Diagnostics and Treatment of MSUD in Germany

Prof. Dr. Udo Wendel
University Children’s Hospital
Düsseldorf, Germany

In 2004, fifty years after the first description of MSUD by Menkes, there exist these optimum conditions for diagnosis and treatment of MSUD in Germany:

- due to newborn screening by tandem-MS (since 2002), very early diagnosis and pre-symptomatic start of treatment in classic and variant forms of MSUD are possible;
- everything about diet is well known;
- thorough biochemical monitoring is possible, since, in contrast to other organic acidemias such as propionic acidemia and methylmalonic academia, the toxic metabolites can be readily measured in blood; and,
- there is full knowledge about early intervention during catabolic stress (febrile illnesses, etc.).

As a result:
- normal neurological and intellectual outcome is possible; and,
- independent living, post-secondary education, adult vocation and development of adult relationships, as well as uneventful pregnancies, are achievable.

Demographic data of MSUD patients living in Germany
I know of seventy-eight MSUD patients living in Germany. Thirty-three (42%; 20 classic, 13 variants) are of German origin, forty (51%; 33 classic, 7 variants) are of Turkish origin, and five (6%; all classic) are of Italian/ Spanish origin. At present, around 2.5 million persons of Turkish origin, or 3% of the population, live in Germany. The number of persons of Turkish descent is exceptionally high in North-Rhine Westphalia, where Düsseldorf is located. This is because in the 1960s a great number of guest workers came into this densely industrialized area. Turkey has a high rate of consanguineous marriages, reaching 40% in some rural areas in the eastern parts of the country where the majority of the Turks living in Germany come from. The rate is believed to be equally high in people of Turkish origin living abroad, such as in Germany. In Turkish MSUD patients living in Germany, parental consanguinity is 100%. This total is even higher than the 84% presumed for MSUD patients in Turkey. The high rate of consanguinity is reflected by the exclusively homozygous mutations we found in the three MSUD genes (for the E1a, E1b, and E2 subunits of the branched-chain 2-keto acid dehydrogenase enzyme complex) in our Turkish patient group.

(MSUD in Germany cont. on page 4)

Inside This Issue:

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Photos taken at the MSUD Symposium, July 22 - 24, in Decatur, Georgia. A great time was shared by all!

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MSUD SYMPOSIUM 2006!  Start planning NOW!

SYMPOSIUM 2006 will be held at the Dublin Embassy Suites in Dublin, Ohio (suburb of Columbus) on June 15-17, 2006. The hotel is an all-suite hotel. Each suite includes a private bedroom, separate living area with sofa bed, and a refrigerator. YEAH! Nearby attractions include the Columbus Zoo, Wyandot Lake Water Park, and Olentangy Indian Caverns.

Hope to see everyone in Columbus, Ohio in June 2006!

SYMPOSIUM 2004 REVIEW

SYMPOSIUM 2004 was held in Decatur, GA at the Holiday Inn Select on July 22-24. Approximately 375 people attended the three-day event, which was hosted by Wendy Harsch, Sandy Bulcher, and the Emory Metabolic Team.

MSUD families from twenty-six of the fifty United States were present. Also in attendance were families from Canada, Israel, Brazil, Argentina, South Africa, Australia, and India. Ninety-six individuals with MSUD attended, ranging in age from infant to thirty-six years. For more than twenty families, this was their first symposium!

Registration was Thursday evening, July 22. During this time, the children (and some adults!) enjoyed a variety of carnival activities including a clown, juggler, magician, and various climbing toys. Face-painting and cotton candy completed the carnival experience. As the children entertained themselves, parents enjoyed meeting new MSUD families and renewing old friendships.

During the time the MSUD families participated in the activities at the hotel, the Emory Metabolic Team hosted a reception for professionals at the Emory Conference Center. The primary focus was on research for MSUD. Heartfelt thanks to the Emory staff for their support!

Speakers, topics and activities on Friday, July 23 included:
• Comprehensive Management of MSUD - Emory Metabolic Team
• German MSUD Experience - Udo Wendel MD (see article, cover)
• Understanding What Can Go Wrong-Can We Make It Right - Dean Danner PhD (see article, page 8)
• MSUD Mouse Model - Harbhajan S. Paul PhD
• Parent Breakout
• MSUD-Young Adult Panel
• MSUD group photo

Speakers and topics on Saturday, July 24 included:
• Psychosocial and Behavioral Issues in Families Affected by MSUD - Wendy Packman PhD (see article, page 12)
• MSUD and Liver Transplantation - Robert Squires MD (article in next issue)
• Daily Management and Sick Day Care for MSUD - Rani Singh PhD
• MSUD and Newborn Screening - Paul Fernhoff MD
• Parent Perspective on MSUD - Wendy Harsch
• Cooking with Cambrooke - David Paollela

Special Thanks to-
-United Services Foundation for their generous donation, which allowed many MSUD families to attend the symposium.
-the AJS Foundation for MSD (Richard and Melissa Stamps) for their generous donation which covered the cost of one hotel night for many MSUD families.
-Trish Mullaley (PKU parent from MA) for the great low protein food that she prepared for the MSUD children and adults.

Quotes, taken from the Symposium 2004 surveys, will appear throughout this newsletter in shaded boxes.

"The symposium has helped me have a better appreciation for MSUD, and the information will help me provide better care for my MSUD patients."  Dietician

"This symposium- my first- has been a wealth of information"  Tibby Turner, Maryland
FOCUS ON: Accomplished Adult With MSUD

Nikolai Rudd is a 30-year-old from Massachusetts with classic MSUD. In the spring of 2003 he worked full time as a teaching aide for children in special education while attending a local college as a full time student. He made the Dean's List for academic excellence. On March 1, 2004 he finished his student teaching and is now certified as a teacher in secondary English. Nikolai passed the test and should be certified to teach Theater as well as English for grades 5-12, recently passed the exam to teach the Visual Arts, and plans to apply for that certification shortly.

This year Nikolai took an Essentials of Film class and Latin American Cinema course with Professor Gibens, at MCLA. This Spring he's hoping to take "Global Issues in Communications" which would have a travel component to Venezuela for 10 days—where he would be shooting a documentary with Professor Gibens. Also, Nikolai received the Editor's Choice award for poetry from Poetry.com and has been included in "The Best Poems of 2004". He is still on the finishing touches of his poetry book called "Exposed".

Nikolai recently met with the entire team of doctors in Pittsburgh as part of an evaluation for a liver transplant. "I have a lot of information to sort out before I make a decision. It's a big decision and I have to weigh all the information. I am leaning towards having it done, since it would seem to benefit my lifestyle." says Nikolai.

Congratulations and best of luck to you, Nikolai!

(MSUD in Germany cont. from page 1)

In Germany, until 2002, diagnosis of classic MSUD was usually made between 10 and 25 days of life when the patient was already in deep coma for a couple of days and showed peak plasma leucine concentrations ranging from 2.1 to 4.2 mmol/l. All the patients were in need of extra-corporal toxin removal including blood exchange transfusion, hemodialysis, or hemofiltration. On the whole, the plasma leucine concentration remained in the "neurotoxic" range above 1mmol/l for 12 to 25 days, and in the oldest patients, now around 30 years of age, due to improper treatment up to 35 and 40 days of life. This resulted in permanent brain damage with neurological sequelae, particularly spasticity, and loss of intelligence. Variant (intermittent and intermediate) forms of MSUD usually were diagnosed in infancy during the work-up of developmental retardation in infancy or during a ketoacidotic derangement triggered by inter-current illnesses in childhood.

Newborn screening by tandem MS

Remarkable progress with respect to diagnosis of MSUD among many other inborn errors of metabolism came with the introduction of the tandem mass spectrometry-based newborn screening in Germany in 2002. If the screening procedure is properly applied (blood prick at 36 hrs of life, sending the filter paper blood to a newborn screening laboratory by overnight mail without delay, biochemical testing on the same day), the tentative diagnosis of MSUD should be possible by day 5 to 6. This is sufficiently early for an adequate intervention in a still pre-symptomatic newborn. In patients identified in tandem MS-newborn screening, the increased leucine blood levels could be lowered to a non-toxic range within 24 to 48 hrs without extra-corporal detoxification and intensive care measures. This strongly decreases the risk of brain damage by the branched-chain compounds during the particular vulnerable neonatal period.

Emergency regimen

In the treatment of acute crises during catabolism (destructive phase of metabolism), we were always successful with i.v. glucose / insulin and enteral (by way of the intestine) branched-chain amino acid-free amino acid powder. With that regimen, we could also master dangerous metabolic decompensations following major surgery (6-hours lasting spinal column operation) with extensive tissue destruction and blood effusion.

In MSUD uneventful pregnancy is achievable

One of our Turkish women with MSUD presented at the age of 22 years already pregnant in the 6th gestational week. She had moderately elevated branched-chain amino acid levels (plasma leucine 450 μmol/l) and was feeling well. In order to decrease the blood leucine concentration into the near-normal range, the leucine intake was reduced from 750 mg to 350 mg per day. It was later adapted according to plasma leucine levels. Energy, protein, vitamin, and mineral intake were according to nutritional recommendations in maternal PKU. The plasma branched-chain amino acid levels were measured weekly. Leucine ranged between 100-300μmol/l; valine and isoleucine were in the higher normal range. During the second half of pregnancy, leucine intake had to be increased from 350 to 2100 mg/day. Spontaneous labor was at 36 weeks; a healthy girl was born. Immediately after delivery, the mother's leucine intake had to be reduced from 2100 mg/day back to 350 mg/day. Nevertheless, plasma leucine reached a level of 1.1 mmol/l on the ninth postpartum day.

Conclusions: There were no harmful effects to embryo nor fetus. The mother's plasma branched-chain amino acid levels must be carefully monitored in the critical postpartum period in order to minimize the risk of metabolic decompensation due to tissue catabolism (involution of the uterus, etc.).

(MSUD in Germany cont. on page 5)
Neurological and intellectual outcome

1. Intellectual outcome in MSUD as compared to PKU and normal subjects
The intellectual performance of 22 children aged 3-16 years with MSUD was assessed and compared to a group of early treated phenylketonuria (PKU) children and normal subjects matched by age, sex, nationality, and socio-economic status. All subjects were tested by one examiner using the age-related version of the non-verbal Snijders–Oomen intelligence test. The respective IQ scores are shown in Table 1.

<table>
<thead>
<tr>
<th>Table 1: Intellectual outcome in MSUD and PKU patients and normal subjects</th>
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</thead>
<tbody>
<tr>
<td>IQ-scores (mean ± standard deviation)</td>
</tr>
<tr>
<td>---------------------------------------</td>
</tr>
<tr>
<td>IQ range</td>
</tr>
<tr>
<td>(mildly mentally retarded to average intelligence)</td>
</tr>
<tr>
<td>(average to high average intelligence)</td>
</tr>
</tbody>
</table>

The IQ scores in MSUD patients ranged from a mildly mentally retarded condition to average intelligence and were clearly below those in both early treated PKU patients and the normal population.

2. Intellectual outcome in MSUD as a result of the longitudinal metabolic control
In another investigation, we tried to determine whether there is a relationship between the long-term plasma leucine concentrations and the intellectual outcome as indicated by the IQ scores. Therefore, we evaluated 24 patients with classic MSUD ages seven to twenty-four years. For each patient, the median values of all available plasma leucine concentrations taken from the laboratory reports were calculated over twelve month periods; the courses of the first six yearly medians were grouped by cluster analysis. The profiles in the first years formed three homogenous clusters labelled as low, intermediate, and high plasma concentration (Figure 1).

Figure 1: Profiles of the first six yearly medians for three clusters of low (cluster 1), intermediate (cluster 2), and high (cluster 3) plasma leucine levels

In the cluster “low” (8 patients) the average plasma leucine level was constantly around 180 µmol/L (1.5-fold of normal). The cluster “intermediate” includes 13 patients with an average plasma leucine level of around 400 µmol/L (3-fold normal), and the cluster “high” includes 3 patients with an average plasma leucine level of 650 µmol/L (4.5-fold normal). Our data suggest that for the mode of quality of metabolic control in the individual patient, the first three years of life are decisive since the clusters diverge from the second/third year of age. Furthermore, our data suggest that the mode of quality of control persists into adolescence and becomes even worse. For example, a 20-year-old patient of the cluster “high” showed average plasma leucine levels of 1.5 mmol/L during the last 3 years. Interestingly, the daily life including social behavior and driving a car seemed not to be affected.

In the next step, the IQ scores of 16 patients were correlated with their average plasma leucine levels of the first six years of life. By doing so, it turned out that the quality of long-term metabolic control showed an inverse relationship to the average plasma leucine level and thus to the quality of dietary control. As shown in Table 2, the IQ scores in patients of cluster “low” (5 patients) ranged from 86 to 108 which is normal. The IQ scores in patients of cluster “intermediate” (8 patients) ranged from 57 to 99 and those in patients of cluster “high” (3 patients) ranged from 50-64 indicating mild mental retardation.

<table>
<thead>
<tr>
<th>Table 2: Relationship between the average blood leucine levels during the first 6 years and the IQ-scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster/Group</td>
</tr>
<tr>
<td>No. of patients</td>
</tr>
<tr>
<td>Mean plasma leucine</td>
</tr>
<tr>
<td>-times normal</td>
</tr>
<tr>
<td>IQ scores</td>
</tr>
</tbody>
</table>

(MSUD in Germany cont. on page 6)
(MSUD in Germany Cont. from Page 5)

In this study we could show that, irrespective of neonatal coma, up to fifteen days normal development and intellectual outcome is achievable if average long-term plasma leucine levels are close to normal. This is also illustrated by the data of two siblings with classic MSUD. The first sibling had suffered from a 10 day lasting neonatal coma (peak leucine level of 4.5 mmol/l) and showed during his first 18 years of life average annual plasma leucine levels of 140 μmol/l. His younger sister, now 14 years old, and without neonatal coma, had the same excellent dietetic-metabolic control. Both siblings have IQ scores of 120 and 125, respectively. Monitoring of plasma branched-chain amino acids and diet adjustment in these patients took and still takes place every week.

In Table 3 the outcome in 14 adults with classic MSUD is shown.

**Table 3: Outcome in 14 adult patients with classic MSUD**

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Schooling and professional education</th>
<th>Present circumstances of life</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>University-entrance diploma</td>
<td>Assistant medical technician, nurse</td>
</tr>
<tr>
<td>4</td>
<td>Graduation from secondary school &amp; vocational training</td>
<td>Training as communication technician, Student of Islamic theology</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 office clerks, unemployed, live with parents</td>
</tr>
<tr>
<td>1</td>
<td>Finished school for physically handicapped &amp; vocational training</td>
<td>Woodworker, lives with parents</td>
</tr>
<tr>
<td>4</td>
<td>Finished school for mentally handicapped, no vocational training</td>
<td>Housewife, lives with husband &amp; daughter, Helpers in a bakery &amp;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>shop, kitchen worker; Can or cannot live on their own</td>
</tr>
<tr>
<td>3</td>
<td>Finished school for mentally handicapped; working in a sheltered workshop</td>
<td>Spasticity; Cannot live independently</td>
</tr>
</tbody>
</table>

**MRI changes in the brain**

In another study, we investigated 14 juvenile and adult patients with classic MSUD by means of cerebral magnetic resonance imaging (MRI) and correlated the MRI changes to metabolic -biochemical control measured as median plasma branched-chain amino acid concentrations over 6 to 36 months prior to investigation. Abnormalities consisted of increased signals in the white matter images, which is compatible with a disturbed water content of the white brain matter and “dysmyelination”. The extent of changes correlated with the height of plasma branched-chain amino acid levels during the last 6, 12, 24 and 36 months. In addition, our data indicated that the white brain matter changes are not associated with acute neurological and encephalopathic symptoms, a similar result already known for adult patients with the amino acid disorder phenylketonuria (PKU). We don’t currently know the relevance of the MRI changes which originate during prolonged periods with high branched-chain amino acid concentrations and are reversible with decreasing concentrations for a prolonged period of time.

**Clinical outcome in non-classic MSUD variants**

In another study, we investigated the clinical outcome of non-classic MSUD variants. The data are shown in Table 4.

**Table 4: Analysis of 21 patients with variant MSUD in Germany**

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Clinical presentation</th>
<th>Leucine conc. at presentation</th>
<th>Therapy</th>
<th>Schooling / Education Work</th>
<th>Present age</th>
<th>Type of variant</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Newborn screening</td>
<td>300 – 550 μmol/l</td>
<td>No - alertness with some protein restriction</td>
<td>Normal</td>
<td>1-26 yrs</td>
<td>Mild</td>
</tr>
<tr>
<td></td>
<td>No symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Acute episode at 0.5 - 7 years</td>
<td>1200 - 2000 μmol/l</td>
<td>Protein restriction</td>
<td>Normal</td>
<td>11-22 yrs</td>
<td>Mild</td>
</tr>
<tr>
<td></td>
<td>Delayed symptoms</td>
<td>1200-1800 μmol/l</td>
<td>Strict MSUD-diet</td>
<td>Normal to low IQ depending on treatment</td>
<td>6-30 yrs</td>
<td>Severe</td>
</tr>
<tr>
<td></td>
<td>No acute episodes</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

(IIUD in Germany Cont. on Page 7)
The following are comments about new information that was learned at the symposium:

"The use of IV treatment utilizing insulin along with glucose helps to lower leucine levels." Hank Livingston, AL

"It was great to know that we can get blood results just by sending the filter paper through the mail." Suvasia Family, NY

"I have learned more about where we are with gene therapies and the risks involved with a liver transplant." Daniela Jones, TN

"I learned about liver transplantation as a cure for MSUD."

"I learned that MSUD children can tolerate higher leucine levels as they age, without demonstrating obvious outward effects." Tracy Brassard, FL

"I learned that children with MSUD can develop normally with dietary restrictions. This differs from what I was told in my country." Eduardo Gatica, Argentina

"We have learned to be very thankful for the great care that we have from our doctors."

"I learned a lot about how to help my kids get through each day." Maria and Guillermo Funes, MA

(MSUD in Germany Cont. from Page 6)

From the analysis of the 21 non-classical MSUD variant patients, we can conclude that:

- 20% of all cases of MSUD are non-classic variants with a continuum of BCKD residual enzyme activity from 2 to 40%;

- variant forms of MSUD can be identified by Tandem-MS newborn screening;

- some mild variants never become symptomatic (even without a diet) and develop to normal adults;

- some mild variants have episodes during catabolic stress (febrile infections) in childhood. After making the diagnosis of variant MSUD, the further development seems to be normal; and,

- severe variants (clinical presentation at the end of the first month of age) must be treated like classic MSUD. Their outcome depends on quality of therapy and metabolic control.

We never found a thiamine responsive variant or classic MSUD patient.

References
Understanding What Can Go Wrong and If There are Ways to Correct the Error

Dean J. Danner, Ph.D.
Professor & Vice Chair, Department of Human Genetics, Emory University School of Medicine, Atlanta, GA 30322

Fifty years after the first report of a family whose children died in infancy, all with a distinctive sweet odor to their diapers, we have developed an understanding for some parts of the complex condition that has come to be known as Maple Syrup Urine Disease [MSUD]. The basic problem in MSUD is that branched chain amino acids (leucine, isoleucine, and valine) cannot be broken down and therefore accumulate in blood and tissues to a level that is toxic and thus can kill the cells. Brain cells seem most sensitive to this condition. The inhibited function resides in the second step in the pathway for branched chain amino acid breakdown, with the enzyme called branched chain a-ketoacid dehydrogenase (BCKD). Mom and Dad each have one copy of the affected gene that works; they do not show any sensitivity to protein. Individuals with MSUD have two copies of the defective gene, so BCKD does not work as it was designed. Presently over 120 different mutant alleles have been identified with a near equal distribution between the three genes that can hold mutations to specifically cause MSUD. Except for the sex determining genes, we inherit two copies of a gene, one from Mom and the other from Dad; “allele” refers to one copy of that gene. In families outside of the Mennonite community, most affected individuals have two different mutant alleles for the same gene. Newborn screening programs around the world have been used for detection of individuals at risk for MSUD. This enables early dietary intervention with protein-modified diets to allow growth and development of these infants. Confirmation of MSUD should be done with enzyme assays and gene analysis, usually on blood cells from the patient.

Although some genetic mutations that cause MSUD were identified before the sequence of the entire human genome was completed, new methodology and the reference information for the full human genome sequence has allowed rapid detection of mutations in all regions of the genes encoding BCKD. Once the mutations are known for a family, the specific mutant allele contributed by each parent can be determined by analysis of parental blood cells. With this information, the distribution of the mutant allele within other family members can be easily determined and the information made available to all those who want to know if they carry the abnormal allele. Some individuals find this helpful in family planning. In addition, the genetic information allows monitoring of future pregnancies of parents with an affected child. Using genetic analyses, the testing can be done at an earlier time in pregnancy, by less complicated methods, and with a shortened time for analysis. Our laboratory has done investigations of both types when requested by a family.

One of the questions we address through research in my laboratory concerns brain cell function when branched chain amino acids cannot be metabolized. We are determining what happens to these cells when they are insulted with a high level of leucine, isoleucine, or valine individually and asking if the response is different than when all three amino acids are present in high concentration. We have prepared rat brain cells whose BCKD function can be lowered to levels similar to that found in persons with MSUD. Under these conditions the cells are most sensitive to leucine alone, with abnormalities occurring within 48 hours. Neither isoleucine nor valine was able to cause a similar response under these conditions. We are continuing these studies with new methods that allow us to individually block expression of each of the three genes that can be defective in causing MSUD. These studies will allow us to relate specific responses to each mutant gene and eventually the specific type of mutation within that gene.

Applying this question (whether defects in one gene produces effects different from those resulting from mutations in one of the other genes) to the child with MSUD is difficult to address. This difficulty is due in part to the need for individual tailoring of diet management, as well as the treatment used when a patient presents with a metabolic crisis. General procedures exist, but specificity resides with the care-giving physicians and dietitians. We investigated the results of clinical outcomes in ten families managed by the staff at a single tertiary care facility at a large medical school. The data found little variation in the need for hospitalization in a crisis situation regardless of the affected gene. A slightly better IQ score was found with individuals having mutations in the gene for the DBT component, especially compared with those with a mutation in the alpha

(Understanding cont. on page 9)
subunit. However, IQ cannot be attributed to a single gene and is a component of many genetic factors as well as the environment, so this data is not predictive. In essence, at this point it can be said that early intervention and compliance with a protein-modified diet is a strong determining factor in clinical outcome. Also the family and physician need to be aggressive in managing any condition that can or does result in a metabolic crisis.

Many questions remain to be answered through investigations in the basic research laboratory, with aims for better treatment for the person with MSUD. For example, the individuals with “intermittent” MSUD have not been explained at a genetic level. Recent reports have suggested small molecules are present within cells that can affect the amount of BCKD that is present in a cell. An excess of these small molecules at different times in a person’s life could result in periodic loss of BCKD activity within certain tissues and thus result in elevations in branched chain amino acids. We are devoting significant time to studies in this area. Another area of intense study is aimed at correcting the genetic defects that incorrectly assemble the directions for making one of the proteins in BCKD. We are seeking drugs or dietary supplements that would correct the misdirection to create a functional protein that would then result in a working BCKD enzyme.

Another area that needs investigation addresses whether individuals with MSUD will need additional special care as they age, since an increasing number of individuals with MSUD are now adults. We do not know if these individuals, who have lived on a low protein diet all of their lives, will age in the same way the general population does. We may discover they are actually better prepared for aging; information of this type may have implications for aging in the unaffected population, as well. Gene therapy for MSUD, or any single gene disorder, is not yet ready for general use. How soon it will be possible and effective is not known. Liver transplants have been tried with some success in a limited number of persons with MSUD. Still, one must remember this is a trade off of one form of life-long treatment (protein modified diet) for another after transplant (immunosuppressant drugs). Transplant surgery is extremely serious and must be considered with great care and concern. Therefore we continue to do laboratory research in cells and animals to help us understand more fully the changes that occur and seek ways to alter the observed changes.

MSUD BOARD Update

Current board members include:
Wayne Brubacher..................President
Ivan Martin..........................Vice President
Dave Bulcher........................Treasurer
Tish Fuller.........................Secretary
Anne Fredericks...................Board Member
Denise Pinskey......................Board Member
Tony Kohl............................Board Member

During the symposium, Joyce Brubacher was recognized for her many years of dedication to the MSUD Family Support Group.

Thank you, Joyce, for all you have done to further our cause!

To help fill the void left by Joyce, the following individuals volunteered to take a more active role in the support group:

Karen Dolins, Newsletter Editor (beginning 2005)
Adrienne Geffen, Newsletter Layout
Sandy Bulcher, Symposium Coordinator
Denise Pinskey, Symposium Assistant
Cathy Codner, Symposium Assistant
Matt Koons, Symposium Assistant, Young Adult Activities
Tibbie Turner, NIH Laison
Wendy Harsch, NIH Laison and Research Contact
Cathy Codner, NIH Laison
Tina Sprock, Research Contact
Kay Larson, General Information Contact
Marcia Hubbard, Legislative and Educational Issues Contact
Monica/Navid Falconer, Website Maintenance
Emily Talley, E-group Administrator

"I enjoy the doctors and topics, but the absolute best part is spending time with our extended MSUD family. We forget between symposiums how nice it is to talk to people that share some of the same worries, concerns and triumphs." Tish Fuller, Indiana
**Delectable Desserts!**

### Whoopie Pies

3 cups Dp Baking mix  
1 cup sugar  
3 T. cocoa  
1 tsp. baking soda  
1 1/2 tsp. vanilla  
1 T. vinegar  
6 T. vegetable oil  
1/2 tsp. salt  
1/2 - 3/4 cup water

Combine ingredients and mix until smooth. Adjust the water according to the thickness desired. The larger amount of water will make a flatter cookie. Drop by tsp. onto an ungreased cookie sheet. Bake for 8 - 10 minutes. Cool.

#### Filling:

2 cups powdered sugar  
4 T. Crisco  
1 T. plus 1 tsp. water  
1 tsp. vanilla  
dash salt

Combine ingredients until smooth. Spread filling between 2 cookies to make a sandwich type cookie. Wrap each cookie separately. These freeze very well.

<table>
<thead>
<tr>
<th>Protein</th>
<th>Leucine</th>
<th>Calories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per recipe: 4.4 gm</td>
<td>201 mg</td>
<td>3535</td>
</tr>
<tr>
<td>Divide total protein, leucine and calories by number of cookies.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Orange Sherbet

1 orange Kraft Handi-Snack Gel  
2 T. Rich's Coffee Rich  
2 T. frozen orange juice concentrate  
2 T. sugar  
1/4 cup Cool Whip

Melt contents of gel cup in the microwave or on a low heat in a small sauce pan. Add Coffee Rich, orange juice and sugar. Cool to room temperature. Fold in Cool Whip. Freeze
Recipe by Brenda Wenger

<table>
<thead>
<tr>
<th>Protein</th>
<th>Leucine</th>
<th>Calories</th>
</tr>
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<tbody>
<tr>
<td>Per recipe: 1.2 gm</td>
<td>45 mg</td>
<td>340</td>
</tr>
</tbody>
</table>

### Butterscotch Pudding

1/2 cup Coffee Rich  
1/2 cup water  
2 T. brown sugar  
2 T. butter  
1 tsp. vanilla  
dash of salt  
3 T. cornstarch  
3 T. water

Recipe by Mary Kathryn Martin

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<thead>
<tr>
<th>Protein</th>
<th>Leucine</th>
<th>Calories</th>
</tr>
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<td>Per recipe: .30 gm</td>
<td>48 mg</td>
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<tr>
<td>Per 1/4 cup: .06 gm</td>
<td>10 mg</td>
<td>112</td>
</tr>
</tbody>
</table>

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**Please send recipes to Food News Editor**

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Ephrata, PA 17522  
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HALEY'S STORY

January 21, 2002 was such an exciting day for us as we welcomed a baby girl, Haley Su Kohl, into our family. Since she was our first child, we had no idea exactly what to expect and no idea what the word “normal” meant.

However, we quickly noticed that she was sleeping a great deal and hardly eating. Our initial thought was that we were just not breast-feeding her correctly, as we had been told that it could take babies some time to learn how to receive nourishment in this manner.

Nonetheless, our concern grew quickly and, within the first seven days of her being born, we had made three visits to the doctor’s office. On the seventh day, Haley was admitted back into the hospital. At this point, we felt as if our hearts were being torn from us, as the possibility existed that our baby was not going to survive. We had never before felt pain that was so intense.

Initially, the doctors were at a loss. All they could tell us was that she was extremely dehydrated and apparently was having seizures. Over the next four days she got progressively worse, as test after test came back negative. By now, Haley was in a comatose state and on a respirator as she was unable to breathe on her own.

It wasn’t until day 12 that a second newborn screening test confirmed that Haley had a very rare genetic disorder called Maple Syrup Urine Disease. It turned out that the first test that was taken after her birth was done incorrectly and did not show that she had the disease.

Although we had no idea what MSUD was, our first reaction was one of relief; now that a diagnosis had been made, her treatment could begin. That relief turned out to be very short-lived.

The geneticist who came to see us in the hospital informed us that we would have to fly our baby to the Children’s Hospital in San Diego. It wasn’t that the doctors in Arizona were not qualified to begin treatment, but rather that Arizona’s hospitals lacked the equipment needed to help her.

With Haley Su in critical condition, we flew her to California. For the next three weeks, we watched our daughter fight for her life. If ever there was a time we needed the support of family and friends, this was it – but those friends and family lived elsewhere. Loving our daughter so much and seeing her pain, our family got together and decided to try to make her life better.

We started with the idea of obtaining an Amino Acid Analyzer for the State of Arizona. It was taking up to seven days to get results from her blood test, and this long for a sick child could literally be a lifetime. After finding a local hospital willing to house the machine, run it, and read it, which in itself was no easy task, we went to work to raise $85,000 to buy the Amino Acid Analyzer.

We did fundraisers and garage sales, sold brownies, put on special dinners with restaurants, had a golf tournament, and many more things. This was our first goal, and we did it in seven months! The generosity of our friends and family, not only with their financial support, but also with their time and prayers, has been just breathtaking.

You all know and probably have lived the rest of our story. Haley has been in and out of the hospital several times, with each episode keeping us on pins and needles. Some days she’s great and looks as healthy as any normal child, and other days it’s all a challenge and you’re pulling your hair out by the end of the day.

(Haley’s Story cont. on page 15)
Summary of Symposium 2004 Presentation, Psychosocial and Behavioral Issues in Families Affected by MSUD

Wendy Packman, J.D., Ph.D.
Written by Shelly L. Henderson, M.A. and Wendy Packman, JD, PhD
Dr. Packman is Assistant Professor of Psychology at the Pacific Graduate School of Psychology and Assistant Clinical Professor of Pediatrics at the University of California, San Francisco. Shelly Henderson, M.A. is a graduate student and research assistant in pediatric psychology at Pacific Graduate School of Psychology.

Introduction
Parents and caregivers of children with MSUD have expressed concerns about psychosocial and behavioral issues that affect their chronically ill child. Chronically ill children experience behavioral, emotional, and medical problems that can interfere with daily activities and functioning. Another challenge of childhood chronic illness is the impact of the illness on the family. The purpose of this study was to describe and assess the behavioral, emotional, and psychosocial issues faced by families affected by MSUD. Previous studies have examined cognitive and behavioral issues in children with MSUD. These studies have contributed to our knowledge of the factors that influence developing cognitive capabilities in children with MSUD. For example, researchers have described the importance of early detection and the need to prevent complications during the newborn period (Kaplan et al., 1991; Nord, et al., 1991). Other studies have found that the quality of long-term metabolic control influences IQ and that metabolic stabilization improves problem solving, attention, and concentration (Hilliges et al. 1993; Emory et al. 1992).

In an effort to address the lack of research on psychosocial issues, researchers at Emory University, the University of California, San Francisco, and the Pacific Graduate School of Psychology embarked on a collaborative study. The authors undertook this descriptive study to gain insight into the common issues faced by families of children with MSUD.

Participants
Participants were recruited from the MSUD Support Group and included 55 families with children ranging in age from 5 to 18 years old. Questionnaires used to assess psychosocial and behavioral issues were mailed to participants’ homes. These included a Family Survey, the Behavior Assessment System for Children (BASC) Parent and Teacher Rating Scales (Reynolds & Kamphaus, 1992), and the Pediatric Quality of Life Inventory (PedsQL) (Varni, Seid, & Kurtin, 1999). Demographic data were obtained from the Family Survey. The sample of participants was mostly Caucasian (70.8%), married (84%), residing in the East (39%) or Midwest (33%) of the United States, and had a bimodal socioeconomic status in the low and middle ranges.

Findings
The Family Survey consists of a series of closed and open-ended questions that capture child and family medical and psychosocial information (e.g., “What was your initial reaction to hearing your child’s diagnosis?”). Findings from the Family Survey indicated that families often experience fear and concern upon initial diagnosis. They also reported emotional and financial stressors as a result of having a child with MSUD. In addition, many parents felt that they had less time for other children and themselves, and spent much more time on dietary concerns. Parents reported worrying about the impact of having a child with MSUD on relationships and marriage; however, most couples stated that the experience brought them closer together.
The main themes that emerged from parents’ responses on the Family Survey were: 1) Finances and insurance; 2) Coping with medical staff; 3) What it means to have a child with MSUD; and 4) The child’s experiences in school. These areas of concern identified by parents are described below.

Financial Concerns and Health Care Coverage
Families stated that it was a considerable financial burden to care for a child with MSUD because of inadequate or no health insurance. The vast majority of families had no insurance coverage. Items not covered by insurance include specialty foods and therapies and services outside of school, such as speech, mental health, and child-care.

Coping with Medical Staff
Parents reported both positive and negative experiences with medical personnel. Many parents reported that coping with medical staff was a stressful experience. One participant stated, “My only experience is the fact that I may know more than the doctor does and find myself telling the doctor what to do.” For this participant, finding herself more knowledgeable than the doctor was disconcerting and stressful. Many parents noted feeling stressed for the following reasons: 1) Disrespected by staff; 2) Lack of staff competence or inexperience; and 3) Uncooperative staff.

(Behavior Cont. on Page 13)
A few parents did not experience stress in regards to medical staff and some reported positive experiences such as the following: "Most medical staff... if they don't know about MSUD are eager to learn." Taken together, the participants’ experiences speak to the fact that knowledge is power. Confidence in medical staffs’ expertise and the care they provide is clearly an important issue to families of children with MSUD and can make for a stressful or satisfactory and comforting experience.

Meaning to Parents’ Lives

Parents were asked what having a child with MSUD has meant to their lives. Many parents described finding hidden personal strengths. Common themes that emerged from parent remarks included both negative and positive feelings. These included struggle and stress, becoming grateful, compassionate, more caring and patient, having a shift in perspective and priorities, and a renewed faith in God. For example, one participant commented that the presence of MSUD accompanied any thoughts about the future and the desire for more children. Other participants described what they had learned from their child with MSUD: "Having this child has made me aware of each day as a gift. She thoroughly enjoys life and spreads happiness from rising to bedtime.... Knowing at anytime she could get sick and be gone has made me appreciate even the challenging times." Another participant stated, "It has taught me patience. He has enriched our lives with love and challenge and is extremely rewarding." Others recounted life-transforming experiences stating, "It has changed my life and my outlook on life drastically," and "I have become a more spiritual person as a result of having a child with MSUD." Parents described both positive and negative meanings to their lives as a result of having a child with MSUD, ranging from finding personal strength, to struggling with stressors, to becoming more spiritual. This range of meaning, often present in one individual, mirrors the complexity and challenges of coping with MSUD.

This complexity is also present in the multiple environments in which a child with MSUD must function and parents must navigate. Parents were asked about their child’s experiences in school. Again, parent responses were quite varied and included positive, negative, and mixed experiences. For example, one participant commented, "My son is not treated any different than any other kid at school. The lunch staff is very accommodating," while another parent reported, "the school is mostly uncooperative." Other parents reported a mixture of these experiences.

These varied school experiences are possibly related to the severity of the MSUD, which impacts cognitive functioning and, in turn, may influence school placement (e.g., special education, private school). Several parents commented on experiencing fewer problems in private schools than in public schools. In addition, the age of the child may influence the school experience. Overall, more positive experiences were reported for the 5-7 year olds, whereas experiences became somewhat more negative for older children and teens.

To end the Family Survey, we asked, "How do you maintain your psychological health and social interactions?" The following themes emerged: Family Support, Keeping faith/religion, Friends, Exercise, Think positive, Professional counseling, and MSUD Support Group.

Following the Family Survey, we administered the Pediatric Quality of Life Inventory (PedsQL) (Varni, Seid & Kurtin, 1999). The PedsQL, for children ages 2 through 18, looks at functioning in 5 domains: Physical, emotional, social, psychosocial, and school. We provided participants with a child form and parent proxy. Statistically significant differences between parent and child report were found in all domains except school functioning. In all instances, children reported higher quality of life than parents. When compared to both healthy and oncology sample means (Varni et al., 2002), the mean total and domain PedsQL scores of MSUD children and parents were closer to the oncology sample than the healthy sample.

Finally, the Behavior Assessment System for Children (BASC) (Reynolds & Kamphaus, 1992) was administered to parents and teachers. The BASC- Parent Rating Scale assesses 9 clinical areas including hyperactivity, aggression, conduct problems, anxiety, depression, somatization, atypicality, withdrawal, and attention. Sixteen out of 55 children were found to be in the "at risk" range in the area of attention and 10 children were in the "at risk" range for hyperactivity. Children within the "clinically significant" range require intervention. In this sample, ten out of 55 children fell within the "clinically significant" range for attention and 7 children fell within this range for hyperactivity.

The BASC- Teacher Rating Scale assesses the same 9 clinical areas as the parent scale and also includes learning problems. Sixteen out of 37 children were found to be in the "at risk" range in the in the area of attention, 8 children were in the "at risk" range for learning problems, and 8 children were in the "at risk" range in the areas of anxiety and somatization. Children within the "clinically significant" range require intervention. In this sample, 5 out of 37 children fell within the "clinically significant" range for learning problems.
Behavioral Continued from Page 9
require intervention. In this sample, 5 out of 37 children fell within the “clinically significant” range for learning problems.

Conclusions
Parents reported via the Family Survey that having a child with MSUD is a source of emotional and financial stress. These parents experienced difficulties with medical staff and schools. However, parents also reported that MSUD has had a positive influence on their lives, leading to a shift in priorities and a world-view that is more caring and compassionate.

Confluent with other studies that utilize the PedsQL, there was a discrepancy between child and parent reports of health related quality of life. (Packman et al., 2004; Varni et al., 2002). In the current study, children reported a higher quality of life than parents in most domains. These results on the PedsQL are similar to the findings from a recent study of siblings of cancer patients (Packman et al., 2004).

In addition, similar to other studies of children with chronic illnesses, the majority of children fell within the average range on the clinical scales of the BASC-PRS, though there were some elevations in attention, hyperactivity, and aggression. On the BASC-TRS, the majority of children fell within the average range, though there were some elevations in attention, learning problems, anxiety and somatization.

The findings from this study can be used to alert health care professionals, physicians, and teachers to the importance of continued education in the symptoms and treatment of MSUD. Families want to be taken seriously by medical personnel and to feel confident in the care given to their child with MSUD. In addition, given the tremendous stress and worry that families experience, the results of this study can guide mental health professionals to support families where they need it most — financial and health care coverage resources, time management, child care, and dietary planning. Finally, our findings highlight the complexity of the psychosocial consequences of MSUD and reaffirm the various experiences that families face. While MSUD does place a financial and emotional strain on families, having a child with MSUD can also have a positive impact and allow one to be more compassionate, caring, and appreciative of life and family.

References


"The symposium has become a family reunion for us, and we try to never miss it!" Adrienne and Irv Geffen, NJ

"Everything was very good. Talking with others was great. We could listen to the doctors a lot more." Todd and Carlene Olstad, IA

"The best part was meeting and sharing with the families." Gina Pharris, CA

MSUD TEACHERS GUIDE
The Arizona Department of Health Services developed a booklet to help educate teachers about MSUD. They are available for $2.50 each. Make a check payable to the Arizona Department of Health Services. Send the check and note requesting the booklet to:
Arizona Department of Health Services • Nutrition and Chronic Disease Prevention Services
150 North 18th Ave #310 • Phoenix, AZ 85007-3228 • Attn: Lee Renda
Currently there are approximately 90 members from around the world on the MSUD egroup. If you are a member of the MSUD Family Support Group and would also like to join the egroup, simply send an email to Emily Talley at emilytalley@mindspring.com requesting to be added to the egroup. If you are not a member of the support group, first send an email to Sandy Bulcher at dbulcher@aol.com asking to join the support group. Those that are on the egroup have found it very beneficial and informative.

DR. PAUL
In early 2005, watch for a special mailing regarding Dr. Paul’s MSUD Mouse Project. The MSUD Family Support Group would like your support again this year to fund this important project. More details to follow.

From the mother of a child with MSUD:
When I am absolutely beside myself with my 6 year old’s behavior, first I pray for strength, then I remember a saying I once heard, "When children are acting in an unlovable way, that’s when they need our love the most."

Thank you to Renee Alman, Aunt of Elan Geffen, MSUD, for editing this issue of the Newsletter!

Coming in the Next Newsletter:
Liver Transplantation as a Cure for MSUD
The very significant topic of liver transplantation as a cure for MSUD was presented at the symposium in July. Several MSUD children and one MSUD adult have received liver transplants in the US in the past year. This is a very complex subject, and we hope to devote a large portion of the next newsletter to the pros and cons of this procedure. We plan to include several articles by professionals, as well as by parents whose children have undergone liver transplants. It is our desire to present as much information as possible outlining the benefits and risks of this new option for MSUD patients.

“The MSUD Family Support Group has helped me as much as the speakers. I feel so proud to say that when I go back home, I can tell my family that I belong to two family units on two continents.”
International MSUD parent

“I’ve known that all of these families were out there somewhere, but to actually connect with them has changed my heart, mind, and outlook. I can’t wait for the next symposium.”
Michelle Flanagan GA

DANIELLE FORDE  It is with a deep sense of sadness that we announce the death of Dannielle Forde. Dannielle was the seven year old daughter of Daniel and Anne Forde of Ireland. Dannielle passed away earlier this year. Our thoughts and prayers are with the family during this difficult time.

(Haley's Story cont. from page 11)
Haley- who we call Haze- is for us like any child that is "normal". She is turning 3 in January. She laughs, plays, and watches over her seven-month-old brother like any big sister would. We account for what she eats daily and have been since day one. We are amazed at what she has learned and how she knows what food is hers and what is not.

Everyday we are still learning about her and how she reacts to her MSUD, but we have decided not to take “no” or “that’s how it has always been” for answers. We are going to find an easier and better way for our daughter and help many others while doing so.

We have started our own nonprofit organization called the MSUD Research Foundation and have moved forward to encouraging research in our disease. It is only by taking action that we as a group will be able to beat MSUD. If you are interested in learning more about what we are doing or would like to offer suggestions, we would love to hear from you.
You can visit our website at www.msudresearchfoundation.org. ■

Thank you.
The Kohl Family
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This Newsletter does not attempt to provide medical advice for individuals. Consult your specialist before making any changes in treatment.

The following is the last verse of a poem for caregivers of special children by Maureen K. Higgins sent to our eGroup members by Paula Ruter, Mom of Anna.

But we, sisters, we keep the faith always. We never stop believing.
Our love for our special children and our belief in all that they will achieve in life knows no bounds.
We dream of them scoring touchdowns and extra points and home runs.
We visualize them running sprints and marathons.
We dream of them planting vegetable seeds, riding horses and chopping down trees.
We hear their angelic voices singing Christmas carols.
We see their palettes smeared with watercolors, and their fingers flying over ivory keys in a concert hall.
We are amazed at the grace of their pirouettes.
We never, never stop believing in all they will accomplish as they pass through this world.
But in the meantime, my sisters, the most important thing we do, is hold tight to their little hands, as together,
we special mothers and our special children, reach for the stars.