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FEATURED FAMILY - THE THIRD ONE WAS RHODA

Details

Written by Minerva Zimmerman

Published: 17 July 2009

Aaron and Minerva Zimmerman are an Old Order Mennonite couple from Mifflinburg, Pennsylvania - northwest of the Lancaster area group of Mennonites. I talked to Minerva in PA this summer, and she said she was considering writing. I encouraged her to write for this issue. We were home only a day or two until this arrived. Thank you, Minerva, for your prompt response. This was the only history submitted for this issue.

On a warm, Sunday, summer morning, July 14, 1991 at 5:40 a.m. we were blessed with our second daughter, third child, Rhoda Elizabeth. She weighed 7 lbs. 6 oz. and was 20, in. long. She had long dark hair - quite a bit more than our other children. We didn't realize something could be wrong, as she seemed like other newborns to us.

At 3 days of age, I noticed a different smell when I changed her diaper. I held the diaper to my nose, but I didn't recognize the smell. So I reassured myself it must be her bowels.

The next day at 4 days of age, I didn't really think of that smell. But every time I tried to nurse her, she pulled back and really cried till she'd finally settle down and nurse. I thought our baby must be born with a stubborn streak!

The fifth day was very hot, and I thought Rhoda minded the heat, as she was kind of listless, didn't open her eyes, and hardly cried. She was a very contented baby. That night it changed. She cried, and her mouth was pinched shut when I tried to nurse her. I pried her mouth open with my fingers. She'd suck three times and go back to sleep.

This happened off and on all night. By Saturday morning, the 6th day, I was ready to give up! I called our midwife Mary Hostetler and told her how our baby acts. She asked a few questions concerning her navel. All seemed fine there, so she told us to take her to our family doctor. By that time she couldn't cry anymore, just moan.

The doctor examined her, and said he thinks she might have a blood infection or pneumonia and sent us to our local hospital around ten miles from our place. It was noon by then, and they started an IV. Tests that afternoon showed nothing.

We went home for the night. Sunday morning, when we came to her room, a pediatrician, Doctor Stoltzfus, met us. He questioned us about MSUD. Was it in our families? I had a cousin, Amos Fox (Weaver and Alma's son) who had MSUD. But on Aaron's side, we didn't know of any.

Doctor Stoltzfus said he knows very little about MSUD, and neither did we. He was going to test for it. It was Sunday, so the blood wouldn't be sent till Monday. It would take a couple of days to get the results. So all there was to do was wait and wait.

By this time Rhoda didn't respond anymore and was very stiff. Sunday afternoon my Aunt (a sister to Alma Fox) and Uncle from the Lancaster area came to visit us at the hospital. When she saw Rhoda, she said she acts just like Weaver and Alma Fox's MSUD babies did. They said something to the nurses, and the nurses said everything is taken care of.

That evening back home, Aunt Eva just didn't feel comfortable. She knew something should be done. She called her neighbors, Enos and Anna Mae Hoover, who also have children with MSUD, and told them about our sick baby. Enos called Dr. Morton. By 8:30 p.m. Dr. Morton (someone new to us) called to ask permission to see Rhoda at the hospital. He planned to meet Doctor Stoltzfus at 1:00 a.m. in her room.

We were in a daze; it was like a nightmare. Surely we'd wake up and find it all a dream. But no - at 1:30 a.m. the phone rang. "Please come to the hospital right away. Doctor Morton is 98% sure she has MSUD and wants to move her to Lancaster General Hospital."

Luckily, the children were at Aaron's sister's for the night. But we needed to find someone to do our milking and a driver to take us to the hospital at that time of the night.

At 2:30 a.m. we met Doctor Morton for the first time. They put a tube through Rhoda's nose to give her formula. By 3:00 a.m. we were on our way to Lancaster, all in Doctor Morton's car. We stopped 3 times to give her some formula. At 5:30 we were at this new hospital. There we learned much about MSUD. It looked like a huge mountain before us!

Her highest level was 38 mg/dl. She spent 6 days in the Lancaster General. We were glad to bring her home again, but we had so many questions yet. Could I take care of her, etc.?

She was a very fussy baby and had many ear and yeast infections. Then in Dec '92 when 17 months old, she weighed 21 lbs. and was beginning to loose her hair. We had tubes put in her ears, which we thought would solve the problem. It didn't.

Jan.'93 she was admitted to Lancaster General for 5 days with very low levels and very run down. She had lost all her hair. She was put on 90 gm. S14 and 30 cc. leucine for a whole month till her levels finally stayed at 3 and 4 mg/dl.

At 19 months of age she started to walk. By 20 months she had a nice amount of hair again and weighed 25, lbs. In Feb. '95 she was again admitted to Lancaster General for 3 days. She had the flu and couldn't keep anything down. She was very dehydrated and had a leucine level of 21 mg/dl.

Rhoda is now 4 yrs. old and doing well. She is talking about going to school - how she's going to wear her big sister's school dresses and take chocolate milk in her thermos.J

On June 29, 1995 we were blessed with a healthy son whom we named Curvin Jay. Rhoda loves him dearly. May the Lord bless you all.

Minerva wrote a note for "Tips for Mixing Formula" under the DIET & NUTRITION section. I am quoting from it here as it gives some information about her problem with Rhoda.

"Mixing formula is one of the easier jobs, if you don't loose a blender part.J It's after the formula is mixed when it turns into a challenge! Rhoda, age 4, does not beg for her formula, but needs to be reminded again and again to drink her formula.

A new drinking cup does wonders, but it only lasts so long - till the newness is worn off. Rhoda has seven different drinking cups! When she doesn't want to drink it, we'll use another cup she hasn't used for a couple weeks. Wishing you all much patience and strength to face each new day."

ANMD PARENT CONFERENCE REVIEW

Details

Written by Joyce Brubacher

Published: 17 July 2009

The Association for Neuro-Metabolic Disorders (ANMD) held its parent conference on Oct. 21, '95. There were 8 MSUD families represented in the group of around 80 - mostly parents of persons with PKU, some PKU adults, and several persons representing other disorders.

On Sat. morning the MSUD families met separately in a workshop. Those attending were Peter & Sharon Shaffer, Kentucky; Leon & Diane Kennedy, Michigan; Sandy

Keil, Michigan; Dave & Sandy Bulcher, Ohio; Dave & Laurie Page, Michigan; Ron & Denise Pinskey, Michigan; Wayne & Joyce Brubacher, Indiana and several Grandmothers. Chuck, Betty and Amy Whitfield-PA arrived in time for lunch. Sandy Keil was the parent leader and her report follows.

Workshop From Sandy Keil's Notes:

The MSUD workshop is a family reunion of sorts. It is so encouraging to meet with the other families and we updated each other on how our children have been doing. We were all happy to report we had a healthy year. We were especially honored to be able to welcome Michigan's newest MSUD family - Ron & Denise Pinskey. Newborn screening detected their son Zachary, born September 6.

We discussed many issues. Many families advocated getting the flu shot. Also, with the new chicken pox vaccine available, those children who haven't had the pox yet are planning to get the vaccine.

One family asked about school snacks. Some mothers send special snacks along if they know something is coming up at school. Sandy Bulcher said she let Jordan pick out a package of his favorite regular store bought cookies and she sent these to school for the teacher to keep on hand to give one or two to Jordan for special snack times. The teacher sends a note home with Jordan letting Sandy know how many cookies he had. Sandy can then figure that into her leucine count for the day.

Sandy and Dave Bulcher reminded us of the upcoming MSUD Symposium, June 20-22, '96.

The Pinskey's child, Zachary, was in the hospital at the time with pneumonia. This was his first hospitalization since his release after diagnosis. (He soon recuperated.) This gave Ron & Denise an opportunity to get acquainted with other families and ask questions. We had a lively and interesting time together, as usual. Our MSUD family ties grow stronger.

Program Review from Joyce and Sandy's Notes:

Randy Eisensmith, Ph.D. from the Department of Cell Biology, Baylor College of Medicine in Dallas, Texas spoke on Genetic Therapy and Genetics of PKU and Related Disorders.

Every person has 9 to 10 genetic mutations. We who have children with these diseases, know one of our mutations.

Genetics helps us understand the kinds of PKU, MSUD and other diseases. There are over 300 mutations of the PKU gene. Population genetic studies have shown that certain types are concentrated in specific areas of Euro-Asia. The country from which your ancestors originated may provide a clue as to the type of disease. **(This is true in MSUD as evidenced in the Mennonite population which originated in certain areas of Europe and have a distinctive type of classic MSUD.)**

One method of gene therapy currently being used to correct PKU involves using viruses to carry the corrected gene into the body. The activity level does not need to be nearly 100% to work. However the body's immune system attacks the virus as a foreign body and the new enzyme activity only lasts two to three weeks. Giving an immune suppression drug, as is used in transplants, permits it to continue working. Using a PKU mouse, experiments are continuing, but there are a number of hurdles remaining before satisfactory therapy can be started on humans.

Because of the location of the enzyme in the cell, the process is much more complicated for MSUD. Other diseases, however, will benefit from the PKU research.

Anna Marie Schaefer, R.D., MPH, from the University of Michigan, spoke on Monitoring & Compliance Issues in Metabolic Disorders. She showed charts of blood levels compared with the amount of dietary protein for MSUD patients. Individuals will follow health care advice based on four things: motivation or interest, susceptibility, severity of the consequences of not treating, and benefits and costs. Four barriers to compliance are: the amount of physical discomfort, financial concerns, inconvenience and time factor, and lack of concrete evidence of noncompliance. The latter is especially true in PKU.

Dr. Richard J. Allen, M.D. from the University of Michigan, praised the illustrations in the June '95 National Geographic article on "Quiet Miracles of the Brain" in his speech on "New Technology in Brain Chemistry in Metabolic Disorders." Good illustrations such as these are hard to find and are helpful in understanding brain functioning.

All brain cells have a birth date. Various chemicals insult brain cells depending on the developmental stage of the cell. The brain can be affected by static dementia (physical insult) and progressive dementia (chemical insult), which are different from retardation (low IQ). The insult to the brain is progressive in PKU and MSUD.

Most of the damage to the brain is done in the first few days of life in MSUD. High levels of leucine interfere with myelin (a covering on the nerve cells) formation. The sensitivity of the brain at birth is entirely different than when a person is older.

After a parent presentation by the mother of a child with Galactosemia, William Young, Ph.D., from the Michigan Department of Public Health, described the Michigan State Screening Program. He called it a great program with an excellent State Lab. The ANMD has been very instrumental in influencing the program and preventing it from being downgraded.

HASSLE FREE DIET TRACKING

Details

Written by Edwin & Ruth Leid

Published: 17 July 2009

Displeased with all the books, papers, pencils and time used in figuring Ervin's daily diet, we thought there must be a better way. After some research and phone calls, I came across this handy little Palm Top Computer - similar to a small, hand-held calculator. At first we thought we wouldn't use it much. However, after having it partly programed from the FOOD VALUES book, and after we used it a few days, we realized how time consuming the other way was. It is very easy to use.

Example: Enter 88 grams sherbet - orange, and the screen will display:

FOOD	ITEM	WT	ILE	LEU	VAL	KCAL	UNIT
SHERBET	OR	88	52.2	84.3	57.8	121	2.56

It also adds the amounts to the daily total. If you enter "totals," it displays the values in the same way. Every time you hit "totals" it shows you the amount so far for that day. It holds more information than the current "FOOD VALUES" book, is small enough to set beside your plate, and folds to fit in a shirt pocket.

TIPS FROM MOTHERS

Details

Written by Verna Burkholder

Published: 17 July 2009

Karen Lovrin's son, Nick, likes a cup of hot tea mixed with MSUD diet powder formula. She fixes it by mixing , cup tea with , cup formula and, of course, lots of sugar. It's the only way he drinks the MSUD diet powder and he loves it.

Verna Mae Martin started canning her own low protein mixed vegetables. Her children like rice with salt, butter, tomato juice or spaghetti sauce, and sometimes she adds her own mixed vegetables.

For quick meals, Verna Mae likes to keep instant mashed potatoes and minute rice on hand. French fries, fried potatoes, or tater tots are the usual main breakfast foods along with fruit and cereal for her two children with MSUD.

She substituted apple butter for the applesauce in her low protein bread and used less sugar. Her daughter thought it looked more like the bread the family eats.

For Keith's pancakes, Mary Kathryn Martin substitutes applesauce for , of the oil. The pancakes have a much better texture and are not as fragile.

Tips on Mixing Formula
Recently someone suggested we collect tips on mixing formula. I received almost a dozen responses and summarized them:

- All the mothers weigh the formula powder and use a blender, mixing from a few seconds to five minutes.
- Place water in the blender first, then add formula. Some mothers keep the blender running while adding formula. The blender will not be as sticky, and it mixes well.
- Mix in the evening for the following day.
- Add supplements and vitamins before blending.
- A hand blender works great for traveling and fits into a wide mouth jar. Easy to clean and store.
- Add ice to just mixed formula if your child needs to have it ice cold or add ice to the blender while mixing.
- Set a one quart canning jar on the scales and measure ingredients into the jar. The blender ring fits onto the jar. Blend, cover the jar and refrigerate. You have only the blender attachment to clean.
- One mother measures a week's supply at a time - including supplements - measuring into jars or ziplock bags. It saves time and your child can easily mix his own formula when it's premeasured.
- One mother adds , T blackstrap molasses (per day) to her child's formula as a source of vitamins and minerals, and it also helps constipation.
- Several mothers mentioned that mixing the formula was easy compared to getting the child to drink it or to preparing low protein foods.

How does a mother manage with 3 of her children on the diet?
Following is her account of her formula mixing method.

- Seems I'm always in a hurry when I mix formula as I do it in the morning in the rush hour before school. I make it the fastest and easiest way I can! I have my blender sitting on counter day and night and a case of formula handy on the second shelf of the serving cart. My scales I have to hide as it's such a nice toy. I have it at a handy place. I use an aluminum pie pan and dump MSUD powder in it on the scales. With water in the blender, I bend the pie pan in a scoop-like way and dump the powder into the blender. I blend for one minute while I get the next batch ready, and so on until all three formulas are made. While the last batch is mixing, I grab the isoleucine and valine supplements and measure them into all three formulas. I put water in the blender to soak and that is done for another day. They all enjoy their formula, thankfully, although they do have sprees when they would rather not have it. I can't complain.

QUESTIONS ANSWERED ABOUT LOW PROTEIN FOODS

Details

Written by Joyce Brubacher

Published: 17 July 2009

In our last Newsletter (Spring '95), I reprinted an article from National PKU News in which the editor, Virginia Schuett, asked three companies making medical foods (formulas) to respond to questions about their products. The winter '95 issue of the National PKU News included an article in which Virginia asked the three U.S. companies making and distributing low protein foods - Dietary Specialties, Ener-G Foods and Med-Diet - to respond to questions. The questions were asked by families participating in the American Academy of Pediatrics survey on PKU treatment in the spring of '94. These same questions are asked by families involved with MSUD.

With appreciation for Virginia Schuett's efforts and the response of these companies, and with apologies to you who subscribe to the National PKU News, I am reprinting this article, also. I try to reprint only those articles of special interest to our subscribers. The PKU newsletter has many articles of interest. I think you would find it well worth the subscription fee for 3 issues a year. To subscribe contact:

National PKU News
6869 Woodlawn Ave, NE #116,
Seattle, WA 98115
www.pkunews.org

Why are the foods so much more expensive than regular foods?
(The very frequent complaint was, "We cannot afford them, or we use much less than we should or want to.")

There are many reasons for these differences that make life difficult for all families (except those living in Connecticut and Massachusetts, where the foods are paid for by insurance). First, the number of people who require special low protein foods is very small. Food supplies are plentiful and inexpensive for the general retail market in the U.S. because there are so many people buying. Low protein foods are very expensive because there are so few people buying them.

To produce these foods, certain costs are fixed, despite the number of units produced. The result is that such "fixed costs" are spread over fewer units when the production runs are small. Among these fixed costs are costs of governmental regulations, such as complying with the new label regulations. (Recent costs associated with these regulations have been

large enough to discourage one of the companies from producing a few less-popular low protein foods. Other costs such as labor, ingredients and packaging materials are more expensive per unit as the number of units produced decreases.

Ingredients for low protein foods also are usually more expensive than ingredients for more commonly available foods. The least expensive ingredients are those that low protein products cannot use, such as regular flour, eggs and powdered milk. Packaging, especially vacuum packaging required of some products, is very expensive. Such expensive packaging is necessary to increase shelf-life. For example, this is important for low protein bread bought in bulk and often eaten by only one person in the household.

Some families have asked why the U.S. cannot make its own pasta and other products to reduce the costs, instead of importing many of them. It is very difficult to find manufacturers who will make small quantities. Their equipment is geared to very large runs. For instance, most U.S. pasta companies run their machines 24 hours a day, 7 days a week. They are computer controlled for continuous operation. To ensure that there is no residue of "normal" pasta in the system, the extruders and dryers would have to be cleaned up. This could be very expensive just to make a one or two hour run of specialty pasta. (A four hour run on this equipment would produce nearly a whole year's supply of low protein pasta.) This is the major reason most low protein pasta comes from Italy. They have smaller producing units and also sell their products all over the world. This helps them get "economy of scale." The same is true for low protein bread, cookies, etc. There is a large start-up and cleanup expense associated with producing most food products. Small runs cannot be justified. So it is necessary to import many low protein foods, despite their higher cost.

Finally, shipping and handling costs are higher per package than they are for shipping entire truckloads of generally used foods over shorter distances. Dietary Specialties relates that, despite an average increase of 26% in UPS rates since 1990, their charges for shipping and handling are actually lower than they were four years ago. This is due to increased efficiencies in shipping and their desire to "keep things as affordable as possible."

Editor's note (Virginia Schuett): This attitude of wanting to serve families in the best way possible characterizes all three of the companies. I know this from years of communication with them. They are small companies that started out with an aim to help small numbers of people live better lives. They must make a small profit to stay in business, but they are not out to "gouge" you financially. It is my firm belief that they are all doing their best to keep prices down in the face of high production and shipping costs.

Why can't there be a bigger variety of prepared low protein foods? ("Cooking special meals for my child is a constant problem.")

It certainly would be nice to have a bigger variety of already- prepared low protein foods (those that would need heating only). Again, it is a matter of cost economies. Due to the small production runs and special packaging required, the cost would be $5.00 or more per serving. Are parents ready to pay this much and how many units could be expected to sell? The cost of developing new products is very high. The companies must be absolutely sure that the few consumers who require these foods will buy enough to justify the up-front cost.

If more states follow Connecticut and Massachusetts in getting laws passed requiring

insurance coverage of low protein foods, the general use of low protein foods could increase significantly. This would make it much more feasible to develop new products. In countries such as Canada and England, these foods are paid for by the National Health Service. This stimulates consumption and almost guarantees a market. In those countries, many companies have entered the market because there is less risk, since they know that the product will be paid for by an outside agency.

Why can't the low protein foods be made to taste better?
(Also, "Why can't the foods have salt? Why can't the foods be geared just for PKU [MSUD] and not other conditions requiring low salt?")

The food companies are always trying to develop products that will look and taste like regular foods. As you know, it is a very big challenge to remove almost all the ingredients that contribute to the structure, "mouth-feel" and flavor of a food and still have the food resemble the original. Sometimes it's not possible.

The reason low protein foods are made to be low in salt is so they will be acceptable for renal diets (for kidney failure) where protein and salt restrictions are needed. Making a food that will suit two markets means the company does not have to make two separate products. The cost of these products is very dependent on the size of the production run, so it makes sense to increase the size of the run as much as possible. Also, it means avoiding the costs of carrying two separate inventories, separate packaging, etc. If the companies tried to produce foods tailored to only one group's needs, the flavor could be improved. But they would have an even harder time than they already have in attracting a manufacturer due to the very small volumes.

Why can't a low protein substitute for meat or cheese be developed?

The development of low protein meat or cheese-like foods has many technical barriers. It may not be possible. The chemical and textural properties of proteins are unique and very hard to duplicate. Also, they typically deteriorate rapidly. Refrigeration would be necessary throughout handing and delivery, which is very expensive. The large companies with the research facilities to develop such products are concentrating on developing high protein substitutes for meat and cheese. This is what the public wants.

Why can't the low protein foods be made available in grocery stores?
("It's very inconvenient and expensive to order large amounts through the mail.")

The goal of supermarkets is to sell to the consumer large amounts of products in the most efficient manner and to make a profit. There are so many products that the store has to limit the number of items it carries. To maximize profits, they stock only those items that will produce the highest profits per square foot of shelf space. Unfortunately, low protein products do not fit that profile. Low protein foods are usually not available in the grocery store because turnover is too low to justify their shelf space. To obtain shelf space, many supermarkets also require large "slotting fees," which small companies like Ener-G Foods, Med-Diet and Dietary Specialties cannot afford to pay. Also, they do not have an outside sales force, so it is not possible for them to travel around the country to persuade grocery stores to carry their foods.

Health food stores work with lower turnover items, but higher markups than supermarkets. Low protein foods often do not meet even the lower turnover requirements of health food stores. Drug stores and specialty food shops also are stocked by large distributors, not much different from those that distribute to the regular supermarket trade. This leaves mail order as the only avenue for small volume specialty products. It is the most efficient way of getting these products to consumers.

Several parents in different parts of the country have shown that it is possible to get low protein foods in certain grocery stores. But it is not an easy process. It takes the right combination of good will by the store, persistence by parents, and a large enough PKU clientele who will purchase the products. The companies, in fact, are happy to ship low protein foods to any retail outlet that will stock them. They would be glad to hear from subscribers about retail outlets that would buy their products on a regular basis.

Circumstances are but the trigger that call into action our faith. The same strong wind that capsizes one sail boat moves another to its destination. Faith thrives on the most adverse circumstances.

CEREBRAL EDEMA & MAPLE SYRUP URINE DISEASE

Details

Written by Holmes Morton M.D.

Published: 17 July 2009

Parents be sure your doctor is aware of the information in this article on cerebral (brain) edema. This report on the control of glucose, sodium and water in ill persons with MSUD can be a lifesaver and has already helped save several critically ill children. We want to stress the significance of this information. The terminology may be difficult for many of us, but I encourage everyone to read the article.

Brain edema is the most dangerous complication of MSUD and is usually the cause of death during metabolic crisis. The following recent experience with brain edema markedly changed my understanding and treatment of the problem.

Case summary: In late May 1995 I admitted a 3 year old Mennonite girl with maple syrup urine disease (MSUD) to Lancaster General Hospital. For several days before admission she had poor appetite and intermittent vomiting. There were large ketones in her urine, but her urine DNPH test cleared intermittently. Her serum leucine level was only 5 mg/dl (380 µM) the day before admission and was 6 mg/dl (650 µM) when she was admitted. Twelve hours after admission, when she was receiving MSUD hyperalimentation, and her serum

leucine was 4 mg/dl (300 µM), and her serum 2-ketoisocaproic acid was less than 200 µM, she developed critical brain edema. Her pupils became dilated and her breathing stopped. MSUD hyperalimentation was continued, and her biochemistries remained stable while mannitol and hypertonic saline were used to rapidly increase her serum osmolarity. Over a 48 hour period, it became increasingly apparent to me that her clinical improvement and deterioration were better predicted by changes in serum sodium and osmolarity than by branched chain amino acid levels. Her sensitivity to low serum osmolarity resolved over 36 to 48 hours; she gradually became more stable, then began to recover. Now, four months after the brain edema, she is left with a mildly unsteady walk and run, and her voice is uneven, probably because of injury to the cerebellum. But I remain hopeful that in time she will recover completely.

Critical brain edema in patients with MSUD most often develops after 6 to 24 hours of intravenous therapy. Patients, who may have been alert when admitted, become drowsy, irritable, and disoriented. At a time when amino acid levels are decreasing and the patient would be expected to improve, the important signs of illness such as vomiting, headache, and mental status suddenly worsen. The risk of brain swelling is not predicted well by branched chain amino or keto acid levels. The most severe cases of edema I have managed developed life threatening brain edema when plasma leucine concentrations were only 4 and 9 mg/dl (300 and 650 µM). **Risk factors for critical brain edema include: recurrent vomiting, prolonged ketonuria prior to admission, persistent ketonuria after IV therapy is started, serum sodium less than 135 mEq/l, serum osmolarity less than 275 mOsm/l, rapid increases of blood glucose to levels greater than 200 mg/dl, and the use of intravenous solutions that contain less than 140 mEq/l of sodium**. Critical edema such as the above patient had, can be seen on MRI scan of the brain as an increase in T2 signal (whiteness) throughout cerebral and cerebellar hemispheres and is especially prominent in the basal ganglia and brainstem.

Based upon recent MRI studies done on mildly symptomatic children with MSUD, I now suspect that all patients with MSUD who are ill have some degree of brain edema. Critical edema that causes pressure on the base of the brain and brainstem is a late final stage of a process that begins before the patient is admitted to the hospital. MRI's of the brains of children with neurological signs such as ataxia, vomiting, hyperactivity, dystonic posturing, hallucinations, nightmares, and memory loss show focal areas of edema in the brainstem and cerebellum, the basal ganglia and thalamus, and the medial regions of the temporal lobes. **Neurological signs of brain intoxication develop before generalized swelling of the brain and pressure on the base of the brain. Such signs of intoxication appear to correlate with edema or metabolic derangements within selective regions of the brain**.

The cerebral edema that occurs in MSUD is not unlike that associated with diabetic ketoacidosis and hypernatremic dehydration. In all three conditions, water is pulled from the vascular and extracellular space into the intracellular spaces of the brain by intracellular metabolites with osmotic activity. In diabetes and MSUD, generation of these metabolites is associated with prolonged ketosis. The amount of water that enters the brain under the influence of such metabolites is controlled in large part by the sodium concentration in the extracellular space. The balance of extracellular sodium and pathologic intracellular osmolites determines whether critical edema develops. The use of intravenous fluids that cause rapid expansion of intravascular fluids and low serum sodium concentrations, either

due to dilution with free water or losses through the kidney, favors the diffusion of water into the intracellular space of the brain and other organs.

Figure 1 shows the effect of a decrease in serum sodium from 137 to 126 mEq/l upon intracellular water assuming that the intracellular osmolites are fixed at 1425 mOsm. As the extracellular osmolarity decreases to 252 mOsm/l, because of the decrease in serum sodium concentration, water diffuses into intracellular space to dilute the intracellular osmolites to a concentration of 252 mOsm/l. When the new equilibrium is established, the extracellular osmolarity equals the intracellular osmolarity and intracellular water has increased by approximately 9%.

In most organ systems an increase of intracellular water of 5 to 10% is well tolerated but swelling of the brain is limited by the skull. **Figure 2** shows the tolerance for brain swelling in relation to body weight and age. The neonate and the adult have a slightly increased tolerance of brain edema as compared to the child. The neonate may tolerate an increase in brain water of 10 to 15% because of the open sutures of the skull. A 4 to 9 year old child will only tolerate an increase of brain weight (water) of 5 to 8% before developing critical pressure. The larger ventricles of an adult allow an increase in brain water of approximately 10% before critical pressure develops.

The effects of treatment of acute cerebral edema with hypertonic solutions of saline and mannitol are also represented in **Figure 1**. When mannitol 2 grams/kg of body weight is given, the osmolarity in the extracellular space transiently increases by approximately 38 mOsm/l and causes a 7% decrease in intracellular water. Similarly if hypertonic saline is given to restore the sodium concentration in the extracellular fluid, then intracellular volume is restored to the initial state. In the patient, losses of mannitol and sodium into the urine require ongoing administration of these osmolites to the extracellular space to prevent reaccumulation of intracellular water. Mannitol (2 g/kg) and hypertonic saline should be given slowly intravenously over 20 to 30 minutes to prevent a transient increase in intracranial pressure associated with a rapid increase in central venous and arterial pressures. When lasix is used for diuresis, care must be taken not to cause hyponatremia. Hypertonic saline infusions should be used to keep serum sodium concentrations to the range of 140 to 145 mEq/l. An infusion of 5 mEq/kg of NaCl as 3 or 5% saline will cause an increase in serum sodium of 5 to 6 mEq/l. Sodium, in contrast to glucose, does not cross from the vascular space into the nervous system and opposes the entry of water into the brain. In experimental animals, infusion of 10 mEq/kg of 3% sodium chloride or sodium bicarbonate over 60 minutes causes a sustained **decrease** in intracranial pressure of more than 50 mm H20. (Kravath et al. *Clinically significant changes from rapidly administered solutions: Acute Osmol Poisoning*, **Pediatrics** 46: 267, 1970.)

It is necessary to use high glucose infusion rates to control catabolism associated with MSUD, however, insulin should be used to prevent hyperglycemia, and solutions of glucose in water, without NaCl, should never be used. Glucose rapidly enters the brain and, if unopposed by sodium, pulls water from the vascular space into the central nervous system. In experimental animals, infusion of 20 ml/kg of 5% dextrose in water over 10 minutes causes an abrupt **increase** in intracranial pressure of more than 50 mm H2O. (**Pediatrics** 46: 267, 1970.)

I recently summarized the management of an ill patient with MSUD as follows: successful

treatment of MSUD depends upon inhibition of protein catabolism and sustained support of protein synthesis. Serum and intracellular concentrations of leucine are decreased by sustained rates of endogenous protein synthesis. To induce and sustain the anabolic state, the patient must have a total caloric intake of at least 2 to 3 times his or her basal metabolic rate, and a total protein intake of the MSUD amino acid mixture from MSUD formula or hyperalimentation equal to 2 to 3 grams/kg of body weight per day. Optimal rates of protein synthesis are obtained when 35 to 45% of the total caloric intake is from fat. In the initial few hours of therapy, insulin and propranolol may be needed to overcome counter-regulatory hormones in the severely ill patient. Isoleucine and valine deficiency must also be prevented. These essential amino acids become deficient within 6 to 12 hours after the start of effective therapy and must be provided at a rate sufficient to maintain serum levels of 4 to 5 mg/dl (300 to 400 µM). Isoleucine and valine supplements of 70 to 150 mg/kg-24 hours are typically needed for a neonate and 10 to 30 mg/kg-24 hours for the older child. The central nervous system is especially vulnerable to isoleucine and valine deficiency. Other adjuncts to therapy include glutamine, alanine, thiamine, and pyridoxine which are nutritional supplements added to formula and hyperalimentation solutions to limit the effects of increased leucine and 2-ketoisocaproic acid upon transamination. Recovery from acute metabolic intoxication finally does depend upon control of multiple interdependent variables that serve to sustain protein synthesis, reestablish transamination cycles and amino acid synthesis at other thiamine dependent enzyme complexes.

I would now add to this overview that the prevention and treatment of cerebral edema in a patient with maple syrup urine disease depends heavily upon basic principles of fluid and electrolyte therapy. The biochemical derangements that cause the branched chain amino acids to increase, and that cause prolonged ketosis, appear to produce osmolites within cells of the brain that make MSUD patients vulnerable to brain edema. This is true for patients with MSUD just as it is true for patients with diabetes mellitus and hypernatremic dehydration. In our efforts to gain control of metabolism, what we do with glucose, sodium, and water determines whether the balance tips toward or away from critical brain edema. These are preliminary observations, but I think they will prove to be useful in the care of children with MSUD and other metabolic disorders.

This article was first printed in the summer '95 issue of the Clinic for Special Children Newsletter. I asked Dr. Morton's permission to reprint that article; he kindly agreed. The article as printed here is his 11/17/95 revision. We are always interested in articles on recent treatments for MSUD. Send them to me, the editor, please. Also let me know where to get permission to reprint them, if possible.

THE HISTORY OF OUR SUPPORT GROUP - PART 1

Details

Written by Joyce Brubacher

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Personal Interest Begins

"I'm sorry, but your baby has a rare disease called maple syrup urine disease. I have very little information as there is only one paragraph about it in my largest medical book." Those words changed our lives. During ensuing conversations with doctors, we were challenged with these words: "You will need to know as much as we do about MSUD in order to take care of this child." Wayne and I took the challenge and have been asking questions and searching for information ever since. We also longed to compare experiences with other parents.

Those heartrending and mind-boggling words were issued on the 11th day of the life of our first child. Our son, Monte Merlyn, born March 12, 1965, was the first child in the world to be detected through a statewide screening program. Oregon, where we lived, had added MSUD to the Guthrie screening test along with PKU shortly before Monte was born. (Several individual laboratories in other states were collaborating in this field trial.)

Monte did very well under the care of Dr. Havelock Thompson and later, Dr. Neil Buist in Oregon. He remained remarkably healthy after his release from the hospital at 2 months of age. He had two short hospitalizations in his first two years, for observation only, as we were learning about this strange disease. Monte was soon above the fiftieth percentile in height, weight, and head circumference, and weighed 25 lbs. at 9 months. He sat alone at 6 months, crawled at 7, months, and walked within days of his first birthday.

The challenge of Monte's diet and care seemed to consume all my time. There were no prepared formulas or food back then and everything was mixed from basic materials. I searched for information, and bombarded our wonderful, kind, helpful doctors with many questions. Only years later did we realize how very fortunate we were to have doctors who patiently took time to teach, train and nurture us during this critical time. They were on call day and night for us.

We longed to talk to other parents of children with MSUD. We had very concerned and caring families and friends. But how could they really know or understand our daily challenges, fears and triumphs? My sister seemed insulted, or maybe threatened, when I asked so many questions about her son's development. Her son was 2 months younger than Monte, and they lived 2000 miles away. I wanted so badly to know how Monte's behavior - he was hyperactive - and development compared with a "normal" child. How was she to understand? Demands on my time increased with the birth of our son Ricky Marlyn on Sept. 21, 1966. Monte soon had a lively exploring partner because Ricky walked at 8 months. Maybe I should say ran, because he seemed determined to keep up with his big brother, who never did anything in slow motion.

Meeting Other Families

When Monte was two, we learned of a doctor at the University of Michigan Medical Center

in Ann Arbor who had an amino acid analyzer and was willing to take Monte as a patient. This enabled us to move to Indiana to Wayne's home community. Again we were favored with a good, supportive doctor, Dr. Richard Allen. He had one other patient with MSUD and kindly arranged for us to meet Greg Whitfield and his family.

It was exciting to meet another family experiencing MSUD. Our enthusiasm was tempered by sadness and compassion. Greg Whitfield, 1, yr. younger than Monte, did not have the benefit of early diagnosis. (He was not diagnosed until approximately four weeks of age). Greg could not join our boys in their romping, but he had a beautiful smile and a quiet, sweet personality. (I was more thankful for Monte's hyperactivity, which often seemed to drain my energy.) We admired and were challenged by the total, self-sacrificing devotion of Greg's mother, Betty. She fed Greg every three hours around the clock, because he could not keep his food down. Charles (Chuck) and Betty displayed a deep love for their son and willingly did all they could for him.

I think our friendship with the Whitfields, and later the Paul Kurtz family from Pennsylvania, was the seed time of our desire to do whatever possible to prevent late diagnosis and its devastating consequences. Lena May Kurtz was born in Sept. '67 and was in critical condition before being diagnosed. Lena May sustained both physical and mental disabilities. The Kurtz's were the first Mennonite family in PA to have a child diagnosed with MSUD.

The Kurtz family had their second daughter with MSUD, Pauline, on Feb. 26, 1970, and a little over a week later, we had our first daughter. Five days before Monte's fifth birthday, on March 7, 1970, Shayla Myrene entered our lives. Wayne drove her the 160 miles to Ann Arbor within 24 hours of birth. Three days later we were told she also had MSUD. She was small - 6 lb. 7 oz., 17, in. long - sensitive and colicky. With no one to care for Monte at home, I did not stay in the hospital with her until she was still not doing well at 2, months. When I was able to stay with her for several days at a time, she soon stabilized, coming home at 3, months. Pauline Kurtz only required a short hospitalization and seemed to do very well.

Growing Children

Monte made friends easily and was very lively and outgoing. We did not send him to kindergarten, and he had to repeat the first grade because of his short attention span. From then on he made average grades, and at 8 years of age his doctor said Monte's total mental and physical development was within normal range except for a slight hand tremor. At the age of 9, he was a dependable chore boy on our farm, strong enough to carry 50 lb. feed bags. He worked and played hard and was seldom sick.

At the same time Greg Whitfield was active with leg braces and a walker and doing well in classes at a special school for the physically disabled. He developed a skin rash when he was seven which worsened until his death in the fall of '74. After Thanksgiving of that same year, Monte seemed to have a mild case of the flu. Although he didn't seem very sick and his levels were not highly elevated, he went into a coma and died Dec. 6. It was all so puzzling and we understood so little.

The Whitfields had another daughter, Amy, born on Sept. 15, 1976. Like Shayla and

Pauline, she was diagnosed right after birth and, like Pauline, responded very quickly to treatment. Except for Shayla's poor start, all three girls were healthy physically with few or no hospitalizations.

Shayla walked at 12 months, dressed herself at 2 and taught herself to tie her shoes when 3 years old. We were unprepared for her difficulties when she began school. Her reading stalled at a beginning third grade level; she was hindered by a short attention span, had problems relating to others and limited reasoning ability. This slowed her learning considerably. However she was an expert at jumping rope and had only slight problems with fine motor coordination. Pauline Kurtz had some physical and mental disabilities. Amy Whitfield did well in school and developed normally. Why the differences when they each had the advantage of early diagnosis and why did Shayla have more problems than Monte? As we came to know other families, we learned that the effects of MSUD varied considerably in children. Some did very well, while others experienced mild to severe physical and mental diffiÐculties. Certainly early diagnosis and strict dietary control were critical but were other factors involved?

Seeking Support

When Monte was four years old, I sent a questionnaire to all the parents we knew, asking many questions trying to compare observations. I wrote to a doctor in New York and one in England, who had patients with MSUD, asking them to give the questionnaire to their families. We only received replies from several of the families we knew best, and were concerned when they could not answer many of the questions. Some parents did not know their child's amino acid levels, how much leucine the child was getting, and were not aware of home testing with DNPH.

In 1979 we started a circle letter among eleven families of our acquaintance. Each family added a letter as it circled and then removed their former letter on the next round. It provided a forum for sharing and support. By the beginning of '82 it included 22 families and 2 dietitians - some from Canada. The letter was taking a whole year to make the circle.

Getting Together

In 1980, Jonas and Mary Reiff sent out invitations to the families in the circle letter inviting them to an informal get-together in their home in Missouri. Only Leon Kennedys from Michigan and we could be there. It was a good time of sharing and another step in developing support.

Wayne and I began thinking about getting a group of families and professionals together for a day of learning from each other. Our doctor from Michigan, Dr. Richard Allen, and his staff were enthusiastic and encouraged us. He and his staff had started an MSUD parent group meeting for his patients while Monte and Greg were still living. Dr. Allen had always encouraged parent education and support. His clinic was following seven children with MSUD at that time. He and his staff planned to drive the 3 hours to our parochial school to share their expertise at our first symposium on May 23, 1982.

Of the 22 families, 16 attended (including 15 children with MSUD) traveling from as far as California. Other doctors, dietitians, public health nurses, medical technicians and local

college students, brought the number attending to almost 100 persons. It far exceeded our expectations, and we called on our local church group to help us with the promised free meals and overnight accommodations.

Dr. Janet Milne and Linda Chan, a research nutritionist, from The Hospital for Sick Children at Toronto, Ontario were the first speakers. They gave a summary of the treatment of seven children with MSUD followed at Toronto. Two children had died suddenly from brain edema and the doctors were currently treating high levels with peritoneal dialysis - a common treatment at that time for seriously ill children with MSUD.

Dr. Allen, a pediatric neurologist at the University of Michigan Medical Center, addressed the topic: what do metabolic diseases do to the brain? This was a new topic for many parents and they found it very interesting. He patiently answered many questions from the parents. (We learned we weren't the only ones with questions.)

Our dietitian, Debbie Hufstetler, discussed the goals of dietary treatment and introduced two new MSUD formulas, MSUD1 and MSUD2. Edward Schwartz, a psychologist on Dr. Allen's staff, led an informative discussion on coping with MSUD family problems. Several mothers wrote a sample of their child's daily diet on the blackboard, opening a time of lively discussion on various topics in the afternoon.

Those attending thought it was educational and helpful and proposed having another Symposium in 2 years. We also agreed to replace the circle letter with a newsletter.

This set the general pattern for most future symposiums - sponsored by parents with the help of their health care practitioners. Our first meeting would not have been possible without the enthusiastic help and cooperation of Dr. Allen and his staff. He and his staff deserve much credit for the beginning of our support group.

In the next issue of the Newsletter, I intend to continue this report on the development of our support group, Newsletters and Symposiums.