CLINIC FOR SPECIAL CHILDREN NEWSLETTER

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The understanding, the acceptance, that many common illnesses arise from genetic predispositions and are nonetheless treatable, may be the most important contribution of the Plain People to modern medicine. D. H. Morton, M.D.

PROGRESS

In last summer's Newsletter we wrote of our efforts to plan for the future. We were in the process of identifying the Clinic's primary goals and objectives for the next few years. This past winter, those four goals were refined and objectives for each goal defined more clearly. Progress began quickly, even before the plan was printed.

GOAL I: **Provide effective and affordable diagnosis and comprehensive care for children with biochemical disorders and other heritable conditions.** We continue to improve care for children with many different disorders. We are working on a new, improved formula for infants and children with MSUD; developing more efficient and lower cost diagnostic tests; and actively seeking ways to lower hospitalization costs for our patients and utilizing new preventive measures such as RotaTeq vaccine to prevent serious, life threatening illnesses in patients at high risk for complications from rotavirus.

GOAL II: **Increase the laboratory capacity to incorporate new technology to serve the needs of patients and their families.** With the gift last fall from Affymetrix of a GeneChip scanner, the capability in our lab to develop and perform diagnostic tests at low cost in our own lab increased dramatically. We hired a part time lab tech to assist with routine work to allow Erik Puffenberger more time to develop use of new technology. Over the last few months, we were able to identify and map several "new"disorders in families who sought our help. These discoveries are either now published in the medical literature or in process of publication. We are one of the few clinics in the world with the technology and the clinical experience to translate new genetic information now available for the immediate benefit of patients on an individualized basis.

GOAL III: Develop capability for clinical studies, for education and training in genetic medicine. We continue to develop our capacity for clinical studies at the Clinic and in collaboration with other medical centers. Our IRB (ethical review mechanism) was established through Lancaster General Hospital. Courses and lectures in clinical genetics were given by Dr. Morton, Dr. Strauss and Dr. Puffenberger, and we are now developing a CME course for pediatricians to be given later this year. The clinic also serves as a training site for residents and medical students.

GOAL IV: Secure long term financial stability. We hope support for the Clinic will increase this year. Community support through auctions provide a third of our annual funding needed. We are actively seeking grants from foundations and making appeals to individuals who will help us increase our endowment fund to help meet expenses of clinical studies and educational activities in addition to achieve financial security for the clinic for years to come.

We are working hard in all of our goals and have made remarkable progress the past few months. We ask for your help more than ever.

MODEL OF "GENOMIC MEDICINE"

The clinic was featured in two national publications. *The Dawn of Genomic Medicine* by Lisa Belkin, a cover article in **The New York Times Magazine** 11/6/05, described the unique approach of the Clinic as a model of medicine of the future. Genomic Medicine is a new term used to describe seeking "the promise of treatment in understanding the genes".

Another article, *Medical Sleuth* in **Smithsonian** (Feb '06) by Tom Shachtman quoted G. Terry Sharrer, curator of the Smithsonian's Division of Science, Medicine and Society: "*the clinic's use of genetic information as the basis of diagnosis and the individualized treatment of patients make it the best primary care facility of its type that exists anywhere"*. Dr Sharrer further stated, *"the Clinic for Special Children shows that health care can be reasonably priced, highly tailored to patients and conducted in simply managed circumstances."*

2006 AUCTIONS

Quilts appear in the office daily, we hear talk about special items in the making and estimates for food supplies and tents. It's the time of year that we ask for support, and we are always reminded how meaningful and dedicated community support can be. Auction committees in three regions are busy planning these events, which bring significant support to operate the clinic year after year. Please join us and do some bidding.

SHIPPENSBURG ~ July 15th

The first auction in 2006 is on July15th in Shippensburg, PA at the Shippensburg Produce Auction on Route #11 north of Shippensburg. Starting at 8:30 AM, the auction will feature a new two-seat fiberglass spring wagon, many different hand made quilts, wood crafts, furniture, plants, baked goods, chicken barbecue, hand made ice cream, and much more. Please call Elvin at 717-532-9088 or David at 717-532-5221 for information or to arrange a donation.

BLAIR COUNTY ~ September 9th

This is the 10th year for the auction at the Morrison Cove Produce Auction site on Rt.36 near Roaring Spring, PA. Families from Blair and Somerset Counties help sponsor the event to support the clinic. which serves many children from this region of Pennsylvania. Contact Amos at 814-793-3634, Eli at 814-793-3010 or Paul Ray at 814-224-5442 for information or donations for the auction.

LANCASTER COUNTY ~ September 16th

This will be the 16th annual auction for the clinic in Lancaster County and, we hope, another record-setting event without a hurricane. The gavel will start the sale at 8:30 am at the Leola Produce Auction location. For those who come early, breakfast will be available. Quilts and furniture will be sold after remarks from Dr. Morton and Dr. Strauss around 11:00. Lawn furniture and Gift Certificates will be sold around 1:00. Times for other specific items at the seven different auction blocks will be posted near the registration table.

Featured this year will be many beautiful hand made quilts including the traditional nine patch design pictured in this Newsletter, a Postage Stamp quilt, center diamond, applique designs and many more patterns. Other items include an oak grandfather clock, cherry table with three leaves and six chairs, new Amish carriage, and a new spring wagon. A hand-crafted wood chest will be carved by an Amish artist during the sale and then offered to the highest bidder.

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

FROM LAST YEAR ~ ~ A PREVIEW FOR THIS YEAR

Last year's auctions were great successes and provided at least one-third of the funds needed to operate the Clinic this year. Attendance increased, helped by good weather. Expanded facilities at Leola gave room to spread out. Although people came mostly to support the clinic..... maybe for a bargain on a quilt, to feast on chicken barbecue, or for those amazing donuts that melt in your mouth, ...the auctions always bring people together for many reasons. There are reunions of kinship, of those with shared experiences, of those who lost a special child and those who helped a special child. Many quilts were sold, each with a story in their making. A handsome wooden chest was decoratively hand carved while we watched. Other items like autographed hand carved turkey calls, wooden music boxes with an engraving of the clinic, ponies and carts, new buggies and wagons, and the model Amish schoolhouse/playhouse complete with bell undoubtedly inspired new stories for those who took them home.

At last year's auctions, 35 large quilts sold in Shippensburg, about that many in Blair County, and 96 in Lancaster, where over 2,000 bidders were registered. Roasted pork from 7 pigs sold out by 1:00. Approximately 68 dozen eggs turned into 335 omelets by 10:00 am, 18,000 donuts were made under a tent and sold by the end of the day as were 528 pizzas, 3700 subs, 2,918 pounds of chicken, and countless soft pretzels. The salad bar in a canoe was a big hit.

Just a taste of what to expect this year. We need support for this year more than ever as we work to reach our goals for the next few years. Income from the auctions keep our fees for services very reasonable for the families who need us.- We have not increased fees for regular office visits or lab tests for patients performed in our own lab for over ten years. Fees for immunization services were only recently increased to cover costs, but are still reasonable at $15. In most other medical facilities, pediatric and genetic services including testing such as we provide often cost ten times what the clinic charges. We maintain a commitment to offer our services at the lowest price possible so that families are not burdened - at least from the clinic's fees. It actually costs three to four times what we charge to provide our services. The auctions help by providing funds to meet the balance of the cost of operating the clinic. This support and other donations also help provide special formulas at reduced cost to families and help us pursue better, more effective treatment for children with rare genetic diseases.

SUPPORT FROM OTHER PLACES:

Families in **Shiloh, Ohio** sponsored another auction to benefit the clinic last July. This was the second year for an auction in that region, and we are very grateful for this support and appreciate their help.

In **Springfield, New Jersey**, the third annual Hammer Family Fun Day was held in June to generate support and awareness of the clinic. Many thanks to the Hammer Family, their friends and neighbors.

In **Lancaster,** the new School House at the Amish Farm and House on Lincoln Highway East chose the clinic to receive donations collected from visitors.

We cannot all do great things but we can do small things with great love ~ Mother Teresa

Beanies, Beanies and More Beanies!

For some it was a tough decision to choose, others knew exactly what they wanted, and the clinic staff especially enjoyed the gift of giving after giving "gixes". Every child who visited the Clinic in the last few months ended their appointment by choosing a beanie baby to take home. The Beanie Babies, generously donated by Marty and Scott Schoonover of South Carolina, brought smiles to so many children and we thank them for this thoughtful gift.

Now, the Beanie Box is almost empty and we are hoping someone else will be interested in donating their beanie baby collection. We ask that the beanie babies be in new, pristine condition with the name tags attached to qualify in value as a charitable gift and, more importantly, appropriate condition to give to a child. Please contact the clinic (717) 687-9407 if you are considering this gift.

GIFT FROM AFFYMETRIX

Productive collaboration over the last few years led to the gift of a major addition to the CSC laboratory and to our capability to identify rare genetic disorders in our patients. Affymetrix, Inc. generously donated a GeneChip scanner and associated hardware last fall. This equipment allows us to run and analyze "SNP" arrays in our own lab and improve the speed and efficiency of our mapping projects. SNP (single nucleotide polymorphism) genotyping is a new, efficient method for identifying segments of DNA to map or localize the disease causing genes. This new diagnostic technology is much more efficient and cost effective for patients than some traditional methods for diagnosis. The technology can also lead to very useful information about characteristics of rare disorders.

We thank Affymetrix, Inc. for this amazing gift and for the capability it provides to better serve our patients. We look forward to our continued collaborations.

.....USING NEW TECHNOLOGY.....

PROGRESS IN THE LAB

Over the past 6 months using the new GeneChip scanner, we provisionally mapped over a dozen separate disorders. In several, we also identified the disease gene and the causative mutation. The mapped disorders include the molecular characterization of Cockayne syndrome in the Amish, mitochondrial myopathy-cardiomyopathy in the Mennonites, Bartter syndrome in the Amish, and a Pelizaeus Merzbacher-like syndrome in the Amish. Each of these disease genes was previously identified elsewhere as a cause of the syndrome, but we identified a novel mutation in our patients. Several other disorders have been mapped, but the disease gene has so far eluded us. For these diseases, we are actively sequencing candidate genes in the mapped regions in hopes of identifying the causative gene. In a few cases, we have succeeded in identifying the unique gene for a "new" disease (that is, unpublished in the medical literature). For example, our most recent research publication details a clinical syndrome we call cortical dysplasia and focal epilepsy (CDFE). We studied four Amish children with this disorder and mapped the gene to chromosome 7. Subsequent work revealed a mutation in the CNTNAP2 gene. Our research was the first to report mutations in this gene and was published in the March 30th issue of the prestigious New England Journal of Medicine. (see article on CASPR2)

We are currently working with Affymetrix to develop a custom diagnostic array. This array will detect all the known mutations found in the Amish and Mennonite populations of Pennsylvania. It also will contain thousands of SNPs scattered throughout the genome which will give us the ability to detect changes in DNA copy number in individuals. This analysis allows us to identify chromosomal deletions and duplications. The usual method for detection of chromosomal abnormalities is a test called a "karyotype." These tests are expensive, laborious, and have a limited ability to detect small DNA changes. We have used the new method, which is called a "molecular karyotype", to detect several abnormalities in clinic patients, such as trisomy 21 (Down syndrome), trisomy 13, and Angelman syndrome. We have also found abnormalities that are below the detection level of standard karyotypes. The collaboration with Affymetrix should help us to develop this new technique as a useful and cost effective diagnostic test at the clinic.

A NEW DISCOVERY IN CASPR2

Over the last year, we worked with researchers from the Translational Genomics Institute of Arizona to find the cause of a disabling epilepsy syndrome afflicting Amish children from the Belleville community. All children with the CDFE syndrome had relatively normal development until the onset of seizures in early childhood. Thereafter, they developed autistic behaviors and severe mental retardation. Seizures were difficult to control with medication. Many children had to switch medications, and some needed two or three drugs in combination to control seizures. Three children underwent brain surgery to remove a "seizure focus", but only one child had long-term reduction of seizures after surgery. All children with CDFE had severe learning problems and many did not learn how to talk. Some developed impulsive and hyperactive behaviors that were a challenge to deal with at home and at school.

We used new microarray technology developed by Affymetrix to localize the problem to a mutation in a gene called CNTNAP2, which encodes a protein called CASPR2 (contactin associated protein-like-2). The protein has a well-known role in maintaining physical contacts between neurons and neighboring glial cells in the mature nervous system, but this is the first evidence that CASPR2 is also important for early human brain development. As a result of the defect, many nerve cells in the brain are disorganized, have a peculiar shape, and make

abnormal connections with other nerve cells (termed *cortical dysplasia*). In certain parts of the brain, these abnormal connections cause repetitive spontaneous seizures (*focal epilepsy*). Thus, the acronym CDFE (cortical dysplasia and focal epilepsy syndrome).

Implications of this discovery:

Dr. Kevin Strauss, CSC pediatrician and primary author of the article published in the March 30 *New England Journal of Medicine*, said "previous studies on CASPR2 in isolated cell cultures and genetic 'knockout' mice did not predict its fundamental role in human brain development or cortical electrical activity. The present findings are compelling evidence for such roles, and open new directions for epilepsy and autism research beyond the index population." Dr. Morton also commented: "We expect that other, less severe mutations in the CASPR2 will be identified in other patient populations, with problems ranging from temporal lobe epilepsy, to autism, to subtle disturbances of language use, memory, and behavior. The identification of the mutation in CASPR2 in our Amish patients has already allowed us to recognize affected newborns before they are symptomatic. Our hope is that early treatment and prevention of prolonged seizures in infants will lessen the effects of the disorder upon the lives of these children and their families."

"PRETZEL" SYNDROME

Through a collaboration between families, the Clinic for Special Children, and the Translational Genomics Institute in Arizona, we recently identified a gene defect that causes malformations of the brain, skull, bones, muscles, and heart. This newly identified genetic condition is referred to as "Pretzel" syndrome, so named by the families for the characteristic body posture adopted by many affected children. The defective gene is called LYK5. It has a complicated function that is only partly understood. The LYK5 gene product is part of a chemical "relay" or "messaging" system that controls the growth and function of many cells in the body. In Pretzel syndrome, part of the LYK5 gene is missing, which leads to a complete loss of this signaling function.
The LYK5 gene has an important role in normal organ development. Defective organ development that begins during the earliest stages of pregnancy is not treatable and leads to a variety of medical problems throughout life In affected children studied, the first signs of Pretzel syndrome began during gestation: 80% of mothers had "polyhydramnios," extra amniotic fluid around the affected baby. All mothers also had preterm labor starting anywhere from 25-38 weeks gestation. The brain was large and malformed in all affected children. MRI studies showed extra fluid around the brain, or "hydrocephalus." The nerve cells were not positioned properly and probably did not make normal connections with other nerve cells. As a result, seizures began early in life and were often difficult to treat. Mental development was severely delayed. The muscles were thin and weaker than normal. The combination of low muscle tone and abnormal connective tissue resulted in very flexible joints and allowed children to twist themselves into unusual "pretzel-like" postures. Like other muscles of the body, those that controlled the eyes were also weak, and about 40% of affected children had "strabismus" or "lazy eye." Children with strabismus should be treated by a pediatric eye doctor to prevent permanent loss of vision.

Approximately one third of the affected children had anatomical heart defects. The most common was atrial septal defect--a hole between the two upper chambers of the heart. This defect typically does not cause symptoms of heart failure early in life, but can become problematic later in childhood. In 20-30% of affected children, there was a buildup of calcium deposits in the kidneys, which then lost the ability to conserve water for the body. This condition, called "diabetes insipidus", causes children to urinate frequently. Children with diabetes insipidus should be allowed to drink freely to prevent severe dehydration.

Although the organ defects caused by LYK5 deficiency can not be prevented or reversed, Pretzel syndrome can nonetheless be treated by recognizing problems such as seizures, strabismus, diabetes insipidus, and heart defects, and treating these problems appropriately to optimize the health and well-being of the child. The disease can now be diagnosed at our laboratory with one simple test at a cost of about $50. Early diagnosis helps families and children. It allows doctors to anticipate problems and treat them early and allows families to avoid expensive and unnecessary testing. If you know of a family interested in testing or more information, encourage them to contact our clinic.

The Clinic Parking Lot - Diversity at the Hitching Post
A Honda, A Horse and A "Hog"

COURSE AT FRANKLIN & MARSHALL COLLEGE

Dr. Morton, Dr. Strauss and Dr. Puffenberger taught a senior biology seminar titled, *Plain People, Modern Medicine* during the spring semester at Franklin & Marshall College. The course consisted of 14 three hour lecture / discussion classes on different topics and will be taught again this coming academic year. The three were appointed as adjunct professors and look forward to future involvement with F&M.

CSC AND DR. RICHARD KELLEY RECEIVE BENJAMIN RUSH AWARD

In June the Lancaster City and County Medical Society honored the Clinic for Special Children with the Benjamin Rush Award for "outstanding contribution to the health and welfare of citizens of Lancaster County. Dr. Richard Kelley, CSC Board member, received the individual Benjamin Rush Award for his significant contribution of time, expertise, and guidance to the Clinic and for the services he provides to our patients on a volunteer basis.

Excellence is to do a common thing in an uncommon way.
Booker T. Washington

CSC STAFF CHANGES

Debbie Kennedy LaBerge, gave her last shot at the clinic last summer. Since 1990, Debbie coordinated the Immunization program at the clinic. In addition to her duties as a nurse practitioner, she was also our on site 'horse advisor' as a champion endurance rider, trainer, and specialist in equine thermography. She is now pursuing her profession in this new field. We wish her well in her new endeavor and thank her for her valuable contribution to the clinic for fifteen years and for her friendship which continues. Immunization services are now coordinated by staff member, Christine Hendrickson, RN.

In January we welcomed Roy Martin to our staff as a part-time laboratory technician to assist Dr. Puffenberger with the increasing demand of laboratory work. Roy previously worked for Ephrata Community Hospital, Lancaster General Hospital and Wyeth Vaccines. He assumed some of the daily responsibilities in the lab including amino acid analysis and organic acid analysis. His capability is a great contribution to our staff, so is his humor.

LOOKING AHEAD:

In August, the clinic will sponsor a clinical update on MTHFR disease with Dr. Harvey Mudd. Families with children with MTHFR from the Somerset County region will attend.

August 12, CSC Conference on Nemaline Rod Myopathy.

The Clinic is planning a conference on GA1 for late spring next year. IOGA will help sponsor the conference to be held in the Strasburg area.

The clinic is planning a CME course for pediatricians on diagnosis and treatment of disorders in the Amish and Mennonite populations. The two day course will be offered in late fall. Physicians interested in attending can contact the clinic for further information.

RECENT LECTURES:

National Youth Science Camp, W.V., July 2006, Lectures by Erik Puffenberger, PhD. and Holmes Morton, M.D.

Maple Syrup Urine Disease Family Support Group Symposium, June, 2006, Dr. Morton.

Drexel University, Gold Lecture: ***Medicine and Humanity, Beyond Medical School Learning to Care***, Feb. 2006 Dr Morton.

Dartmouth Medical School, Visiting Professor Pediatric Grand Rounds and Medical Student Seminar, March 2006, Dr. Morton.

P**ittsburgh Children's Hospita**l Grand Rounds, June, 2006, Dr. Morton

Ontario, Canada - Workshop - ***Diagnosis, Newborn Screening and Care of Amish, Mennonite and Hutterite People of Canada and SNP Technology,*** April, 2006, Dr. Puffenberger and Kevin Strauss, M.D.

Bologna, Italy -European Conference on Crigler Najjar Disease, Keynote Lecture, April, 2006, Dr. Strauss.

Paris, France -SSIMD International Meeting, ***Influence of Newborn Screening on Clinical Outcome in Patients with MSUD***, September, 2005, Dr. Morton.

Clinic for Special Children Conference for Midwives: ***The Neonate At Risk for Genetic Disease: Standards of Care for Screening and Management***. Dr.Morton, Dr. Strauss and Dr. Puffenberger, July 2005.

RESIDENTS AND STUDENTS AT CSC

Dr. Nicholas Rider, Chief Resident, Internal Medicine-Pediatrics Residency Program at The Penn State Milton S. Hershey Medical Center spent the month of May at the clinic for a clinical training rotation. Dr. Rider focussed on immunodeficiency syndromes and on complications of genetic disease in older patients.

Bommy Hong, senior medical student at New York Medical College participated in a month long assignment at CSC in November for a pediatrics/genetics rotation. Her focus was on severe congenital microcephaly.

Daniel Lapp, first year medical student at Penn State/Hershey Medical School did his first year preceptorship at the CSC as an introduction to clinical work.

RECENT PUBLICATIONS FROM CSC

Strauss KA, Puffenberger EG, Huentelman M, Gottlieb S, Dobrin SE, Parod JM, Stephan DA, **Morton DH**. Cortical Dysplasia and Focal Epilpsey Syndrome (CDFE):Clinical Description, Genetic Mapping, and Molecular Characterization of a frameshift mutation in the contactin associated protein-like 2 gene (CNTNAP2) (N Engl J Med 2006;354:1370-7.)

Strauss KA, Robinson DL, Vreman HJ, **Puffenberger EG**, Hart G, **Morton DH**. Management of hyperbilirubinemia and prevention of kernicterus in 20 patients with Crigler-Najjar disease. Eur J Pediatr. 2006 Jan 25;:1-14.

Strauss KA, Mazariegos GV, Sindhi R, Squires R, Finegold DN, Vockley J, **Robinson DL, Hendrickson C**, Virji M, Cropcho L, **Puffenberger EG**, McGhee W, Seward LM, **Morton DH.** Elective liver-transplantation for the treatment of classical maple syrup urine disease. Am J Transplant. 2006 Mar;6(3):557-64.

Morton DH, Strauss KA. Liver transplant as treatment for Maple Syrup Disease: Our Perspecitve as Pediatricians. MSUD Parent Support Group Newsletter, Summer 2005.

Strauss KA, Puffenberger EG, Craig DW, Panganiban CB, Lee AM, Hu-Lince D, Stephan DA, **Morton DH**. Genome-Wide SNP Arrays as a Diagnostic Tool: Clinical Description, Genetic Mapping, and Molecular Characterization of Salla Disease in an Old Order Mennonite Population. American Journal of Medical Genetics (2005) 138A: 262-267.

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2006 BENEFIT AUCTIONS

SHIPPENSBURG, PA ~ JULY 15

BLAIR COUNTY, PA ~ SEPTEMBER 9

LANCASTER COUNTY, PA ~ SEPTEMBER 16

MISSION

The Clinic for Special Children was established in 1989 is a non-profit medical service for children with genetic disorders from the Amish and Mennonite communities. The Clinic seeks to serve its patients by translating advances in genetics into timely diagnoses, accessible and comprehensive medical care and by developing better understanding of heritable diseases.

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