



# CLINIC FOR SPECIAL CHILDREN NEWSLETTER

VOLUME I NUMBER 9

\* LANCASTER COUNTY, PENNSYLVANIA \*

SUMMER 1995

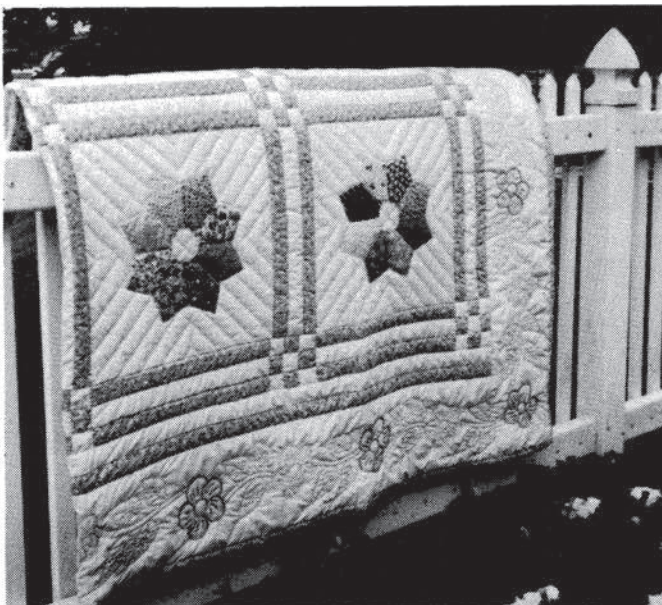


*Join Us for the*

**5th Annual Benefit Auction  
Saturday, September 16, 1995**



*Now is the time of year the road to the Clinic forms a channel between the corn stalks. The corn seems to envelope us each day as we approach and force us to focus. In the Clinic we strive to think about our work, about how to serve this community, how to care for special children. Our focus is specialized : to diagnose and care for children with inherited disorders, particularly metabolic disorders that are difficult to treat, and to study how to improve their medical care. But, all of the work here follows from the ability and opportunity to diagnose children as early as possible before they suffer and are unable to recover from the ravages of their disease. In this issue of the newsletter we report efforts to screen infants, test older children, and through carrier tests, determine who may be at risk for a disorder, so that diagnosis is early and children have the chance to live as fully as possible. We have made progress over the last five years but continue to build roads toward more effective diagnoses.*



*A quilt made for the auction this year by the mother of a clinic patient. It features old fashioned calico prints in a traditional pattern, hand quilted with a beautiful hand embroidered border.*

## THE 5TH ANNUAL AUCTION

Plans for the fifth annual benefit auction are in progress as all of us involved with the Clinic eagerly look forward to this special event. For those of you who attended in the past we hope you can join us again this year. For anyone who will attend our auction for the first time this year, we welcome your support ! Barbequed chicken, fresh subs, strawberry pies, donuts and soft pretzels baked on site, freshly squeezed lemonade, hundreds of pies, cakes, cookies, and breads should provide nourishment for bidding on beautiful local handmade quilts, wall hangings, toys, furniture, crafts, farm supplies, and hundreds of other items all donated for the sale. Among items donated so far is an oak bedroom set made by a local Amish furniture maker.

Unlike many other auctions conducted on a consignment basis, all items sold are donated by many individuals in Lancaster County, other Amish and Mennonite settlements, and from supporters of the Clinic in other regions of the country. All proceeds go directly to support the operation of the Clinic. Funds from the auction each year help the Clinic continue its immunization services for all families, keep fees for diagnostic services and medical care reasonable for all families who need our services, help pay for maintenance and supplies for laboratory equipment needed to diagnose and monitor children with metabolic disorders, and help finance our efforts to improve diagnosis and treatment protocols for all children with such disorders as maple syrup urine disease, glutaric aciduria, and medium chain MCADD.

Please join us for this special day to support the Clinic, but also to celebrate the joy special children bring to all of us who know them. Directions to the sale are included on the announcement on the back of this newsletter as are the telephone numbers of sale committee members if you wish to donate an item for the auction. If you need additional information, please call the Clinic (717) 687-9407.

***We hope to see you on September 16th!***



## STATEWIDE NEWBORN SCREENING

One of the first tasks the Clinic addressed when we started in 1990 was to set up a service to test infants of Lancaster Old Order Amish background for glutaric aciduria, type I. GA is an inherited metabolic disorder which causes selective brain injury in children, often suddenly and in context with ordinary childhood illnesses such as ear infections or diarrhea. The brain injury produces movement disorders resembling cerebral palsy. Within a year and a half the Clinic, using urine organic analysis by mass spectrometry / gas chromatography was testing approximately 94% of all Amish infants in Lancaster County. The carrier rate for GA in the Lancaster Amish population is estimated at 1 in 10 with a birth rate of 1 in 400 births. In the last few years we have tested nearly 3000 infants and diagnosed 7 infants soon after birth. The first principal of treatment of GA1 remains that the disorder **must be found before brain injury has occurred**. We now know GA1 is found in Amish settlements throughout the state. The disorder is not restricted to Lancaster Amish families. Several of the recent cases are in the non Amish population and were found by a supplementary screening program set up by Dr. Edwin Naylor of Pittsburgh.

For the past few years the Clinic worked closely with Dr. Naylor, Director of Neo Gen Screening in Pittsburgh to include the test for GA 1 in his panel of disorders screened through his supplemental screening service. Using state of the art laboratory techniques including fast atom bombardment and tandem mass spectrometry on a filter paper blood spot, Neo Gen screens for 35 different disorders in infants with the most effective, efficient technology and with minimal cost. Maple syrup urine disease, GA1, and medium chain, MCADD are now among the 35 disorders detected in the Neo Gen test at a cost of \$17.50. This is the most advanced newborn screen available in the world. Currently all hospitals in Lancaster County and we hope all midwives send newborn filter papers to Neo Gen in addition to the required state laboratory. Neo Gen now screens 47% of all newborns in Pennsylvania and has contracts with 50% of the hospitals for screening services.

The Neo Gen method has the advantage of using blood spot filter paper instead of a urine sample which is much easier to collect, ship, and store for analysis. The method also allows screening to be expanded readily to include other disorders.

**Based on the quality, practicality, and value of this test, the Clinic now recommends that all newborns in Pennsylvania, particularly infants of Amish and Mennonite heritage be screened by Neo Gen.** In addition to glutaric aciduria and maple syrup urine disease, Neo Gen screens for 33 other genetic disorders including several of high risk to families in the central region of Pennsylvania, such as medium chain (MCADD), cystic fibrosis, adrenal insufficiency and adenosine deaminase deficiency.

By shifting the newborn screening to Neo Gen the Clinic's lab can be used more effectively to confirm diagnosis, monitor

children with metabolic disorders, and allow more time for clinical research activity. **For Amish and Mennonite families at high risk for GA1, maple syrup urine disease, or medium chain acyl dehydrogenase deficiency (MCADD), the Clinic will continue to test these high risk infants as soon after birth as possible** and provide the followup care when necessary. The advantage of the Clinic's laboratory approach is that it gives more detailed, specific information which is important for immediate follow up care for infants with positive results.

For additional information on Neo Gen, contact: Dr. Edwin Naylor, Neo Gen Screening, Inc. 110 Roessler Road, Suite 200 D, Pittsburgh, PA 15220, phone: (412) 341-8658.

## CARRIER TEST UPDATE

Testing to detect carrier status for maple syrup urine disease has been available at the Clinic for a year. To date over 200 individuals of Mennonite heritage have been tested and 29% had a positive result for carrier gene status. Of this number, many of those tested were relatives of families who had a child with MSUD, which reflects the high number of positive results. The estimates of the carrier rate for MSUD in the Mennonite population stemming from Lancaster County is 1 in 10, with an occurrence of 1 in 500 births. Carrier testing is also available for medium chain acyl dehydrogenase deficiency (MCADD) and we hope difficulties will be resolved soon to provide carrier testing for the Amish variant of glutaric aciduria type I. Carrier status information is of great value in allowing the earliest possible diagnosis for a baby before any symptoms of the disease can cause complications, therefore giving an infant as healthy a start in life as possible. For those interested in learning more about the carrier tests or to schedule an appointment, please call the clinic (717) 687-9407.

## AMISH DIABETES STUDY

The lower level office at the Clinic is now occupied by Dr. Alan Shuldiner of Johns Hopkins University and his research team to study Type II diabetes. The study, funded through Glaxo and Johns Hopkins, hopes to identify the gene involved in this adult on-set type of diabetes which tends to run in families. There is an unusually high prevalence of type II diabetes in the Lancaster Amish community. The disease is caused by insulin deficiency or insulin resistance, marked by high levels of sugar in the blood with symptoms including increased thirst, frequent urination and fatigue. If untreated complications can be severe with damage to the heart, kidneys, eyes, legs, feet and nervous system. In addition to the genetic research the study also offers diabetes and cholesterol screening for at risk families and services related to arrangement for follow-up care. As of the first of August, 207 individuals from the Amish community had participated in the testing. It is hoped this study will lead to improved methods of early diagnosis, early intervention to prevent or delay symptoms of



## PROGRESS NOTES:

### Cerebral Edema & Maple Syrup Urine Disease Holmes Morton M.D.

**Brain edema** is the most dangerous complication of MSUD and is the usual cause of death during metabolic crisis. The following recent experience with brain edema markedly changed my understanding and treatment of the disorder.

In late May I admitted a 3 year old Mennonite girl with maple syrup urine disease (MSUD) to Lancaster General Hospital. For several days before admission she had poor appetite and intermittent vomiting. There were large ketones in her urine but her urine DNPH test cleared intermittently and her serum leucine level was only 5 mg/dl (380  $\mu$ M) the day before admission and was 6 mg/dl (650  $\mu$ M) when she was admitted. Twelve hours after admission, when she was receiving MSUD hyperalimentation, when her serum leucine was 4 mg/dl and her serum 2-ketoisocaproic acid was less than 200  $\mu$ M, she developed critical brain edema. Her pupils became dilated and her breathing stopped. She survived because of quick reactions by her primary nurse, Donna Robinson, and the respiratory therapists on the pediatric floor and with the help of the staff of the Lancaster General neurological intensive care unit. Now, two months after the brain edema, she is left with an unsteady gait and an uneven voice because of injury to the cerebellum but I remain hopeful that in time she will recover completely.

All patients with MSUD who are ill have some degree of brain edema. This edema can be seen on MRI as an increase in T2 signal throughout cerebral and cerebellar hemispheres and is especially prominent in the brainstem. Central nervous system edema can develop when leucine concentrations are low. The risk of brain swelling is not predicted well by branched chain amino or keto acid levels. The most severe cases I have managed developed life threatening brain edema when plasma leucine concentrations were only 4 & 9 mg/dl (300 & 650  $\mu$ M). **The risk of critical edema is highest after recurrent vomiting and prolonged ketosis and when the serum sodium is less than 130 mEq/l and intravenous solutions are used that contain less than 75 mEq/l of sodium.**

The cerebral edema that occurs in MSUD is not unlike that associated with diabetic ketoacidosis and hypernatremic dehydration. In all three conditions water is pulled from the vascular space into the intracellular spaces of the brain by intracellular metabolites with osmotic activity. In diabetes and MSUD generation of these metabolites is associated with prolonged ketosis. The amount of water that enters the brain under the influence of such metabolite is controlled in part by serum sodium and glucose concentrations. The balance of these factors determines whether critical edema develops. The use of intravenous fluids that cause rapid expansion of intravascular volume, high serum glucose levels, and low serum sodium concentrations favors the diffusion of water into the brain. Prevention of brain edema requires careful management of water, glucose and sodium.

Treatment of acute cerebral edema requires the use of mannitol and hypertonic saline solutions. Mannitol (2 g/kg) or hypertonic saline (3%, 5 mEq/kg) should be given slowly over

15 - 20 minutes to prevent a transient increase in intracranial pressure caused by an increase in central venous and arterial pressures. When lasix is used for diuresis care must be taken not to cause hyponatremia. Hypertonic saline infusions should be used to restore serum sodium concentrations to the range of 140-145 mEq/l. An infusion of 5 mEq/kg of NaCl as 3% saline will cause an increase in serum sodium of 5-8 mEq/l. Sodium, in contrast to glucose, does not cross from the vascular space into the nervous system and opposes the entry of water into the brain. In fact, increases in serum sodium will pull water out of the nervous system. In experimental animals infusion of 10 mEq/kg of 3% sodium chloride over 60 minutes causes a sustained **decrease** in intracranial pressure of more than 50 mm H<sub>2</sub>O. (Kravath et al *Clinically significant changes from rapidly administered solutions: Acute Osmol Poisoning, Pediatrics* 46: 267, 1970)

It is necessary to use high glucose infusion rates to control catabolism associated with MSUD, however, insulin should be used to prevent hyperglycemia and solutions of glucose in water, without NaCl, should never be used. Glucose rapidly enters the brain and, if unopposed by sodium, pulls water from the vascular space into the central nervous system. In experimental animals infusion of 20 ml/kg of 5% dextrose in water over 10 minutes causes an abrupt **increase** in intracranial pressure of more than 50 mmH<sub>2</sub>O. (*Pediatrics* 46: 267, 1970)

I recently summarized the management of an ill patient with MSUD as follows: Successful treatment of maple syrup urine disease depends upon inhibition of protein catabolism and sustained support of protein synthesis. Leucine concentrations are decreased by high, sustained rates of endogenous protein synthesis. To induce and sustain the anabolic state the patient must have a caloric intake of at least 2-3 times his or her basal metabolic rate and protein intake of the MSUD amino acid mixture equal to 2-3 grams/kg of body weight per day. Isoleucine & valine deficiency must be prevented - these essential amino acids become deficient within 6-12 hours after the start of therapy and must be provided at a minimal rate of 20 mg/kg-day. The central nervous system is especially vulnerable to isoleucine and valine deficiency. Glutamine, alanine, thiamine, and pyridoxine are nutritional supplements added to formula and hyperalimentation solutions to limit the toxic effects of increased leucine and its keto acid analog, 2-ketoisocaproic acid.

I would now add that the prevention and treatment cerebral edema in a patient with maple syrup urine disease depends heavily upon basic principles of fluid and electrolyte therapy. The biochemical derangements that cause the branched chain amino acids to increase and cause prolonged ketosis produce osmotic metabolites within cells of the brain that make these patients vulnerable to brain edema. This is true for patients with maple syrup urine disease just as it is true for patients with diabetes mellitus and hypernatremic dehydration. In our efforts to gain control of metabolism, what we do with glucose, sodium, and water determines whether the balance tips toward or away from critical brain edema. These are preliminary observations but I think they will prove to be useful in the care of children with MSUD and other metabolic disorders.

# CLINIC FOR SPECIAL CHILDREN

## LIST OF METABOLIC DISORDERS & SYNDROMES

January 1990-August 1995

The metabolic disorders and syndromes listed below were seen at the clinic over the past 5 years. Of the 29 disorders of metabolism listed below, 4 are lethal, 3 are minor biochemical variants of little clinical significance, and 22 are treatable disorders.

(McKusick Catalog #) (Phenotype D-dominant, R-recessive, X-linked, Sporadic)

### DISORDERS OF METABOLISM

Adenosine deaminase deficiency (102700.0016-D)  
Autoimmune polyglandular syndrome type 2 (26920-R)  
Congenital adrenal hyperplasia II 3 $\beta$ -hydroxysteroid dehydrogenase deficiency (20181-R)  
Congenital growth hormone deficiency (McKusick lists 5 syndromes -D)  
Corticosterone methyl oxidase II deficiency (Aldosterone deficiency) (20341-R)  
Crigler-Najjar syndrome type 1 (21880-R)  
Cystinuria (220100-R)  
Diabetes mellitus, familial (125850-D?)  
Familiar hypercholesterolemia, type B (14389-D)  
Galactosemia, Duarte Variant (Galactosemia & Duarte genes present)  
Gaucher disease, noncerebral, juvenile (230800-R)  
Gilbert syndrome (14350-D)  
Glutaric aciduria type 1, glutaryl CoA dehydrogenase deficiency (Amish variant) (23167-R)  
Glycogen storage disease, type 6 (Liver phosphorylase deficiency) (23270-R)  
Infantile GM1 gangliosidosis (Beta-galactosidase deficiency) (23050-R)  
Hyperthyroidism with male gonadal failure (sporadic)  
3-Hydroxy-3-methylglutaryl-CoA dehydrogenase deficiency (24645-R)  
3-Hydroxy long-chain acyl-CoA dehydrogenase deficiency (Unlisted-R)  
Isovaleric aciduria, isovaleryl-CoA dehydrogenase deficiency (24350-R)  
Maple syrup urine disease, branched chain 2-keto acid dehydrogenase deficiency (24860-R)  
Medium chain acyl-CoA dehydrogenase deficiency (20145-R)  
3-Methylcrotonylglycinuria, 3-methylcrotonyl-CoA carboxylase deficiency (21020-R)  
Mevalonic aciduria - Mevalonate kinase deficiency (25117-R)  
Phenylketonuria - phenylalanine hydroxylase deficiency (Amish Variant) (26160-R)  
Propionic acidemia, propionyl-CoA carboxylase deficiency (23200-R)  
Pyruvate kinase deficiency of the red cell (26620-R)  
Sitosterolemia (210250-R)  
Thyroid binding globulin deficiency (?18860-D, ?31420 X-linked)  
X-linked adrenoleukodystrophy (30010-X-linked)

### SYNDROMES

Alagille syndrome, intrahepatic biliary atresia (11845-D)  
Bartter syndrome hypokalemia alkalosis & renal cysts (241200-R)  
Biliary atresia, extrahepatic biliary atresia (21050-sporadic)  
Byler's disease (21160-R)  
Cartilage-hair hypoplasia dwarfism - Metaphysial hypoplasia (25025-R)  
Congenital familial microcephaly (lethal) (Unk-R)  
Congenital supraventricular arrhythmias (Unk)  
Dermatomyositis (Sporadic)  
Ectrodactyly syndrome with omphalocele & cardiac malformations (Unk-?D)  
Ellis-van Creveld dwarfism (22550-R)  
Hereditary spherocytosis (18290-D)  
Hirschsprung disease with & without Waardenburg syndrome (24920,27758-R)  
Familial deafness (Several forms-McKusick lists 45 inherited forms - 15D/30R)  
Familial episodic fever with abdominal pain (Unk, Not Israeli genotype 24910-R?)  
Familial manic-depressive illness (Unk)  
Immune deficiency caused by Zap-70 kinase deficiency (t-cell signaling defect)  
Infantile nemaline rod myopathy - Amish variant -R  
Macrocephaly with congenital heart disease (Sotos syndrome?) (11755-D)  
Milroy's syndrome - familial lymphedema (15310-D)  
Moyamoya disease (252350-R)  
Neurofibromatosis (1010000-D)  
Omenn syndrome, familial histiocytic reticulosis (267700-R)  
Optic atrophy, congenital deafness with episodic ataxia & psychosis (Unk-R)  
Osteogenesis imperfecta with opalescent teeth, fractures (166240-D)  
Polycystic kidney disease, infantile type (263200-R)  
Riehl syndrome (? acute infantile Pelizaeus-Merzbacher, autosomal, 260600-R)  
Rett syndrome - progressive encephalopathy in girls (31275 X-linked Sporadic)  
Werdnig-Hoffmann disease (Infantile spinal muscular atrophy) (25330-R)  
Wilms tumor, increased frequency, type unknown (194090-R)



the disease, and to develop more effective medications. More information can be obtained by calling the diabetes clinic (717) 687-8371 or Dr. Shuldiner at Johns Hopkins in Baltimore at (410) 550-1832. The diabetes clinic operates as a separate entity from the Clinic for Special Children although we share the pleasure of serving many of the same families in the same building.



## CYSTINURIA

Cystinuria is an inherited disorder of the kidney which usually presents with cystine kidney stones in the young adult, however, children may form stones, suffer chronic, recurrent stomach and back pain and have severe kidney damage before the condition is recognized. Affected adults may be asymptomatic then develop sudden severe back or flank pain from acute urinary tract obstruction. Cystinuria is a very common disorder in the Mennonite families of Lancaster County. The carrier rate in the population may be as high as 1 in 5 people. All individuals of Mennonite descent who have kidney stones and all siblings and children of known cases should be tested for cystinuria. It is a treatable disorder.

Urine samples should be submitted to the Clinic for Special Children for testing. A random sample of 5cc (1 teaspoon) will be adequate. The compounds to be analyzed are stable for long periods at room temperature but the specimen should be delivered to the laboratory within 12 hours after collection or, if stored for several days before delivery, frozen. To encourage screening of children for cystinuria we have developed a rapid, inexpensive method in the Clinic laboratory. Samples will be analyzed twice monthly and the screening fee will be \$15 per sample. Each sample should be labeled with a name, date of birth, and date of collection. Also provide parent names, home address, phone, and brief remarks about the occurrence of kidney stones or cystinuria within the immediate family. Samples can also be analyzed on an emergency basis at a higher fee for urine amino acid quantitation.

*Clinic for Special Children*

P.O. Box 128 Strasburg, PA 17579 (717) 687-9407

## NEW GLUTARIC ACIDURIA SUPPORT GROUP

For parents challenged with the complexities of caring for a child with a disorder like glutaric aciduria, a lifeline to other parents facing similar challenges is a vital source of help and comfort. Several parents of children with glutaric aciduria type1 recently decided to organize a support group for families and professionals involved in the care of children with GA1. Those involved in the formation of the International Organization for Glutaric Aciduria-Type1 are interested in including other parents in the ground work to define the organization's purpose and goals. Parents interested in participating should contact Mike Metil and Cay Welch at RD #3 Box 167A Jersey Shore, PA 17740 or call (717) 321-6487 for more information. The group tentatively plans to have an informal gathering in Strasburg, PA the evening of September 16th after the Clinic's benefit auction.

## IN TRAINING

This spring and summer two residents and a nursing student participated in the life and work of the Clinic. From Lancaster General Hospital's family practice residency program, Jean Cochrane, M.D. and Myron Glick, M.D. each spent a month's rotation assigned to the Clinic. Mary Ellen Francescani also spent a month here as a senior nursing student from Johns Hopkins University. We hope their time here provided them with a valuable experience and perspective on the art of medicine.

## OUR NEEDS

With the Auction approaching it is always helpful to outline the Clinic's need for support. Although revenue from fees for services is gradually increasing, support from the community through the Auction and from donations from foundations and individuals is vital to our ability to meet operational expenses. Last year our sources of support were as follows:

Contributions from individuals and foundations: 36 % ;  
Clinic fees: 34 % ; Auction funds: 30 %.

This year we hope to increase our staff to include a full time nurse and a second full time pediatrician. Both positions are badly needed to help with the current demands for the Clinic's services. These additions are dependent on increasing our level of support. We are very grateful for all those who contribute directly to our operating fund and for all who participate in the Auction. ***We thank you for your 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 does not seek or accept federal or state support and is tax exempt under IRS 501 (c)(3). ID # 23-2555373.*

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



5th Annual  
**Benefit Auction**  
to support



**THE CLINIC FOR SPECIAL CHILDREN**

*Quilts Handmade Toys Furniture Crafts Baked Goods Chicken Barbeque*

*Donations Appreciated*

**September 16, 1995**

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, 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

The Clinic for Special Children is a registered charitable organization. In accordance with Pennsylvania law, we are required to advise you 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.

