Moving Forward

This year marks the 10th year of the Clinic for Special Children. In these years hundreds of children have presented with medical problems due to over 80 different genetic disorders or syndromes. Some problems are one of a kind, others affect large numbers of children. Our goal is to help our patients be as healthy as possible despite their genetic disease. Our efforts encompass newborn screening and carrier testing for early diagnosis; laboratory tests to confirm and monitor their condition; preventive and comprehensive pediatric care specialized for each child; critical care in hospital when necessary; and clinical research to advance care plans and treatment protocols for children with many of the disorders. In this issue we list the genetic disorders seen in children at the clinic over 10 years, we offer a “genetics primer” to increase understanding, we list new tests available, new studies underway and we describe several new experimental therapies which we think offer hope for many of our patients. And, we offer our thanks to children who have taught us, to their parents and to many who have given us support over 10 years to do this work.

9TH ANNUAL BENEFIT AUCTION
SEPTEMBER 18, 1999

The third Saturday of September, the 18th, is on the minds of many volunteers who coordinate the clinic’s annual benefit auction. The auction grows each year and much thought is given to how much chicken to barbecue, subs to make, soft pretzels to bake, ice cream to freeze, what to bake or what to make? Last year’s auction was another great success and provides some clues as to what to expect this year: 3,000 lbs. of chicken were cooked and sold, 4,000 soft pretzels were made, 9,000 donuts baked, 200 fresh strawberry pies prepared, and 230 gallons of ice cream consumed by an estimated several thousand people. Last year 84 large size quilts were sold and many pieces of hand made furniture - tables, chairs, cabinets, bedroom sets, benches and a grandfather clock. Outside, lawn furniture, swing sets, storage sheds, farm supplies, a pony & cart, and many other items including a donated shipment of Rubbermaid products were sold to over 1500 bidders by 25 volunteer auctioneers. Amish children enjoy counting and comparing the number of out of state license plates on vehicles in the parking lot. Last year they counted 13 states. The ultimate thrill will be to find one from Hawaii!

We hope all who attended the auction last year will return and we welcome newcomers. Donated items for this year begin to appear: a postage stamp quilt, a cross stitch rose quilt stitched by a special young lady who visits the clinic, many traditional quilts, country love, sunshine shadow, and other appliqued and patchwork designs. A beautiful cherry bed room set was handcrafted especially for this auction. (continued page 2, col. 1)

CRIGLER - NAJJAR SYMPOSIUM:

Bright blue light beamed from many windows of a Strasburg inn in mid-June. The lights were there for children with Crigler - Najjar syndrome who came to Strasburg with their parents for the second symposium on this rare and complex disorder. The conference was sponsored by the Clinic for Special Children with co-sponsors, The Rockefeller University and The University of Vermont and included 16 families and physicians and scientists from the United States, Canada and Europe. Twenty children (or youth) with Crigler- Najjar attended including 4 who have had liver transplants.

Children with Crigler-Najjar suffer high levels of bilirubin causing jaundice and other complications such as gall stones, muscle weakness, lethargy and are at high risk during any illness for neurological injury. When well, children enjoy a fairly normal lifestyle but must spend hours under light therapy to control bilirubin. Their disease is always apparent in the yellow tones of their skin and eyes. The only definitive treatment for Crigler-Najjar has been liver transplant.

Dr. John Crigler, who identified the disease in the late 1940's while at Johns Hopkins, opened the conference with history. When first identified there was no effective treatment for the disease, no hope and the children all died. Dr. Crigler, a professor at Harvard Medical School and Children's Hospital, Boston, continued to work on the disease. One of his former students, Dr. Holmes Morton, now cares for 16 Mennonite and Amish children with Crigler-Najjar at the Clinic for Special Children. (continued page 2, col. 2)

Dr. Crigler with children who have Crigler - Najjar Syndrome at recent symposium in Strasburg
(auction, cont.) The sale begins at 8:30 am and ends when all
is sold at Leola Produce Auction Center, Brethren Church
Road (north off of Rt# 23), Leola, PA. Dr. Morton will make
a few remarks around noon.
If you have items to donate please call one of the following at
area code (717): 626-4863; 354-5415; 636-9694; or 733-2645

The auction provides a substantial portion of the
clinic's annual operating expenses. It builds our
research fund and lowers the cost of office
visits, house calls, laboratory fees, and
diagnostic services for families who need the
clinic. It helps give Dr. Morton and the Clinic
staff time and support to think, study, and
improve care for many children with biochemical
and other genetic disorders.
We thank the many individuals who have
contributed by their presence at the auction, by
their volunteer efforts, and by their generous
spirit. We are very grateful for the interest, time
and contribution that so many give to the Clinic.
The support makes our work possible and helps
many families receive medical care for children
with biochemical and other genetic disorders.

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A SECOND AND A THIRD BENEFIT AUCTION
The Clinic benefits from two additional auctions planned by
plain communities in other areas of Pennsylvania.

MARTINSBURG AUCTION
On September 11th, Old Order Mennonite families in the
Martinsburg area (Blair County region) will hold their third
benefit auction for the Clinic at the Morrison Cove Produce
Auction Center, Rt.36 north of Woodbury or 6 miles south of
Roaring Spring, PA. Last year's sale doubled in participation,
items donated, and results from the first year. The auction
features hand made furniture, quilts, food, crafts, farm goods
and many other donated items. Please call one of the
following for information or to donate items, all at area code
(814): 793-3634; 793-3010; 793-2423; 832-2731.

NEW SHIPPENSBURG AUCTION
Mennonite and Amish families in Shippensburg, PA, held a
benefit auction in the spring and another on July 24th to
support the Clinic. The auctions were held at Leinbach's
Auction Center north of Shippensburg. A highlight of the sale
was a wood three dimensional painting of the Clinic made by
an Amish craftsman. The painting brought cheerful, generous
bidding and was given by the new owner to the Mortons to
hang in the Clinic where it has attracted much attention. The
Clinic thanks the Leinbach family and other members of the
sale committee who gave their time and effort to make these
first sales such a success. The committee hopes to make the
July date an annual event.

NEW YORK PIG ROAST
The Clinic again thanks the family and friends of the Colby
family in Rochester, NY, who continue to sponsor an annual
fundraiser in early October to support the Clinic.

(Crigler, cont.) Dr. Morton presented issues based on the
clinical management of children with this complex disorder.
All of the Clinic's patients have avoided liver transplant, but
their care has stimulated much investigation in the
pathophysiology of the disease and avoidance of bilirubin
toxicity. Dr. Maarten Sinaasappel, Sophia Children's
Hospital, The Netherlands, also discussed clinical experience
with a group of Dutch children with Criglers 1 & 2. Aspects of
the disorder that were presented and followed by open
discussion among physicians and parents included the impact
of the disorder on the brain due to bilirubin toxicity.
Contributors to understanding the neurological impact of the
disease included Michael Johnston MD, Alec Hoon MD, and
Richard Kelley MD, from Kennedy Krieger Institute and Johns
Hopkins and Dr. Jerold F. Lucey, University of Vermont.
Control of bilirubin and its toxicity through light therapy
was presented by Hendrik Vreman PhD, Stanford University.
Co-sponsor Dr. Atallah Kappas, Rockefeller University,
discussed control through medication such as Tino-
Mesoporphrin. Alex Robertson MD, East Carolina presented
effects of medications upon bilirubin albumin binding; Gerald
Salen MD, VA Medical Center, East Orange, NJ, and Clifford
Steer M.D., University of Minnesota discussed effects of
ursodiol upon bilirubin transport through the liver; and Jeffrey
Maisels MD, William Beaumont Hospital, MI. moderated
questions and discussion. Professor Wiese, Mrs. Annie Becker
and Mr. Bachmann presented an impressive state of the art
photo-therapy bed developed in Germany.
Liver transplant as a therapeutic option was presented by Jorge
Reyes MD, University of Pittsburgh Transplantation Institute
and Ira Fox MD, University of Nebraska discussed experience
with liver cell transplant as treatment for Crigler-Najjar.

GENE THERAPY
The role of gene therapy has gained greater significance for
Crigler-Najjar in recent months. Jayania Roy-Chowdhury MD,
Albert Einstein College of Medicine, NY; Clifford Steer M.D.,
University of Minnesota and Michael Blaese MD, NIH &
Kimeragen presented the progress toward a possible gene repair
for children with Crigler-Najjar with a procedure called
chimeraplasty. This aspect of the conference gained much
media attention including comprehensive articles in the NY
Times, Newsday, Lancaster New Era, and Associated Press.
Dr. Steer's work on site directed mutagenesis involving the
delivery of chimeric RNA/DNA templates to hepatocytes
(liver cells) advanced the method of gene repair along with Dr.
Chowdhury's experiments with the Gunn rat using site directed
mutagenesis. Their work paves the way for Dr. Blaese, who
directed gene therapy at NIH for many years, to initiate the
first clinical trials of chimeraplasty to repair an abnormal
gene in humans. Due to the form of gene mutation in Crigler-
Najjar syndrome and that the Amish and Mennonite patients
share an identified mutation, the first attempts at gene repair
will be performed on C-N children from the Clinic for Special
Children. Clinical protocols have been developed by Dr.
Blaese, Dr. Steer and Dr. Morton for FDA consideration and we
hope trials will begin in the Fall. It is hoped that enough
cells in the liver will correct to restore enough liver function to
reduce bilirubin significantly and alleviate complications
generated by bilirubin toxicity. As the children involved say
"and no more sleeping under those lights" !
PROGRESS NOTES
Holmes Morton M.D.

DYSTONIA: New approaches to the control of intractable dystonia caused by basal ganglial injury in children with glutaric aciduria type 1.

Children who have been injured by GA1 suffer from a generalized dystonia that is refractory to treatment with medication and leads to a collection of problems that are miserable, difficult to manage, and often are life threatening. Dystonia is defined as sustained spasms of opposing muscle groups causing fixed, twisting, postures of the limbs and trunk. The strength of muscle contraction typically increases with activity. Dystonic movement is typically superimposed upon or disrupts movements initiated by other regions of the brain. Dystonia is associated with many genetic disorders that affect the basal ganglia including some forms of Parkinsonism, Huntington disease, and many different biochemical disorders that cause degeneration or intoxication of the putamen or globus pallidus. In children with maple syrup disease transient episodes of dystonia are very common and can be suppressed or reversed by tyrosine. Dystonia can also be caused by birth asphyxia, strokes, near drowning, carbon monoxide poisoning, and, particularly in infants, may develop after open heart surgery.

DYSTONIA CONFERENCE
On February 8th 1999 several physicians and scientists met at the Clinic with parents present to discuss the basal ganglion injury caused by glutaric aciduria type 1. Physicians who attended included Dr. Andres Lozano, University of Toronto and Dr. Fred Lentz, Johns Hopkins, both of whom perform neurosurgery to control severe movement disorders; Dr. Rachel Saunders- Pullman, a neurologist from the Beth Israel in New York who has been involved in the research related to two different forms of inherited dystonia found in the Mennonite populations here and in the west called DYT1 & DYT6 dystonias. Three physicians sponsored by IGNA attended: Dr. Tom Freeman and Dr. Robert Hauser from the University of South Florida College of Medicine and Dr. Evan Snyder from Harvard Medical School. Dr. Freeman is a neurosurgeon who does fetal cell transplant as treatment for Parkinson disease and Huntington disease and Dr. Hauser is a movement disorder specialist who works with Dr. Freeman. Dr. Snyder is a pediatric neurologist whose research aims to develop neuronal stem cell lines to be used to repair regions of the brain injured by accidents or genetic disorders. Two neuroradiologists helped with the review of MRIs, Dr. Elias Melhem, Chief of Pediatric Neuroradiology at Johns Hopkins and Dr. Jill Hunter from Childrens Hospital of Philadelphia. Dr. Richard Kelley and Dr. Alec Hoon attended from Kennedy-Krieger Institute in Baltimore. Dr. Hoon is a neonatologist and developmentalist who works with Dr. Michael Johnston in the Movement Disorder Clinic at Kennedy-Krieger. Dr. Kevin Strauss, resident at Boston Children's Hospital attended the meeting. Several parents were invited to bring seven children with GA1 who have moderate to severe dystonia. Although all of the physicians at the meeting are involved in the diagnosis and management of patients with movement disorders, most had not met a child with dystonia caused by GA1.

CELL TRANSPLANTS AS THERAPY
Drs. Freeman, Hauser, and Synder presented research related to brain repair using cell transplants. Dr. Freeman reported that transplanted cells from the substantia nigra have been used with limited success in the treatment of Parkinson syndrome, but, he has had little success rebuilding the caudate and putamen in patients with advanced Huntington disease. Research is ongoing to determine if cell transplants can be used to prevent deterioration of these ganglia in Huntington patients. Dr. Snyder hopes to develop cultured neuronal stem cell lines that can be used to rebuild any region of the brain in the same sense that bone marrow stem cell lines are used to rebuild multiple cell lines in patients who have a bone marrow transplant. Cultured neuronal stem cell lines are not yet available for clinical trials and before such trials are started Dr. Snyder and others will need to show restoration of neurological function in animal models. Some of the research in Dr. Synder’s lab is being supported by Mike Metil and the International Organization for Glutaric Aciduria to determine if neuronal stem cell lines can be used to rebuild the basal ganglia in experimental animals after quinolinate mediated injury of the ganglia.

PALLIDOTOMY AS THERAPY
Dr. Kevin Strauss and I have used MR images and careful neurological examinations to argue that the dystonia seen in children with GA1 arises from injury and degeneration of the putamen. We found that the most severe cases of dystonia develop when the putamen is destroyed and the globus pallidus is still visible on MRI. We were particularly interested in reports about suppression of dystonia by a surgical technique called pallidotomy. In patients with Parkinsonism the recovery of function after pallidotomy is often dramatic and immediate. Patients with an inherited form of dystonia called DYT-1 dystonia recover more slowly but over weeks to months after surgery may make gradual but remarkable recoveries. Andres Lozano described one of several cases from Israel, a 9 year old boy with DYT 1 dystonia who underwent bilateral posterior ventral pallidotomy. The case was reported in Movement Disorders 1997;12:865-870. Dr. Lozano showed a series of videos of the boy before surgery when the boy was fully disabled by generalized dystonia. One to two weeks after surgery the boy could stand and walk with help. Three months later, he could walk independently and within six months he could run. Two years after surgery, the boy was fully independent and off all medications. He can now play soccer and has learned to ride a bicycle. Seeing this video with parents and seven GA1 patients who are terribly disabled by dystonia was a remarkable experience.

In April 1999 the first patient with GA1 and generalized dystonia was operated on by Dr. Lozano and his team at the University of Toronto. This ten year boy was selected for experimental pallidotomy because of severe dystonia with recurrent aspiration pneumonias, progressive lumbar scoliosis with intractable lower back pain, and severe dystonia of the legs that placed him at high risk for hip dislocation. His
dystonia was not responsive to medications. He had been injured at four months of age before diagnosis of GA1 and was fully dependent upon others for care. He had not learned to sit alone or stand and had little or no purposeful use of his hands. The MRI's of his brain showed complete degeneration of the putamen, normal caudate lobes, and residual tissue in the internal globus pallidi. The brain was otherwise normal and he did not have enlarged subdural spaces.

There were few changes immediately after surgery. His dystonia at rest was decreased. He indicated soon after surgery that his lower back pain was gone. He could sit straighter in the wheel chair without his feet being strapped in place to prevent extension and scissoring of his legs. His hands were more often open and relaxed. Improvement in dystonia was more apparent in his lower trunk, legs and hands than in the shoulders and neck.

Most of his progress after surgery has come from working with a therapist, Judy Hurbut, who has worked with several children injured by GA1 at the S. June Smith Center in Lancaster. Judy reports week to week progress in his control of movements and does not think this progress would have been possible before surgery. He continues to have dystonic turning of his head to the right but he can overcome this positioning by following objects with his eyes. He can sit alone on the floor in a crossed-leg position and use his arms to maintain balance for extended periods of time. He can lean forward to the floor with his legs under him then lift his head and shoulders and push-up to a sitting position and can roll from front to back. Lying with his back on the floor he can hold the therapist's hands and pull-up to a standing position while maintaining his head and trunk in the midline. A hand control lever was recently installed on his wheel chair and it appears that he will now be able to drive his wheelchair using hand control.

The boy's parents, Judy, and I agree that his dystonia was not eliminated by the surgery but we continue to see improvements in control and function that we would not have expected without the surgery. The effects of pallidotomy in a child who has always been disabled - who was injured before he learned to sit or walk, may be completely different from the effects in a patient with adult onset Parkinson disease or from a child such as the Israeli boy with DYT-1 dystonia who was able to walk and run until age 6 years and then became disabled. I am hopeful that in our patient the surgery has suppressed the abnormal outflow from the basal ganglia and the remaining dystonia movements are residual, learned patterns of abnormal movement that can gradually be retrained.

Time, work and careful observations will tell.

NOTE:
Palidotomy in children with GA1 is an experimental therapy. Very few medical centers have experience in neurosurgery to treat dystonia, even fewer centers have experience with such surgery in children. I have referred children to Dr. Andres Lozano at University of Toronto and to Dr. Jerrold Vitek at Emory University School of Medicine. Cases should be selected carefully. Parents and children should understand the risks and that the surgery is experimental. I expect that patients who are most likely to respond to this surgery will be those who have focal degeneration of the putamen with preserved regions of internal globus pallidus and an otherwise normal brain. Pallidal lesions need to be placed accurately using electrophysiological studies and bilateral lesions will probably be necessary. Intensive physical therapy after surgery may be especially important in children who have been disabled for many years. Improvement in the control of movements will be gradual rather than dramatic.


CEREBELLAR ATAXIA SYNDROME

Ataxia refers to jerky and uncoordinated movements. Cerebellar ataxia implies that the abnormal movements arise from malformations, or poor function of the cerebellum. Ataxias are caused by many inherited and acquired problems.

A Cerebellar Ataxia Syndrome recently recognized in several children of Amish descent is characterized by a truncal ataxia with minimal effect upon hand use or eye movements. Walking is usually delayed until 20-24 months and the gait in older children is wide based and unsteady but their muscle mass and strength are normal. Affected children cannot do tandem walking or balance on a scooter and they often cannot learn to run. Sensation and position sense of the legs and arms are normal. Tendon reflexes are normal or increased. The infants I have seen have decreased tone, poor head control with head-bobbing or titubation, and, usually, the infants have not learned to sit independently before 8-10 months of age. Speech is also usually delayed until 3-4 years of age and in the older child or adult speech may have an unusual cadence or be monotone.

The neurological signs suggest the syndrome arises from poor function of the vermis of the cerebellum. No biochemical abnormalities have been found in blood or urine. An MRI of the brain of an Amish woman in her 20s with the syndrome showed moderate underdevelopment or degeneration of the cerebellar vermis. MRIs of three boys ages 1, 4, and 9 years show only mild vermal underdevelopment with prominent sulci and folia and decreased volume of white matter in the anterior lobe of the vermis. I suspect the syndrome is similar to a form of cerebellar ataxia reported in a large series of patients from England by Dr. AE Harding in 1981. I also suspect the syndrome is common and that many adults may have the disorder. I am particularly interested in learning more about how the disorder affects teenagers and adults.

In preparation for discussion of the role of gene therapy in the treatment of Crigler-Najjar, Erik Puffenberger PhD, Clinic for Special Children presented a primer on genetics at the conference. Many parents and several of the professionals commented on the clarity of this presentation and its helpfulness in understanding basic genetic terms and concepts. This "Genetics Primer" is printed in the newsletter insert section for other parents and interested readers.

**OHIO FAMILIES VISIT THE CLINIC**

Last winter four families from Middlefield, Geauga County, Ohio, visited the Clinic with their children for evaluation. All of the children have complex genetic disorders with neurological involvement. Although we were not able to advance more specific diagnoses, Dr. Morton reviewed care plans for each child, addressed questions and concerns, and continues to work on their cases. We were excited to learn that the families left our clinic with the inspiration to start their own clinic in Geauga County. With support of the local bishops, a board of trustees was formed, a mission statement created and the Das Deutsch Center for Special Needs Children is taking form. Support is promised from a number of sources in the area, including the Cleveland area, building sites are under consideration, and the search is under way for "another Dr. Morton". Dr. and Mrs. Morton visited with the families in Ohio in June to hear progress, see the children, answer many questions about how our clinic works, and to offer encouragement. Dr. Morton and Dr. Richard Kelley will offer their medical expertise when it is needed. The families estimate there are at least 250 children in their region who have special medical needs that could be met by a local clinic.

**HAY HOLE HAZARDS!**

Clinic staff are working with representatives of the Lancaster Farm Safety / Safe Kids organization and several nurses from Penn State to develop a board game to help increase awareness in children of safety precautions around a farm. Farm related accidents in Lancaster County and other Pennsylvania farming regions affect the lives and health of far too many children. The board design by an Amish artist depicts a typical farm scene and we hope the game rules will lead to a fun, worthwhile game. Local school teachers and students helped list questions and made suggestions. Two games will be given to each of the Amish/Mennonite schools in Lancaster County for their use. If the game gets good reviews, more will be produced. The project was funded by the Children's Miracle Network and is directed by Kathleen Fisher. Children's health leads us in interesting directions!

**UNDER THE CLINIC ROOF**

In addition to the Clinic's operation, space is provided for the following on-going programs:
* Studies and clinic on the genetic basis of adult-onset diabetes directed by Dr. Alan Shuldiner, University of Maryland, Baltimore;
* Studies on the genetic basis of osteoporosis;
* Studies and clinic on genetically based vision problems and eye disease directed by Dr. Dwight Stambolian, University of Pennsylvania;
* New lipid research study to examine blood sitosterol (a form of plant sterol) as a risk factor of early heart disease. The study is directed by Dr. Peter Kwitterovich, Johns Hopkins, Dept. of Pediatrics;
* Special Hearts Circle meets Wednesday-Thursday-Friday.

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THANKS to Doris Dunkle for her regular volunteer contribution to the clinic. Her help is much appreciated. STUDENTS Eden Haverfield, University of Pennsylvania, and Laura C. Morton, University of North Carolina completed senior internships at the Clinic during the past few months. We enjoyed their presence, their questions, their perspective.

**LECTURES:** July-December, 1999

*From Gene to Disease: The neurobiology of an inborn errors of metabolism, National Youth Science Camp Lecture, Bartow, West Virginia. July 1999.*


**RECENT PUBLICATIONS:**


Higgins JJ, Morton DH, Loveless JM: Posterior Column ataxia and retinitis pigmentosa (AXPC1) maps to chromosome 1q31-q32. Neurology 1999; 52.

**PAPERS SUBMITTED:**

Bolk S, Puffenberger EG, Hudson J Morton DH, Charkavarti A: Two novel mutations in nephrin cause congenital nephrotic syndrome, Finnish type (NPHS1, in Mennonites.

Morton DH, Salen G, Batta AK, Shefer S, Tint GS, Belchis D, Shneider B: Abnormal hepatic sinusoidal bile acid transport in an Amish kindred is not linked to mutation in FIC1 & improved by Ursodiol.

Morton DH, Puffenberger EG, Levy HL: Detection of maple syrup disease during the first 24 hours of life.

Morton DH, Robinson D, Strauss K, Levy H, Kelley R: Diagnosis, treatment, and outcome of 32 neonates with maple syrup disease.

THE CLINIC FOR SPECIAL CHILDREN, INC.
P.O. BOX 128
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Ninth Annual Benefit Auction

to support
THE CLINIC FOR SPECIAL CHILDREN
Quilts Handmade Toys Furniture Crafts Baked Goods Chicken Barbeque
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September 18, 1999

Bring your checkbook, no credit cards accepted

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. #23 east, turn left (north) on Brethren Church Rd. past Leola.
From Rt. 30 east: 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 who suffer from a high incidence of genetic diseases such as glutaric aciduria and maple syrup urine disease. Clinic services include infant testing programs for early diagnosis, primary medical care 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 exempt under IRS 501(c)(3), ID # 23-2555373.
P.O. Box 128 Strasburg, PA 17579 (717) 687-9407

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