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GENE REPAIR THERAPY FOR MSUD

Details

Written by R. Michael Blaese, M.D.

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What is it, and when might it become available?

We have all heard about the possibility that gene therapy could be developed to treat MSUD and other serious diseases that are caused by a defective or misspelled gene. So far that possibility has seemed to be just out of reach. Traditional methods of gene therapy try to take a "normal copy" of the gene that is causing the disease, and deliver it to the cells in the patient's body that are crippled by the defect with the hope that this new "normal" gene will reverse the disease. This treatment has worked in some very special cases where the diseased cells from a patient can be removed from the body and the corrective gene inserted while the diseased cells are growing in a test tube.

Unfortunately, for MSUD and the majority of other serious genetic diseases, the "diseased cells" cannot be removed for treatment in a test tube, and therefore the corrective gene needs to be delivered to the cells where they ordinarily live inside the body - for example, the liver or brain. Most of the traditional ideas for gene therapy have run into this "delivery" brick wall and their development has been stopped at this stage.

Many genetic defects can be thought of as a "typo" that causes the code contained in the gene to be misspelled. Such typos in the spelling of the gene, called mutations, can occur while a gene is being duplicated during cell division or as a result of external factors such as radiation exposure, etc. Since genes are inherited, once a misspelled gene develops for any reason, it has the potential to be transmitted from generation to generation, just as the normally spelled genes are passed on. For many genetic diseases, a misspelling involving only a single letter in a gene that is made up of thousands of letters (or bases) can cause disease. As an "ideal treatment," physicians would like to have tools to correct the typo in the spelling of the gene in those cells in the body where that genetic defect is causing a problem.

Recent research at Kimeragen, a biotechnology company, has led to the discovery of a way to correct, or mutate, the spelling of a gene directly in the cells of the body. Now, rather than needing to replace an entire gene that does not work, because just one letter out of the thousands in the gene is misspelled, it will be possible to treat genetic disorders with a much simpler idea - gene repair. This new gene repair technology is very different from the usual pharmaceutical product, because it uses a small molecule that is custom designed and produced for each individual or family in order to correct the unique gene defect that is found in that family. The molecule, called a chimeraplast, is a combination of both DNA and RNA sequences that direct the body's own molecular tools used to repair genes in order to change the defective gene sequence to a normal sequence. To test the feasibility of this idea, rats with inherited genetic defects affecting the liver have been treated using a simple intravenous infusion of a chimeraplast which was specifically designed to correct their mutations. Because early results in two different genetic disorders in rats have shown such promising results, active plans are now underway to begin treating an inherited human disease of the liver, called Crigler-Najjar syndrome, beginning next summer.

Is this a treatment that could be used in MSUD, and when might it be available? Theoretically, many (but probably not all) of the mutations leading to MSUD should be correctable using this new technology, but no work has been done yet to actually test mutations from different MSUD families.

Kimeragen plans to develop this new treatment for patients with many kinds of genetic defects involving the liver including MSUD, PKU, OTC deficiency, hypercholesterolemia, hemophilia, etc., etc. When treatment will become available for each of these diseases will depend on the success of early human clinical trials in Crigler-Najjar patients, as well as cooperation from the FDA in helping move this treatment from the experimental trials to general availability. Also, Kimeragen is a small company with limited resources. We are working to establish partnerships with larger pharmaceutical companies in order to fund more rapid development of this treatment for a broader range of diseases. If the early clinical trials show promise, clinical trials testing this treatment in MSUD could begin sometime in 2000 or 2001.

Dr. Blaese was the last speaker at Symposium '98. He explained a very technical subject in a simple way we could all understand. However, we wondered if we really were understanding? One mother said she looked around the room and saw many of us sitting with our mouths hanging open. Just the idea that there is hope for a cure in the not so distant future was hard to fathom. Previously, cures were only dim hopes - always many years away. Dr. Blaese sounded so certain of this technology.
Dr. Blaese submitted this article on Nov. 19 and plans to keep us updated on developments. We need to keep our hopes from soaring too high just yet. Funding is the major delay in getting testing started. FDA approval is still pending. So parents PRAY; pray for the success of this company and gene repair.

SYMPOSIUM '98 REVIEW

Details

Written by Joyce Brubacher

Published: 20 July 2009

A strong, united effort by the families of children with MSUD in Pennsylvania, along with the support and involvement of the Clinic for Special Children, paid off in a highly commended symposium. Over eighty families from across the United States and six other countries gathered at the Willow Valley Conference Center, south of Lancaster in the middle of June. Many parents brought their families for a great vacation in the heart of Pennsylvania Dutch Country. One hundred children and adults with MSUD, along with their siblings, a number of grandparents, other family members, and many professionals, brought the total to 480 at lunch on Friday, the day with the highest attendance.

Following are two reports on the Symposium reprinted from the Clinic for Special Children Newsletter (Spring 1998 issue). The Clinic chooses to call MSUD Maple Syrup Disease (MSD), but we have changed the name in the following articles to MSUD for clarity. Following these reports on the medical meeting held on Wednesday, June 17 and the Symposium (on 18 and 19), is a report of responses from persons who attended the Symposium and kindly filled out the questionnaires. I hope those who could not attend will gain a little information and an idea of the importance of these meetings to many of the families.

MSUD SCIENTIFIC MEETING

Details

Written by Joyce Brubacher

Published: 20 July 2009

The National Biennial Symposium for Maple Syrup Disease was held in June in Lancaster County with an overwhelming turnout of families and professionals from this country and overseas. Lectures and discussions followed the theme of "Progress, Problems, and Promises." Prior to the two day symposium for parents, the Clinic sponsored a day long scientific meeting to examine neurological effects of MSUD and to provide an overview of the clinic's approach to management of MSUD as presented in a first draft of a Manual for Care. Dr. Morton and Dr.

Kevin Strauss, Resident in Pediatrics at Boston Children's Hospital who spent four months of his senior year of Harvard Medical School in study at the Clinic, discussed a "new" disease model for MSUD which recognizes the greater role of leucine as a modulator of amino acid transport into the brain and out of the cells. Much of the information presented at the Scientific Meeting was based upon work by Dr. Halvor Christensen who attended the meeting. Dr. Christensen remarked that some of his most important observations about how leucine influences the transport of other amino acids were made at Boston Children's Hospital in 1949. His early experiments led to the discovery of the transport system that regulates entry of the neutral amino acids into the brain and provided the first observations that increased concentrations of leucine and phenylalanine cause intracellular entrapment of selective amino acids. Dr. Christensen's discoveries are key to clearer understanding of how high serum leucine causes a complex neurologic syndrome that includes sudden changes in level of consciousness and coordination, brain edema, as well as chronic malnutrition of the developing nervous system. After Dr. Christensen's remarks, Dr. Morton and Dr. Strauss presented their studies of the neurological signs and MRI findings of acute leucine intoxication, described management protocols that allow recovery from cerebral edema, usually irreversible and fatal, and presented MRI findings of patients after prolonged imbalances in serum amino acids caused arrests of brain growth and development.

Douglas Wilmore, MD, Professor of Surgery, Harvard Medical School and Brigham & Women's Hospital in Boston discussed biochemical, endocrinologic, and inflammatory variables that must be controlled to prevent endogenous protein catabolism and sustain protein synthesis in ill or injured patients. His studies and recommendations of the use of glutamine in nutritional management were important contributions to the meeting.

Quentin R. Smith, PhD, Chairman, Department of Pharmacology, Texas Tech University, presented data about neutral amino acid transport across the blood brain barrier and what that suggests about acute neurological dysfunction and chronic amino acid deficiencies in the central nervous system of patients with MSUD.

Attended by approximately 35 physicians and researchers (including Dr. Hugo Moser of Kennedy Krieger Institute and an early supporter of the Clinic's work), the scientific session concluded with discussion of new strategies to prevent illness and injury in patients with MSUD. The current strategy, based on the central idea of simply lowering leucine to control MSUD, does not necessarily promote optimal growth and development. Children survive but are often compromised with some degree of malnutrition, poor brain growth, and mild to severe physical impairment. The new strategy developed by Dr. Morton and used by the Clinic seeks to balance the ratios of the amino acids leucine, isoleucine and valine by modifications in formulas and uses glutamine and alanine to help promote protein synthesis and catabolism in muscle and liver. This strategy has enabled many of the younger MSUD children in care by the Clinic to achieve and maintain normal growth and development.

Following the day long meeting, we enjoyed a Lancaster County supper graciously hosted by friends and neighbors, Marilyn Lewis and Marian Ware. We thank them for such a lovely evening to conclude our meeting.

THE MSUD '98 SYMPOSIUM

Details

Written by Joyce Brubacher

Published: 20 July 2009

Parents of children with MSUD from this region of Pennsylvania dedicated much time and energy as hosts of the two day meeting held at the Willow Valley Resort, located a short distance from the Clinic. The Symposium provided opportunity for parents and physicians to present and discuss the latest in research and treatment protocols, for teenagers to discuss their issues together and for younger children to simply have fun.

Dr. Holmes Morton's lecture to open the meeting entitled "Progress, Problems, and Promises" gave an overview of the evolution of treatment of MSUD for Mennonite families in Lancaster County. He introduced the first draft of a Manual for Care for MSUD based on the Clinic's ten year experience and approach of diagnosis and care of 30 neonates and 60 patients who range in age from a few months to 33 years. The manual is intended for use by physicians and parents and will be revised for a more complete version during the coming year.

Other speakers included Dr. Harvey Levy, Harvard Medical School and Boston Children's Hospital, who presented an update on newborn screening for MSUD in the U.S.; Dr. Vivian Shih, Harvard Medical School and Massachusetts General Hospital, discussed how neonates and children with MSUD are managed in centers in other regions of the U.S. as well as other countries; Dr. Phyllis Acosta, Director of Metabolic Diseases for Ross Products Division discussed formulas and special foods necessary to children and MSUD and Dr. Neil Buist, Professor of Pediatrics at Oregon Health Sciences University in Portland, assessed nutritional problems associated with MSUD's very restrictive diet and how certain problems can be prevented. In a second lecture Dr. Morton analyzed effects of MSUD on the brain such as cerebral edema, muscle weakness, appetite and sleep patterns, and the development of myelin. Contrasting MRI images with clinical observations he gave all of us a greater understanding of the complex involvement of the brain in this disorder and provided parents, children and practitioners a frame of reference for their daily observations. In other presentations, the liver transplant and progress of a 7 yr. old MSUD patient with liver failure due to vitamin A toxicity was described by Dr. Morton and by Dr. Paige Kaplan, metabolic specialist of Children's Hospital of Philadelphia where the transplant was preformed. This experience demonstrated there are possibilities of "curing" MSUD with correction through the liver. Dr. George Mazariegos of the Thomas Starzl Transplant Institute in Pittsburgh described all that is involved with liver transplant. Transplant bears high risks and requires lifelong medication to prevent rejection.

Dr. Richard Kelley, Kennedy Krieger Institute & Johns Hopkins and the Clinic, discussed the nature of metabolic diseases in light of recent developments in the field of gene therapy. Dr.

Rody Cox, Dean and Professor of Internal Medicine at the University of Texas, Dallas, outlined progress of gene repair by viral vectors and insertion of new genes. The final presentation of the symposium revealed the promise of a new approach to gene therapy called chimeraplasty, presented by Dr. Michael Blaese, Chief, Clinical Gene Therapy Branch of NIH. In chimeratherapy, gene correction is achieved through infusion by IV of a chimera gene which corrects the abnormal gene sequence in the liver of MSUD patients (also potentially in Crigler-Najjar patients). With low risk to the patient, this therapy has the potential to be effective for infants as well as older children. Dr. Blaese, the Kimeragen Company, and the Clinic hope to begin trials within a year.

- Reprinted from the Clinic for Special Children Newsletter (Spring 1998)

SYMPOSIUM '98 GREATLY APPRECIATED

Details

Written by Joyce Brubacher

Published: 20 July 2009

At the Symposium, I asked the audience to write down what they liked about Symposium '98, and to share what they learned while attending the Symposium. Each family and professional received a questionnaire to complete. I said I would use this information in a review in the fall/winter issue of the Newsletter. I received responses from 30 family members and five professionals.

Following is a summary of these responses.

"Did you enjoy the Symposium?"
Yes, yes, yes! No one marked "no" in answer to this question. Some even emphasized their "yes." They would all consider attending another one. Motel accommodations were rated excellent on 11 questionnaires; other ratings included: very good, superb, very nice, and good. The comments on accommodations included some advice:

- *Excellent facility although a smaller facility makes it easier to interact with each other.*
- *Excellent, gets better with every Symposium.*
- *They were very nice, though the lecture room was often cold.*
- *Very well organized.*
- *It was wonderful, but as Ivan said during the Symposium, "I'd attend in a tent to be with these families and hear the latest."*
- *Very nice, but a little over-priced.*
- *Fine; there was plenty of room, and I didn't get lost going from place to place.*
- *Very nice - I think you should only offer the discount to parents who need it, and allow parents who can pay the full fare to do so. It is too much money to*

raise, and many families could have paid the extra two hundred or so dollars. (The fund-raising by Pennsylvania families provided enough money to pay a percentage of the hotel bill for each of the attending MSUD-affected families.)

This is how families answered the question: What did you like best about the Symposium '98 experience?

- *Sharing with parents our experiences and learning from doctors and also parents.*
- *Substance-there was a lot of medical information.*
- *That I didn't have to do any work this time. I liked all the speakers. (from Reneé Eck who helped with Symposium '96)*
- *As always, the interaction with the families can't be beat.*
- *Everything nice and complete. Day was not long enough to get all topics in.*
- *It was great to hear from many different "experts" who work with people who have MSUD. The idea of parents and professionals sharing information is helpful. I enjoyed seeing the children with MSUD and how well many are doing. Also keeping up with families that have moved away and talking with professionals.*
- *Accommodations, good food, good organization, and amount of information given.*
- *I liked renewing old friendships, learning more dietary necessities - comparisons of leucine, isoleucine and valine quantities.*
- *Learning from Dr. Holmes Morton.*
- *Doctors and professionals' views and discussions.*
- *Talking, sharing with other parents and just being here and part of the big family.*
- *Everything was special! I liked having activities for children while we were in the conference room.*
- *The sense of a big family and the children all eating the same; comparing notes with other parents and seeing the kids growing up. Everything was great. I hope two years from today it goes just as well.*
- *Meeting new families! New information.*
- *Gene therapy update; leucine and isoleucine relationship and supplements; visiting with old friends and meeting new families.*
- *The discussion in the evening with the parents. Also Dr. Morton's speeches.*
- *It is always a highlight seeing and visiting with other MSUD families. Just the gathering is a blessing.*
- *Information! Networking; sharing experiences; catching up with families and seeing growth and development among the MSUD kids; socialization for Elan with other MSUD teens.*
- *Information; hearing accomplishments of research; meeting with other families.*
- *1) The kindness and respect (love) that was prevalent. 2) The bringing together of, and the opportunity to befriend, people from all different cultures.*
- *That the information I'm taking back may improve my daughter's health.*
- *The baby sitters were wonderful!! I didn't need to worry.*
- *Can't say which - it was just GREAT!*

What the professionals liked best:

- *Just being with the families, learning their experiences and seeing the progress of their children.*
- *The genetic and medical information was extremely well presented, informative and timely. I enjoyed the biochemistry explanations.*
- *1) The health care providers sessions, especially Wednesday at the Clinic. 2)Meeting new patients/families.*
- *Dr. Morton's talk on how MSUD affects the brain; seeing adults and children with MSUD. The meeting was well run and organized. I learned quite a bit.*
- *Sharing experiences with families. Very well paced. Excellent job of keeping people on schedule.*

When asked if there was something they did not like about the Symposium, most answered no, or nothing, and some left a blank space. There were a few comments and suggestions:

- *Everything was interesting; I think that the genetic research and gene therapy was a little confusing.*
- *We would have liked more small groups of parents with children of same age. We found the doctors meeting the most valuable.*
- *Some talks were more technical than they needed to be.*
- *Not enough time to talk in groups about common MSUD problems.*
- *We did not have enough time to get into small groups for discussion. More Dr. Buist - he's very entertaining!*
- *Too many scheduled meetings and speakers; too short a lunch break.*
- *Not enough time for all the questions, but could easily understand with all the people attending.*
- *Never seems to be enough time to cover all questions.*
- *Not all the questions on the index cards were answered.*
- *Excellent speakers, but some needed to put lectures on level we parents could understand.*
- *Gene therapy talk was over my head; it's so exciting and I wanted to better grasp it.*

Professionals' suggestions:

- *It is hard to sit all day and into the evening. I would recommend 1, hours be scheduled into the program for exercise.*
- *It was difficult to keep comfortable, warm temperatures.*

The parts of the program families enjoyed most and the reasons they were special:
In answer to these two questions, the three most frequently mentioned parts of the program were the three that most directly involved the families: the Coping Workshops, the Personal Perspective Panel, and the Question and Answer Panels.

Coping Workshops:
Families could choose to attend a workshop for parents of teens, one for parents of children between the ages of 6 to 12 years, or one for parents of newborns to 6 years old. These sessions proved to be very emotional and extremely interesting and helpful to the parents. Here are some comments on the Coping Workshops:

- *I enjoyed everything, but I found very stimulating the Coping Workshops - seeing all that parents are going thru and understanding what you are going thru. You can really realize that you are not alone and your feelings are normal.*
- *Sharing personal thoughts and ideas about MSUD.*
- *The families discussing their personal experience with their child or children was interesting.*
- *I liked the splitting of the big group, for a part of an afternoon, into several smaller groups. People are more apt to share their experiences when the group isn't so large.*

Question/Answer Panels:
Twice during the program, a panel of doctors fielded questions from the audience. The questions were written on 3x5 cards and handed to the moderators who recorded them on large flip sheets. Each flip of the paper revealed another question. This kept the answering very orderly. Following are comments:

- *Learned day-to-day coping skills.*
- *The parents got a chance to ask questions; we need the professionals.*
- *Real concerns were answered by many different people to get more than one view.*
- *Good communication between parents and doctors.*
- *Everyone had a chance to ask just about anything.*
- *We picked up some useful information to take home with us on daily management.*

Personal Perspective Panel:
On this panel were adults with MSUD who gave their views on questions asked by moderator Bobbi Wanta, and also answered questions from the audience. Many persons mentioned this as being particularly interesting. But the only specific comments were: that it was very interesting as far as coping with diet and peer pressure; and that it was very encouraging.

Dr. Morton's speeches:
Dr. Morton made sense when he explained the many aspects of MSUD that tend to puzzle parents. His knowledge of MSUD and personal interest in each child were evident and appreciated.

- *Dr. Morton's explanations: It is encouraging to know that he is trying to comprehend the complexity of this disease, so that all of our children can benefit.*
- *Dr. Morton's presentations: His responses to questions were in layman's terms; very knowledgeable about MSUD. Also appreciate his research findings.*
- *I've been wanting to meet/hear him speak about MSUD since I had my daughter (3 yrs.).*
- *The amount of knowledge that Dr. Morton has and passed on to us parents. Especially the MSUD effects on the brain.*
- *I am really glad Dr. Morton wrote all his information down, so maybe our doctors will get a better idea on how to treat the children they see with MSUD.*
- *He was so easy to understand and everything made so much sense. Gave me some direction to consider to improve the treatment of my son.*

Liver Transplant:
Families found the information presented on the topic of Kathryn Burkholder's liver transplant of great interest; most stating that it was interesting and educational.

Genetic Research:
The possibility of gene therapy aroused a great deal of hope and fascinating interest. Some specific comments were:

- *I enjoyed learning about genes.*
- *That MSUD may have a cure soon - I felt like it would not happen in my child's life time.*
- *Dr. Blaese's genetic discussion: it's hard to beat the kind of hope he's given that some day, in the not too distant future, we may have a cure for MSUD (or MSUD).*
- *Explanation of liver transplant and gene therapy gave us hope for the future*
- *Obviously the highlight and surprise was the announcement of a possible cure. Dr. Blaese probably never should have gone so far out on a limb, but now, I hope you can follow up and keep us informed.*
- *The session on gene therapy was very difficult to understand, but feel that the research being done is very hopeful for the future.*

Comments from professionals about the parts of the program they enjoyed and why they found them interesting:

- *The professionals' day at the Clinic on Wednesday was a unique experience.*
- *I only attended Friday but enjoyed the entire day. The speakers were interesting and interested in the MSUD young people themselves.*
- *1) I enjoyed the health professionals session at the Clinic most. I enjoyed hearing about Dr. Morton's unique experience. He has what many of us dream of, the ability to get "STAT" labs and MRI's - which leads to insights and documentation of objective and quantitative changes needed to improve our understanding and ability to treat. 2) Also enjoyed visiting and "interpreting" for our patients and families. Our patients are always special.*
- *Arguments for better treatment.*

How could the Symposium be improved?
Two persons felt the Symposium couldn't be improved. Others had some comments, ideas and suggestions:

- *You all did a great job and the children enjoyed their workshops, which is important, too.*
- *Considering how many issues there were, I don't think it could have been much better.*
- *I wish it was closer. But then all the great people who made it possible probably would be too far away to attend! And it wouldn't even come close to this year's symposium. I've never met so many nice people in one place. How can we be kept up-to-date on the research?*
- *We need organized activities in the evenings so that families can interact.*
- *It would be good for parents to introduce themselves and give the name of their child when they speak from the audience. It would help to get to know the different families better. Possibly have introduction of families during a separate*

session - maybe the first night, so families can learn to know each other sooner.

- *I think it would be good to allow parents with children similar in age to talk together for 2 to 3 hours. I think every group would then benefit from a "round table" discussion with parents from the next age group older to theirs. For example, parents with new babies might enjoy talking to parents of children 6 to 8. And parents of pre-teens would enjoy talking to parents with teens. What about more business time - not to talk about finances or anything else like that, but maybe things we feel the general support group should vote on. Or do we just leave all decisions to the board? (For example, name change from MSUD to MSUD)?*
- *One doctor was talking in terms I could not understand, and took it for granted that we all understood him. He was very hard to follow.*
- *I would be very interested in having the children with MSUD in a panel to express their feelings about their disease, like the young adults with MSUD did. Have them divided into different ages, so the parents can have a better idea of what to do better, or what to expect from the children as they grow.*
- *It would be helpful if the doctors could present their information in a more simplified form for ease of understanding by families who don't have a medical background. Some speakers did a better job with this, such as Dr. Buist, Dr. Kaplan, Dr. Mazariegos, and Dr. Blaese. I'd like to hear more about the day-to-day management of MSUD, such as how families do the diet, count milligrams of leucine, or count grams of protein? Do they keep daily diet records? Are low protein foods used? What is frequency of blood tests? Is urine testing routinely done and how often?*
- *Allocate more time for parent-to-parent interaction.*
- *It would be great if we could add a day and spend more time in smaller groups discussing our personal questions and problems. It would be great to have a list of all the people/places who are in attendance. This way we could seek friends and make new acquaintances of those in our areas. Unless you have met them before, or are introduced, you may not get a chance to meet.*
- *Need more than one hour for the break-out groups. Also, a medical professional could be added to each group.*
- *Group time for workshops increased to 1, or 2 hours; have a 3-day symposium vs. a 2-day symposium.*
- *Emphasis on managing day-to-day problems*
- *More professional interaction with patients and educate in the newer aspects of treatment and theory.*

Suggestions for improvement from physicians and dietitians:

- *More "doctors' panels" to answer patient questions from the audience - it is helpful for patients to have their doctor up there with other doctors treating the disorder and get everyone's opinion on issues.*
- *More recipe sharing - maybe a cooking class for parents and teens with advice on how to improve your own cooking.*
- *Sessions combining patients, their parents and professionals all together. When I am in professional and adult meetings, I feel that I am missing what the kids or their parents are saying.*

- *A workshop/talk on diet to see if we all manage it the same, or what other methods are used. A cooking class for parents to exchange ideas/tips/recipes and to help new parents overcome the fear of working with the low protein products.*

Persons were encouraged to write more about what they learned from the speakers and in what way the Symposium helped them and their families:

- *We attended the MSUD Symposium in Lancaster and want to extend our heartfelt thanks to all of those involved in the planning and implementation of the meeting. In addition to the meeting itself, the level of support from the community was also impressive. Unfortunately, we were only able to attend on Friday, and as we were traveling with our 3 toddlers, did not have much opportunity for conversation with other families. Hopefully we will be able to remedy this at the next Symposium, which we will look forward to. - Karen & Jerry Dolins*
- *Obviously, we feel this way because Nikolai was on the panel, but it was touching to hear from the adult MSUD for the sake of the younger ones. It probably helped the parents. I'm sorry not more younger children attended.*

  I think the location was the key to having so many attend. If Boston is chosen next time, there may be interest in new speakers - only if Dr. Shih takes an active role. But it will be much more expensive. Nevertheless, no future symposium can be planned now without specific attention given to the progress of the cure. It may be necessary to direct the location around that company.

  I think all parents should take a moment to consider how difficult it is to have 400 people, with kids who have special needs, come to talk, eat, sleep, play, and learn. We are so busy, even this evaluation is late. Our hats are off to the organizers! Barbara and I think they did a fabulous job, down to the details of having gifts in each room!

  The only other issue which may be raised is the silent one of how the doctors disagree with one another. It can be difficult for parents to be convinced of one approach in a lecture, recommend it to their doctor, only to be told that it is a wrong, or at least not necessarily the best, approach. That is the conflict of getting parents involved, but as you know, it is needed.

  Nikolai's comments: He liked it. The only negative: kids didn't have much time to get to know each other again, because they kept being separated. Everything else is positive. - Eric & Barbara Rudd
- *The information I have learned at the Symposium will be brought back to my son's metabolic physician to update her on new findings and research. - Jody Carrington*
- *I always enjoy attending the Symposium even if I don't leave with more information. Just the discussions with other MSUD parents makes it worth attending. My problems don't seem so bad after I talk with other parents. It is nice to just visit with everyone. It also gives my MSUD child an opportunity to be around other MSUD children, and she doesn't feel like she is the only one with the disease. - Mary Ann Peters*

- *I have been reading and re-reading the manual that we received at the Symposium. There is a wealth of information that can benefit all of our MSUD children. At the Symposium, I learned a great deal from Dr. Morton including the relationships between leucine, isoleucine, and valine and other amino acids. Also, the effect on the brain and development of MSUD children when these amino acids are not balanced correctly. It was encouraging to learn that Dr. Morton has gained an understanding of cerebral edema in MSUD children.*

  Dr. Naylor from PA spoke about the benefits of mass tandem spectrometry for newborn screening. Wouldn't it be wonderful in the future if all newborns could be screened so quickly for so many rare diseases? Dr. Michael Blaise from the NIH explained about chimeroplasty. It seems to be the most promising gene therapy for our kids. It is encouraging to know that someone is working to improve our children's future and that the liver will likely be the targeted organ - Sandy Bulcher
- *Maybe we don't need another MSUD Symposium in two years if these children can all be healed!J We appreciate the good clinic and care we get in this area after hearing of the care some others are getting. Really appreciated that Neil Buist could be here and sure enjoyed his talk. We need more people like him. Very thankful for what Dr. Blaese is doing and sure hope it will work out. - A parent*
- *I had a great time and my son too. Even with the long drive ahead, I would do it every year. I can see there is a lot of hard work and time put into it. God bless everyone who did this Symposium. We really enjoyed this time we had together. See you in two years in the year 2,000. - Lucy Silva*
- *This one child threw us into a frightening world. But now it is a big part of our life, and we love it. We are happy to be a part of this family. Life would seem so empty without it. We made more friends through this one child than through all our others combined. This includes not just the families, but the professionals as well. Our love to all. - Ivan & Katie Fox*
- *After her liver transplant, Kathryn Burkholder asked her mother why she was never 6 or 7 years old. "I was 4 and 5, then 8 and 9, but I wasn't 6 or 7." (The years she was very sick.) "Other children are 6 and 7 years old but I wasn't." - Kathryn's grandmother, Mrs. Isaac (Rachel) Newswanger*
- *My nephew (who has MSUD) enjoyed the socializing. For me (great aunt, aunt, grandmother, and mother), it was wonderful talking to parents of children the same age as my great nephew, finding similarities of problems, hearing other doctors, of course, especially Dr. Morton. All were wonderful. Dr. Blaese (God willing the cure) and Dr. Kelly and Dr. Cox so brilliantly explaining the chain reaction of trouble cells. Thank you. - Sheila Wasserback*
- *I feel grateful for Dr. Morton's help for our problems over the years, and for the doctors that traveled from Philadelphia, Pittsburgh and many other states to help with the "forward movement" of new information to help or cure MSUD patients. Thanks so much to all who made the Symposium possible. - Norman & Mabel Burkholder*
- *We learned that we have much to be thankful for to have Dr. Morton as our doctor. Talking with some other parents you find out some doctors are still doctoring the way they did 15 to 20 years ago. We also found it very interesting to see all the adult MSUD doing so well. - unsigned*

- *I have benefitted greatly from this Symposium and will now take back ideas on how to better care for my daughter, Samantha. Her life will be better because of this.*

  Thank you for making it so well organized. Every minute was utilized to the fullest to bring us the most information possible in two days. Thank you for the nice gift basket. It was a nice touch to the end of a hectic, long journey.

  I admire and appreciate the strength and comradery of this community and wish I lived closer. We are looking forward to the next Symposium. A million thanks. - Barnfather family

Comments from the professionals:

- *The biochemistry was so interesting! I only deal with MSUD on a personal basis and to delve into the disorder itself was very educational and fascinating. - Patti Lee, CNM*
- *I am a health care provider, so my perspective is a bit different from a parent's. I am responsible for a unit at the state health department in Maryland that works with 8 children (at the moment) with MSUD. Our hopes for the program were to learn about new ideas in the treatment and diagnosis (through newborn screening) that might help us better care for our MSUD patients and to find them more quickly*

  The unique experience of Dr. Holmes Morton (with a large number of very compliant patients, from a very similar genetic background, living in a relatively small area, allowing him to follow them very closely) has produced a number of insights that we hope will help us to manage our patients better. We are pursuing a series of strategies to speed up our newborn screening test turn-around time and some insights into doing this were also gained.

  Specific efforts will be made to implement DNPH monitoring, to set up full amino acid profiles from fingerstick dried blood spots with HPLC and isoleucine/valine supplementation. (Na balance measures are already in more general use.) We also would like to try the sick day regime. But implementing this on a population basis in a state system will require educational efforts with our metabolic specialists, working together with our families to do the therapeutic trials, and scraping up a few dollars for the improved lab capability.

  Immediate major efforts in newborn screening will be focused on improving transit time from the hospital (where a specimen is drawn on day two) to lab for testing. Tandem mass spectrometry is a longer term goal. - Susan Panny, MD
- *I liked the way questions were handled when there was not enough time to address them after the particular speech. The flip chart was a great idea! - A professional*
- *I don't think I got across the idea that I wanted to, namely that the powdered beverages are an excellent source of total nutrition, albeit providing an inappropriate protein/calorie balance for older children and adults. We need to devise ways of giving them either a flexible source of more protein (i.e., amino*

acids), or calories, and/or vitamins and trace elements. Anything that is manufactured with this in mind to treat PKU, MSUD, etc. could be classified as a medical food. - Neal Buist, MD

The Symposium Committee worked very hard and did a splendid job. They had good support from many other families in Pennsylvania who were all asked to help with fund-raising. They raised well over $30,000 mostly through individual donations of a few dollars to $1000, except for $10,000 given by the families in Blair County from the proceeds of a fund-raiser auction. Families and their relatives prepared low protein foods, helped with child care, planned the teen program and entertainment for the children, provided for transportation needs and other details. A united effort paid off in a truly successful symposium.

Low protein foods, formula displays, food supplies and monetary contributions came from Applied Nutrition Corp., Dietary Specialities, Inc., Ener-G Foods, Inc., SHS North America, and Ross Products Division. Their contributions and support are so needed and appreciated.

United Service Foundation, Inc. provided $12,500 specifically to help families attend who had never been to an MSUD Symposium before, but were now able to attend with some financial assistance. These families genuinely appreciated this opportunity. Our sincere thanks to the Weaver family who administers this foundation.

The committee greatly appreciated the wonderful cooperation of the staff at the Willow Valley Resort where Symposium '98 was held. They were willing to do everything possible to accommodate our MSUD group. They graciously worked with the committee in planning the menus around foods appropriate for those with MSUD, even making the low protein pastas. A hearty thank you to the staff at Willow Valley Resort.

SHARING - MY EXPERIENCE BREAST FEEDING OUR MSUD BABY

Details

Written by Mark and Lorraine Martin

Published: 20 July 2009

Mark and Lorraine Martin are a Mennonite couple from Lancaster County, Pennsylvania. Lorraine is a sister to Glen Wenger; Glen and his wife Brenda have two girls with MSUD. So Mark and Lorraine were tested and found to be carriers before they were married. They had two unaffected children before Crystal was born. Crystal had the advantage of being detected right after birth and has done well.

Does breast feeding sound appealing? Can you breast feed an MSUD child? What are the pros and cons you will need to face in the process? I'd like to share our experience in hopes of answering some of those questions.

Our third child was born October 28, 1997, and we named her Crystal Lorraine. As usual, I started breast feeding her. At the age of 24 hours, she was diagnosed with having MSUD. One of my first thoughts was, "Oh no, now I can't even breast feed!" But I also knew that Dr. Morton was interested in trying breast milk for an infant with MSUD. The mother would pump, expressing milk for her baby, and add the milk in measured amounts to the formula as needed. So we bought an electric, dual pump to begin our journey. Colostrum is too high in protein so it wasn't until the fourth day that I could give Crystal some of my own milk.

One immediate change was that Crystal took her formula better. Up to that point, she cried and gagged over it. It just seemed she liked the taste better with my milk added.
At first, I did fairly well with my milk production. I was making up to a quart a day until she was about 4 months old. So we put the excess in the freezer. Once she was 6 months old, I stopped pumping, and we began using the freezer supply. She is now 9 months old and still getting mom's milk.

Crystal seemed to be a very healthy baby, which Dr. Morton contributes to the breast milk. He definitely feels it played an important role in keeping her level's stable. We noticed her first ear infection once we switched to frozen milk. We believe some of the antibodies were frozen out. Although she was exposed to many colds and flues the first half year, she never got really sick. She did have a respiratory infection at 8 weeks old which made her leucine level go up to 4 mg/dl. But she was never on a sick-day formula till after 6 months old, and that's when she developed her first ear infection and a cold, which caused her leucine level to reach 8 mg/dl. But it wasn't long until she was her happy self again.

Now, what about the disadvantages? When my baby was quite small, she'd wake up at night and cry - and guess what Mom had to do? That's right, pump! So Dad had to be available to do nighttime feedings the first while. Also, if you have other young children, it can be stressful being tied to one spot while pumping. Putting a phone by the chair was a plus, as it seemed to ring as soon as I was ready to pump. One other disadvantage that comes to mind: it's a lot of paraphernalia to pack up if you need to be away. Then once you reach your destination, you'll also need a private spot to pump. Bathrooms work well, providing you're not holding up a line of people! You'll also need to have sterile storage containers for the milk at all times. Those are the disadvantages.

But to me, the advantages far outweighed the disadvantages. I'm still thankful that I chose that route. It meant everything to me to see my baby enjoy her formula. It was one thing that I could do for her. And if it meant a healthier baby, the disadvantages were all worth it to me. Then there is an added financial benefit as well. At 6 months, we figured we went through only 4 , cases of MSUD formula versus 6 to 8 cases without the breast milk. Because my breast milk is lower in protein than Similac or any other formula, we could use more mother's milk which in turn meant less MSUD formula. Plus we didn't have the added expense of Similac or other formula.

Best wishes to all of you mothers who may give this a try. If you have questions or would like to rent the pump, please feel free to call us. We'd be glad to help where we can. Our phone number is (717) 733-3070.

PERSONALLY FROM THE BRUBACHERS

Details

Written by Wayne, Joyce & Shayla

Published: 20 July 2009

When we returned from the Symposium, I was so eager to share all the excitement and wonderful experiences along with the knowledge we gained at this meeting. I wanted to get a special, early issue of the Newsletter ready within a couple months. But here I am as usual, trying to get the fall/winter issue out before the end of the year. Maybe this issue will refresh the memories of those who attended so they can feel the wonder of it all again.

I do hope this Newsletter conveys some of the atmosphere of Symposium '98. The families were thrilled to be together and to gain new insights and share mutual feelings and concerns. However, several of the adults with MSUD were disappointed. They were too mature for the teen activities and found some of the talks too boring. This group of adults is increasing - good news - and we need to consider their needs. You adults with MSUD, send in your ideas for the next Symposium. You are a very important part of these meetings. The Personal Perspective Panel was one of the most appreciated parts of the agenda. Don't sit and stew, write your views for the Newsletter.

Rick Finkel, with Applied Nutrition Corp., made an interesting observation at the Symposium. Rick attends many conferences to introduce his products. He told me our Symposium differed from the conferences of PKU and other diseases in that we are such a social group. He was impressed that the interaction of the families was so intense, that it was difficult to get the people to quit talking and back into the conference room after breaks.

We were thrilled to have so many Spanish-speaking families at this Symposium. Maria English from the state of Washington sacrificed her time and served graciously as a medical translator for those who couldn't speak English. These families are so scattered (even from as far away as Chile); it was a joy to learn to know them and to give them the opportunity to participate.

I should explain a little about the term Maple Syrup Disease (MSUD). Several families said their children were embarrassed by the word "urine" in the name of their disease. So the Clinic for Special Children in Pennsylvania chooses to use the name MSD.

FOOD NEWS

Details

Written by Joyce Brubacher

Published: 20 July 2009

Ice Cream Solution:
Here is a solution for families who want to stop for an ice cream treat at a fast food restaurant. Some families have found these places very accommodating when they ask for a non-dairy creamer cone for their child with MSUD. Dairy Queen and others will often use their pressurized whipped topping to fill a cone. They may even put sprinkles on it. Some places may use real whipped cream which is higher in leucine. *Food Values of Portions Commonly Used* gives these values:

Pressurized whipped cream:
1 T. = 9 mg leucine or 0.1 gm protein, cup = 72 mg leucine or 0.8 gm protein

Non-dairy whipped topping, pressurized:
1 T. = 4 mg leucine or 0 gm protein, cup = 32 mg leucine or 0.3 gm protein
Add 30 mg leucine for a regular cone. Waffle cones have 90 mg leucine, and sugar cones are the highest with 1 gm leucine.

NEW - Uncle Henry's Low Protein Pretzels:
At Symposium '98, the children loved Uncle Henry's low protein pretzels. These great, special Pennsylvania Dutch pretzels are stone-hearth baked, hand twisted, regular-sized pretzels.

Mrs. Glen (Brenda) Wenger, the mother of two girls with MSUD, developed the recipe and worked long and hard to help the company start making the low protein pretzels.

Since all the equipment has to be thoroughly cleaned to run a batch of these pretzels, they are made only when orders total 100 lbs. You may have to wait a week or two for your order to be filled, but then they are always shipped fresh. The demand has increased considerably since the pretzels were mentioned in the *PKU News* and many persons with PKU are ordering them by the case. So they are being made more frequently. Leucine is 12 mg/oz. and protein is .13 g/oz. Each pretzel weighs about 18 gm or a little more than , oz.

Delicious regular pretzels are also available. If you order enough pretzels to fill a case, you can reduce the shipping costs. It pays to fill out your order with regular pretzels if you just want to order a few low protein pretzels to try. Expect some breakage in shipment. The low protein pretzels break easily because they do not contain gluten.

The cost of low protein pretzels (prices subject to change):

8 oz. bag is $1.85 9 (8 oz.) bags/case is $16.65.
11 oz. bag is $2.20 6 (11 oz.) bags/case is $13.20.
2 lb. bag is $6.20 2 (2 lb.) bags/case is $12.40.

Shipping costs $5.00 to $6.25 depending on the order and destination. If order is only 1 or 2 bags, shipping cost is $7.50. For orders outside the continental U. S., call the office number below. Order forms available: Uncle Henry's Pretzel Bakery, P.O. Box 219, Bowmansville, PA 17507
Phone: 717-445-4690 Fax: 717-445-8334
E-mail: pretzels@ptdprolog.net
Web site: www.unclehenry.com

Hints From Mothers:
Brenda Wenger's girls love the low protein pretzels dipped in salsa. Some of the children like them stewed in water or in a non-dairy creamer. Makes a good after-school snack.

Ruth Leid wrote of several products she uses and really likes for her son with MSUD. "I'm glad you found that Rice Dream. We use the vanilla-flavored and put a small amount of cream or coffee creamer in it - then it's as white as our milk." She wonders if others know that Lipton Recipe Secrets Onion Soup mix makes a good flavor when added to other foods. The Major Chicken Style Soup Base is another almost free protein source of flavoring. Her son calls Tomato Bisque soup mixed with heavy cream or coffee-creamer his "best soup."

Elsie Newswanger likes the oatburger recipe that was printed in the Spring 1995 issue of the Newsletter. She made the oatburger into meat balls, browned them in butter, and then made gravy with the drippings. The recipe also made good Sloppy Joes. Elsie loves to cook, but her son with MSUD doesn't readily like new things, so the rest of the family enjoys them. Her son's favorite meal is potato, made any way, lots of low protein noodles, and a vegetable. His favorite vegetables are corn and peas, very high protein vegetables. He knows he can have only one teaspoon, so he scatters them over everything on his plate to make it look like more! Elsie uses the low protein noodle recipe in the Spring/Summer 1996 issue of the Newsletter. Using a cheap source of wheat starch available in Pennsylvania, many of the families make their own noodles cutting the cost considerably. Elsie uses chopped low protein macaroni in place of eggs to make "egg salad" for her son's school sandwiches.

International Food Bank:
National Food is a nonprofit food bank serving persons with inherited metabolic diseases in Canada. It provides a variety of formulas and low protein foods from many suppliers in the U.S. and Europe. The products have been approved by dietitians and doctors and are distributed directly to hospitals and clinics, which serve as distribution agents for families. As a result of many requests, National Food has set up the International Food Bank on the Internet as a distribution center for special formulas and foods. Products include those from Mead Johnson, SHS (Scientific Hospital Supply), Ross Products and Applied Nutrition (formerly FoodTek). For those who cannot locate some of the special foods in their country, check out their Web site: www.international-foodbank.org. If you don't find what you are looking for, write to the Food Bank and they may be able to help. They welcome suggestions and comments. E-mail: cust.service@international-foodbank.org.

FAMILY HISTORY - A GOOD FIRST YEAR

Details

Written by Shawn Kelly

Published: 20 July 2009

I received the following account from the Kellys at the end of September. Ed and Shawn live in Michigan where their daughter with MSUD, Sydney, was detected through the state screening program soon after she was born on Sept. 10, 1997. This is a success story which is a joy to share with other families.

As the end of the first year approaches, I sit and say to myself, "Where has this last year gone?" We have had a daughter for one whole year. Our daughter, Sydney, was diagnosed with MSUD at ten days of life. Sydney is the most important person in our life. I look up as she says, "Ma Ma" to find her standing at the entertainment center turning the TV on and off. I tell her "No no," and Sydney smiles and shakes her head "no no."

I have thought about writing about my experiences with MSUD for a long time - I just never got around to it. My name is Shawn Kelly, and I work full time for a marketing company in Michigan. My husband's name is Ed, and he is a fireman for the City of Detroit (Sydney and I are very proud of him!). Aside from working, I spend every additional hour with my daughter and my husband. Together Ed and I have read all the newsletters, found information on-line, and talked to other families who have children with MSUD.

I can still remember the Friday that Ed and I received the phone call. I was in the shower and Ed said, "We have to go to the University of Michigan right now; Sydney has MSUD." I was so upset! We were called on Wednesday and told to have Sydney retested for MSUD, at which time her test came out slightly positive. From Wednesday until Friday, all I could do was cry. I just knew she had it.

I called a friend of mine who is a nurse and she told me the little bit that she knew about MSUD. "MSUD causes mental retardation, brain damage and death in infants if left untreated." My friend said not to worry, because it's such a rare disease. "This can't be happening," I must have said over and over.

Sydney, Ed and I entered the hospital on Friday, September 19, 1997 and met with Anna Marie Schaefer (nutritionist on the Pediatric Neurology Metabolic Team). Anna Marie confirmed for Ed and me that Sydney definitely had MSUD. Anna Marie answered all of the questions that Ed and I had and tried to ease our fears. I couldn't understand it; Sydney didn't show the usual signs of having MSUD. She was fully alert, ate, slept, cried and did all the things a new baby does. However, we didn't recognize that the cry was a little high, as this was our first child. Sydney wouldn't nurse, so I would pump the breast milk and feed her

with a bottle. She was drinking. She was sucking. She was smiling and cooing like a baby does. Until that Friday.

While we were on our way to the hospital, Sydney was very quiet. She wouldn't drink the Pedialite we gave her, and she became very fussy. We sat in the waiting room for a short time while the nurses took a blood sample from her and put her on an IV to prevent dehydration. Sydney screamed so loud that I became frantic! The doctor said, "Relax Shawn, that means that she is awake and not in a coma."

Ed and I were shown to a room and told that if Sydney wouldn't drink the formula, she would have to be fed through an IV. At that point, I was out of control with grief, and Ed said he didn't want Sydney to need an IV. Ed made the MSUD formula and fed her the formula from a bottle. Ed actually got her to drink! If Sydney wouldn't drink, Ed put a cool cloth on her face or took off her clothes to wake her up. It seemed Sydney would drink just to make Ed leave her alone!

By Saturday, Sydney was much better, however, I wasn't. Ed took full responsibility for Sydney. He fed her, changed her and rocked her. I was scared. In the afternoon, a woman named Sandy Kiel called me. Sandy has two kids with MSUD. At that point, these words eased my fears a bit. I began asking Sandy questions such as: "What will Sydney eat when she goes to school?" "What do your kids eat?" Questions that I shouldn't have been worrying about at that time, as Sydney was only eleven days old! I should have been paying attention on how to make her formula, listening to the neurologist on call, and to Anna Marie, who came in with all the information she had. I finally calmed down enough to listen, and that night, when Ed was worn out from being up for two days straight, I took over. I sat up and rocked Sydney until 3:00 a.m. We bonded. I told Sydney that I wouldn't let anything happen to her, and she smiled at me and went to sleep.

We were discharged on Sunday, only three days later! Anna Marie and Dr. Allen couldn't believe it. Sydney's leucine went from 43 mg/dl to 16 mg/dl in just three days. Sydney was awake, alert, eating and going home! It was a miracle. We came home to four dozen pink balloons and a big WELCOME HOME SYDNEY sign from Ed's twin sister, Denise. Denise came over and cleaned for us and made it comfortable for when we came home. It was a wonderful welcome.

Well, this last year has been pretty easy. Sydney was sick only once, and her leucine levels only went to 7 mg/dl. She was back to her normal self in two days. We have never stayed overnight in a hospital since that day almost one year ago. I tried to write about our experiences quite a few times, but my story could never match the ones that I read. Anna Marie finally said, "You need to write about your experience, whether Sydney was sick or not. All the children are different. People will want to read about how well she has been. New MSUD families will like to hear the positive information."

Since I have to work, my mom takes care of Sydney during the day. My mom is wonderful with her, and I couldn't ask for anything more. She loves Sydney more than I could imagine, and Sydney loves her too! You can just tell. They play little games with each other. I call my mom every day to see how much she ate, if she napped, or if her diaper smells like syrup. Sydney has a very large family. She has 19 cousins, 10 aunts and 8 uncles, and they all adore her. Sydney is the 17th grandchild on Ed's side, and his 6 sisters still fight over her.

The cousins always want to hold her. At first, I wouldn't let them hold Sydney because I was overly cautious. When Sydney was a few months old, my niece Shelby asked if she could hold her. Shelby smiled and said, "I'll wash my hands." I let the kids hold her now, and I just keep her away when they are sick. It's hard, because our family is very close - when one person is sick, it goes on down the line.

Sydney is a very bright little lady, and she has to have her hands in everything. She likes to swim, and she loves her dog, Bailey. Sydney takes her little pink baby doll, that her Aunt Kimberley bought for her, everywhere. We now have four of these little dolls. Sydney sucks the ribbon around the baby doll's neck to go to sleep, so the dolls are constantly getting dirty and need washing. One day without the doll equals a very crabby Sydney.

Our experience with the disease has been fairly easy. I always inquire about the other children. Zack Pinsky and Anna Rueter are always in our thoughts. We finally met the Kiels and the Page family at the ANMD picnic. We went to the Pinksy's and met the Bulcher family. Tyler, Zack and Sydney, all in one house at the same time. We held our own Symposium!

Sydney, Ed and I would like to thank everyone for all their support, pictures, letters and calls. It has really helped our family and gave us the knowledge and understanding that we needed. I look forward to the newsletters, recipes, as well as how other families experience MSUD.