Approach to Care for Patients with Metabolic Disorders

What is a Medical Home for Child or Adult with a Metabolic Disease?

D. Holmes Morton MD
Pediatrician, Clinic for Special Children
Strasburg, Pennsylvania
In 1986-1988, my fellowship years, the 6 physicians at CHOP who specialized in *Biochemical Genetics* followed 150 patients - total. Richard Kelley provided general pediatric care for 87 of these cases.

The 6 physicians at CHOP cared for 10 Mennonite children with MSUD but no other founder-disorders from the Amish & Mennonite populations of Lancaster County, only 40 miles west of Philadelphia. Victor McKusick started his studies of the Amish in 1963 & published *The Medical Genetic Conditions of the Amish* in 1978.

The first Amish patient I saw as a fellow in Biochemical Genetics was a 4-year-old boy with glutaric aciduria type 1, June 19, 1988.
WERE THESE POPULATIONS “UNDERSERVED?”

Today two pediatricians at the Clinic for Special Children care for over 2000 patients from these populations with 115 different recessive disorders.

Edwin Naylor’s *Expanded Newborn Screening Program* using MS/MS started in 1993-94.

In 2012 we follow more than 400 patients from the Plain Communities that were diagnosed through Newborn Screening including:

- >90 Mennonite patients with classical MSUD
- 57 cases of the Amish variant of glutaric aciduria type 1
- 34 children with propionic acidemia
- 42 cases of MCADD
- 20 cases of a severe, but treatable, form of MTHFR deficiency
NEWBORN SCREENING CORE PANEL OF 29 DISORDERS
MENNONITE 6 & AMISH 8 ~ # pts

FATTY ACID OXIDATION DEFECTS
MCADD (M+, A-) 42
VLCAD (M-, A+) 2

ORGANIC ACIDEMIAS
GLUTARIC ACIDURIA TYPE 1 ((M-, A+) 93
3-METHYL-CROTONYL COA DEFICIENCY (M+, A+) 30
PROPIONIC ACIDEMIA (M+, A+) 34

AMINO ACID DISORDERS
PHENYLKETONURIA (M+, A+) 6
MAPLE SYRUP DISEASE (M+, A-) 134
HOMOCYSTINURIA (M-, A-) (A+ MTHFR) 22
TYROSINEMIA TYPE 3 (M-, A-) (M+ Tyr 3) 8
CONGENITAL HYPOTHYROIDISM (M+, A+) 22
BIOTINIDASE DEFICIENCY (M+, A+) 6
CONGENITAL ADRENAL HYPERPLASIA
21-hyd def
3-beta OL,
Methyl oxidase-2
CLASSICAL GALACTOSEMIA (M-, A+) 6
HEARING LOSS (M+, A+) Many different forms, common problem

Total 433
Other inherited disorder found within the Plain populations for which treatment outcomes justify diagnosis in the pre-symptomatic infant by family targeted carrier testing & newborn testing.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Patients</th>
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<tbody>
<tr>
<td>Crigler-Najjar disease</td>
<td>24</td>
</tr>
<tr>
<td>RBC Pyruvate Kinase Deficiency</td>
<td>30</td>
</tr>
<tr>
<td>Cystinurases</td>
<td>25</td>
</tr>
<tr>
<td>MTHFR Deficiency</td>
<td>22</td>
</tr>
<tr>
<td>Bile Salt Transport/Synthesis Disorders</td>
<td></td>
</tr>
<tr>
<td>TJP2</td>
<td>30</td>
</tr>
<tr>
<td>BAAT</td>
<td>10</td>
</tr>
<tr>
<td>Byler Disease</td>
<td>6</td>
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<tr>
<td>SCID Syndromes</td>
<td></td>
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<tr>
<td>CHH RPMR with hypo-immune function</td>
<td>33</td>
</tr>
<tr>
<td>IL7 Receptor Defects</td>
<td>10</td>
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<tr>
<td>RAG1 Mutations</td>
<td>10</td>
</tr>
<tr>
<td>Adenosine Deaminase Deficiency</td>
<td>2</td>
</tr>
<tr>
<td>Nephrotic Syndromes</td>
<td></td>
</tr>
<tr>
<td>Pierson Syndrome with retinal detachment</td>
<td>13</td>
</tr>
<tr>
<td>Congenital Nephrotic Syndrome NPHS1 &amp; 2</td>
<td>10</td>
</tr>
<tr>
<td>Dopa-responsive dystonia TH mutation</td>
<td>2</td>
</tr>
<tr>
<td>TOTAL</td>
<td>227</td>
</tr>
</tbody>
</table>
MSUD - Emergency Admissions to Lancaster General Hospital for Acute Metabolic Care. n=267, 1990-2012

Neonatal presentations ~10%
- Down syndrome VSD repair, congenital bowel obstruction (HMC)
- Sepsis SCID (IL7-SCID)
- Sepsis & pneumonia Group B Strep
- +Newborn Screens & Illness (34 of 69)*

Infectious illnesses ~78%
- Gastroenteritis (Rotavirus)
- Pneumonias (RSV)
- Otitis media
- Strep pharyngitis
- Bacterial/fungal sepsis
- Herpes simplex 1 stomatitis

Surgery & Trauma ~12%
- Appendicitis
- Hirschsprung Disease with distal colonic resection (HMC)
- Cholecystitis
- Ovarian torsion & Cyst
- Hysterectomy
- Fracture femur, skull fracture

*NOTE: 35/69 newborns with MSUD were <24 hrs of age & asymptomatic when diagnosed because of carrier testing or family history. These infants were managed out-of-hospital.
## Cost Analysis for RotaTeq & No RotaTeq n=100, at LGH

<table>
<thead>
<tr>
<th></th>
<th>CSC RotaTeq (n=50)</th>
<th>No RotaTeq (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of vaccine</td>
<td>$8,450</td>
<td>$0</td>
</tr>
<tr>
<td>Cost of administration</td>
<td>$4,700</td>
<td>$0</td>
</tr>
<tr>
<td>Work-Lost</td>
<td>$1,275</td>
<td>$0</td>
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<tr>
<td>Travel cost</td>
<td>$2,700</td>
<td>$0</td>
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<tr>
<td>Total cost of RotaTeq</td>
<td>$17,125</td>
<td>$0</td>
</tr>
<tr>
<td># of infants hospitalized for Rotavirus</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td># of days of non-ICU care</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>Costs of non-ICU Care ($3,335/day)</td>
<td>$7,003</td>
<td>$66,700</td>
</tr>
<tr>
<td># of ICU days</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Costs of ICU Care ($3,335×2.5=$8338)</td>
<td>$0</td>
<td>$83,380</td>
</tr>
<tr>
<td>Direct cost of hospitalization</td>
<td>$7,003</td>
<td>$150,080</td>
</tr>
<tr>
<td>Cost of RotaTeq + Hospital</td>
<td>$24,128</td>
<td>$152,833</td>
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</tbody>
</table>

**Hospital cost savings from vaccine**  **$128,705**

(Based upon Yount LE et al. Pediatrics 2004;114;1606-1611)
Patients with many different genetic disorders are at risk for severe illnesses induced by common, seasonal, preventable infections: Rotavirus, Influenza A&B, Hepatitis A&B, Varicella, Hemophilus Influenza, Pneumococcus, Pertussi, and RSV

- Glutaric Aciduria *
- Propionic Acidemia*
- Crigler-Najjar Disease*
- Maple Syrup Urine Disease*
- Medium Chain Acyl Dehydrogenase Deficiency
- Adrenal Insufficiency Syndromes

Ellis van Creveld with pulmonary hypoplasia
Cartilage hair hypoplasia with pulmonary hypoplasia or immune deficiency
Down Syndrome
Prader Willi Syndrome
Immune Deficiencies
Amish Lethal Myoapthy, Troponin 1 Deficiency
Generalized dystonia, spasticity, and other disabilities
Congenital Heart Disease, many variants
Seizure syndromes, many variants
Diagnosis: MCAD Deficiency

MCAD Deficiency
Homozygous A985G

mass / charge
CASE - A 10 day old male infant was referred to me because of a positive neonatal screen for octanoylcarnitine.

Serum and urine analysis GC/MS in my lab showed increase serum octanoate & cis-4-decenoate, urine hexanoyl & suberylglucose and supported the diagnosis of MCADD.

Molecular tests showed that the parents and the three other healthy children carried the common delta 985 mutation.

A sibling of this child died 16 months before. She was found dead in her crib 18 hours after her first DPT/OPV/H Flu immunization. A Reye-like fatty infiltration of the liver was noted at autopsy, regardless, her death was attributed to SIDS.

MS/MS & molecular studies of her newborn filter paper confirmed that this infant in fact had MCADD. She died a metabolic illness provoked by a respiration tract illness & an immunization, not from SIDS.

What is the immediate cause of these deaths?
FATTY ACID OXIDATION DISORDERS DETECTED in 2,300,000 infants tested.

- MCAD Deficiency: 176
- VLCAD Deficiency: 37
- LCHAD Deficiency: 35
- CPT-II Deficiency: 18
- SCAD Deficiency: 10
Figure 27-16
Biochemistry, Sixth Edition
© 2007 W.H. Freeman and Company
## Mennonite MSUD Patients Born 1963-1984: Mortality from Cerebral Edema 11/20 (55%); Cognitive & Physical Disabilities 100%

<table>
<thead>
<tr>
<th>Year of Birth</th>
<th>Patient</th>
<th>Age</th>
<th>Age at Death</th>
<th>Illness Provoking Brain Edema</th>
<th>Cognitive &amp; Functional</th>
<th>Physical Disability</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1984</td>
<td>IA Ho</td>
<td>26</td>
<td></td>
<td></td>
<td>-2</td>
<td>-1</td>
<td>moderate cognitive impairment, Full Scale IQ 55 &amp; mild motor impairment</td>
</tr>
<tr>
<td>1983</td>
<td>MK H</td>
<td>Dead</td>
<td>3 yrs</td>
<td>infection &amp; vomiting</td>
<td>-2</td>
<td>-1</td>
<td>moderate cognitive impairment, Full Scale IQ 57 &amp; severe spasticity</td>
</tr>
<tr>
<td>1982</td>
<td>Da E</td>
<td>Dead</td>
<td>6 yrs</td>
<td>infection &amp; vomiting</td>
<td>-2</td>
<td>-3</td>
<td>profound MR, moderate spasticity</td>
</tr>
<tr>
<td>1980</td>
<td>Mar Z</td>
<td>30</td>
<td></td>
<td></td>
<td>-3</td>
<td>-2</td>
<td></td>
</tr>
<tr>
<td>1980</td>
<td>Ne N</td>
<td>31</td>
<td></td>
<td></td>
<td>-3</td>
<td>-2</td>
<td></td>
</tr>
<tr>
<td>1980</td>
<td>Ch Mar</td>
<td>Dead</td>
<td>8 yrs</td>
<td>mycoplasma pneumonia</td>
<td>-3</td>
<td>-2</td>
<td></td>
</tr>
<tr>
<td>1979</td>
<td>Na H</td>
<td>Dead</td>
<td>3 yrs</td>
<td>infection &amp; vomiting</td>
<td>-2</td>
<td>-1</td>
<td>moderate cognitive impairment &amp; mild motor impairment</td>
</tr>
<tr>
<td>1979</td>
<td>Ja H</td>
<td>Dead</td>
<td>5 yrs</td>
<td>infection &amp; vomiting</td>
<td>-2</td>
<td>-1</td>
<td>moderate cognitive impairment &amp; mild motor impairment</td>
</tr>
<tr>
<td>1978</td>
<td>Ke Mar</td>
<td>33</td>
<td></td>
<td></td>
<td>-2</td>
<td>-1</td>
<td>moderate cognitive impairment &amp; mild motor impairment</td>
</tr>
<tr>
<td>1976</td>
<td>El H</td>
<td>Dead</td>
<td>4 mos</td>
<td>infection &amp; vomiting</td>
<td>-2</td>
<td>-3</td>
<td>moderate cognitive impairment, good language &amp; memory</td>
</tr>
<tr>
<td>1974</td>
<td>Ed H</td>
<td>37</td>
<td></td>
<td></td>
<td>-2</td>
<td>-3</td>
<td>severe lower extremity spasticity &amp; foot dystonia</td>
</tr>
<tr>
<td>1971</td>
<td>Su F</td>
<td>Dead</td>
<td>4 yrs</td>
<td>infection &amp; vomiting</td>
<td>-2</td>
<td>-2</td>
<td>moderate cognitive impairment &amp; mild motor impairment</td>
</tr>
<tr>
<td>1970</td>
<td>Me H</td>
<td>Dead</td>
<td>13 days</td>
<td>neonatal illness</td>
<td>-2</td>
<td>-2</td>
<td>moderate cognitive impairment &amp; mild motor impairment</td>
</tr>
<tr>
<td>1970</td>
<td>Sh Br</td>
<td>42</td>
<td></td>
<td></td>
<td>-3</td>
<td>-2</td>
<td>severe cognitive impairment &amp; mild motor impairment</td>
</tr>
<tr>
<td>1970</td>
<td>P Ku</td>
<td>42</td>
<td></td>
<td></td>
<td>-3</td>
<td>-2</td>
<td>severe cognitive impairment &amp; mild motor impairment</td>
</tr>
<tr>
<td>1967</td>
<td>Le K</td>
<td>45</td>
<td></td>
<td></td>
<td>-3</td>
<td>-3</td>
<td>severe cognitive &amp; severe lower extremity spasticity &amp; dystonia</td>
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<tr>
<td>1967</td>
<td>El F</td>
<td>Dead</td>
<td>13 days</td>
<td>neonatal illness</td>
<td>-3</td>
<td>-3</td>
<td></td>
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<tr>
<td>1965</td>
<td>Mo Br</td>
<td>Dead</td>
<td>9 yrs</td>
<td>infection &amp; vomiting</td>
<td>-3</td>
<td>-3</td>
<td></td>
</tr>
<tr>
<td>1963</td>
<td>Wi F</td>
<td>Dead</td>
<td>3 mos</td>
<td>infection &amp; vomiting</td>
<td>-3</td>
<td>-3</td>
<td></td>
</tr>
</tbody>
</table>
CLASSICAL MAPLE SYRUP DISEASE
Mennonites, homozygous T->A in exon 9 at aa position 1312
Acute Brain dopamine Deficiency

Acute Brain Serotonin Deficiency
Plasma branched chain amino acids and tyrosine concentrations during the first four days of therapy in an ill neonate with MSUD.

Plasma BCAA & Tyrosine Concentrations

Leucine rate of decrease = 1587 umol/L-24 hrs
(goal Leu <300 umol/L)
# VARIABLES OF PROTEOLYSIS AND PROTEIN SYNTHESIS

<table>
<thead>
<tr>
<th>MUSCLE</th>
<th>PROTEOLYSIS</th>
<th>PROTEIN SYNTHESIS</th>
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<tbody>
<tr>
<td></td>
<td><strong>Stimulates</strong></td>
<td><strong>Inhibits</strong></td>
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<tr>
<td></td>
<td>Interleukin-6</td>
<td>Glucose</td>
</tr>
<tr>
<td></td>
<td>Interleukin-1</td>
<td>ECF amino acids</td>
</tr>
<tr>
<td></td>
<td>Tumor necrosis factor</td>
<td>Glutamine uptake</td>
</tr>
<tr>
<td></td>
<td>Prostaglandin E2</td>
<td>Insulin</td>
</tr>
<tr>
<td></td>
<td>Sepsis</td>
<td>Insulin-like GF-1</td>
</tr>
<tr>
<td></td>
<td>Starvation</td>
<td>Cell hydration</td>
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<tr>
<td></td>
<td>Amino acid deficiency</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low intracellular Gln</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cell dehydration</td>
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</tr>
<tr>
<td></td>
<td>Muscle denervation</td>
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</tr>
<tr>
<td></td>
<td>Cortisol (permissive)</td>
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<tr>
<td></td>
<td>Hypoinsulinemia</td>
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<tr>
<td>LIVER</td>
<td>IL-6, IL-1, TNF</td>
<td>Insulin</td>
</tr>
<tr>
<td></td>
<td>Glucagon</td>
<td>IGF-1</td>
</tr>
<tr>
<td></td>
<td>Epinephrine (beta-1)</td>
<td>ECF BCAAs + alanine</td>
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<tr>
<td></td>
<td>Cell dehydration</td>
<td>Cell hydration</td>
</tr>
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Variables of management of Maple Syrup Urine Disease 
MSUD-TPN

1. Glucose infusion rate (10-12 mg/kg-min.) & total daily caloric goal (2 x BMR or >) 120-140 Cal/kg-24 hrs with lipid infusion providing 40-50% of total calories.

2. Insulin infusion rate 0.05 – 0.15 units/kg-hr to keep blood glucose 80-140 mg/dl with infusion rate of 10-12 mg/kg-minute.

3. Protein grams/kg as MSUD amino acid mixture, enriched with L1-NAA & conditionally essential AA 2-3 g/kg-24 hrs. Glutamate, Glutamine, and Alanine are given as conditionally essential amino acids ~100-200 mg/kg-24 hrs each).

4. Valine & Isoleucine mg/kg-24 hrs. (60-120 mg/kg-24hrs)

5. Sodium & potassium adequate mEq/kg-24 hrs to replace Na deficit, urine Na/K losses, and maintain a stable serum osmolality. Na+ losses & replacement may be 10-15 mEq/kg-24 hrs; K+ are also increased by furosemide & mannitol diuresis used to control cerebral edema.
Genomics & A Medical Home

A Medical Home is the place where, when you have to go there, they have to take you in, And, they know how to care for you.

D. Holmes Morton MD
Pediatrician, Clinic for Special Children
Strasburg, Pennsylvania
Transport Competition & Outcome in MSUD
Chronic amino acid malnutrition & the developing brain
ARRESTED HEAD GROWTH
HYPOMYELINATION
ACRODERMATITIS/HAIR LOSS
NORMOCYTIC ANEMIA
GROWTH FAILURE
IRRITABILITY/ANOREXIA

Photo with parental permission
Poor growth in terms of weight, length & head circumference were the result of prolonged essential amino acid deficiencies during the first 6 months.

The calculated valine uptake into the CNS from birth to 6 months of age was less than 3% of normal – Z-score <-3.3 - over a prolonged period.

This data predicts poor neuro-cognitive outcome as compared to our Mennonite patients who also have a severe MSUD variant.

DOB 7/4/2008. Adm. to NICU at age 7-days. Dx with MSUD at 14-days. Discharged age 44-days. Time until Leucine < 400 uM was 18 days, age 30-days. Leucine intoxication lasted for 4 weeks.
Fine Cortical Branching
The Neuropathological Correlate of Mental Retardation in Protein Malnourishment Syndromes

MSUD Poorly Treated

Normal
Growth related protein accretion & leucine tolerance related to age in Classical MSUD
On admission to LGH his prescribed Leucine intake at 33 months 55 mg/kg-day, all from 8 oz of cow’s milk. Isoleucine 34 & Valine 37 mg/kg.

No supplements of Ile or Val were being used to prevent deficiencies.

Ketonex-2 provided 36 grams of protein as free amino acids.

Profree formula provided additional calories to total 93 Cal/kg-day.

Parents did not have a sick day protocol. No monitoring was done to detect increases in leucine caused by common illnesses. No adjustments in leucine intake were made when a high leucine or when isoleucine or valine deficiency was found.
On discharge from LGH his prescribed Leucine intake at 33 months 17 mg/kg-day with an expected range of 15-25 mg/kg, all from Similac 20 grams.

Isoleucine 9 mg/kg & Valine 17 mg/kg
Supplements of Ile 0, Val 10 ml 100mg. To be adjusted as needed based upon weekly amino acid results.

Applied Nutrition MSUD Complex Jr. 185 grams provided 2 gm/kg-day as amino acids.

Total Caloric intake 74 Cal/kg-day.

Calculated BMR 37 Cal/kg-day, 2 X BMR = 74 Cal/kg-day.
**Leucine & KIC**

**ACUTE INTOXICATION**
- Vomiting
- Hallucinations
- Imbalance
- Coma
- Brain swelling
- Stroke or sudden death

**CHRONIC PROBLEMS**
- Arrested brain growth
- Developmental delay
- Mental retardation
- Spastic cerebral palsy
- Chronic mental illness
- Physical and mental disability
The newborn in this report, Rachel W, was born with the severe Mennonite variant of MSUD in November of 1989. (Case #33 in Morton 2002) She was the first infant from the Lancaster County population to be managed with MSUD-parenteral nutrition. She has been cared for at the Clinic for Special Children for 22 years. Her growth and development were normal. She was an “A” student in school, is now married, and recently underwent a curative liver transplant.

We began using MSUD-parenteral nutrition at LGH in 1990 and have successfully rescued more than 250 ill cases of MSUD. MSUD-PN is
**Diffuse basal ganglial, brain stem & cortical Edema in MSUD**

The increased T2-signal in cortical & deep gray matter is low-diffusion, intracellular edema. In metabolic disorders like GA1 & propionic acidemia such low-diffusion edema indicates irreversible cyto-toxic or ischemic injury of the tissue.

The gray-matter edema of MSUD is unique in its sensitivity to changes in serum osmolality: increases in free water & progressive hyponatremia cause worsening cyto-toxic edema & tissue death. Decreases in systemic free water through the effects of furosemide & mannitol upon kidney & brain, combined with the prevention of hyponatremia by hypertonic saline are cyto-protective.

*MRI from Morton DH et al Pediatrics 2002*
Figure 1-1: Edema in an eleven-day old infant with Maple Syrup Urine Disease in acute metabolic crisis. **Left:** T2-weighted images: Generalized swelling is evidenced by overall hyperintensity in the brain as well as decreased subarachnoid and ventricular space. Focal areas of accentuated hyperintensity are present in the (a) posterior centrum semiovale (b) posterior limb of the internal capsule (c) midbrain and (d) cerebellum. **Right:** Diffusion-weighted images: increased intensity represents decreased diffusion. The images are overall hypointense, reflecting increased diffusion. Localized hyperintensities, reflecting restricted diffusion, are found in (a) the posterior centrum semiovale (b) the posterior limb of the internal capsule (c) the midbrain, and (d) the cerebellum. Image slices correspond with those on the left.
KZ was admitted to LGH 24 hours after being discharged from another hospital. He had a minor infectious illness but had become catabolic, was intoxicated with leucine, and had become encephalopathic. MSUD-parenteral nutrition was not available. The CT scan in the upper two panels was done at the time of release from the hospital and was read as “normal.” The lower panel shows dangerous progression of the brain edema over a 24 hour period.
JoB was admitted to LGH 24 hours after onset of metabolic illness. He was intoxicated with leucine, and had become encephalopathy. The CT scan was done before the start of MSUD-TPN. The left panel shows CSF anterior to the brain stem, in the 4th ventricle, and posterior to the cerebellum. Also open ventricles & CSF in the left Sylvian fissure.
Prior to Discharge
48 hours after the brain CT
MSUD Admissions to Lancaster General Hospital for Acute Metabolic Care 1990-2012

Neonatal presentation acute illness 13% 35
   Down syndrome VSD repair, congenital bowel obstruction (HMC)
   Sepsis SCID (IL7-SCID)

Infectious illnesses 77% 203
   Gastroenteritis (Rotavirus)
   Pneumonias (RSV)
   Otitis media
   Strep pharyngitis
   Bacterial/fungal sepsis

Surgery & Trauma 10% 25
   Appendicitis
   Cholecystitis
   Ovarian torsion
   Hysterectomy
   Fracture femur, skull fracture
Liver transplant is recommended for patients who do not have access to medical care specifically designed to manage the complex problems of MSUD, regardless of age.

Control of MSUD by liver transplant does not reverse spasticity, dystonia, or mental retardation. Transplant does however prevent progressive loss of neurologic function and greatly reduces the risk of stroke or death from cerebral edema.

Teenagers and adults with MSUD are especially vulnerable to loss of motor skills, attention deficit disorder, emotional illnesses, and poor cognitive function because of acute illness and chronically poor dietary control.

Adults with MSUD often have no access to medical care by physicians who are experienced with out-patient and in-patient management of MSUD in the setting of common adult illnesses and medical problems.
Maple Syrup Urine Disease

21 years of “TRANSLATIONAL GENETICS” at the Clinic for Special Children

- Presymptomatic diagnosis of high-risk newborns
- Parent education & home dietary management
- Metabolic monitoring and early detection of decompensation
- Improved MSUD-TPN to reverse metabolic intoxication
- Reversal of critical brain edema & prevention of strokes caused by cerebral edema
- Elimination of dialysis as an invasive & costly treatment for metabolic crisis
- Recognition of brain under-nutrition as a major cause of mental and physical disability
- Improved formula design for prevention of long-term dietary complications
- Recognition and treatment of mental illness in older children and adults
- Collaborative development of a protocol for liver transplantation
- Monitoring of patient outcomes with both conservative and transplant management
IQ CONTROL GROUP

IQ
MSUD-
Mennonite

IQ

TC

M

M

M

MM

M

M

X

60 70 80 90 100 110 120 130 140
After transplant
Off diet & formula
Leu 202 +/- 51 uM

Medically treated MSUD
Leu 253 +/- 185 uM
Post-Transplant – Plasma Amino acid Profiles on unrestricted diet not supplemented with LAT1 amino acids. The BCAA have high CNS uptake z-scores: Leu +2.6, Ile +4.1 & Val +2.8 while neuro-chemical precursors are low: Trp -1.2, Tyr 1.1, His -1, Met -1.1, & Thr -1.3. ARE POST-TRANSPLANT PSYCHOLOGICAL PROBLEMS RELATED?
Among the 7 patients with Adaptive & IQ Scores <70 were patients from South America & India where MSUD formula, Ile/Val supplements, blood amino acid monitoring, & sick day treatment protocols are not available. In Vietnam where screening for MSUD was recently introduced medical services are not available – 11 of 12 infants diagnosed over 3 yrs of the program are dead. The 1 survivor is disabled. Unfortunately, several of these transplanted patients were from regions of the United States where medical care is inadequate & outcomes are poor even for infants diagnosed through newborn screening.

Regardless of their disabilities, medical reasoning suggested to us that cure of MSUD by liver transplant was likely to stabilize the medical condition, thereby decreasing the risk of further injury. Ethical reasoning suggested cure of MSUD would improve the quality of life for patient & family.
Liver transplant is recommended for patients who do not have access to medical care specifically designed to manage the complex problems of MSUD, regardless of age.

Control of MSUD by liver transplant does not reverse spasticity, dystonia, or mental retardation. Transplant does prevent progressive loss of neurologic function and greatly reduces the risk of stroke or death from cerebral edema.

Teenagers and adults with MSUD are especially vulnerable to loss of motor skills, attention deficit disorder, emotional illnesses, and poor cognitive function because of acute illness and chronically poor dietary control.

Adults with MSUD often have no access to medical care by physicians who are experienced with out-patient and in-patient management of MSUD in the setting of common adult illnesses and medical problems.
Amish Cerebral Palsy, ca. 1989
Mitochondria

Tissues (brain), blood, urine

Lysine
Hydroxylysine
Tryptophan

Glutaric acid?

Glutaryl-CoA Synthetase?

Glutaryl-CoA → Glutaric acid

FAD → FAD\(\cdot\)2H

Glutaconyl-CoA

↓

Acetyl-CoA

Glutaric acid

3-Hydroxyglutaric acid 2 TMS (MW 304)

Glutaric acid 2 TMS (MW 276)

glutaryl carnitine
Not Screened (N=171)

- Dystonia: 93%
- Healthy: 7%

Screened (N=31)

- Dystonia: 35%
- Healthy: 65%
Figure 1. Before 1989, Amish children with glutaryl-CoA dehydrogenase deficiency (GA1) were fully disabled by their second birthday and often misdiagnosed with cerebral palsy. The first genetic study at the Clinic for Special Children identified GA1 as the cause of “Amish cerebral palsy” in 16 children. Beginning in 1989, the Clinic offered on-site diagnostic screening, comprehensive pediatric follow-up care, and inpatient management for children with GA1. The incidence of brain injury decreased from 94% to 36% by 1990. There have been no brain injuries among our 12 GA1 patients born after 2006.
Crippling dystonia follows acute striatal necrosis in an Amish child with GA1
Transport Competition
Effects free amino acids upon the plasma Lysine/Arginine Ratio

Pathophysiology and treatment of glutaryl-CoA dehydrogenase deficiency: Lysine restriction coupled to arginine fortification improves neurological outcome.

Accepted for publication June 30, 2011 by Molecular Genetics & Metabolism, exactly 23 years after my first visit to Lancaster County to examine Danny Lapp, the first Amish infant diagnosed with glutaric aciduria type 1.
Transport Competition
Effects free amino acids upon the plasma Lysine/Arginine Ratio
Injury or Disease?
GA1: Intracranial Hemorrhage
Retinal hemorrhage
Glutaric Aciduria Type 1
Nikki GA1, non-Amish, diagnosed by screening
Transport Competition
Effects free amino acids upon the plasma Lysine/Arginine Ratio

Nikki H - N
Steve M - X

[Graph showing correlation between plasma Lysine/Arginine ratio and brain lysine uptake]

LYSx r = 0.36, p = 0.009
A Medical Home is the place where, when you have to go there, they have to take you in, And, they know how to care for you.

D. Holmes Morton MD
Pediatrician, Clinic for Special Children
Strasburg, Pennsylvania