the difficult work of caring for infants and children before and during the crisis that led to brain injury or death. I also began to realize that the medical care and research necessary to successfully treat these disorders could not be offered at a university medical center. I was advised in Philadelphia that the GA1 project was not fundable by NIH and the research could not be supported at CHOP.

I had developed a deep interest in the neurobiology of GA1 and I believed that terrible disability of the disorder could be prevented. I replied, stubbornly, that this kind of patient centered research was interesting, necessary, and fundable. I moved from CHOP to Dr. Kelley's new lab in Baltimore at the Kennedy Krieger Institute in October 1988. Dr. Hugo Moser, then President of Kennedy Institute, encouraged my work in Lancaster County, which became the basis of an NIH grant that was submitted in January of 1989. Despite letters of support from Drs. Moser & Kelley, my grant proposal was not funded, which seemed unfortunate at the time, but was one of those important failures that led me along a *Road Less Traveled*.

I always remember an evening in August 1989. I was driving from Baltimore to our home in St. Davids. I stopped along the highway to think about what to do. By then I knew there would not be grant money from National Institutes of Health or Johns Hopkins to support my studies of glutaric aciduria. By then I knew my research fellowship at the Kennedy Institute would soon end, and there would be no job. By then I was supporting our family entirely by working nights and weekends in the newborn intensive care units of Bryn Mawr and Harrisburg Hospitals, which was difficult work and would not help the Amish families with glutaric aciduria. I had on that August day decided to come to Lancaster to work as a pediatrician, but I had no experience starting a practice, setting up the laboratory that I would need, or building a Clinic. My former teachers in Boston at Harvard Medical School and Children's Hospitals in Boston and Philadelphia, and Dr. Hugo Moser, told me the move to Lancaster County would end a promising career in academic medicine. They said I should stay at a university hospital and let patients come to me. Dr. Richard Kelley, my wife, and my father were supportive, but they were understandably worried. A few Amish and Mennonite families knew about the idea Caroline and I had to start the Clinic, but they were skeptical that such a clinic could be supported by them or that other members of the Plain Communities would help. On that rainy day in August, the Clinic for Special Children, as we know it today, seemed unlikely.

I cannot say how long I sat by the road that day, or what new ideas I may have found. I remember at one point there were tears of frustration and disappointment. I said to myself, "If this ever works out, I hope you will always remember this day. I hope you remember how difficult this time really was." Every year as I look out over the crowd at the benefit auction, I do remember that uncertain time.

Many know about the writer Frank Allen and how his story about the effort of Caroline and me to start our Clinic appeared on the front page of the Wall Street Journal on September 19, 1989. His writing changed our lives, and the lives of many. Whatever new ideas were found that gray day along the highway from Baltimore are long forgotten. The solutions to the problems we faced were unimaginable.

Caroline and I established the Clinic for Special Children as an independent non-profit organization in the Spring of 1989. Our initial efforts to raise money within the Plain Communities to help pay for laboratory equipment and support the medical practice failed, but finally the seed money for the Clinic came through the help of a writer for the Wall Street Journal named Frank Allen and the paper's front-page editor, a man of Mennonite ancestry, named Paul Martin. With support from this article, and office space donated by Lancaster General Hospital, Caroline and I began to work in Lancaster County full-time in December 1989. Work at the Clinic for Special Children was the patient-centered, case-study-model of Richard Kelley, who has been a consulting geneticist, helps care for patients, and makes house calls regularly. Dr. Kelley was a founding member of the Clinic's Board and has maintained the written record of Board Meetings since 1989. Newborn screening for glutaric aciduria in the Clinic's new laboratory started in January of 1990. Urine sample #6 was positive. The successful treatment of this first infant was a Gift that gave all of us hope and sustained us through many difficult failures in the years to come.

As Dr. Kelley and I expected, the Clinic became a place where the practice of medicine could be translated into science, and, not only for MCADD, MSUD and GA1. Over the first 10 years, our work at the Clinic had identified 65 disorders, 37 genetic syndromes in the Amish population and 28 syndromes in the Mennonite population. Of the 65 disorders 42/65 could be diagnosed by history, physical exam, biochemical testing, and several like MCADD, MSUD, GA1, and propionic acidemia were added to the expanded newborn screening panel because these disorders were common in the Plain populations throughout Pennsylvania. Today the Clinic's medical staff of three doctors and two nurses provides medical care for 1029 active cases with 107 different genetic disorders that affect every organ system and range from highly treatable to invariably lethal. The 25 most common problems managed at the Clinic include 525 patients.

A Path to Understanding

Kevin A. Strauss, M.D.



It was 1993. I was working as a surgical orderly at a small hospital in Allentown. It was my job to transport patients from their hospital room to the operating suite. At the end of each day, I cleaned and repacked the surgical instruments. Then I returned home to study, late into the night,

for the medical school entrance exam. I liked to talk to patients as I wheeled them through the halls. They taught me about the difference between disease and suffering. Within the narrow confines of the operating room, doctors describe disease in objective terms: damaged cells and failing organ systems. But people—not just their component parts—suffer. And my encounters with such people, although brief, were the start of my medical education.

One encounter I will not forget. I entered the hospital room to find a boy of about nine years twisted painfully in bed. His limbs were thin and pale, and as I tried to lift him to the gurney, I was startled by the force of his muscle contractions. He had a feeding tube in his stomach. His breathing was thick and labored. Forceful neck spasms locked his head to one side, and he could not turn to look at me. Could he hear me? Did he understand? How did this happen?

"Low oxygen levels when he was born," said his mother. "He has cerebral palsy." She sat near the window, beside two wheelchairs and a portable suction pump, knitting a bright pink sweater. "He understands what you say." Stretched across her lap was a younger boy, also crippled. "He can't talk, but he understands." She did not look up and she did not stop knitting. "Both of them were born with the cord wrapped around the neck. Doctors said low oxygen levels to the brain caused the damage. That's how they explained it. I didn't have any more children after that."

I had no reason to doubt her story. I knew little about childbirth and even less about cerebral palsy. But that mother and her two sons were fixed firmly in my mind the day I met Dr. Morton. Prompted by a relative, I sought him out for advice about where to attend medical school. When I arrived at the Clinic, he was in the laboratory. We stood and talked. Actually, we moved and talked (I tried to keep up.) Somehow, amid many distractions, he managed to give me his full attention. Or so it felt to me. He was testing a urine sample for glutaric and 3-hydroxyglutaric acids—mysterious words to me at the time—searching for a disease he called glutaric aciduria type 1 (GA1).

He told me about his discovery of GA1—Amish cerebral palsy—and how his experience with a few special children convinced him and his wife Caroline of the need for this clinic. One case among 17—an Amish girl who had escaped brain injury without the benefit of therapy—was living proof that prevention was possible. The first requirement, however, was to start with healthy children, and this he intended to do. So during the Clinic's first four years (1989 to 1993) Dr. Morton screened 1223 asymptomatic Amish infants for GA1. If a diagnosis was made, treatment entailed a low-protein diet, vitamin supplements, close surveillance, and frequent hospitalizations to treat infections and other illnesses. This did indeed keep the children healthy.

I drove home in astonishment, moved by the work of the Mortons and the community of people that supported them. But moved also by a core idea behind the Clinic: the idea that science, constrained by conscience, could do much to prevent human misery. This was the aim of medicine, but never had I seen so powerful an example. My thoughts kept returning to my encounter with the mother and her two boys. What if Dr. Morton had tested them for GA1 soon after they were born? Would they be running through the house? Climbing trees? Racing across the yard?

In 1994, I began my medical studies in Boston and took special interest in the biology of the nervous system. I wanted to understand how GA1 and diseases like it injure the developing brain; I knew intuitively this was the key to prevention. I returned to the Clinic as a student in 1997, prepared this time by three years of training. Although Dr. Morton wanted to learn more about the fundamental cause of brain injury, he was motivated to find relief for the many children already disabled. And so we turned our attention to experimental new brain surgery—called pallidotomy—that was being used with good success to treat Parkinsonism. After a detailed study of the neuroanatomy and physiology of the basal ganglia, we convinced ourselves that the surgery could work for GA1.

Over the years, GA1 has dealt many humbling blows. This was my first. A boy under Dr. Morton's care traveled to Canada for the surgery. It was performed by a physician who pioneered the technique. He did a fine job—placed the pallidal lesions with exquisite precision. But it didn't work. To be sure, this was a censure to confidence. But we were right to try it; we had to try it. So many children, who could not speak for themselves, depended on it.



We refocused our efforts on prevention. Through the early and mid 1990s, we thought of GA1, propionic acidemia, and maple syrup disease in much the same way. We imagined that certain chemicals produced endogenously (from within) acted as neural toxins. The prevailing idea was this: during infections or other physical stresses,

muscle tissue degrades protein—a process called catabolism—to provide amino acid building blocks that are used by the liver to make sugar and by the immune system to make antibodies. This is a normal adaptation. It happens in all of us, every time we get sick. In GA1 and diseases like it, an enzyme deficiency prevents the complete breakdown of these amino acids. As a consequence, certain chemicals accumulate to high concentrations in the blood and poison the brain. Dr. Morton and others had clearly shown that brain injuries in GA1 almost always occurred during infections and other catabolic states.

Two concepts grew out of the “circulating toxin” model. First, we assumed that the poison in GA1—either glutaric or 3-hydroxyglutaric acid—came primarily from muscle, moved through the bloodstream, and ultimately had to enter the brain through a special obstacle, called the blood-brain barrier, to cause damage. Second, we believed that effective treatment depended on interrupting this chain of protein degradation, toxin accumulation, and brain injury by treating the earliest stages of catabolic illness with special nutritional therapy (usually delivered by IV) that forced amino acids back into muscle protein. At the time this model was plausible; it was a good starting point for therapy.

And it worked. Before 1989, the incidence of brain injury among Amish children with GA1 was greater than 90%. By the end of 1990 it was 50%, and by 1995 it had decreased to 36%. However, between 1995 and 2005, risk remained unchanged. Clearly, we had run up against the limits of our understanding. Over this same decade, facts began to accumulate that challenged our basic tenets about GA1:

Not all brain injuries occurred during catabolic illness. Before 1995, at least two thirds struck during an infection, but after 1995 only 3 of 9

injuries occurred during an illness. The other 6 occurred with no obvious triggering stress. Direct metabolic testing during catabolic illness, and even during the acute phase of a brain injury, showed that glutaric acid levels in blood and urine were seldom elevated, and sometimes lower than expected, in children who were sick. This challenged the idea that toxins “accumulate” during acute illness. Several experiments in animals showed convincingly that glutaric and 3-hydroxyglutaric acids in the bloodstream do not enter the brain.

In the spring of 2001, as I neared the completion of my pediatric training, Dr. Morton invited me to join his practice at the Clinic. That first winter in Strasburg, I witnessed the cruelty of GA1 firsthand. An Amish girl was diagnosed with GA1 as a newborn and treated at the Clinic. She grew normally, sat independently at age 6 months and by age 11 months was cruising. Shortly after her first birthday, she developed a lung infection and high fever. Her mother went to awaken her from a nap to find her flaccid and paralyzed. A brain MRI showed acute injury to the basal ganglia and a “diffusion” scan showed that the damage was irreversible—just like a stroke. She is now nine years old, confined to a wheelchair, fed through a tube, and unable to speak or use her hands.

Over the four years that followed, five more children were injured. We struggled to gain our footing. Meanwhile, studies were underway that would transform our thinking about GA1. In Canada, Dr. Funk and his colleagues studied six children who died from complications of GA1. They described basal ganglia lesions indistinguishable from those caused by stroke. And more importantly, found that concentrations of glutaric and 3-hydroxyglutaric acids in brain tissue were 100- to 1000-times higher than levels in the blood or spinal fluid. This solved an intractable puzzle: Why couldn't the risk for injury be predicted by measuring chemicals in blood or urine? Because blood and urine concentrations do not reflect the concentration in the brain—which is the concentration that matters.

In 2005, I wrote an editorial about this study in which I speculated that glutaric acid does not enter the brain from the bloodstream, but rather is produced within the brain from two precursor amino acids, lysine and tryptophan. Studies in animals soon confirmed this hypothesis. When extra lysine was fed to experimental GA1 mice, they accumulated large amounts of glutaric acid in the brain, developed brain lesions, and died.

The clinical implication was clear enough: to understand GA1, we had to look at the inner workings of the brain. Here, stroke could prove a useful model. Strokes occur when the brain lacks the energy to meet its basic needs. Most commonly this is because of a vascular obstruction. However, stroke can also occur if either glucose or oxygen levels are low in the blood, or brain cells cannot utilize them for some reason. This has been called metabolic stroke. So here was a simple set of variables to explore. If chemicals accumulating in GA1 cause an injury like a stroke, they must do so by interfering with the brain's oxygen use, glucose use, or blood supply.

Answers to these questions depended on new methods to image the brain, ones that provided functional data about brain energy production and blood flow. Many collaborators donated time and services to make this possible: Jelena Lazovic, Alan Shuldiner, Patrick Donnelly, Max Wintermark, and the neuroimaging staff of Lancaster General Hospital. With their help, we collected and interpreted a large amount of functional imaging data over the last 8 years. These observations are summarized in two large studies, one completed in 2007 and another due out this Fall. Eric Sherman, a high school student from Ephrata, worked with Dr. Puffenberger to fill in another key piece of the puzzle. He mapped the gene for glutaric aciduria type 3 (GA3), an apparently benign condition, which gave us more precise knowledge about the chemical toxicity of GA1. Collectively, this is what we found:

Glutaryl-CoA, which cannot be produced in GA3, appears central to the toxicity of GA1. The location of its production is likely key to its

toxicity. It is made in mitochondria-- numerous compartments within the cell that produce energy.

Glucose use by the basal ganglia is about 30% below normal in children who are not injured. This suggests that something about the mitochondrial trapping of glutaryl-CoA or its derivatives (e.g. glutaric acid) interferes with energy metabolism in the brain. This can be observed in asymptomatic infants (and perhaps all infants) with GA1, and does not necessarily lead to brain injury.

In non-injured GA1 infants, blood flow is reduced by 18-26% throughout the brain. A larger volume of blood flows through the brain, but it moves more slowly. This pattern has been seen in other conditions associated with brain damage. In GA1, it may be a response to abnormal energy metabolism.

Cerebral veins appear congested with blood. This can impede arterial flow, and rarely leads to complications like bleeding under the skull or within the nerve layer of the eye. Venous congestion is also a source of extra fluid in and around the brain, which might account for large head size, a common feature of GA1.

During an acute brain injury, two striking changes take place. Cells from both the right and left basal ganglia suddenly and collectively lose their ability to produce energy and they become swollen. Meanwhile, blood flow to the brain speeds up, is reduced in volume, and becomes unevenly distributed. Changes in blood flow and glucose use are most pronounced during the first few years of life, and appear to correlate closely with the brain's rapid phase of growth.

What do these findings mean? First, they suggest that growth itself puts the brain at risk. To grow, the brain must import lysine, expend a lot of energy, and recruit a large blood flow. These forces likely interact to create a precarious state: the brain might produce the most glutaryl-CoA at a time when its energy demand is highest. If this is true, then during the brain's rapid growth phase in the first two years of life, brain concentrations of glutaryl-CoA and glutaric acid are probably continuously high and change rather slowly. Infections and other stresses can definitely trigger injury, but probably not by causing more toxins to accumulate. What we do know, unfortunately, is that no such trigger is necessary for an injury to take place.

The real value of knowledge is revealed by its practical consequences. What practical wisdom do we take away from this long and difficult struggle with GA1? We certainly take away humility; GA1 is an elusive disease, hard to understand, and there is much more to learn. But we also have learned that Dr. Morton's basic intuition in 1989 was correct: if we start with healthy children and try to take care of them, over time knowledge comes, slowly and deliberately, and it does make a difference.

Beginning late in 2006, we entered a new phase of practice. Collaborating with a company called Applied Nutrition in New Jersey, we developed an infant formula (Glutarade) for the treatment of GA1. It was designed to provide a larger percentage of calories as carbohydrates (i.e. glucose)— the same amount, in fact, that children receive by IV when hospitalized. It is also enriched with certain essential amino acids. These probably serve at least two functions. First, they improve the overall quality of tissue growth and promote better general health. Second, they may improve the efficiency of energy production in mitochondria by a process called anaplerosis.

Does it work? It is too early to tell for certain, but there is reason to be hopeful. Since August 2006, we have diagnosed six newborns with GA1, five of whom were started on Glutarade. All six children are healthy and free from injury. Four have passed their second birthday. We still lack a precise understanding of how the new therapy works, but such is the history of medicine. We must often act on incomplete knowledge, especially when risks are certain. We are satisfied to alleviate some misery, admit our ignorance, and keep moving forward. At least, it seems, we are on the right path.



CLINIC STAFF: seated, Holmes and Caroline Morton, standing, left to right, Miriam Echtermach, Christine Hendrickson, Donna Robinson, Nicholas Rider, Kevin Strauss and Erik Puffenberger. Not pictured are Rebecca Smoker and Cris Mitchell.

In June, Dr. Kevin Strauss was named Medical Director to coordinate day to day clinical work and clinical research projects. Dr. Morton continues as the Clinic's Director and is happy, confident and gratified to share responsibilities with his colleague.

UPDATES FROM OUR LAB

Erik Puffenberger, Laboratory Director

Disease Gene Mapping

When there is no strong clinical or biochemical evidence linking a genetic disease to a known gene, then it is necessary to map the general location of the disease gene among the 22 human chromosomes. For many disorders that we have identified in the Plain populations, the clinical or biochemical evidence is strong, implicating a single causative gene. In these cases, we simply sequence the gene in one or more patients to identify the mutation. Unfortunately, there are dozens of disorders seen in clinic patients where the gene and/or its location are unknown. Without knowledge of the gene location, efforts to identify the disease gene among the 40,000 human genes are extremely difficult.

We have performed several dozen mapping studies using DNA samples collected with permission from clinic patients. To date, we have mapped and identified the causative gene for 14 separate genetic diseases. Many of these diseases, such as LYK5 deficiency ("Pretzel" syndrome) and CDFE (cortical dysplasia and focal epilepsy), were previously undescribed in medical literature. We also have preliminary mapping data for 11 other disorders; that is, we know the location of the gene on a chromosome, but not the specific gene within that region. This is analogous to knowing the street where someone lives, but not the specific house. We are actively working to sequence candidate genes for several of these disorders. Unfortunately, there are many genes to sequence and this requires much time, money, and effort.

This summer we embarked on a collaboration with the **Broad Institute** in Cambridge, MA, to improve mutation identification through gene sequencing. Dr. Stacey Gabriel, director of the National Center for Genotyping and Analysis at the Broad Institute, was a graduate school classmate of the clinic's laboratory director, Dr. Erik Puffenberger. They have been organizing a joint project which would provide whole-genome gene sequencing on selected clinic patients. This work would be performed for free, although the resulting DNA sequence data will need to be deposited in a national database for other researchers to access. The first five disorders for this project have been selected and three DNA samples have been shipped to the Broad Institute. This will save the clinic much-needed resources and will lead to development of diagnostic testing and to potential treatments for these disorders.

DNA Sequencer Upgrade In March 2000 the clinic purchased an Applied Biosystems 310 Genetic Analyzer. This single-capillary DNA sequencer was acquired to facilitate molecular genetic research and improve diagnostic testing. Through gene mapping and mutation identification studies, the DNA sequencer has greatly improved our diagnostic capabilities over the past nine years. The laboratory can presently detect about 80 gene mutations found in the Old Order Amish and Mennonite populations of Pennsylvania. The ability to accurately and inexpensively diagnose patients in a timely manner through DNA-based testing is invaluable for preventing the devastating effects of many genetic disorders.

Since acquiring the 310 Genetic Analyzer, we have isolated DNA from over 4350 individuals. A wide variety of DNA sequencing projects have been conducted on these samples, both for clinical and research purposes. We perform about 400 sequence-based carrier and diagnostic tests yearly. In addition, we can perform complete gene sequencing for several disorders such as phenylketonuria (PKU), Crigler-Najjar syndrome, and medium chain acyl-CoA dehydrogenase deficiency (MCADD). Over the past nine years, we have completely sequenced the PAH gene in 79 PKU patients, identifying 97.5% of their mutations. As time and resources permit, we also perform candidate gene sequencing for our mapping studies. To date, we have sequenced 137 different human genes to identify mutations. Unfortunately, the volume of laboratory work now far exceeds the capacity of our single-channel 310 DNA sequencer. In order to alleviate this problem, we recently replaced the ABI 310 Genetic Analyzer with a larger and faster ABI 3130 Genetic Analyzer. The acquisition of the new sequencer was made possible through a generous gift from **Lancaster General Hospital**. The increased speed and higher throughput of the new 4-channel sequencer will help us keep pace with the ever-increasing workload.

We thank Lancaster General for this very significant gift and the improved capability it brings to our lab.

ULTRASOUND DONATED

In our previous Newsletter we wrote of our need to have our own ultrasound equipment with compelling justification of the value of this technology in diagnosis and assessments for many children with genetic conditions seen at the Clinic. We are happy to report we received the ultrasound equipment in June and are very grateful to the **Phillips** company for their support.

SCID: CREATING A BONE MARROW DONOR DATA BASE

Dr. Nicholas Rider

Severe combined immunodeficiency (SCID) is caused by inherited defects of T-cell function. Without treatment, SCID is uniformly fatal early in life. Hematopoietic stem cell transplantation (HSCT) allows SCID patients to survive in good health. Stem cell match and patient age at transplantation are two critical determinants of outcome after HSCT. Immune cell engraftment and patient survival are best when a child less than one month of age receives stem cells identical, or HLA matched, to their own.

SCID affects at least 1 in 75,000 newborns worldwide, but is more common among Old Order Amish and Mennonite (Plain) communities of the United States due to a high prevalence of "founder" mutations in four different genes (ADA, IL7R, RAG1, and RMRP). The RAG1 c.2974A>G variant alone has an estimated carrier frequency of 1 in 20 among Lancaster County Amish. We know of 44 Plain children born with SCID between 1978 and 2007. Only half of them received a transplant and 33 (75%) died from infections at an average age of 5 months. Compared to other SCID populations, mortality is unusually high among Plain children, largely due to poor medical access, delayed diagnosis, and the prohibitive costs associated with treatment. We are developing strategies to diagnose SCID early in life, before the onset of illness; make HLA matching quick, accurate, and affordable; and provide comprehensive local care that allows affected children to safely get to HSCT before 1 month of age. Studies show that 95% of SCID patients transplanted within this time frame survive long-term with restored immune function.

Currently, we offer rapid testing for the 4 genetic causes of SCID described above. Cord or peripheral blood samples may be sent to our laboratory for diagnosis within hours. We can also use this technology to determine whether parents are carriers of the mutation and provide appropriate counseling to the family. Finally, we are constructing a database of HLA or transplant types to facilitate quick and affordable stem cell matching for affected infants. One of the most important parts of this effort is enrollment within the National Marrow Donor Program (NMDP) and also within our HLA database at the Clinic for Special Children. To begin the process of helping a sick baby with SCID, potential stem cell donors may sign up to attend a 'bone marrow drive' which will be held on Friday November 6 at the Clinic for Special Children. A second drive will be held in Union County Pennsylvania on Saturday November 7. Please contact us for further details.

SCHOLARSHIP AT WORK

During the past year we have had several students stretching their brain at the Clinic and contributing significant work for the benefit of patients. We asked them to reflect on their work:

Eric Sherman *I have been volunteering at the Clinic for two years and have helped with a variety of projects during that time. I have mapped genes, discovered new mutations, developed new protocols, and assisted with day-to-day laboratory operations. One of my current projects involves optimizing a bisul-*

fitte sequencing protocol which, when completed, will allow easy molecular differentiation and diagnosis of Angelman and Prader-Willi Syndromes. Another current project includes the development of a computer program to identify possible bone marrow donors for a significantly lower cost than traditional methods. I enjoy volunteering at the Clinic and will be furthering my education at Swarthmore College this fall. I hope to build upon what I have learned at the Clinic by earning a degree in biology or genetics, with the ultimate goal of earning a Ph.D. or an MD/Ph.D. and becoming a research scientist.

Eric is the son of Donna and Don Sherman of Ephrata and a recent honors graduate of Ephrata High School. Eric just received news he was named as a Davidson Fellow Laureate by the Davidson Institute which includes a substantial scholarship award for his future studies at Swarthmore College. He received the Morton Scholarship Award last summer.

Nikolas Muenke *I have had the privilege of studying at the clinic for almost a year now and continue to learn new things every day. The pleasure of meeting so many families is a big part of what drives me to bring my best every day. My main project has been working with the mass spectrometer; the tool we use to identify certain markers of metabolic defects. With help from Dr. Morton, I am getting closer to more accurate analysis and quantitation of many important organic acids. We hope to have the automatic software analysis running smoothly so anyone, even those unfamiliar with the complexity of the data can derive meaning of sample results. In addition to simplifying this powerful research tool, it has been my goal to set up an age and gender matched database of control samples in order to compare patient lab values to the normal average and standard deviation. This will allow us to ask questions beyond simply looking for the presence or absence of a particular pathologic metabolite, giving us a more detailed picture about how certain disorders affect other normally functioning pathways. I thank you all sincerely for inviting me into your communities and allowing me to meet so many of your children. The time I have spent here has been a blessing in many ways.*

Nikolas received the Morton Scholarship Award this year and also works part time in the Clinic's lab. He is in the process of submitting his applications for medical school.

Krysta Brown *My involvement with the Clinic for Special Children began when I took "Plain People and Modern Medicine," a class offered at Franklin and Marshall College, that is taught by the Clinic doctors. I had to petition the chair of the biology department to let me in the course. I was a junior Biochemistry major, and preference was given to senior Biology majors. I am happy that I did—by the time the class ended I was completely fascinated by the work being done at the Clinic. So much so that I made an arrangement with the doctors and F&M that allowed me to do research at the Clinic through the Howard Hughes Medical Institute Grant.*

I started my independent research at the Clinic in September of 2008. In the past months I have immersed myself in the study of pyruvate kinase deficiency, a red blood cell abnormality of the Amish population. This disease is characterized by ineffective red blood cell function and abnormal iron metabolism. I am specifically interested in discovering the origin of the iron imbalance because iron overload becomes a major problem in aging pyruvate kinase deficient patients. I am hoping that my work will help to define better treatment protocols for this aspect of the disease. In retrospect, I realize that taking "Plain People and Modern Medicine" was one of the wisest choices of my college career. My views about patient care and effective medicine have been forever altered by my work at the Clinic. As I enter the medical profession I will take with me the valuable lessons I have learned about translational medicine and the success of a healthcare system that is based on understanding the unique needs of the patient, rather than the patient's disease.

Krysta received the Eyler Award from Franklin & Marshall College which funds a ten-week summer internship at the Clinic. She is also in the process of her application to medical school.

Tara Flick, a high school biology teacher at Conestoga Valley High School, participated in a six-week summer research internship in bioinformatics at the Clinic. Franklin and Marshall College, through a Howard Hughes Medical Institute grant, partnered with the Clinic to offer this opportunity as well as a one-week seminar for teachers.

Tara worked on finding a genetic mutation that leads to cerebral cavernous malformation (CCM). CCMs are vascular abnormalities of the brain that can cause hemorrhagic stroke and seizures as well as headaches. Some individuals with CCMs are asymptomatic. Dr. Erik Puffenberger guided Tara through the process of finding a mutated, inherited gene in a family with four affected individuals. Tara used SNP microarrays to narrow the entire human genome to more specific areas where the mutation might occur. She sequenced a gene, KRIT 1, that is associated with causing CCMs and is looking for a mutation within that gene. This entire experience will help Tara bring real-world and cutting edge applications to her students. As part of this internship, she is developing lessons that use bioinformatics in hopes that her students will find the topic very interesting and realistic.

CLINIC FOR SPECIAL CHILDREN
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CSC FELLOWSHIP

Olivia Wengerd, M.D. will be working part time with the Clinic for Special Children during the coming year to improve communication and participation in newborn screening services among lay midwives and Plain families in Central Pennsylvania. Partially funded by Dr. Morton's MacArthur Award, the goal of her Clinic Fellowship includes identifying ways to improve follow up services to children from that region of PA who are diagnosed with genetic conditions through newborn screening or subsequent testing. In the following paragraphs she reflects on her involvement with the Clinic and this new project.

I remember my first meeting with Holmes Morton very clearly. He spoke about "meaningful work" at my graduation from Elizabethtown College nine years ago. I sat in the audience, filled with ideals about the kind of physician I wanted to be. I soon left rural PA for medical school at Albert Einstein College of Medicine in New York City, followed by a pediatric residency in Akron, Ohio. I now practice pediatrics in my hometown—Lewisburg, PA. Lately, I have realized that physicians can be crippled by cynicism, anxiety, and exhaustion. Our handicaps are not as obvious as developmental delay, seizures, or dwarfism. However, they can be just as debilitating. I am very grateful for the chance to learn about providing excellent medical care to special children from the physicians and staff at the Clinic for Special Children. One could say that the CSC has provided a "medical home" for me—a young pediatrician with special needs of her own.

PLEASE consider a donation to the Clinic for Special Children. We need support more than ever.

Staff

Holmes Morton, M.D., Director
Caroline S. Morton, EdM., Executive Director
Kevin A. Strauss, M.D., Medical Director
Nicholas L. Rider, D.O., Pediatrician
Erik Puffenberger, PhD., Lab Director
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LOOKING AHEAD

GLUTARIC ACIDURIA FAMILY DINNER SEPTEMBER 18

Families with children with glutaric aciduria will share dinner and fellowship on Friday, September 18th, before the Clinic's benefit auction in Lancaster County. As in previous years, the dinner will be held at the Clinic and sponsored by IOGA.

CME FALL COURSE The next CME course sponsored by the Clinic is scheduled for **October 15-16, 2009**. Held at the Clinic, the course is designed for pediatricians, family practice physicians, medical students or residents. Please call the Clinic 717-687-9407 for additional information or to register.

BONE MARROW DONOR DRIVE DATES:

November 6 at Clinic for Special Children and November 7, Union County, PA.

OUR WISH LIST

General support for patient services

Matching donor fund challenge

SCID clinical studies and bone marrow donor project

Support for clinical studies

Major gifts for the Research and Endowment Fund

MISSION

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

CLINIC FOR SPECIAL CHILDREN

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PA law requires us to advise 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