This winter marks the fifth anniversary of the Clinic for Special Children. Although work by Dr. Morton with special children with glutaric aciduria and maple syrup urine disease had begun, the vision of the clinic actually took shape in the late fall and winter of 1989-90 with help from contributions received from many of you. We reflect on the last five years in this issue to look at our progress. The knowledge gained, the care given and the inspiration always in evidence here were achieved by long hours of hard work and through generous gifts of support. But this progress was also a gift from children who have suffered much. They teach us, inspire us, challenge us to improve medical care, lead us all in meaningful work and we thank them.

SEPTEMBER'S HARVEST: THE AUCTION

Once again the Annual Benefit Auction lifted spirits, fed us abundantly, and feasted us with the caring generosity of many who gave, baked, built, and quilted. With thanks to all the proceeds netted a record $105,430!

Community members donated hundreds of pies, cakes, cookies, and loaves of bread which helped raise a considerable amount of support. The barbecued chicken upheld its reputation as the best in the county which is no easy feat in Lancaster County. Freshly squeezed lemonade was a refreshing treat with strawberry pies, sticky buns, soft pretzels straight from the oven and tasty subs as fast as volunteers could make them. To give some idea of the dimension of food prepared...
and sold for the day, consider 55 cases of chicken (which is over a ton), 90 large bags of charcoal to keep the fires going; 8 pounds of pepper, 20 pounds of salt, and 26 gallons of vinegar to flavor the chicken; 280 pounds of provolone cheese for subs, and 6 cases of lemons all squeezed by hand for lemonade!

Seventy four large quilts and as many wall hangings brought very good prices this year. Many of these quilts were made by mothers, grandmothers, aunts and friends of families with special children. Popular patterns that inspired lively bidding included broken star, postage stamp, quilted all white designs, sunshine shadow, log cabin, center diamond patterns, drunkards path, rubiks cube and favorite applique designs. Hand made furniture such as desks, cedar chests, pencil post beds; wagons, toys, crafts, housewares, lawn furniture, bird feeders, mail boxes, kennels, farm supplies, a pony and puppies all contributed much to the sale. As a special surprise, Dr. Holmes and Caroline Morton were presented a lovely quilted wall hanging featuring an embroidery of the Clinic building. It was made by the sister of a clinic patient, presented as a gift from the community, and was deeply appreciated by the Morton's.

In his noon time remarks to thank participants, Dr. Morton noted this was the first auction without a special friend of the Clinic in attendance. Frank Allen, formerly with the Wall Street Journal whose stories helped launch initial support to build the Clinic, moved from Pennsylvania to Montana this past summer. Frank has a gleeeful penchant of running up bids in spirit of the purpose of the day. A handy talent at benefit auctions. Others tried to fill in and did very well judging by the totals, but Frank was missed. We hope he and his family feel at home in Montana, but there is always a special place for them among folks in Pennsylvania.

Thank you to all who gave of themselves through their time, effort, talents or bidding to help the Clinic continue its work. These gifts not only provide needed support for the Clinic to meet its budget each year, but the spirit in which they were given inspire its doctor and staff and strengthen hope for all families with special children. Each pie, loaf of bread, quilt or craft was appreciated and contributes to the care of special children. Thank you to the members of the Auction Committee who for the fourth year gave tirelessly of their time and energy to make the auction such a success: Mr. and Mrs. Leonard Hurst, Mr. and Mrs. Enos Hoover, Mr. and Mrs. Harvey Hoover, Mr. and Mrs. John Fisher, Mr. and Mrs. Steve Huyard, Mr. and Mrs. John Stoltzfus, Mr. and Mrs. Steve Beiler, Mr. and Mrs. Jacob Zook, Jr., Mr. and Mrs. Daniel Stoltzfus, Mr. and Mrs. Ernest Zimmerman, Mr. Ralph Atkinson, and Miss Rebecca Huyard.

The work supported through the auction directly benefits local children with inherited disorders, but it also helps many others and those yet to come. Funds from the auction each year help the Clinic continue immunization services available to all families, help maintain all the laboratory equipment and supplies needed to monitor children with metabolic disorders, help fund research to improve care and support the infant testing service for glutaric aciduria available for all Amish infants. Auction funds also enabled the Clinic to start the carrier tests for maple syrup urine disease and MCADD (medium chain acyl dehydrogenase deficiency) which will identify more infants at risk for these disorders and lead to early, more successful treatment.

Mark your calendars! Next year's Auction will be Saturday, September 16, 1995.

EQUIPMENT FOR CARRIER TESTS

The Lancaster General Hospital recently donated $8,455 for the purchase of laboratory equipment and supplies to help establish carrier testing services at the Clinic. Tests are now available to determine carrier status for families potentially at risk for classical maple syrup urine disease (MSUD), Mennonite form, medium chain acyl dehydrogenase deficiency (MCADD), and soon, glutaric aciduria type 1, Amish variant. Conestoga Wood Specialties, Inc. donated the additional cabinets and counters in the Clinic's lab to house the new equipment. Dr. Richard Kelley and Lisa Kratz, Ph.D. from the Kennedy Institute in Baltimore, MD, developed the laboratory methods and coordinate the carrier testing for the Clinic. The Clinic is very grateful for the support from Lancaster General Hospital, from Conestoga Wood Specialties, and for the expertise of Dr. Kelley and Dr. Kratz.

Carrier tests will lead to early diagnosis of infants with these disorders as soon after birth as possible, allow more effective treatment with little or no hospitalizations in the neonatal period. Infants diagnosed early respond more readily to treatment with fewer complications and have a healthier long term prognosis. Among Mennonites in Lancaster County the estimated carrier rate for MSUD is 1 in 7, and for glutaric aciduria in the local Amish community, the rate is 1 in 10. An infant has a 1 in 4 chance of inheriting a recessive disorder if both parents are carriers of the gene.

Although for some parents the knowledge that they are carriers of a gene which may cause such a serious disease in their unborn child is a difficult burden, this information is so important for the health of a baby and makes a profound difference in how his or her life begins. The diseases for which we test are all treatable and the opportunity for the earliest diagnosis we hope parents can accept as a gift for their child rather than as a burden of unwelcome knowledge. There is no
In December 1989 , Dr. Morton listed factors that he then expected to determine neurological outcome in Amish children with glutaric aciduria. After five years of clinical work, diagnoses of infants, laboratory analyses and observations, we offer a summary of progress toward understanding this disorder. Glutaric aciduria type 1 (GA 1) is an inherited biochemical disorder caused by a deficiency of the enzyme glutaryl CoA dehydrogenase. If not treated, episodes of biochemical intoxication cause degeneration of the basal ganglia of the brain and progressive paralysis. Children who have glutaric aciduria and have suffered significant brain injury often mistakenly are given a diagnosis of cerebral palsy. In 1988 when Dr. Morton diagnosed the first case of GA 1 in an Amish boy in Lancaster County, the disorder was little understood, only 8 cases were reported in the medical literature, and it was considered to be an untreatable, crippling, often fatal disorder. One Amish family led him to another and soon observations and histories of children's injuries from the disorder led him to consider it could be treated, injury possibly prevented, and that the number of families affected by the recessive disorder in the Amish community here required an infant screening program. The need for medical care and clinical research related to this disorder along with MSUD inspired the formation of this Clinic. Progress in understanding and treating GA 1 in part defines the Clinic's progress and at five years of work, we assess that progress.

PROGRESS NOTES:
Toward an understanding of glutaric aciduria
Holmes Morton, M.D.

Glutaric aciduria, as is true for most inherited disorders, has a complex natural history. Infants have an abnormal gene, enzyme, and biochemistry at all times but illness is episodic. Brain injury appears to be caused by transient changes in biochemistry but selective regions of the brain, the caudate nucleus & putamen, are destroyed by episodic biochemical intoxication. A metabolic illness severe enough to destroy the caudate, and leave the child helpless, is usually of little significance to other regions of the brain or other organs. Brain injury is also age dependent - injury almost always occurs between 2-18 months of age. My efforts to explain the natural history of the disease and prevent brain injury has emphasized the biochemical basis of episodic illness and, more recently, emphasizes that the catabolic state itself is fundamental to producing the injury. However, the selective injury of the basal ganglia and the peculiar vulnerability of the infant brain to injury could not be explained in a satisfactory way by systemic changes in biochemistry. Recent research has provided new insight into the mechanism of injury of the caudate and has yielded a promising new approach to prevention of injury.

In December 1989 I listed six factors that I expected would determine neurological outcome in Amish children with glutaric aciduria. Our approach to care of infants and children was based upon these factors. I thought an interesting way to present the progress in the understanding and treatment of glutaric aciduria would be to comment upon my old list.

1. Neurological Condition at Diagnosis: The first principle of effective treatment of GA1 remains that the disorder must be diagnosed in asymptomatic infants. Patients diagnosed because of an abnormal neurological examination, poor development, or at the time of metabolic crisis have in almost all cases suffered moderate to severe brain injury before the diagnosis was made. Once such injury has occurred recovery is slow and incomplete.

Screening of the neonate is essential. Through our screening program at the Clinic more than 3000 Old Order Amish infants have been tested for GA1 in the past 5 years and 6 cases were diagnosed for a prevalence of 1/500 infants. In the past 2-3 years more than 90% of Amish infants were tested through the Clinic's voluntary testing program.

Recently Dr. Edwin Naylor in Pittsburgh added a test for GA1 into his innovative statewide program which now tests 80,000 infants per year in Pennsylvania, including all infants delivered in hospitals in Lancaster County and approximately half of the Amish and Mennonite infants delivered at home. The most recently diagnosed case of GA1 was from a family that is no longer Old Order Amish, was not tested by the Clinic laboratory, and would have been missed were it not for Dr. Naylor's program. The newborn screening tests are also available to Amish & Mennonite populations throughout Pennsylvania and central New York. Screening is by analysis of dry blood spots on filter paper and results are available within 24 to 72 hours after sample is received. Sophisticated analytical methods are used to test for 28 different inherited disorders including GA1, MSUD, galactosemia, medium chain acyl dehydrogenase deficiency (MCADD), cystic fibrosis, and a form of adrenal insufficiency - all found in Amish and Mennonite populations from Pennsylvania. The charge for the screen is less than $20. We now suggest that all infants in Lancaster County and the outlying settlements be screened through Dr. Naylor's program.

Efforts at the Clinic will shift from population wide screening to the use of geonelogical information and the GA1 carrier test to help identify high risk couples, and to rapid analysis of amniotic fluid or cord blood by mass spectrometry to allow recognition of infants within a few hours after delivery. The two most recently diagnosed infants were significantly ill within the first week of life. Each had marked biochemical abnormalities, lethargy, focal seizures, and required emergency care. Although these two infants now, at 6 and 12 months of age, appear to have escaped brain injury, their illnesses as neonates indicates that metabolic intoxication in the neonatal period is more significant than previously recognized. Biochemical data gathered over the past 5 years show rapid increases in serum and urine glutaric acid and other pathological metabolites within 6-24 hours after delivery. These metabolic changes occur before the infants are fed and probably reflect normal post-partum catabolism.

2. Frequency and severity of catabolic illnesses, especially during infancy: Two concepts have become increasingly important to my understanding of GA1: (1) the age dependent vulnerability of the brain to injury, and (2) the primary role of the catabolic state in the generation of an intoxicating metabolite other than glutaric acid. Of the 17 injured Amish children followed by the Clinic the ages by which the brain injury occurred ranged from 2-36 months. Patients older than 4 years tolerate infectious illnesses and marked elevations of pathological metabolites without apparent loss of neurological function. In 15 of 17 cases the injury took place in association with an infectious illness and, once started, the injury evolved very rapidly - parents can give the day and hour the child became disabled.

Research in Dr. Michael Johnston's laboratory at the Kennedy Institute in Baltimore suggests that the age dependent vulnerability to injury in GA1 may be explained by changes in the glutamate receptor type and density found on the caudate nucleus of
the infant brain during a particular interval of maturation. We now think the injury is mediated through the glutamate receptor and is either caused by abnormally high concentrations of the excitatory amino acid glutamate itself or by a false excitatory neurotransmitter generated during catabolic illness. Dr. Richard Kelley has pointed out that glutaric acid combined with glycine, or one of several other amino acids, forms a compound that has a chemical structure similar to other known excitatory toxins whose effects are mediated by glutamate receptors. He has suggested that the catabolic state may be important because biochemical pathways are opened that lead to conjugation of glutaric acid with glycine, or another amino acid, to form a toxin.

The importance of this new thinking about the mechanism of biochemical injury is that it leads to the use of glutamate receptor blockers during acute illnesses as a more direct means to prevent acute brain injury. The most widely available glutamate receptor blocker is dextromethorphan, which is the cough suppressant in many over-the-counter cold formulations. Dr. Johnston and others have shown that dextromethorphan can be used to protect the basal ganglia of animals from excitatory-toxin mediated injury. Dr. Johnston has also reported that dextromethorphan is safe and helpful for management of another metabolic disorder, non-ketotic hyperglycinemia, which causes degeneration of the basal ganglia and severe seizures not unlike that caused by GAI.

3. Rate of clearance of glutaric acid by the kidney and concentrations of the acid in the blood: There have been significant changes in my thoughts about the role of abnormal blood and urine metabolites in patients with GAI. The original model of the disorder suggested that protein catabolism within liver and muscle released large amounts of glutaric acid which, if not cleared from blood by the kidney, would accumulate in blood, enter the nervous system and cause focal intoxication and damage. Several observations have undermined this model: clearance studies show the urine glutaric acid increases independently of the blood glutaric acid concentration. Glutaric acid is secreted by the kidney and the rate of clearance of glutaric acid from blood does not correlate well with serum concentrations. For clinical purposes, risk of intoxication is better predicted by the rate of caloric intake, degree of catabolic stress, and by hyperglycinemia than by random blood or urine concentrations of glutaric acid. An increase in blood or urine concentrations of the pathological metabolites glutaconate & 3-hydroxyglutarate are better biochemical predictors of intoxication than glutaric acid.

4. Dietary protein intake, especially during infancy: In my original writing about GAI I suggested that age specific vulnerability to injury may be related to introduction of cow's milk and other high protein foods between 6-18 months of age. My opinion about the contribution of dietary protein to biochemical illness has changed considerably. We know that infants tolerate mothers milk well: nursed infants with GAI grow and develop normally, the urine and blood concentration of glutaric acid arc as low on human milk as on artificial formulas. Dietary protein contributes little to the intoxication caused by illnesses and fasts - intoxicating metabolites in neonates and older children are primarily derived from catabolism of endogenous protein.

The last three factors listed that were expected to determine the course of Amish children with glutaric aciduria I are inter-related:

5. Parent's ability to recognize the onset of significant metabolic illness, to initiate first level of care

6. Availability of knowledgeable primary care providers who can provide routine pediatric care and evaluate infants during intercurrent illnesses

7. Rapid access to a hospital with personnel and facilities to provide care for a child with a metabolic illness

Metabolic crises in patients with GAI are caused by common illnesses. Of the 32 admissions to Lancaster General Hospital for patients with GAI over 5 years, 23 (72%) were for metabolic crises provoked by common infections such as colds, otitis media, and diarrhea. Otherwise minor respiratory tract infections, flu-like illnesses, and diarrhea led to 12 of 15 serious metabolic illnesses and injuries in GAI patients who were injured before the Clinic was established. For children who have GAI combined primary and specialty care is important. Two of the infants diagnosed through the Clinic's neonatal screens were injured during minor infectious illnesses. Delay in initiation of hospital therapy by 1-2 hours directly contributed to their severe injury. I hope that routine use of receptor blocker therapy during intercurrent illnesses will make us less dependent upon emergency hospital therapy. Such therapy would greatly facilitate the care of infants with GAI in other regions of Pennsylvania and the US.

Progress at the Clinic takes many forms. The clinic screening program has served to educate parents and health care providers about glutaric aciduria in particular and about genetic diseases in general. Carrier tests for MSUD, MCADD, and GAI will help identify asymptomatic infants and allow care to be more effective and less costly. These tests will also add to our understanding about the distribution of genetic traits in the Amish and Mennonite populations and help families better understand and discuss the risks of genetic diseases. The Clinic newsletters, lectures, meetings, laboratory reports, letters to physicians, and admissions to Lancaster General Hospital have all made local health care providers in the region more aware of the importance of recognition and care of children with genetic diseases.

Although the Clinic was founded to provide care for Amish & Mennonite children in Lancaster County who have GAI & MSUD, the Clinic has become a regional resource for the diagnosis of unusual medical conditions. Over 5 years children with 27 different biochemical disorders and 32 unusual syndromes have been seen at the clinic. Some of these disorders like mevalonic aciduria and 3-methylcrotonylglycinuria affect only 1 or 2 children in a family but the presence of the recessive trait shows that carriers are found in the population and suggests that more cases may be found in subsequent generations. Other disorders like cysantinuria, hereditary spherocytosis, pyruvate kinase deficiency, and medium chain acyl dehydrogenase deficiency are common, treatable, and are much too often overlooked until the health of the patient is severely affected. Other disorders point to the need for research. We are hopeful that a common, lethal form of microcephaly will be prevented by folie acid. Research continues to find the cause and a treatment for pigeon breast disease which is the most common recessive trait found among the Lancaster County Amish.

For most of the children seen at the Clinic, their medical care and progress depend directly on efforts at the Clinic to understand their disease and refine treatment. The needs of our patients will continue to guide our work in clinical research, and insights gained will contribute directly to their care and hopefully, the care of other children elsewhere with similar disorders.
question that the earliest diagnosis prevents serious complications and brain injury to the baby and allows more normal growth and development.

NEW HELP FOR CRIGLER-NAJJAR DISEASE

In October several families whose children have classical Crigler- Najjar Disease, a disorder of bilirubin conjugation, met at the Clinic for Special Children with Dr. Morton, Dr. Jerold Lucey of Vermont-Oxford Neonatal Network and the University of Vermont Medical Center, Dr. Kappas and Dr. Drummond of Rockefeller University, and Dr. Vesell of Hershey Medical Center. The Clinic follows six children with this rare disorder. Brain injury caused by free bilirubin is similar in many ways to the brain injury caused by glutaric aciduria: the injury is most severe in the basal ganglia and causes a cerebral palsy-like paralysis, brain intoxication is episodic, affected children can experience normal growth and development for many years followed by sudden injury which typically is provoked by infectious illnesses, catabolic stress, and a rapid increase in free serum bilirubin.

The purpose of the meeting was to discuss a new therapy to prevent rapid increases in free bilirubin developed at Rockefeller University by Drs. Kappas and Drummond. A medication called Tin-mesoporphyrin inhibits the production of bilirubin and has been shown by Dr. Kappas' group at Rockefeller to protect neonates with hemolytic disease from bilirubin intoxication. We are hopeful that the medication will prove to be an effective way to prevent the dangerous increase in free bilirubin associated with common intercurrent illnesses. Drs. Lucey and Kappas also plan to organize a national meeting to discuss the care of children affected by Crigler-Najjar disease. (Note: Dr. John Crigler, who helped describe this condition more than 40 years ago, was one of my teachers at Childrens Hospital of Boston. Dr. & Mrs. Crigler came to Lancaster County 2 years ago and had a memorable visit with an Amish family with 3 affected children. Dr. Crigler will be an advisor for the study and seems interested in making more house calls in Lancaster County.)

HOUSECALL TO KENTUCKY

Most of our work is here in Lancaster County. But, increasingly we are called to help when new cases of inherited disorders such as maple syrup urine disease (MSUD), glutaric aciduria, or medium chain deficiency (MCADD) are diagnosed in other regions and local physicians and hospitals are not equipped to manage such cases.

This fall the Clinic was involved in the care of two infants born in Kentucky with maple syrup urine disease. Both infants were transported to Lancaster General Hospital for care by Dr. Morton but their cases were significantly different in severity. The first baby was diagnosed at 16 days of age and by then in critical condition at the University of Kentucky Medical Center with cerebral edema. MSUD had not been suspected and took time to diagnose, provisions for care and specialized formula were not readily available. He was transferred to Lancaster on a ventilator by air ambulance and after a few days of intensive care, MSUD was controlled, seizures stopped, cerebral edema resolved but he remained in the hospital for two weeks because of a severe fungal infection. He is now home in Kentucky and progressing well for all he has experienced since birth. His parents have learned a great deal about MSUD, also his local doctor and midwife.

The second baby was born several weeks later to a neighboring family in the same Mennonite community and delivered by the same midwife. By the fifth day MSUD was suspected, therapy was started with MSUD formula, and the baby and his parents travelled by car to Lancaster for definitive diagnosis and care. The baby spent a week in the hospital, did not experience cerebral edema, and is now home in Kentucky progressing well. The experience of these two families was difficult not only for the families involved but for their entire community in Kentucky. Where there are large extended families, implications that come with the recognition of a genetic disorder resonate through the community. In the case of plain sect communities which do not participate in any form of medical insurance the financial burden of large medical bills is shared by the church community.

Based on this community's experience with poor access to needed supplies and medical services to diagnose and treat MSUD, the Clinic developed a "care package" for the local community, area physicians, midwife, and the University of Kentucky Medical Center. Guidelines for early recognition of MSUD, laboratory sample instructions for confirmation of diagnosis and detailed immediate care plans were sent to Kentucky. The formula company was alerted and has special formula readily available. Dr. Morton, on what is likely his longest house call, lectured on MSUD and medium chain (MCADD) at the University of Kentucky Medical Center, met with local physicians who will provide immediate care for these infants, and met with Mennonite families from the community to explain the disorder, outline daily care involved, and discuss carrier tests which are now available to determine risk of having a child with MSUD.

Some distance from a medical center, most couples in the community plan to be tested through the Clinic for MSUD carrier status which will identify infants at risk and lead to an early diagnosis. (More than half of the Mennonite couples in child-bearing age from Casey County have now been tested for carrier status.) Our challenge and hope is if ever a third baby is born in that region of Kentucky with MSUD, diagnosis will be made no later than a day or two after birth and care will be immediate.

A MEANINGFUL AWARD IN LANCASTER

In September the Lancaster City and County Medical Society honored Dr. Holmes Morton with the first Edward Hand Award for his work at the Clinic for Special Children treating genetic diseases among Amish and Mennonite children. The Award, named for the Revolutionary War general and physician who served with George Washington at Valley Forge and who was an active civic leader in Lancaster, was established by the
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 does not seek or accept federal or state support and is tax exempt under IRS 501 (c)(3). ID # 23-2555373.

JOURNAL ARTICLE PUBLISHED

The talk given by Dr. Holmes Morton at the 125th anniversary celebration of Children's Hospital of Boston was published in the journal *PEDIATRICS* in the December issue as the lead feature article. Reprints will be available in limited supply at the Clinic upon request. The response to the article from many pediatricians is gratifying and appreciated.

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