CLINIC FOR SPECIAL CHILDREN NEWSLETTER

VOLUME I NUMBER 11 * LANCASTER COUNTY, PENNSYLVANIA * SUMMER 1996

Please join us!

6TH ANNUAL BENEFIT AUCTION

SATURDAY, SEPTEMBER 21, 1996

PLANS FOR THE 6TH ANNUAL AUCTION

The third Saturday of September, otherwise known as Auction Day at the Clinic for Special Children, is fast approaching and preparations are well under way. The wedding ring quilt design on this newsletter was the pattern of the first quilt we received for the sale this year. It is a softly multi-colored crib size made by the mother of one of our patients. Other quilts from a long winter's work have started to make their appearance as the special children who inspired them come in to the Clinic for their latest check-up.

In addition to many beautiful quilts are handmade crafts, toys, wagons, furniture including a locally made oak bedroom set, housewares, and various farm supplies. A special item for this year is a children's log cabin playhouse which is now under construction using real logs. A friend of the clinic in California donated two beautiful handmade wooden bowls turned with many varieties of wood. They are works of very fine craftsmanship. As in other years, there will be a bake sale featuring breads, pies, cakes, and cookies baked by families and friends of special children , chicken barbequed at the sale grounds using Steve's well tested auction recipe, freshly made subs, pig roast, soft pretzels that disappear as fast as they come out of the oven, hand squeezed lemonade, and much more.

If you have items to donate for the auction or need more information, please contact one of the following numbers: (717) 626-4863, (717) 354-5415, (717) 656-9694, or (717) 733-2645. Unlike other auctions, all items to be sold are donated and there are no consignment items. All proceeds go directly to support the Clinic. Directions to the sale at the Leola Produce Auction Center are listed on the back page of this newsletter. Information is also available from the Clinic (717) 687-9407.

Please join us for this special day

Log cabin playhouse similar to one under construction for auction

THE MEANING OF THE AUCTION

The annual benefit auction serves several important purposes. It is a primary source of support for the Clinic to meet its expenses each year so that our schedule of fees for services can continue at very reasonable rates for families who are faced with constant medical costs. Most of our families do not have insurance and do not participate in any public support such as medicaid. Our fees are currently at a fraction of what is charged for the same services at other medical centers. The benefit auction also enables the Clinic to provide services such as our immunization program, helps maintain lab equipment, and supports clinical research to improve treatment for the children who come here for care.

The auction is also an expression by this community of the richness and joy that special children bring to those who know them and care for them. It is a time of reunion among families who share a bond, a time of celebration and fun.

ABOUT GENETIC DISEASES ....

As we talk, lecture, write about the genetic disorders and syndromes of children we treat here at the Clinic, we often hear questions such as "Why are there so many unusual diseases among the Amish and Mennonites? Are these diseases on the increase? Is intermarriage a factor? "

All of us, no matter of what genetic background, carry on average 5 to 10 abnormal genes among the hundreds of thousands of genes that make up our individual genetic material . Most of us are fortunate that these defective genes are of little consequence and we never know we have them. However, the defective genes are passed on to our children and thus retained in the population of our descendants. About 3 of every 100 babies in the U.S. are born with genetic disorders that require medical attention. Of admissions of children to hospitals in the U.S. 25% are for treatment of a genetic condition. Asthma, arthritis, heart disease, osteoporosis, diabetes, are all examples of common medical conditions that may have a genetic basis. In less mobile communities that have endured over generations, abnormal genes often become more apparent or frequent due to factors such as the "founder effect". An early settler of a community passes an abnormal gene on to the next generation. After many generations, descendants who may not consider themselves "related" actually carry the same "founder" gene. In the Amish and Mennonite communities, rare recessive genetic diseases occur at a higher rate than the general population due to this "founder effect". Usually in those who carry an autosomal abnormal gene, the disease is not expressed. However, if a baby inherits an abnormal gene from each parent, he or she inherits the disease. These diseases are known as autosomal recessive diorders and include many of the metabolic disorders.

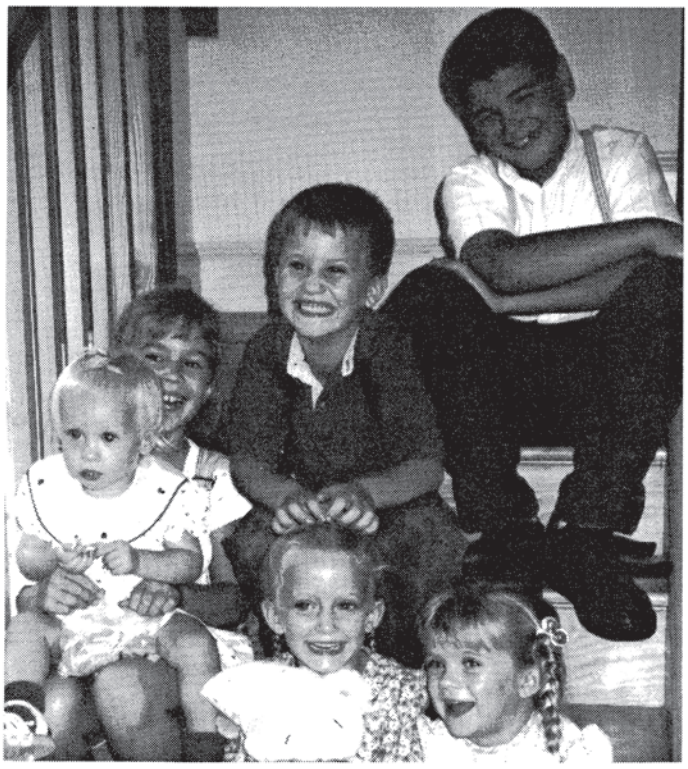
The awareness of genetic diseases in the Amish and Mennonite populations has grown for several reasons, often giving rise to the perception that genetic disorders are occurring here with alarming frequency. Most recessive disorders related to the founder effect reach a plateau in frequency. Disorders such as maple syrup urine disease or glutaric aciduria-1 will continue to occur in this community at an estimated carrier rate of 1 in 10 and 1 in 15 respectively. Awareness of genetic diseases in this community has grown in part because children with these disorders are now being diagnosed and treated - that is the Clinic's mission. Studies of modern genetics have been advanced due to the willingness of many Amish families to share their histories with those committed to the science over the last fifty years. We owe these families gratitude for their contribution to medical science that gives hope to all of us.

CRIGLER- NAJJAR CONFERENCE IN NEW YORK

While others celebrated Memorial Day in traditional ways, physicians, scientists and families of children with Crigler - Najjar syndrome assembled at Rockefeller University in New York. The conference was organized by Dr. Jerold Lucey of the University of Vermont and the Vermont-Oxford Neonatal Network and Dr. Kappas of Rockefeller University. The opening lecture was given by Dr. John Crigler who helped describe the disorder more than 40 years ago while a young physician at Johns Hopkins. Drs. Lucey and Kappas visited the Clinic in 1995 to meet our patients with Crigler's disease and the conference grew out of their sincere efforts to improve the care of these children. Along with Dr. Morton who was one of the conference presenters/ moderators and Lillie Rizack, R.N., four of the Mennonite families attended the conference with their children.

The purpose of this gathering of scientific experts in the genetics and biochemistry of bilirubin metabolism was to review the current approaches to care and stimulate research for this very rare disease. Crigler - Najjar disease is caused by several gene defects that selectively block the transport of bilirubin through the liver. Liver function is otherwise normal and high bilirubin levels in blood are of little medical consequence unless the bilirubin dissociates from serum albumin and enters the brain as free bilirubin. Bilirubin causes a pattern of brain injury similar to that seen in type 1 glutaric aciduria and can occur at any age. Control of bilirubin with current therapies becomes especially difficult in adolescents.

The only definitive treatment for Crigler-Najjar now available is liver transplant which is a therapy with high risks and costs. As one parent remarked, *with a transplant you just trade one set of serious problems for another, and at a high price too.* At least two methods of gene therapy are technically possible now but the methods produce only low or transient levels of gene activity in the liver cells where bilirubin is processed and would be expected to cause only small or transient decreases in serum bilirubin. This, combined with the need for prolonged immune suppressive therapy to prevent destruction of the gene vectors probably renders the use of current methods unwise. Until modern genetics offers less problematic methods of repair for the gene defects, the continued good health of these children will depend upon our understanding of, and control of the biochemistry of bilirubin which is where the work at the Clinic remains focused.



Children with Crigler- Najjar syndrome at the Clinic

CLINIC FOR SPECIAL CHILDREN RESEARCH PROGRESS REPORT

Each year, the Clinic identifies several new diseases that appear to be common among Amish and Mennonite children in the Lancaster area. Whereas some of these disorders occur in other populations and have been studied in depth by scientists and physicians, other disorders that we find are either unique to this community or are so rare elsewhere that almost nothing is known about their cause or treatment. Although collectively these disorders constitute a major health problem among the Amish and Mennonites, the increased number of patients in our area also affords a valuable opportunity to learn more about these diseases and, with this knowledge, develop better therapies. Over the past year, the Clinic has made a concerted effort to learn more about several of these diseases and to recruit other physicians and scientists to assist the Clinic in these endeavors.

Chicken Breast Disease

One of the most common disorders among the Lancaster Old Order Amish is a lethal infantile muscle and nerve disease that appears to be unique to this community. The condition is often called "chicken breast" disease by the Amish because of a characteristic protrusion of the breast bone that develops in the terminal stages of the disease. Although very striking abnormalities of the muscle, called "nemaline rods," are found microscopically, the disease impairs the function of nerves as well as muscle. Most of the children die before their second birthday, either from weakness and respiratory failure or from heart failure. About two new infants a year with the disease are born in Lancaster County and more than 50 other affected children who have died in the past 25 years are known. Because we have been unable to find any biochemical clues to the cause of chicken breast disease, we have asked a former colleague from Johns Hopkins, Dr. Joseph Maher, to search for the gene that causes chicken breast disease. Using new methods for finding genes more rapidly, Dr. Maher, who is now at the University of Mississippi, hopes to localize the gene for chicken breast disease to a specific chromosome within the next six months and then begin work to isolate the gene itself. Knowing the gene structure should tell us much more about the biochemical cause of chicken breast disease. In addition to Dr. Maher, another physician from Johns Hopkins, Dr. Tom Crawford, is working hard to understand better the neurological aspects of the chicken breast disease and thereby suggest better treatments for the disorder.

Sitosterolemia (Phytosterolemia)

Sitosterolemia is a rare disorder in which there are high blood levels of cholesterol and several "phytosterols," compounds closely related to cholesterol that are found in all vegetable products with a high fat content, such as corn oil and peanuts. Sitosterolemia is a serious disorder that causes premature coronary artery disease and death from heart attack in young adults and even teenagers. The disorder closely mimics other disorders with high blood cholesterol levels ("hypercholesterolemia") but requires a completely different therapy. In fact, a low cholesterol, high vegetable oil diet will make sitosterolemia worse rather than better.

Although one Amish family with sitosterolemia was found in Lancaster County more than 20 years ago, since then there has been no regular testing for the disorder and no other affected individuals in our area have been identified. However, our study of the family tree of the one known Lancaster County family indicates the the gene for sitosterolemia came into the Old Order Amish community in the early 1800's. Thus, there almost certainly are other Amish and Amish descendants in our area who have sitosterolemia or who have died from it, either undiagnosed or misdiagnosed as "ordinary" familial hypercholesterolemia. For this reason, the Clinic has established a diagnostic program for sitosterolemia and has begun to test for sitosterolemia in individuals with early coronary artery disease or those with just high blood cholesterol levels. We are also providing dietary counseling and regular monitoring of blood sitosterol levels in affected individuals. Dr. Gerald Salen, one of the world's experts on sitosterolemia, visited the Clinic on August 1st and will be providing assistance to our work on sitosterolemia. If several other families with sitosterolemia are found in the next year, studies will be set up in collaboration with Dr. Salen to isolate and learn more about the gene that causes sitosterolemia.

Amish Microcephaly

Microcephaly, which means "small head" in Greek, is a common characteristic of many genetic conditions associated with physical and mental disabilities. In the last 50 years, an unusually severe and lethal form of microcephaly has appeared with apparently increasing frequency among the Older Order Amish. The affected children have extremely small brains at birth and head circumferences as small as 10 or 11 inches (normal is 13 to 15 in). Although there are no other physical abnormalities, the children are often frail and die at an average age of 6 months. In the past 35 years, there have been more than 40 children born with this severe form of microcephaly. This is a frequency of at least 1 in every 500 Old Order Amish births, making the disorder one of the most common genetic diseases of the Amish. Most of the affected children are descendants of an Amish couple who lived in Lancaster area in the early 1800s, but the gene can also be traced back to the earliest Amish settlers of the 1700s.

Another form of severe congenital microcephaly that occurs in both the Ohio Amish and non-Amish populations, Smith-Lemli-Opitz syndrome, is caused by the inability of the fetus to make adequate amounts of cholesterol. Unlike many other nutrients, cholesterol is not supplied by the mother to the developing baby. Many children born with Smith-Lemli-Opitz syndrome will die or fail to thrive in the first few months, but can be greatly helped by providing extra amounts of cholesterol in their diets. We suspect that the Amish microcephaly may also be caused by a prenatal nutrient deficiency, possibly even treatable through the mother's diet. Accordingly, we will be testing for a similar chemical deficiency in the next child born with this form of microcephaly. In the meantime, we have made arrangements with Dr. Les Biesecker of the National Institutes of Health to begin looking for the gene that causes this microcephaly

syndrome. Dr. Biesecker believes that the chromosomal localization of the microcephaly gene can be found within the year. Dr. Biesecker and one of his colleagues from NIH, Dr. Claire Francomano, have also offered their assistance in finding the genes causing other common syndromes among our patients.

Cerebral Arteriorvenous Malformations

In the past 2 years the clinic staff has been consulted by neurosurgeons from Lancaster & Philadelphia about three Amish children, ages 6, 9, & 10 years, who presented with sudden severe hemorrhages caused by an isolated cluster of malformed blood vessels in the brain. All three children were asymptomatic before the hemorrhages, all developed sudden severe headaches then within minutes lost consciousness. All made remarkably complete recoveries after emergency surgery and full resection of the vascular malformations.

Medical histories of the extended families of these children revealed 9 other confirmed cases of cerebral arteriorvenous malformations (CAVM). Patient ages at the time of hemorrhage ranged from 6 to 55 years. Two children and an adult with CAVM's died before medical care could be obtained. There were also three unexplained infant deaths within these families. Dr. James Argires who has worked as a neurosurgeon in Lancaster County for more than 25 years recalls at least 40 such cases and believes that most of these CAVMs were in people of Amish descent.

Reports in the New England Journal of Medicine within the past year describe the genetic basis of two vascular malformation syndromes: **hereditary hemorrhagic telangietasia**, found in many ethnic & racial groups, and a cerebral **cavernous malformation syndrome** of Hispanic Americans. Now that gene markers are available for these particular vascular malformations a blood test can be used to screen those at high risk and allow detection & treatment before life-threatening problems develop.

We have asked Dr. Alan Guttmacher of the University of Vermont & Dr. Douglas Marchuk at Duke University, both authorities on hereditary hemorrhagic telangietasia, to help us develop a similar test for the Amish CAVM syndrome. As part of the initial phase of this research, Dr. Paul Leslie, a neuroradiologist at Lancaster General Hospital, designed a new rapid MRI sequence to search for the CAVM's and 31 brain MRI's were done for parents & siblings of affected children within 4 large Amish families. All studies were donated by the Lancaster General Hospital. None of the parents of children with CAVM's had vascular malformations and only two at-risk siblings were found to have sites of old hemorrhage. Geneological studies and brain MRIs suggest that the Amish CAVM syndrome has an autosomal recessive pattern of inheritance which makes it highly probable that a gene marker can be found for the disorder.

Bile Salts: A New Variant of Byler Syndrome

Byler syndrome was first described in 1969 by Dr. McKusick & colleagues in a paper entitled **Fatal intrahepatic cholestasis in an Amish kindred**. The disorder typically presents in infancy with poor weight gain because of intestinal malabsorption, bleeding due to vitamin K deficiency, and severe itching and jaundice associated with high serum bile salt concentrations. Studies by Linarelli et al in 1971 concluded that the disease was caused by a defect in bile acid & bilirubin transport from the liver cell into bile ductals. Recent studies by Dr. Knisely and colleagues at Children's Hospital of Pittsburgh have identified gene markers of patients with the form of Byler disease found in the Amish population of western Pennsylvania.

Within the past year we have diagnosed 4 Amish infants in Lancaster County with a Byler-like syndrome. Although our patients had fat soluble vitamin deficiency and markedly increased serum bile salts, as in classical Byler disease, our clinical studies suggested they had a unique disorder of bile salt metabolism. Their liver disease was less severe and the response of these infants to therapy with the artificial bile salt urosdiol (Actigall) was dramatic. Dr. Knisely subsequently found that these Lancaster County infants do not have the gene markers for classical Byler disease. Studies of bile salt metabolism done by Dr. Gerald Salen and colleagues suggest a selective defect in the sodium dependent transport of bile acids from blood into the hepatocyte. In our patients ursodiol is apparently transported by a different, functional transport system. More important, ursodiol appears to restore the circulation of bile from intestine to liver and suppress markedly increased rates of bile salt synthesis within liver cells. Normalization of liver enzymes and liver function on our current therapy suggest that progressive liver damage may be prevented in these infants.

Research on other disorders

There are many other metabolic and genetic diseases that bring patients to the Clinic. At last review, we had treated children with 35 different metabolic diseases and 45 other genetic syndromes. Like chicken breast disease and the lethal microcephaly, at least six of these disorders have not been been found in other populations. We have undertaken a large number of special laboratory studies in an attempt to discover the biochemical bases of these disorders, and we continue to work with many other physicians and research scientists to understand the genetics and metabolism of the most serious of these diseases. We have also begun similar collaborative research efforts for several disorders not unique to the families we treat. Some of the conditions for which there are active or planned research projects include Werdnig-Hoffmann disease, Crigler-Najjar syndrome, cystinuria, 3-methylcrotonylglycinuria, a newly recognized syndrome of retinitis pigmentosa & sensory ataxia in addition to our on-going studies of glutaric aciduria-1 and maple syrup urine disease.

We are hopeful that our research will lead to effective therapies for as many of these disorders as possible. For our work on all of these disorders, the Clinic is very grateful for the interest and tremendous assistance we have been provided not only by national and international scientists but also our patients and their families and the many contributors to our research fund.

Richard Kelley, M.D.,Ph.D. & Holmes Morton, M.D.

AN ALERT: TOXICITY OF VITAMIN A

We are reminded often that successful treatment of a metabolic disorder requires more than an understanding of the specific biochemical disorder. Common and uncommon medical problems interact with the underlying genetic disease to cause complex problems. A 7 year old patient with MSUD was found recently to have end-stage liver failure caused by the chronic ingestion of vitamin A. Doses of vitamin A of 50,000-100,000 were originally suggested by a physician who is an advocate of natural therapies. The child's mother was told that such high doses of vitamin A would boost the child's immunity and make control of her MSUD less difficult. The result of years of intermittent megadoses of vitamin A is severe liver damage that may not be reversable.

Vitamin A when improperly used is the most toxic of the vitamins. Doses in excess of 25,000 units early in pregnancy are associated with birth defects that range from brain & facial malformations to congenital heart defects. Using megadoses of vitamin A to mistakenly treat morning sickness may have terrible consequences for a newly forming fetus. Acute vitamin A poisoning causes vomiting, bone pain, and cerebral edema. We now suspect that one case of life-threatening cerebral edema in a young child with MSUD was the result of vitamin A poisoning. Having reviewed the role of chronic vitamin A overdose as the cause of progressive liver failure, there is concern that high dose vitamin A therapy may contribute to degeneration of liver function in patients with biliary atresia and Byler disease and we have asked specialists at the Children's Hospitals in Philadelphia & Pittsburgh to review specific cases of children who had liver transplants to determine if prescribed doses of vitamin A may have contributed to a decline of liver function.

DIABETES RESEARCH PROGRAM

The Diabetes Research Clinic directed by Dr. Alan Shuldiner of Johns Hopkins and located in the lower floor offices of the Clinic has seen over 600 Amish individuals since it began in February, 1995. With these studies Dr. Shuldiner and colleagues hope to identify genes that cause diabetes so that new medications can be developed for treatment and prevention. Of those tested, approximately 1 of 8 were found to have diabetes in this high risk population. The study finds there is a threefold increase in the likelihood that diabetes will occur in first degree relatives (parent/ child / sibling) of a diabetic. For more information or to request testing if you are from an Amish family with a history of diabetes, please contact Dr. Shuldiner on Mondays and Tuesdays at the clinic office (717) 687-8371 or by calling collect to(410) 550-1832.

CLINIC ASSIGNMENTS

Jeff Martin, M.D., a resident at Lancaster General Hospital's Family Practice Residency Program spent a month at the Clinic this spring to learn more about attitudes toward medical care by those in the plain cultures, how critical decisions are weighed, and how payment of major medical expenses are met. This summer, Marieke Dekker, a medical student from Erasmus University in the Netherlands studied at the Clinic to learn more about genetic metabolic disorders. Some of these disorders also occur in Europe and she focused on comparisons of treatment. It was a pleasure to have both Dr. Martin and Marieke spend time at the Clinic and we hope their experiences here enriched their approach to the practice of medicine. Prior to his high school graduation this spring, Nathan Kelley spent several weeks at the Clinic. His father, Dr. Richard Kelley, sees patients here a few days a month. Nathan gathered information to help improve the effectiveness of light therapy for children with Crigler-Najjar syndrome. Nathan also discovered his father does take time every now and then to eat lunch. We enjoyed Nathan's insights, his time here and wish him well in his studies this fall at MIT.

CARRIER TESTS AVAILABLE

The carrier test for the Amish form of glutaric aciduria, type 1, is now available through the Clinic for Special Children. The test is performed using a blood sample and can determine if that person carries the gene for glutaric aciduria. People who are "carriers" do not have the disorder, but they can pass it along to their baby. GA 1 is a recessive disorder which means a baby must inherit two genes, one from the mother and one from the father to have the disease. Carrier testing gives a family information which is helpful to make early diagnosis of infants and allow medical treatment to begin before a baby suffers illness or complications due to the disorder. We also offer carrier testing for the Mennonite form of classical maple syrup urine disease.

IMMUNIZATIONS

The Clinic offers childhood immunizations for families in the local community. Immunizations are scheduled on Tuesdays and cost $5.00 per visit. Please call 687-9407 if you wish to schedule your baby or school age child for an appointment.

GREETING CARDS

We still have a limited supply of greeting cards for sale to benefit the Clinic. The 5x7 cards feature photographs by noted Pennsylvania photographer, Bill Coleman. They come as a set of eight at a cost of $10 plus 6% sales tax and shipping cost.

We welcome your gift of support !

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 tax exempt under IRS 501 (c)(3), ID # 23-2555373.
P.O. Box 128 Strasburg, PA 17579 (717) 687-9407

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

6th Annual

Benefit Auction

to support

THE CLINIC FOR SPECIAL CHILDREN

Quilts HandmadeToys Furniture Crafts Baked Goods Chicken Barbeque

Donations Appreciated

September 21, 1996

All Day from 9:00 A.M.

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.

Come enjoy the fun, food, fellowship, and lend support !

If you wish to make a donation for the sale, please call one of the following for information:
(717)-626-4863 ; (717) 354-5415 ; (717) 656-9694 ; or (717) 733-2645