CLINIC FOR SPECIAL CHILDREN NEWSLETTER

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BUILDING BLOCKS

This Log Cabin design builds piece by piece to create a stunning quilt. The Clinic for Special Children is also building. We are building Hope. We are building our capability to treat rare genetic conditions, building our laboratory equipment, building our staff, and building our support to sustain the Clinic. In this issue we discuss our work and how we approach difficult problems to find solutions to help children. We also highlight how we are building collaborations and partnerships to strengthen the Clinic, provide better services and to educate others.

OUR GOALS

GOAL I: Provide effective and affordable diagnosis and comprehensive care for children with biochemical disorders and other heritable conditions.

GOAL II: Increase the laboratory capacity to incorporate new technology to serve the needs of patients and their families.

GOAL III: Develop capability for clinical studies, for education and training in genetic medicine.

GOAL IV: Secure long term financial stability.

2007 AUCTIONS

Shiloh, Ohio ~ July 14

This is the fourth year Mennonite families in Shiloh, Ohio, are sponsoring a benefit auction for the Clinic. We are very grateful to families in that area for this support.

SHIPPENSBURG ~ July 21

The auction in Shippensburg, PA is on July 21st at the Shippensburg Produce Auction on Route #11 north of Shippensburg. Starting at 8:30 AM, the auction will feature a new two-seat spring wagon, many different hand made quilts, wood crafts, furniture, nursery 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 8th

Morrison Cove Produce Auction on Rt.36 near Roaring Spring, PA is the site for the Clinic's benefit auction in that area on September 8th. Families from Blair and Somerset Counties help sponsor the event. The Clinic 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 15th

The 17th annual auction for the Clinic in Lancaster County will start at 8:30 on September 15th at the Leola Produce Auction location. Breakfast will be available this year for those who come early. Last year 500 omelets and 19,000 donuts were made for breakfast. Quilts and furniture will be sold after remarks from Dr. Morton and Dr. Strauss around 11:00AM. Lawn furniture and Gift Certificates will be sold around 1:00PM. Times for other specific items at different auction blocks will be posted near the registration table.

Featured again this year will be many beautiful hand made quilts including another Postage Stamp quilt, Center Diamond designs, applique and many more traditional patterns. Other features are beautiful locally made furniture including a cherry roll top desk and a cherry grandfather's clock, garden and farm items, crafts, baked goods and as always, fresh subs, and the best chicken and pork barbecue.

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)

Each of these auctions requires the hard work of many and the generosity of so many more. Without this help, the Clinic could not continue. We express our thanks to all who make the benefit auctions possible, to all who attend, contribute, bid and especially we thank the children who inspire all of us to work harder.

Note: We sadly report that one of the faithful volunteers for the Blair Auction, Leah King, died in an accident this winter on her way to teach school. She prepared breakfasts every year for the Blair auction. She is sadly missed and remembered for all her contributions to help so many.

A CHALLENGE FOR A MATCH

The Clinic recently received notice of a generous matching gift challenge. A family foundation has designated a gift to the Clinic of $50,000.....

..... if we can match this amount by other donors!!!!

We hope supporters of the Clinic will help us make the match! We need this support. Not only have our operational expenses increased in the last few years, but our research and clinical studies expenses have also grown with more extensive work to describe, understand, and improve treatment for many of the genetic conditions of the children in our care. Even though our expenses have increased we have not increased our fees for services substantially over the last 18 years. The Clinic is committed to keeping fees at minimal cost to families to provide affordable access to care. But to do this, we need to raise more support. Clinic fees charged only cover 25% of the actual cost to run the Clinic. Our annual budget is now $1.3 million.

One of our major goals is to increase our Research & Education Endowment Fund so that a portion of the interest earned will support the Clinic's research and teaching programs each year. This fund also serves to secure the Clinic's future. Dr Morton is donating funds he received with his MacArthur Fellowship to help fund the research, new equipment, and educational programs we describe in this Newsletter. But that only meets part of the cost.

We need to invest in new lab equipment, a LightCycler, that will allow us to do timely diagnostic work that is so critical to the success in treating difficult diseases such as SCID. Cost estimate, equipment and materials: $160,000; related research costs for 1 year: $180,000.

Additional support is needed to establish a Genetics of Hearing Lab and pediatric screening program. Cost estimate: $48,000 for equipment and $60,000 for screening and research.

Finally, by next summer we hope to have enough support to hire a third physician on our staff to care for patients and participate in clinical research.

We need your help to meet the challenge match, and to realize our goals for the next few years.

PLEASE CONSIDER A DONATION !

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

The Clinic is a registered charitable organization in PA and designated non-profit under IRS 501(c)(3) ID# 23-2555373.Contributions to the clinic are tax deductible.

BUILDING ON A CASE

The Clinic's first priority is medical care for children with genetic disorders. This will always be our first priority. In recent years our efforts to understand these genetic disorders has led us to engage more extensively in clinical studies. This research is based on the needs of our patients and helps to answer questions, solve problems, and provide better care. In every case, what we learn benefits many other children.

The decision to allocate time and resources to address the need of a patient is fast and easy....if it needs to be done, we have a responsibility to our patient to do it. The actual work however, the clinical research, is far from easy. It takes time and sometimes more resources than the Clinic has on hand. We take care of children who have rare, complicated diseases who need our help, now. They can not wait on grants to come through for next year or for funding priorities to change. We do not bill the patient for this research, but cover the cost through donations, auctions and proceeds from a portion of the interest earned on our Research and Education Endowment Fund. Eventually we hope to raise enough money for our Endowment Fund that a portion of the yearly earnings on this fund will support all the costs of our clinical research each year. Not only do these resources help the children here at our clinic, but we are finding the problems we solve here, the questions for which we find answers, help children in many other places.

In the following articles we will summarize progress on treating children with Severe Combined Immune Deficiency (SCID), which has been a focus of clinical investigation in recent months. As always, our work began with one patient who came through the Clinic's door.

HANNAH.....

Hannah (not her real name) was brought to our clinic shortly after her birth with a severe skin condition and hair loss. With treatment and special formula she improved briefly, but returned to the Clinic within three weeks, pale and with swollen lymph nodes. Subsequent lab work indicated acute anemia and *Staphylococcus* infection requiring acute care as well as indicators of immune system dysfunction. Her family history included a sister born fourteen years before her who had similar complications that were consistent with Omenn Syndrome. The sister died at 3 months of age.

Using DNA samples from the infant and her 7 siblings, the Clinic's lab was able to locate the disease causing gene, a process called SNP genotype mapping. Erik Puffenberger and Mary Morton were then able to sequence two candidate genes, called RAG1 and RAG2, to identify the disease causing mutation, which confirmed the diagnosis of Omenn syndrome, a lethal disorder treatable only by bone marrow transplant. Then, using the SNP genotype data generated during the mapping study, Dr. Puffenberger was able to study the inheritance pattern of a cluster of genes on chromosome 6 called the HLA region and determine that one of Hannah's 7 siblings was a perfect match as a bone marrow donor. This series of studies was accomplished at the Clinic in less than two weeks, at very low cost to the family

Her case and the urgency of response it required generated a cascade of work at the Clinic that benefitted her, but also inspired a course of action that will help other children, hopefully before severe complications of SCID develop. We describe some of the work that took place, much of it is still in progress.

Time is that wherein there is opportunity, and opportunity is that wherein there is no great time. . . . Healing is a matter of time, but it is also a matter of opportunity.
—Hippocrates, *Epidemics*

Photo courtesy of Bill Coleman

ABOUT SCID.....

Kevin A. Strauss, MD

The human immune system is a network of specialized cells distributed throughout the tissues of the body. These cells cooperate in complex ways to recognize, neutralize, and eliminate microbes (bacteria, viruses, and fungi) that invade the body. Microbes are all around us: they live in the air, the soil, on the foods we eat, and on our skin surfaces. Normally, the immune system provides a flexible and powerful barrier to prevent microbes from entering the body and causing harm.

The severe combined immune deficiencies (SCID) are a large group of disorders that result from mutations in genes required for the normal development of immune (T) cells. Throughout the world, approximately 1 per 75,000 children are born with SCID and without treatment they die of infections early in life. Transplantation of bone marrow-derived immune cells from a healthy donor can allow children with SCID to survive in good health. Two critical determinants of outcome following cell transplantation are the donor source and the patient's age at the time of transplantation. **Immune cell 'grafting' and survival are best when a child less than one month of age receives immune cells that are structurally similar to their own**, a process called HLA matching. Often these cells come from a sibling.

Among Amish and Mennonite children, SCID can be caused by at least six different gene mutations (Table 1). With the help of many cooperating families,

we recently collected information about 41 of these children born between 1978 and 2007. Only half of these children received a bone marrow transplant and 26 (63%) of them died of infections at an average age of 5 months. Mortality from SCID was much higher for Plain children than for other SCID populations studied over a similar time period, largely due to delayed diagnoses and the prohibitive costs associated with bone marrow transplantation.

Table 1. Severe combined immune deficiency disorders of the Plain people, 1978-2007

Disorder	Gene	# of Patients	# Transplanted	Died
Adenosine deaminase deficiency	*ADA*	12	2	10
Omenn syndrome	*RAG1*	4	2	2
Cartilage hair hypoplasia	*RMRP*	2	2	1
Interleukin-7 receptor alpha chain deficiency	*IL7A*	5	3	2
CD3 delta chain deficiency (Dadi et al., 2003)	*CD3D*	3	1	2
ZAP-70 kinase deficiency (Arpaia et al., 1994)	*ZAP70*	3	3	0
Undetermined (Amish)	-	12	8	9
TOTALS		**41**	**21 (51%)**	**26 (63%)**

STRATEGY TO ADDRESS THE PROBLEM.....

The Clinic's strategy to address this problem consists of three main goals: 1) to develop a method for diagnosing SCID early in life, before the onset of infections, 2) to make HLA matching for family members quick, accurate, and affordable, and 3) to have systems of care in place so that affected children can receive bone marrow transplantation before 1 month of age. Previous studies have shown that 95% of children with SCID transplanted within this time frame survive long-term with restored immune function. To achieve these goals we went to work as follows.

1) Early Diagnosis. To achieve the first goal, we are raising money to buy a new instrument called a LightCycler. This machine will allow us to simultaneously test Amish and Mennonite newborns for all the different SCID-causing mutations (Table 1). The testing will be fast and inexpensive. Beginning in the fall of 2007, we hope to start offering young couples carrier testing for these mutations, so that we can identify babies who are at high risk for SCID.

2) HLA Matching. Following a diagnosis of SCID, the first obstacle faced by an uninsured family is the cost of finding a potential HLA-matched donor. Using current methods, HLA matching costs between 3,000 and 12,000 (U.S.) dollars per individual and take several weeks. Using the GeneChip Analyzer donated by Affymetrix, Drs. Puffenberger, Strauss, and Morton have developed an alternative approach to HLA typing that is fast, accurate, and affordable. It should reduce the cost of HLA matching by more than 95% and allow this testing to be completed within a few days.

3) Timely Therapy. The third goal of early bone marrow transplantation will be achieved through collaborations with experienced specialists at Children's Hospital of Philadelphia and elsewhere. Following a diagnosis, affected babies will be transferred to medical centers that have experience transplanting children with SCID and that work closely with Drs. Strauss and Morton. Through a combination of community education, carrier testing, newborn diagnosis, and efficient HLA matching, we expect a diagnosis of SCID can be confirmed and a cell donor identified before a baby is two weeks of age.

COLLABORATION.....

In March, the Clinic hosted a meeting on ***Diagnosis and Treatment of Primary Immune Deficiencies in the Plain Populations*** which included several families. The meeting reviewed our strategy to develop faster, more efficient methods at the Clinic for diagnosing SCID and discussed our collaboration with other groups to follow through with treatment options.

Drs. Nancy Bunin, Kate Sullivan and Jordan Orange, physicians involved in bone marrow transplant and immunology from Children's Hospital of Philadelphia, discussed the bone marrow transplant program at CHOP. *Fred and Vicki Modell,* presented information from the Jeffrey Modell Foundation on the national and international incidence and treatment of Immune Deficiencies. *Katie Buck, Affymetrix, Inc.* reviewed the current state of technology available and *Dr. Nicholas Rider, fellow in allergy and immunology at Penn State Hershey Medical Center,* presented his findings on the Clinic's SCID patients.

MEETING WITH FAMILIES.....

Dr Nick Rider and Dr. Kevin Strauss traveled to Indiana in June to meet with the Amish and Mennonite SCID Families Support Group to brief families on the Clinic's progress on SCID and to discuss our current research on SCID mutations and plan to provide early diagnostic tests for newborns at risk for these disorders. Approximately 20 families are involved with this support network who had 41 children born with SCID. Twenty six died of this disease.

RESEARCH.....

Dr. Nicholas Rider, Fellow in allergy and imunology at Penn State Hershey Medical Center, is collaborating with the Clinic in research on Cartilage-hair hypoplasia (CHH) and in the development of diagnostic and treatment strategies for SCID. A summary of his work:

Cartilage-hair hypoplasia (CHH) is a syndrome characterized by short stature and immune deficiency, including severe combined immunodeficiency (SCID). Mutations in the RMRP gene result in CHH; however, the mechanism for immune deficiency in this disorder is unknown. Many patients with CHH are well without a predisposition to suffer severe or unusual infections. Others become severely ill in early childhood. The Clinic cares for 25 patients with CHH. Two patients (8%) have had SCID requiring bone marrow transplantation; six other patients (24%) have had recurrent infections.

We have identified clinical and laboratory parameters that suggest which CHH patients will be affected with immune deficiency. Low birth length, low levels of the most prevalent blood antibody (IgG) and the antibody that coats respiratory and gastrointestinal mucosa (IgA), in addition to elevated blood levels of important virus fighting cells (natural killer cells) correlate strongly with SCID in CHH. Additionally, in the immunodeficient CHH patients white blood cells do not proliferate well when stimulated in laboratory experiments.

Our goal is to use the clinical and laboratory markers to diagnose immune deficiency in CHH during infancy, and therefore treat patients before they become ill. We will also begin work to understand why patients with CHH become immunodeficient. This will provide insights into the disorder and help understand other immunodeficiency disorders.

Dr. Rider presented his study at the American Academy of Allergy & Immunology at San Diego in Feb, 2007.

Our strategy to diagnose and treat SCID grew out of the needs of sick children in our community. The experience teaches us that in caring for special children, we make important discoveries that will help us prevent pain and suffering in the future. Like many studies at the Clinic, these lessons have wide medical relevance; they need not be limited to the Amish and Mennonites. If we communicate our discoveries to others, they can benefit children, families, and communities throughout the world.

We also note that the cost of these studies is not billed to our patients, but covered by our Research Fund. The recent studies on SCID and CHH as outlined, cost the Clinic over $50,000, not including the cost of new equipment. The amount we saved just one family and the local community in costs was much greater than $50,000. We need much more support to continue our clinical studies program to solve difficult problems of genetic diseases.

FOLLOW UP NOTE:

Hannah was transplanted 62 days after her birth with bone marrow from her sister. After approximately two weeks in the hospital (CHOP) she returned home and is doing well. She now has no signs of Omenn Syndrome.

Workshop on Inherited Disorders that May Be Mistaken for Child Abuse, Neglect or Sudden Infant Death

The Clinic sponsored a workshop on July 11 to discuss genetic disorders found in the Amish and Mennonite populations that cause unexpected deaths in infancy, chronic malnutrition, intracranial and ocular hemorrhages, bruising, pathological fractures, and which may be mistaken for problems such as child abuse, neglect, shaken baby syndrome or Sudden Infant Death Syndromes. *Dr. Lucy Rorke, neuropathologist, Children's Hospital of Philadelphia, Dr. Julie Mack, pediatric radiologist, Hershey Medical Center, Dr. James Eastman, pathologist, LGH, Dr. David Turkewitz, Chairman of Pediatrics, York Hospital, and Dr. John Plunkett, forensic pathologist from Minnesota* contributed to the workshop. Dr. Turkewitz is current president of the American Academy of Pediatrics of Pennsylvania. Dr. Rorke, Dr. Turkewitz and Dr. Morton all serve on the Attorney General's Advisory Board about Child Abuse.

The Clinic's catalogue of Inherited Disorders of the Plain Populations includes 105 genetic syndromes. For 74 of these inherited conditions a specific disease causing mutation has been identified and can be used for diagnosis. Seven of the conditions are invariably fatal, but many affected infants live for months before succumbing to a lethal disorder. In the course of diseases like Cockayne Syndrome or Troponin Myopathy, affected patients develop generalized wasting, which may be mistaken for neglect. Approximately 26 of the 105 disorders are highly treatable, but if unrecognized and untreated may cause severe neonatal illnesses, malnutrition, bruising, intracranial hemorrhages, or overwhelming infections with unexpected deaths. Although many of these inherited disorders do have distinctive clinical features and can be diagnosed by an informed physician, most of the conditions are unfamiliar to physicians, social workers, and coroners who have little training in genetics and little contact with the Plain Populations.

The goal of the workshop was to collect lecture materials, case studies, and key references that will become part of a Continuing Medical Education Course that will be offered regularly at the Clinic and will be directed to Pediatricians and other members of child abuse investigation teams. The material will also be adapted for Pediatric Grand Rounds presentations at hospitals that serve Amish and Mennonite populations in Pennsylvania and the Midwest. As part of a proposed two year collaboration between the Pathology Department of Lancaster General Hospital and the Clinic for Special Children, Dr. Jim Eastman has developed a presentation specifically for Pathologists and Coroners in Pennsylvania about this specific group of disorders seen at the Clinic.

Although our meeting was focused on recognition of the inherited disorders of the Plain Communities, we hope this material will help others to be more informed who have the difficult task to investigate child abuse and unexplained deaths in other populations of the United States.

Acknowledgements: The July 11 workshop, the proposed pediatric lectures, CME courses and collaboration with Dr. James Eastman to improve the investigation of genetic causes of unexpected death by pathologists is part of Holmes Morton's John D. & Catherine T. MacArthur Fellowship. This work is inspired by memories of Sara Lynn Glick and Lucas Mendez.

MSUD TRANSPLANT SYMPOSIUM

On June 12 the Clinic for Special Children and Children's Hospital of Pittsburgh jointly sponsored the Third Annual Symposium on Transplantation for Maple Syrup Urine Disease Approximately 75 gathered to hear *Dr. George Mazariegos, Director of Pediatric Transplantation at Children's Hospital Pittsburgh* discuss the long term outcomes in liver transplantation. *Dr. Rakesh Sindhi, Associate Professor of Surgery, CHP*, provided an update on research on liver transplant. *Hilary Feldman, PhD, from the Child Development Unit at CHP and Diana Shellmar, PhD.* discussed aspects of pre and post transplant cognitive and neurodevelopmental findings. *Dr. Strauss, CSC*, outlined the neurological benefits of transplantation for MSUD patients and *Dr. Morton, CSC*, added perspectives on the choice or decision for transplant. The meeting was attended by transplant patients and their families and families of children with MSUD who are interested in more information about the choice for a transplant.

To date, 23 patients with MSUD have received transplants at Children's Hospital of Pittsburgh.

KARTEGENER DAY AT THE CLINIC

On May 2, the Clinic sponsored a clinical review on Kartegener syndrome, also referred to as primary ciliary dyskinesia. This is a rare recessive genetic disorder that causes multiple problems with the respiratory tract due to a defect in the function of the cilia, microscopic hairs that line the respiratory tract. A common characteristic of this disorder is the reversal of organs such as the heart and lungs. The Clinic sees a group of Amish families with this syndrome and organized the day to include clinical evaluations for patients by the visiting specialists.

Contributors to the meeting in addition to Dr. Morton, Dr. Strauss and Dr. Puffenberger included the following specialists. *Dr. Carlos Perez, Geisinger Medical Center,* reviewed clinical evaluation and disease course of Amish children with primary ciliary dyskinesia: and *Erik Puffenberger, CSC,* discussed SNP-genotype mapping of DNAH5 c.4348C>T in three families.

Dr.Margaret Leigh, University North Carolina, presented pathophysiology and treatment of ciliary dyskinesia: a guide for parents and families.
Dr. Hank Mayer, Children's Hospital of Philadelphia, talked on the clinical management of abnormal mucociliary clearance: lessons from cystic fibrosis and primary ciliary dyskinesia. *Dr. Tom Ferkol, Washington University, St. Louis,* led question and answer session with group discussion
Also present: *Dr. Mike Knowles,* University of North Carolina, expert in the basic science and pathophysiology of cilia function and the principal investigator on a study of a large number of PCD patients (including the Amish); and Dr. *Maimoona Zariwala*, molecular biologist from UNC.
After the presentations, discussion and consenting process, rotating clinical evaluations were provided to each of the children in attendance.

RECENT LECTURES IN OTHER PLACES BY CSC STAFF

Erik Puffenberger,PhD. Association of Biomedical Resource Facilities, Orlando, FL.

Kevin Strauss, M.D. and Erik Puffenberger, PhD., McKusick Nathans Institute of Genetics, Johns Hopkins University.

Erik Puffenberger, PhD., Hershey Medical Center, Department of Biochemistry.

Donna Robinson, CRNP, Lancaster General College of Nursing; LGH Pediatric Update Conference; and Lancaster County Career & Technology Center, LPN Training.

Dr. Morton, Liver Transplant as Gene Therapy for Crigler-Najjar Disease. Pittsburgh Children's Hospital, May 2007

Dr. Morton, Dr. Strauss and Dr. Puffenberger, Elizabethtown College, International Conference on The Amish in America.

Dr. Morton, Dr. Puffenberger- National Youth Science Camp, WV.

Dr. Puffenberger, Dr. Strauss, Franklin & Marshall College.

RECENT PAPERS PUBLISHED BY CSC STAFF

Polyhydramnios, megalencephaly and symptomatic epilepsy caused by a homozygous 7-kilobase deletion in LYK5. Puffenberger EG, Strauss KA, Ramsey KE, Craig DW, Stephan DA, Robinson DL, Hendrickson CL, Gottlieb S, Ramsay DA, Siu VM, Heuer GG, Crino PB, Morton DH.

Brain. 2007 Jul;130(Pt 7):1929-41. Epub 2007 May 23. PMID: 17522105 [PubMed - in process]

Multimodal imaging of striatal degeneration in Amish patients with glutaryl-CoA dehydrogenase deficiency. Strauss KA, Lazovic J, Wintermark M, Morton DH.

Brain. 2007 Jul;130(Pt 7):1905-20. Epub 2007 May 3. PMID: 17478444 [PubMed - in process]

Prevention of brain disease from severe 5,10-methylenetetrahydrofolate reductase deficiency. Strauss KA, Morton DH, Puffenberger EG, Hendrickson C, Robinson DL, Wagner C, Stabler SP, Allen RH, Chwatko G, Jakubowski H, Niculescu MD, Mudd SH

Mol Genet Metab. 2007 Jun;91(2):165-75. Epub 2007 Apr 3. PMID: 17409006 [PubMed - in process]

Mutations in methylenetetrahydrofolate reductase or cystathionine beta-synthase gene, or a high-methionine diet, increase homocysteine thiolactone levels in humans and mice. Chwatko G, Boers GH, Strauss KA, Shih DM, Jakubowski H.

FASEB J. 2007 Jun;21(8):1707-13. Epub 2007 Feb 27. PMID: 17327360 [PubMed - indexed for MEDLINE]

Seated, Dr. Victor A. McKusick and Dr. Morton. Standing l to r, Mike Fox, Mary Morton, Dr. Puffenberger, Dr. Claire Francomano, Dr. Strauss. back row, "Bowie".

Recent Visitors to the Clinic

In addition to guests who participated in recent Clinic workshops we welcomed several visitors in the last few months who are interested in our progress.

Dr.Victor A. McKusick, McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University and Dr. Clair Francomano, Greater Baltimore Medical Associates

Dr. Lubert Stryer, Winzer Professor of Cell Biology and Professor of Neurobiology at Stanford University. His textbook, Biochemistry, now in it 6th edition, is used in many colleges and medical schools.

Johnathan Pevsner PhD. Associate Professor, Department of Neuroscience, Johns Hopkins University. Author of the book Bioinformatics and Functional Genomics. Dr. Pevsner will act as an advisor to the course at F&M College, and collaborate with us on other projects at the Clinic related to the new complex field of Bioinformatics.

Dr. Stephen Eck, Vice President, Pfizer, Inc.

UPDATE FROM THE LAB

It has been a busy year in the laboratory. Roy Martin continues to perform most of the routine amino acid and organic acid analyses. His technical assistance has provided much needed time for Dr. Puffenberger to develop and expand the capabilities of the lab. As outlined in previous newsletters, we began a collaboration with Affymetrix to develop a custom diagnostic array. This array was designed to detect all the known mutations found in the Amish and Mennonite populations of Pennsylvania. In addition to specific mutations, it was designed to contain thousands of polymorphisms (i.e. genetic markers) scattered throughout the human genome which would enable detection of DNA copy number in individuals. Copy number analyses are an alternative method to identify chromosomal deletions and duplications which are found in some genetic diseases. Standard methods for detection of chromosomal abnormalities are expensive, laborious, and often have low yield. We have hope for this new test; unfortunately, the development of a diagnostic array has encountered several technological hurdles which have stalled the project.

We strongly believe in pre-symptomatic detection and much of our work is devoted to development of testing to increase our ability to diagnose genetic diseases in children. Since our custom array appears to be far from completion, we began exploring other technologies for rapid mutation detection earlier this spring. After careful examination of the competing technologies, we chose the option of the Roche LightCycler 480. This equipment detects DNA sequence variants (such as mutations) rapidly and inexpensively. Once the assays for each mutation have been optimized on the new system, we expect to be able to test individuals for all Amish and Mennonite mutations in 3-4 hours. In theory, during an office visit, a patient could know which mutations he/she carries before they leave the clinic. This rapid testing will be especially useful for newborn screening. We hope to test "at risk" babies at birth to identify affected children and begin therapy before the children become ill.

To facilitate the design and implementation of this new testing, we accepted a summer student, Mike Fox, who recently graduated from Franklin and Marshall College and plans to attend medical school at the University of Pittsburgh this fall. He was one of 12 students who enrolled in the first class co-taught by Drs. Morton, Puffenberger, and Strauss at F&M. This summer, he will develop and optimize the mutation detection assays for the LightCycler. If all goes well, he will have the first 24-mutation panel complete before he departs for medical school.

Over the past six months Mary Morton has been using her lab skills to help search for new disease-causing mutations in clinic patients. Her hard work has helped the lab immensely. See her article on her work at the Clinic.

We continue to perform mapping studies to identify the genes underlying the disorders in clinic patients. Recently, we published a paper in the journal Brain detailing the cause of a new disorder found in the Old Order Mennonite population. This disorder was locally known as "pretzel" syndrome. Our studies identified the deletion of a gene called LYK5 in all the "pretzel" syndrome patients. We named the disorder PMSE (polyhydramnios, megalencephaly, syndromic epilepsy). Similar studies over the past several years have determined the genetic basis for the 8 different disorders below (the gene name is in parentheses):

Bartter syndrome (CLCNKB)
Bronchiectasis and situs inversus (DNAH5)
Cortical dysplasia and focal epilepsy (CNTNAP2)
Mitochondrial myopathy and cardiomyopathy (SLC25A4)
Pelizaeus-Merzbacher-like syndrome (GJA12)
"Pretzel" syndrome (LYK5)
Salla disease (SLC17A5)
Sudden infant death with dysgenesis of the testes (TSPYL1)

Additionally, we have mapped the following disorders to a small chromosomal region, but have not yet identified the causative gene. We are actively sequencing candidate genes in the mapped regions in hopes of identifying the causative gene:

Posterior column ataxia and retinitis pigmentosa
"Schrock" syndrome
Retinitis pigmentosa
Usher-like syndrome
"Yoder" dystonia
Craniosynostosis
Primary microcephaly
Lethal seizure disorder
Non-syndromic mental retardation

Erik G. Puffenberger, Ph.D., Laboratory Director

NOTE: Mapping is the process by which a cluster of genes are found that are shared by all patients with a specific disorder and within which we expect to find a specific disease causing gene. A mapped region often contains hundreds of genes which are sequenced to find a disease causing mutation. In Hannah's case Mary and Erik only sequenced two small candidate genes RAG1 and RAG2 to find the disease causing mutation. In other syndromes, like Posterior column ataxia and retinitis pigmentosa, Yoder dystonia, and Usher-like vision and hearing loss, 20 or more candidate genes have been sequenced but the disease causing mutation has not yet been found. The cost of sequencing a gene at the Clinic ranges between $500-$1000 **These costs are paid through our fund for research - patients are not billed for these studies.**

From Mary Caperton Morton, F&M '05.....

The Clinic lab is always busy- filled with hot machines humming around the clock churning out amino acid levels, diagnostic and carrier tests, and cutting edge genetics research. This winter and spring I helped to put a dent in the workload by keeping the gene sequencer running at full steam. Powerful sequencing technology combined with new bioinformatics data is allowing us to pinpoint the location of the gene mutations that underlie many of the genetic disorders seen at the clinic. In the past six months I have found the mutations for Kartagener's Syndrome, Omenn's Syndrome, Chronic Granuloma's Disease and Restrictive Dermopathy. Once the location of the disease gene and mutation is discovered, the ensuing cascade of problems can be better understood and may lead to more effective therapies. This gene mapping can also be used to create conclusive diagnostic tests that can identify patients at a very young age, before their bodies are damaged by the effects of their disease. With prevention-based treatment implemented from birth, many children are spared devastating brain and organ damage and can go on to lead full, healthy lives. My foray into genomic medicine has given me a unique experience that will lend itself well to my studies in scientific and medical journalism this coming year at Johns Hopkins University.

RECENT ROTATIONS AT THE CLINIC

In February, the Clinic hosted Jirair Bedoyan, M.D, PhD., a third year resident in pediatrics at Children's Hospital of Pittsburgh for a two week rotation. Jerry will continue his interest in genetics later this year with a fellowship at the University of Michigan.

BUILDING PARTNERSHIPS

One of the Clinic's goals for the next five years is to develop course material for teaching others from college students to CME courses for practicing pediatricians. Last year Drs. Morton, Strauss and Puffenberger taught a senior level seminar at Franklin & Marshall College. The course was regarded as a significant contribution to F & M's curriculum and especially meaningful to the students who took the course. Most of these students are now heading to medical school or graduate programs in genetics.

The success of this first course led to consideration for further collaboration that will contribute to each institution's goals. With the new Life Sciences and Philosophy building, the College is expanding their curriculum in the biological sciences. **Richard Fluck, PhD., F & M Associate Dean of the Faculty**, worked with the Clinic to determine areas of mutual interest that contribute to the partnership.

Drs. Morton, Strauss and Puffenberger were invited to join the F&M faculty and will teach their evening seminar course, "Medical Genetics and the Plain People"on a regular basis.

The Clinic will work with the College to develop a program on Bioinformatics, an interdisciplinary approach involving the fields of biology, genetics, biochemistry, statistics and computer science. It engages in the effective use of the emerging human genome data base. The Clinic practices "bioinformatics" on a daily basis to inform and solve clinical problems.

Drs. Morton, Strauss and Puffenberger will present a series of "Clinic for Special Children MacArthur Lectures" for F & M, the scientfic and medical communities over the next five years. The first lecture by Dr. Morton will be scheduled early next year.

Qualified students from F&M will also participate in independent research and summer internships at the Clinic. These internships will enhance the student's educational experience and assist the Clinic in its work. This summer the Clinic welcomed Mike Fox, F&M '07 who is working with Dr. Puffenberger to set up new diagnostic methods using LightCycler technology. Mike will begin medical school in August at the University of Pittsburgh.

Joining the partnership, Lancaster General will establish a teaching laboratory at the College's new science facility with a gift of $500,000. The new lab at the College is established in honor of the Clinic for Special Children and will serve as a teaching and resource center for students in biology, genetics, biochemistry and bioinformatics.

Tom Beeman, President & CEO of Lancaster General noted " It is not often we are presented with the opportunity to support an endeavor that recognizes one of our community's medical pioneers and advances clinical research and education". **Dr. Lawrence Bonchek**, a cardiothoracic surgeon affiliated with both F&M and LGH, spoke of the intellectual value of the collaboration and the contribution this will provide to the medical community as well as the community at large. Dr. Bonchek related that he was aware that the Clinic was well known for its work. That was recently underscored when he was giving a lecture in Kuala Lumpur, Malaysia, and was asked if he "came from the place where the Amish children with metabolic errors were studied"!

Franklin & Marshall College President John Fry said "Together, we are inaugurating a relationship that will help Lancaster sustain The Clinic for Special Children, while enhancing the quality of science education at Franklin & Marshall College and making a contribution to the applied sciences as they relate to the care of children at Lancaster General".

INVESTING IN THE FUTURE

F&M is generously assisting the Clinic in investing $30,000 toward the purchase of the LightCycler equipment and related costs of research projects for the Clinic's lab. F&M students working with the Clinic will gain first hand experience using this technology to assist the Clinic in our research programs. We are very fortunate that F&M's high standards and commitment to its students to provide a quality education also embraces the mission of the Clinic. Over the next five years F & M will assist the Clinic in fund raising goals for the Research and Education and Endowment Fund.

REMARKS FROM STUDENTS

From Austin D. Williams, F&M '07

"As I walked out of an Amish farmhouse into cold rain and darkness, I paused to think about the dead boy and the gathering of the people in the room behind me. Special children are not just interesting medical problems, subjects of grants and research. Nor should they be called burdens to their families and communities. They are children who need our help, and, if we allow them to, they will teach us compassion. They are children who need our help, if we allow them to they will teach us love. If we come to know these children as we should, they will make us better scientists, better physicians, and thoughtful people."

I quote this anecdote, Death & Life written by Dr. Holmes Morton, not to tell you about the incredible work accomplished daily at the Clinic for Special Children. I think that is self-evident. Instead, I use these reflections to tell you about what I as a student learned from Drs. Morton, Strauss, and Puffenberger; lessons from which many Franklin & Marshall students will benefit as they go on to contribute to society as scientists and physicians as a result of this partnership.

As a student in the course that Drs. Morton, Strauss and Puffenberger recently taught at Franklin & Marshall, it is true that I grappled with the complex medical problems of the patients about whom we were learning. Dr. Strauss never failed, however, to clarify the intricate biochemical pathways involved with a larger-than-life diagram on the blackboard. And Dr. Puffenberger highlighted for us the key aspects of why the Amish and Mennonites are such an interesting population to study, genetically speaking. I must confess that I have tackled similar material in other courses as a Biochemistry and Molecular Biology major at Franklin & Marshall. What made this experience different was the additional component of the course: thinking not exclusively about the disease but about the patient.

I had the opportunity to stand at a white board in a nurses' station at Lancaster General Hospital with Dr. Strauss and several other students to discuss the differential diagnoses of a newborn who had been admitted to the hospital for testing that evening. But, it was interacting with the parents in the moments that followed that truly defined the experience. They were first-time parents, timid and concerned about their son. The partnership of Franklin & Marshall with the Clinic for Special Children will afford students these meaningful experiences in the Lancaster healthcare community.

Discussions in our class promoted my understanding of the way in which the healthcare system operates; the frustrations and benefits that come in tandem. Dr. Morton highlighted aspects of newborn screening, and health policy. We also touched on health insurance and hospital billing, figures that astounded us all, inflated costs we will never forget.

In total, the basic science and pre-medical components of this course have prepared me incredibly well for a future career in medicine. The addition of the expertise and resources of the staff of the Clinic for Special Children to the strong science curriculum at Franklin & Marshall will be an invaluable experience for other Franklin & Marshall students.

Dr. Puffenberger, Dr. Strauss, Austin Williams F&M'07 and Mike Fox, F&M '07

From Mike Fox, F&M '07

I enrolled in Medical Genetics and the Plain People last spring knowing only that the course was being taught by two MD's and a PhD who had a clinic in the middle of an Amish farm. I expected that the course would provide me with a better knowledge of the Amish and Mennonite communities, and that we would spend a great deal of time learning about some uncommon medical disorders that are frequently associated with these populations. What I didn't know, however, was that this course would provide such a holistic view of these disorders and medicine as a whole, and how much of a profound effect it would have on my plans as a future physician.

Drs. Morton, Strauss, and Puffenberger taught a course that I feel truly embodies the liberal arts beliefs we hold so dear at Franklin & Marshall College. Yes, we learned a great deal about the genetics and pathophysiologies of such disorders as maple syrup urine disease, glutaric aciduria type 1, and medium-chain acyl-CoA dehydrogenase deficiency (not to mention the fact that you can save a lot of breath by referring to these diseases as MSUD, GA1, and MCADD). We also learned about the societal, economic, and ethical impacts that testing for and treating these diseases has on communities, through a combination of lectures, readings, and group work. We were all bright students with a strong background in the sciences, but it was essential that we learned to utilize a more complete skill set than that required of any other course we had previously taken at F&M. In so doing, we became much better students who learned the importance of thinking outside the biological box when examining the kinds of scientific and medical issues important in today's society.

But even more important than the knowledge we took away from the actual course material was the wisdom we gained from our one-on-one interactions with Drs. Morton, Strauss, and Puffenberger. Whether we were interested in medicine or genetics, all three of them always made themselves available to provide guidance and opportunities to observe them in action, both here at the Clinic and at Lancaster General Hospital. We didn't just stand idly by and observe them as they tended to patients or studied their data. They always made us active participants in the process. In fact, I fondly recall an off-the-cuff lecture on the pathophysiology of MSUD given to three of us while shadowing Dr. Strauss at Lancaster General Hospital that lasted over two hours, and likely would have lasted even longer had his wife not called to remind him about bowling night with the Cub Scouts.

On a more personal note, these men are my primary inspiration as I continue my journey towards becoming a doctor. Because of my work with them both in and out of the classroom, I know that I want to pursue a career in some area of pediatrics, and I will consider myself lucky if I should one day be even half the doctor that all three of these great mentors have been to so many of their patients. Dr. Morton, Dr. Strauss, Dr. Puffenberger, thank you for all that you have done for me and for all that you will continue to do for Franklin & Marshall College. But most importantly, thank you for making a difference in our world, and inspiring others to do the same.

LOOKING AHEAD

October, 16 & 17, 2007, CME Course at the Clinic for pediatricians and other physicians.
October, Holmes Morton, M.D., F&M
November 11, 2007, Holmes Morton - MacArthur Lecture and Clinic for Special Children benefit concert with noted cellist, Matt Hamovitz,. Trinity College, Hartford, CT.

MACARTHUR LECTURES

The MacArthur Lectures will discuss the work at the Clinic with a broad perspective on the implications of this work for medicine and biology interwoven with ideas about education and art.

Trinity College, invited Dr. Morton to give the first of these lectures on Novemeber 11, 2007. Dr. Morton's MacArthur Lecture at Trinity College will be a Sunday evening lecture addressed to students, faculty, supporters of the Clinic from the region of New England, and will be open to the general public. The title of the lecture will be ***Roads Not Taken - Inspired Choices and Difficult Learning, Reflections about an Education***.

The Trinity College Lecture will be preceded by a cello concert for supporters of the Clinic in New England and will be a fund raising event for the Clinic's Research and Education Fund. The Concert will feature world-renowned cellist Matt Haimovitz, in the Trinity Chapel. A reception and dinner at the College will follow.

The second MacArthur Lecture will be at F&M College on March 27, 2008. F&M has offered to donate $25,000 to the Clinic's Research and Education Fund.

The Clinic for Special Children in Spring, photo by Mary Morton

Clinic for Special Children
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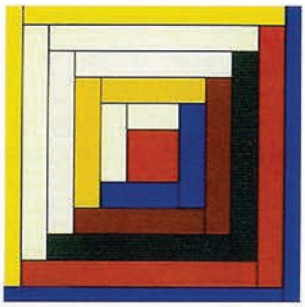
2007 BENEFIT AUCTIONS

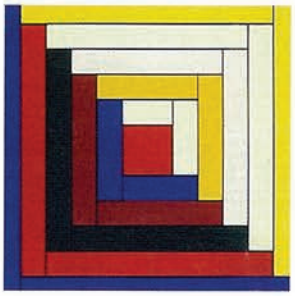


SHILOH, OHIO ~ JULY 14

SHIPPENSBURG, PA ~ JULY 21

BLAIR COUNTY, PA ~ SEPTEMBER 8

LANCASTER COUNTY, PA ~ SEPTEMBER 15



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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