

Aunt Cathy's Guide to Nutrition Why Are Children with Chronic Illnesses or Handicapping Conditions at High Risk of Receiving Suboptimal Nutrition?



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Subtopic: Inborn Metabolic Errors

Adventures in Metabolic Nutrition 1982-Present In North Dakota and Northwestern Minnesota:

I sat down to make a list of all the inborn metabolic error conditions I could remember working with in preparation for this conference, and I was surprised by the number of different inborn metabolic errors I have encountered just in North Dakota and NW Minnesota (and I was also surprised that I could actually remember them! ☺)

For many of these conditions I have worked with only one or two patients, but for others like PKU and Beta-Oxidation Disorders there are actually quite a number of individuals affected. I'm sure I've missed some, but here's a quick list of metabolic error conditions seen in here, arranged by general categories. In the pages following the list I have noted the number of individuals seen with each condition and there are some comments and stories of possible interest about many of these. Feel free to not read all this ... I am just waLking (or typing) down memory lane a bit.

I. Protein / Amino Acid Metabolism Problems

Aminoacidopathies

Homocystinuria (HCU)

Glutaric Acidemia Type I (GA-I)

Isovaleric Acidemia (IVA)

Maple Syrup Urine Disease (MSUD)

Methylmalonic Aciduria (MMA)

Phenylketonuria (PKU) [the most common of the aminoacidopathies.]

Tyrosinemia

Urea Cycle Disorders

Argininosuccinic Acid Synthase Deficiency (Citrullinemia)

Ornithine Transcarbamylase Deficiency

II. Carbohydrate Metabolism Problems

- Congenital Disorder of Glycosylation Type 1a (CGD-1a).
- Congenital Fructosemia
- Galactosemia (Classic and Duarte Variants)
- Glycogen Storage Diseases
- Mucopolysaccharidosis
- Sucrase-Isomaltase Deficiency

III. Lipid Metabolism Problems

- Beta-Oxidation Disorders (AcylCoA Dehydrogenase Deficiencies)
 - Medium-Chain (MCADD);
 - Long Chain (LCADD)
 - Very Long Chain (VLCADD)
- Carnitine-Insufficiency-Related Conditions:
 - Primary Carnitine Synthetase Deficiency
 - Secondary Carnitine Insufficiency Conditions
 - Carnitine Palmitoyl Transferase I Deficiency (CPT-1)
 - Prader-Willi Syndrome (PWS)
- Elongation and Desaturation Defects of Essential Fatty Acids
- Lipoprotein Lipase Deficiency
- Smith-Lemli-Opitz Syndrome (SLO)

IV. Miscellaneous Vitamin or Mineral-Related Metabolic Errors

- Iron-related Metabolic Problems
 - Hemochromatosis
 - Sickle Cell Anemia
 - Thalassemia Minor
- Copper Metabolism Problems:
 - Menke's Kinky Hair Syndrome (Menke's Disease)
 - Wilson's Disease
- Cystic Fibrosis
- Genetic Defects in Bone and/or Skin Construction
 - Ectodermal Displasia
 - Epidermolysis Bullosa
 - Ichthyosis
 - Osteopenia Imperfecta
- Calcium and/or Vitamin D Metabolism Problems
 - Hydroxylation Defects in Vitamin D Metabolism
 - DiGeorge Syndrome
 - Williams Syndrome

Protein / Amino Acid Metabolism Problems

Aminoacidopathies:

Homocystinuria (HCU)
Glutaric Acidemia Type I (GA-I)
Isovaleric Acidemia (IVA)
Maple Syrup Urine Disease (MSUD)
Methylmalonic Aciduria (MMA)
Phenylketonuria (PKU) [the most common of the aminoacidopathies.]
Tyrosinemia

In these conditions, the ability to excrete the waste products of certain amino acids (the bits that link together to make up all proteins) is impaired, so the amino acid or a metabolite can build up and cause serious neurologic injury.

Additionally, some necessary substances usually made from that amino acid may be unavailable. For example, people with PKU can't make the amino acid tyrosine in a normal amount. In Maple Sugar Urine Disease, the branched-chain amino acids (leucine, isoleucine and valine) cannot be used as they normally would be as a critical back-up fuel source during illness. Because of this problem, people with MSUD may need to receive life-saving emergency room iv glucose if they get sick.

People with all of these “aminoacidopathy” conditions need to severely limit protein intake, and they must replace the protein that would normally have been obtained from the diet with a unique “Medical Food” that contains all the missing protein needed minus the one or more amino acids the individual cannot handle. The Medical Food (a formula) is an absolutely essential part of the management of these conditions ... trying to manage this kind of problem by just eating a low protein diet without the Medical Food is extremely dangerous.

These days, the Metabolic Food products are always being improved because There are several production companies in competition now. When I first took over as the metabolic nutritionist, I was startled to find that none of the PKU products the children were on contained ANY selenium or vitamin D, and they were inadequate in the amino acid tyrosine. **The scientific research was reporting consequences like cardiomyopathy and osteoporosis in children who carefully followed the PKU diet. The relative inadequacy of tyrosine (the amino acid that is unable to be made in the usual way in PKU) also was found to contribute to neurologic problems.**

Even now, not all PKU Metabolic Foods contain optimal amounts of many nutrients, so a careful look at the person's total intake of vitamins and minerals is still very important. It is also important to be sure that children learn to eat lots of fruits and vegetables. (Many foods are “low pro” but extremely non-nutritious; some people tend to end up with essentially the “Medical-Food-Plus-Skittles-Diet.”)

In addition to the required Medical Food, most of the people with aminoacidopathies also have to buy expensive low-protein versions of many foods, such as bread, noodles and rice in order to keep their protein intake.

The carefully formulated Medical Foods, however, are extremely expensive, in part because they are so hard to make and research. Additionally, the market for each product in a company's line of Metabolic Foods is typically extremely small. That means that unlike regular infant formulas, for example, all the cost of Research and Development of these products is distributed over a very tiny population. As a result, even with the high cost of the product to the consumer, these special Medical Foods are usually not profitable for the manufacturer.

As an example, at least 30 of my patients have required a phenylalanine-free Medical Food because they have been diagnosed as having the most common of the aminoacidopathies: PKU. But for each of the other protein and amino acid metabolism conditions listed above, I have worked with only one patient. That means that there is only a very tiny market for the manufacture and sale of each of the Medical Foods uniquely required by each individual.

Failure to obtain the appropriate Medical Food causes serous brain injury, the products are extremely expensive, and many insurance companies do not cover their cost. In North Dakota we are extremely fortunate to have a program that provides Medical Foods for infants and children with PKU and Maple Syrup Urine Disease. It also covers women with PKU through child-bearing age. Minnesota has no such program.

Unfortunately, males in ND do not receive any more Medical Food after age 23 because at the time the program was set up it was believed that the need for the special diet and Medical Food would only continue if a person were pregnant. However, the current medical understanding is that the use of the special diet and Medical Food is required for life, because very serious problems do develop if the diet is discontinued. Whereas some of the adult men have jobs and insurance to take on the cost of the Medical Food for themselves, others struggle and fail to get what they need. This is true for women over child-bearing age as well.

Because I work with families on both sides of the ND/MN border, I regularly see how remarkably difficult it is to obtain Medical Food for PKU on the Minnesota side. If the family has good insurance, they may have it covered, but if they have no insurance, or have insurance through certain companies, the family may have no help. For lower income families, Medical Assistance and WIC programs also vary across the borders. They may help ... or not. And there is no help there for the families with incomes above 185% of the poverty level.

In Minnesota, one family I worked with had insurance but the company simply refused to cover the Medical Food, and because it was a smaller company, there was a loophole in the law that allowed them to refuse payment if the company so chose. The

family had to choose between buying their child's brain-protecting Medical Food or making their house payments. They lost their home.

These "No Medical Food Coverage" scenarios are just one of many dilemmas from both sides of the border that our intrepid Social Worker Lindsey Scholar LSW struggles with daily on behalf of the families with Inborn Metabolic Errors. The physicians and I also write letters to insurance companies. In spite of great effort, we often do not succeed. Coverage for Medical Foods for inborn metabolic errors have also been denied by some insurers because they consider them a "pre-existing condition."

We all are extremely grateful for the present ND program that provides the critically needed medical foods for the age groups and genders with PKU and MSUD currently identified as eligible to receive this help. The cost is considerable, but it is a bargain compared with dealing with the severe mental retardation and other serious health consequences of being off-diet.

In addition to issues about stopping provision of Medical Foods in men and in women with PKU or MSUD, there is also another problem to work on: the individuals with any **other** Inborn Error of Metabolism are currently not provided with any needed Medical Food by our otherwise wonderful ND program, and often they also are not helped by other sources.

The threats to their brain development, overall health and quality of life are the same as for those we recognized earlier for untreated PKU or MSUD. We now screen newborns for many more conditions than just PKU and MSUD to identify those infants whose medical condition requires this kind of lifetime nutrition intervention. We do this screening because it is clear that starting the diet right away and following it for life can help prevent permanent injury and debilitation. We need to figure out some way to assure that the rest are protected somehow as well, although I do not know how this might be accomplished, or even if it can be done.

Because PKU represents such a large percentage of our IEM population, there are many interesting anecdotes that could be included here. One of the most memorable was my first visit with teenage female athlete who was very thin and who had very high phe levels in spite of severely limiting her protein intake. She had been advised to cut her protein intake more and more because her phe level was still too high. She was accused of sneaking high protein foods, and she was also suspected of having some kind of eating disorder.

After evaluating her intake, it turned out that she was so thin and had such high phe levels because she had been prescribed too low an intake of protein and calories. That resulted in muscle breakdown, which freed up phe from her own tissues. She was a very cooperative girl who always worked very hard at following her (inadequate) prescribed diet even though she felt very hungry most of the time.

Happy ending: fixing the prescription fixed all the problems and she went on to have fine control of her PKU. She is now all grown up, a college graduate with a professional career, married and the mother of two. This case illustrates how critical it is for the health care professional to carefully evaluate the prescribed diet ... and not just blame the person with the high phe level and assume that she is “cheating” on the diet.

Quantifying the Number of People seen here for Inborn Errors of Metabolism

Occasionally I have been asked to help quantify the number of non-PKU and non MSUD individuals with aminoacidopathies or other inborn metabolic errors that we see in order to estimate the cost of offering the same kind of Medical Food support we now provide just to people with MSUD and PKU. Here is the all-time list of individuals with non-PKU/non-MSUD inborn metabolic errors that I have seen in the past 25 years, and their current status:

1. Aminoacidopathies

Glutaric Acidemia Type I (GA-I) The baby is the one patient we have ever seen with this condition. He is on Medical Food formula currently provided by the WIC Program in ND, which he can receive only until he turns five. If this child were not from a family in ND below 185% of the poverty level, he would get no help. WIC programs in each state have their own rules about providing Medical Foods; some simply do not provide it. This baby is lucky to be here and to be from a family with an income low enough to qualify for WIC. (His Medical Food is not currently provided by the state program that assists with PKU and MSUD.)

Homocystinuria (HCU) The one patient we have seen was diagnosed late (as a 20-year-old) because no screening was done for this condition at the time of his birth. The diagnosis was made based on the phenotype of untreated children and adults, including significant brain, connective tissue and visual damage already present, and now confirmed by lab tests. We checked for a variant that is responsive to high-dose B vitamins and were fortunate to find that he had that type; HCU Medical Food turned out not to be necessary, but had he needed it, the necessary Medical Food would not have been provided by the state program that assists with PKU and MSUD.

Isovaleric Acidemia (IVA) The family of the one baby with this condition moved out of the region when he was about 9 months old.. He was part of an Air Force family and he also qualified for WIC until he turns five. (This product is not provided by the state program that assists with PKU and MSUD.)

Maple Syrup Urine Disease (MSUD) We have had only one child with this condition, and he has been receiving his Medical Food from the ND program. Now he is nearly twenty years old, in about three years he will no longer be eligible to receive his Medical Food through the program.

Methylmalonic Aciduria (MMA) The one child we have seen with this condition passed away at age seven. He was severely handicapped and medically fragile by the time the condition was identified because newborn screening for this condition was not yet done. He spent most of his life in and out of a hospital elsewhere because of many health problems. **This child is a good example of the potential cost of NOT doing neonatal screening and NOT initiating and maintaining an appropriate dietary regimen.** (This product is not provided by the ND program for PKU and MSUD.)

Phenylketonuria (PKU) in people over the age of participating in the ND program. In ND most people with PKU have access to necessary Medical Food either from our state program or through their own insurance as working adults. However, there are at least five individuals too old to receive Medical Food from our program and because of general debilitation they are not able to obtain it elsewhere or to succeed in efforts at employment that might provide insurance. Their continued poor control of PKU results in a downward spiral and increased health problems, which ironically ARE paid for as part of the usual medical programs for low income people. However treatment with standard medicine will not get at the source of the continued physical and mental problems related to poor control of PKU, so the medical problems will continue.)

Tyrosinemia Many years ago, one baby had this diagnosis and he then received a liver transplant to correct this disorder; Medical Food was only necessary for less than one year while awaiting transplant. (This product is not provided by the state program that assists with PKU and MSUD.)

Urea Cycle Disorders:

In normal metabolism any nitrogen waste left over from unneeded protein is converted into a harmless product called urea and the people pee it out (a technical term I use.) In Urea Cycle Disorders, there is compromised ability to convert nitrogen waste to urea. The nitrogen waste backs up and then shows up as high ammonia in the blood (hyperammonemia) which can hurt the brain. The different Urea Cycle Diseases reflect which step along the urea cycle is compromised. We have had patients with two types of Urea Cycle Disorders.

Argininosuccinic Acid Synthetase Deficiency (AASD, also called Citrullinemia) The one child we had with AASD was diagnosed only after she had gone into a coma from high ammonia levels in her blood a few days after birth. She survived a long intensive-care hospitalization, but her mental and physical development were never beyond the three-month-old level and she died at age four. All her life her family provided the appropriate Medical Food and managed her ammonia level beautifully, but the injury she experienced prior to diagnosis could not be corrected. She had multiple hospital admissions over her short life.

Her case illustrates the kind of harm that may be able to be prevented or ameliorated because of newborn screening. However, although the screening would have picked her up before she went into a coma and prevented the huge insult to her brain and the cost of multiple hospitalizations and therapies, the Medical Food products needed for her urea cycle disorder (very similar to the products for the aminoacidopathies like PKU and MSUD) are also not included in the ND Medical Food program. Luckily, this family had insurance coverage.

Ornithine TransCarbamylase Deficiency (OTC) This condition comes in more than one form. There are several patients with milder forms of OTC that usually result in risk of severe hyperammonemia only when there is metabolic stress, such as during an illness or pregnancy. Some people are diagnosed quite late in life because the pattern was not identified. There are **four young children** in the area with milder forms, and there was **one other child** who was diagnosed only a few months before she passed away. She was severely brain-injured and she and her family struggled with multiple health problems and hospitalizations during her seven years.

There are **two adult women** who are known to have a form of OTC as well. One of the women is in her 60s and she has only recently been identified as having this inborn error. The other woman was diagnosed as a child but taken off diet; she has some intellectual compromise, and pregnancy in women with this condition can be life-threatening. The younger woman came to our attention because she was already pregnant and had been off diet, which is a very high risk situation for her and the baby. We were able to obtain Medical Food for her through the WIC Program because she was currently 6 months pregnant, although initiating dietary control only after conception is not ideal in terms of birth defects, and this is especially the case when so much fetal development/construction would have already taken place.

Once she delivered the baby (who survived birth and has been in intensive care with the potential for very guarded outcome) she no longer qualified for Medical Food from WIC, and she will qualify again only if she becomes pregnant again. **The problem for those state WIC Programs that can provide Medical Food is that they can do so only after the pregnancy is advanced enough to be recognized and considerable fetal development will have occurred in a toxic environment.**

The effort to prevent birth defects and optimize pregnancy is the reason women continue to receive Medical Food through ND's PKU/MSUD program until past the child-bearing years. However, the Medical Food needed for other similar metabolic conditions is not provided even during actual pregnancy, and certainly not prior to conception. Had this young woman not had an income low-enough to qualify for WIC, she would have received no Medical Food at all.

Carbohydrate Metabolism Problems

[Not counting any genetic pre-disposition element as in development of Type I (Insulin Dependent) Diabetes and other Auto-Immune Disorders.]

Congenital Disorder of Glycosylation Type 1a (CGD-1a) **Two children** were found to have this disorder that features developmental delay, severe hypotonia, poor coordination, and severe seizures. Many children with this condition control seizures in part by using a ketogenic diet and they may need a carbohydrate-free formula (a Medical Food) for that reason. Accounting for a variety of drug/nutrient interactions and some other nutrition adjustments are usually necessary as well. In general (for all kinds of patients) vitamin/mineral supplements are not covered by either insurance or the WIC Program.

Congenital Fructosemia This condition is characterized by an inability to convert the simple sugar fructose (a common dietary component) to glucose in the liver. Fructose builds up and causes injury. Managing it requires an extremely restrictive diet that allows no fruit, no sucrose (table sugar) and no fructose, including any foods that might contain them. In addition to the very difficult diet for the family to manage, it also requires careful nutrient supplementation because so many foods must be removed from the diet.

No fructosemia-specific Medical Foods are used, although it may be necessary or helpful in some cases to use a special carbohydrate-free formula and replace the carbohydrate with glucose. This is because some formulas use corn syrup that may contain fructose, or sucrose which clearly does. This condition is rare and the **one child** with this was picked up after age three, and only after significant permanent injury had occurred because no screening was available. The outcome has not been good.

Galactosemia (Classic and Duarte Variants) In galactosemia it is the simple sugar galactose that cannot be converted into glucose in the liver, and the build-up of galactose is injurious to the brain. Milk sugar (lactose) also contains galactose, so all milk sugar must be avoided. Certain other foods (e.g. tomatoes and persimmons) contain galactose as well so they must be avoided.

The difference in the two variants is that the classic form is not outgrown and galactose must be avoided life-long. In the Duarte variant, the ability to metabolize galactose improves over time so that by about one year of age the need to so carefully avoid galactose decreases markedly. This condition does not require a specific Medical Food because soy-based formulas are easy to obtain. We have worked with families of **two children with classic galactosemia, and 5-10 with the Duarte variant.** That Duarte variant number is vague because I only see these babies once or twice before they can go to a normal diet so I am relying on memory here.

Our oldest child with Classic Galactosemia was identified only after going into a coma with e. coli sepsis because no regular neonatal screening for galactosemia was available at that time. She was transferred to our NICU and stayed there with us for quite a while because she was very sick. **Neonatal screening will prevent this formerly typical scenario associated with this disease.**

Glycogen Storage Diseases result in a build-up of storage carbohydrate in the form of glycogen in the liver. The dietary management component includes limiting carbohydrate quantity and type, and timing its intake. Fasting must be avoided. We have had at least **two children** with this kind of condition. Dietary adjustments do not involve special Medical Foods but attention needs to be paid to nutrient replacement because of the restricted diet. As usual, vitamin/mineral nutrient replacement is not covered by insurance.

Mucopolysaccharidosis (Hurler and Hunter Syndromes) These conditions result from a defective enzyme so that there is a build-up of glycoaminoglycans (formerly called mucopolysaccharides.) The result is disfigurement, impaired development and it is usually fatal in childhood unless treated. Treatments include liver transplant and a new approach using enzyme-replacement therapy. There is no effective dietary or nutritional treatment for condition, so no special Medical Foods are utilized. Attention to nutrient density and micronutrient replacement is important because of the generally very small total food intake. Again, the vitamin/mineral replacement is not covered by insurance.

Sucrase-Isomaltase Deficiency This is a very rare absence of a digestive enzyme and the effect is chronic malabsorption, diarrhea, severe irritability and failure to thrive. We have had **two siblings** with this diagnosis who had other digestive problems as well. They ultimately did well on a special carbohydrate-free Metabolic Food with the carbohydrate then replaced in the form of glucose so no digestion was required. One child needed a true elemental formula for two years.

Paying for the Medical Foods was a huge burden to this family because insurance did not cover it, they were not quite below the 185% poverty level in order to qualify for WIC, and the state program for PKU and MSUD Medical Food did not include these Medical Foods. This family split up over this stressful situation.

As the children matured they had better tolerance of some other carbohydrates, and this was especially so when an experimental sucrase-replacement enzyme product was taken with meals. Interestingly, one of the children was later diagnosed as having celiac disease in addition, although all testing for celiac had come back negative until she was about six years old.

Lipid Metabolism Problems

Beta-Oxidation Disorders:

**Mitochondrial AcyCoA Dehydrogenase Deficiencies
affecting metabolism of various chain-lengths of fat molecules, including:**

Medium-Chain	(MCADD)	<u>(at least six children)</u>
Long Chain	(LCADD)	<u>(two children)</u>
Very Long Chain	(VLCADD)	<u>(one child)</u>

Beta-oxidation is a process that “chops up” fat molecules to a size small enough bit to fit into the cell’s furnaces (the mitochondria.) If fat can’t fit into the furnace it can’t be burned efficiently for fuel to run the body. The size markers in the name tell how far the fat molecule gets chopped before the process can’t go any farther. Fasting is avoided. A lower-than-average fat content and higher carbohydrate proportion in the diet is helpful. Interestingly, VLCLADD usually requires using MCT oil instead of long chain fat for fuel, whereas MCT is precisely the fat that children with MCADD can’t use.

Carnitine has a key role in carting fat into the mitochondria in the cells so it can be chopped up and used for fuel. (You can remember Car-ni-tine as “Cart-it-in” ... works for me.) Most of these conditions also benefit from providing extra carnitine to help remove unusable partially chopped up fat remnants that must be carted back out of the mitochondria.

If a child with one of these conditions becomes ill, emergency carbohydrate treatment may be necessary to prevent severe hypoglycemia. MCT oil is generally not covered by insurance, nor is it covered by ND’s program for PKU and MSUD.

Carnitine-Insufficiency-Related Conditions:

Primary Carnitine Synthetase Deficiency (one child)

In this condition one fails to make adequate carnitine because the enzyme that does the job is not operating appropriately. It means that many fats (from dietary intake or those in baby’s fat stores) cannot be burned for fuel, so the baby is unable to switch from burning carbohydrate to burning fat when fasting ... sort of like having a “dual heat” furnace the switches back and forth to electric fuel or gas, but then having one of the systems down. In that situation, the baby can only burn carbohydrate fuel, and then it can burn up more carbohydrate than it can afford to burn. The result is a injuriously low blood sugar causing brain damage or death.

It used to be thought that primary carnitine synthetase deficiency did not exist because no diagnosis of it had been made. But what was actually happening was the affected baby would often be a victim of SIDS (Sudden Infant Death Syndrome) and the true cause was not identified.

Happily, this potentially life-threatening condition can be easily managed if it is picked up by newborn screening ... which it now is. We met our first case of this condition only a few months after it began to be screened for in ND, and I am happy to report that our little princess with this condition is healthy and thriving, and she can expect to live a totally normal life. She doesn't need me to nag her about her diet ... she just needs to keep taking her carnitine and having the physician adjust the amount upward as she grows. Lifetime carnitine replacement is needed, so treatment is providing oral carnitine throughout the day. No special Medical Food is required.

Secondary Carnitine Insufficiency:

**Conditions related to other metabolic problems including Beta-oxidation disorders, familial hypotonia, and the use of certain medications.
(many ND children and some adults)**

Secondary carnitine insufficiency can result from conditions that increase requirements (like MCADD, as described earlier) or from impaired production due to the use of medications like the epilepsy medication valproic acid. Regardless of the cause of carnitine insufficiency, it is treated by providing supplemental carnitine. No special Medical Food is required.

I have found that many children and adults have demonstrated significant improvement in exercise tolerance, hypotonia, muscle strength and/or weight management with appropriate carnitine supplementation, including some who had been labeled at a medical center as having "familial hypotonia of unknown origin." At least two of our patients with PKU have also demonstrated clear benefit from carnitine supplementation. In several situations, the carnitine replacement was life-changing, allowing the individual to lead a much more normal life. In all cases I do know why each one had the symptoms of carnitine insufficiency or how the supplementation helped, but doing a trial on supplementation in symptomatic individuals is reasonable and it can be very helpful.

For more information about carnitine, please see my handout
"By Request: A Short Carnitine Discussion that Might Be Helpful."

Carnitine Palmitoyl Transferase I (CPT-1) Deficiency (two children)

No special Medical Food is required. Carnitine replacement is helpful for different reasons in each type. Carnitine Palmitoyl Transferase-1 Deficiency is a metabolic defect in

transferring long-chain fats into the mitochondria to burn them for fuel. The nutritional management of CPT-1 includes a diet with a relatively high percentage of calories provided as carbohydrate (about 70%) and a relatively lower proportion coming from fat (<20%) to provide fuel from glycolysis (glucose metabolism) and to avoid having to rely on fat fuels being available.

The enzyme defect is less of a problem if some of the fat fuel used is in the form of MCT (medium chain triglycerides) because MCT does not require the enzyme system for crossing into the mitochondrial membrane. Carnitine supplementation does not correct the enzyme defect, but it IS helpful in converting potentially toxic long-chain acyl-CoAs to safer acylcarnitines.

Infants would benefit from using a special formula that is fat free or very low in fat. An example is a product that consists of just the protein, vitamins and minerals of infant formula but contains no carbohydrate or fat. This would allow the clinician to add the fats and carbohydrates of choice in appropriate amounts. No special Medical Food are generally needed in older children, except for possible supplemental MCT oil, and consideration of micronutrient adequacies as always.

Prader-Willi Syndrome (PWS) (over ten children)

This condition is caused by the partial deletion of an arm of the 15th chromosome. It has many potentially detrimental effects on the body and development, but a traditionally seen pattern of features is extremely low muscle tone, excessive weight gain exercise intolerance and a powerful drive to eat. No specific Medical Food is required for this condition, but some caloric adjustments of formula can be useful (e.g. to use the fat and carbohydrate-free formula powder to prepare a product with addition of a lower than average carbohydrate and fat proportion but normal vitamin, mineral, protein and fluid volume. Example: One can produce a 10 kcal/oz or 15 Kcal/oz infant formula with the protein, vitamin and mineral content of a standard 20 Kcal/oz formula for children who need many fewer calories while having typical requirements of other nutrients.

Additionally ... and importantly ... it appears that at least some of the hypotonia, excessive drive to eat and weight gain can be much improved by supplementing carnitine and CoQ10. We have many patients who have responded very well to this intervention. One therapy commonly employed in children with PWS is growth hormone therapy. It is quite expensive and precious ... so it is useful to realize that correcting any carnitine and/or CoQ10 relative insufficiency will be necessary to allow the hormone to be maximally effective.

I have encountered two older children who already had severe obesity and problems with high blood sugar. They had been treated for some time with Glucophage (Metformin) to control the high blood sugar. Because this medication impairs vitamin B12 absorption I asked to have this vitamin level checked. Both were found to be quite vitamin B12 deficient. Vitamin B12 deficiency can cause serious neurologic injury and

failing to monitor it is a serious problem for anyone on the medication. They were also very low in several other nutrients, including vitamin D.

PWS is a condition in which nutrient adequacy is rarely evaluated, in part because the children are often at least overweight (even with treatment) and so they look “well nourished.” A closer look usually detects compromised intake of essential nutrients.

For more information on nutrition issues in PWS, please see my handout “About the Prader Willi Syndrome Association’s Food Guide Pyramid for Weight Control (with Some Editorial Comments from Me.)”

Elongation and Desaturation Defects of Essential Fatty Acids

These defects in altering the chain length and number of double bonds in a fat molecule make the usually non-essential fatty acids EPA, ARA and DHA be essential along with linolenic and linoleic acid. It appears that some degree of compromise of these pathways may be quite common but often unrecognized. Interestingly, there are a number of studies now suggesting that the provision of some ready-made EPA, ARA and DHA is potentially beneficial in some people with PKU, and that it can have a positive influence on intellectual development in that population. I have had **one patient** with PKU who clearly demonstrated that he also had a defect in this area that was contributing to some attention deficit problems. Regular fish-oil supplementation was clearly beneficial in an ABAB trial.

A poor elongation/desaturation situation is looking to be common enough that the American Heart Association recommends that everyone either eat fatty fish twice weekly or take 1000 mg fish oil daily to assure an intake of ready-made EPA and DHA (EicosaPentanoic Acid and DocosaHexanoic Acid). These fats have many health roles; they are well known to affect inflammation, blood clotting, vision and brain function. There is no reason to assume that people who happen to have some inborn error of metabolism do NOT need to follow the same advice unless it is specifically contraindicated.

For more specific information on this issue, please see my handout “My Current Top Five Easy Ways to Improve Your Family’s Nutrition.” Additional details and illustrations are included in my handouts “Nutrition and Breast Cancer” and “OTHER Nutrition Issues in Diabetes.”

Lipoprotein Lipase Deficiency (LLD) (one child)

This condition impairs removal of fatty acids from lipoprotein carriers in the bloodstream, so the fatty acids do not enter the cells as they should. The amount of fat that remains in the blood stream is too high. That is, the person has hypertriglyceridemia. Limiting long-chain fats is a typical intervention. Providing some of the fats in the form of MCT (which is not dependent on the lipoproteins needed for transport of long chain fat

in the blood) can be useful. Additional interventions that may assist with particular types of metabolic-defect-related triglyceride problems are supplemental carnitine and fish oil. Both are benign and reasonable to consider.

Smith-Lemli-Opitz Syndrome (SLO) (a Defect in Cholesterol Synthesis)

Cholesterol is critical for the health of all cell membranes, for myelin production in the nervous system, and for steroid hormone production. The SLO metabolic defect impairs the conversion of 7-dehydrocholesterol to cholesterol, with potentially devastating results on development. We have had **two children** with this condition ... one who has a less severe defect than the other. Treatment includes providing ready-made cholesterol, traditionally with making them eat a ton of egg yolks (difficult and frequently unsuccessful,) and now with the use of a special Medical Food that consists of a powdered additive form of ready-made cholesterol to be added to the diet.

There are some circumstances where it is also beneficial to avoid giving a diet high in substances that tend to increase cholesterol production in some people, like a high saturated or trans fat intake. This is because any metabolic effort on the part of the child with SLO to produce more cholesterol will (of course) fail at that aim, but in the process it may result in increased production of precursors to cholesterol like 7-dehydro-cholesterol. Excessive accumulation of these precursors appears to be potentially detrimental.

This is one reason why some old recommendations to give heavy cream as a “good cholesterol source” (instead of using egg yolk or the cholesterol in the Medical Food form) are particularly deserving of going away. Not only is it a lot of saturated fat and extremely low in essential fatty acids, but it isn’t even a rich source of ready-made cholesterol.* (“Oh, fine!”) Unfortunately, I have found that this old recommendation is still being described as useful in some guidelines in spite of the clear reason to avoid it.

[* Comparison: One Tablespoon of heavy whipping cream has 21 mg of cholesterol which is only 1/10 the amount provided by a single egg yolk (210 mg cholesterol.)]

The provision of generous pre-formed cholesterol can help with many problems of a peripheral type, like skin issues and cell-membrane functions. Unfortunately, though, it does not seem to be very successful at causing cholesterol to enter the brain because of the blood-brain barrier. The cholesterol molecule is simply too large to cross from the blood into the brain. The brain has to rely on making its own cholesterol to make myelin, the greasy coating on nerves that speeds up the messages being sent. That means that some of the intellectual development issues are not as amenable to improvement from providing pre-formed cholesterol. The cholesterol additive Medical Food is not covered by the ND program for PKU and MSUD.

Miscellaneous Vitamin or Mineral-Related Metabolic Errors

Iron-related

Hemochromatosis (3)

Inability to limit absorption of iron from the intestine results in injurious abnormal deposition of iron in soft tissues. Excessive iron load affects oxidation status and antioxidant requirements. One adult patient that I saw somewhat accidentally had severe anemia, and overt scurvy (plus other micronutrient deficiencies) because of erroneous (but not uncommon) nutrition advice for treating his disease.

An interesting note: vitamin C deficiency (scurvy) often presents in the US with bleeding gums, and it is seen most often in association with alcohol abuse impairing the individual's nutrient intake. A second physical marker of scurvy is distinctive cork-screw curls in the chest hair of vitamin C deficient men. This patient had both symptoms along with very severe fatigue.

More generous than usual intake of selected nutrients can be critical in supporting the treatment of this condition (phlebotomy) because it allows for more frequent phlebotomy activity and also for improved daily functioning. This man was unable to have any more phlebotomy treatments because his hemoglobin was simply too low. In other words, he still had plenty of iron on board --- way too much -- inappropriately deposited all over his body. But the only way to get it out again is to use it to make new red blood cells, and then remove the red blood cells by phlebotomy. If hemoglobin is too low, phlebotomy cannot occur, and the toxic excessive iron stays in place..

His low hemoglobin also impaired energy production which contributed to his severe fatigue. Antioxidant nutrients and phytochemicals minimize some oxidative damage to organs from iron deposits. Supporting active production of new red cells facilitates more frequent phlebotomy to help reduce the iron load and it also results in much better physical strength and endurance.

(Please see my "Nutrition Support of Hemochromatosis Therapy"
handout for specific guidelines.)

Sickle Cell Anemia (3)

People with this condition have shorter red blood cell life because of breakage of the oddly shaped red blood cells. The need for transfusions may contribute to problems with iron accumulation and oxidative damage to tissues, so generous antioxidant intake is important. Additionally, the short life of the red blood cells means that the individual will be trying to make new red blood cells at a faster than normal rate. Failure to provide a generous intake of key non-iron nutrients required for red blood cell production (e.g.

protein, vitamin B6, B12 and folic acid, zinc and others) can necessitate more frequent transfusions. This trait is most common in people of African heritage.

Thalassemia Minor (1)

This condition also results in shorter life span of red blood cells and chronic microcytic anemia. (Thalassemia Major is much worse, but I have not had a patient with that form.) The condition is most common in people of Mediterranean ancestry. The one case of Thalassemia Minor I have encountered was at a conference for health professionals in northern Minnesota. A young dietitian asked me during a break for suggestions for her chronic anemia, which persisted in spite of taking really huge prescription amounts of iron. (When it did not improve, more and more inorganic iron was prescribed.) After discussing and ruling out some other possible causes of her anemia and noting her dark hair and olive complexion, I asked her if she had any ancestry from the Mediterranean area. Her parents were originally from Lebanon.

I suggested that she ask her doctor to consider Thalassemia Minor as a possible cause of the anemia. She called me later to say that it turned out to be the correct diagnosis and so the treatment plan had totally changed. The case was memorable primarily because it illustrated another problem: recognizing conditions that are rare in a particular region. She lived in a Nordic/Germanic heritage region. In other parts of the country (or even elsewhere in the state) she would likely have had the condition diagnosed much more quickly.

Copper Metabolism Problems:

Menke's Kinky Hair Syndrome (Menke's Disease) (2)

Infants/Children with this condition have an inability to absorb copper at the intestinal level. The condition is characterized by brittle kinky hair (if they have hair yet), developmental delay, bone malformations and fragility, and "cherub facies." It is invariably lethal. The two cases I have encountered both illustrate the importance of identifying metabolic conditions like this even though the child's ultimate lifespan and development will not be aided by the diagnosis.

The first child had been admitted to the hospital (again) at about age one, and he was unable to go home because he was unable to maintain his temperature and because of other problems. He was in intensive care for months and no diagnosis had yet been determined, although many tests were being run. The family struggled for a long time to be both at the bedside and home with siblings.

I was on educational leave and came up to Pediatrics just to visit. One of the nurses asked me to look at the little guy. I noted his unusual hair and suggested checking a ceruloplasmin level for copper deficiency. The physician agreed and the diagnosis was made. The child went home on hospice. This allowed the family to have him with them

at home for the rest of his short life. It also saved a great deal of money because the continued testing and hospitalization could be appropriately ended. It is likely that this child too was slow to be recognized because of his Germanic/Nordic heritage ... it tends to be associated in many of our babies (including this one) with remaining essentially bald until a year of age, so the distinctive hair showed up later.

The second child was even more memorable because he was in foster care and his Daddy was in jail, having been charged with child abuse. The baby had radiographic evidence of a history of several fractures, which along with his extreme developmental delay was presumed to be a result of maltreatment. The child wore a helmet to protect against head injury. He was attending one of our pediatric clinics for children with developmental issues for the first time.

The alert pediatric dietitian in our Coordinated Treatment Center, Nicole Welsch RD, saw that he had amazingly dry and kinky hair. It had always been attributed by his caretaker and home physician as being caused by wearing his helmet. As Nicole and I know many children with helmets and normal hair, this explanation was unsatisfactory. She suspected Menke's Disease, and asked me to take a look at the boy. I agreed with her and she asked the physician at the clinic to check for it.

As a result, the correct diagnosis of the copper metabolism defect was made and Daddy was let out of jail. The bone issues and developmental delay were classic for that condition and no abuse had ever occurred. Additionally, because that condition is invariably lethal, besides the grief of losing his child, the father could have been unfairly charged with murder and carry that label the rest of his life. It had already caused the break-up of the family. So even though the child with an inborn metabolic error may have an extremely poor prognosis regardless of what we may do, there are many other reasons why early diagnosis can be very beneficial.

Wilson's Disease (1)

People with this condition have an inability to excrete copper normally in the bile, so over time it builds up and is deposited in tissues, including the liver, brain and other organs. This young man was a college student being worked up for an enlarged liver, and he was found to have some characteristic eye changes as well. Another name for Wilson's Disease is hepatolenticular degeneration.

The diet/nutrition-related features in the treatment of this condition include limiting copper-rich foods (while replacing the other nutrients they would have provided,) administering oral zinc acetate to compete with copper for absorption at the intestinal level, and providing generous (low copper) antioxidant nutrients and phytochemicals to help protect against the additional oxidative damage associated with the build-up of copper. Medical interventions may include chelation therapy to remove copper, and in the extreme a liver transplant may be needed. If the condition is identified and then managed well, the person with Wilson's Disease can live a normal life.

Cystic Fibrosis (Sodium/Chloride metabolic defect)

This condition tends not to be categorized as an inborn metabolic error in part because it is so common (and “inborn metabolic diseases” are assumed to be rare,) and also because the actual sodium/chloride-related basic genetic defect has been elucidated relatively recently. However, it results from an inborn disruption of the transport of the minerals sodium and chloride due to a malfunctioning CFTR gene.

CF is well-known to contribute to a wide range of potentially life-threatening nutrition-related problems due to intestinal malabsorption of many nutrients and other consequences of the primary defect in many organs including the lungs. Special nutrition interventions to prevent the serious malnutrition that would otherwise develop have made a big difference in the growth, health and longevity of people with CF. They usually need digestive enzymes with meals, treatment for stomach acid reduction, and higher levels of a variety of nutrients. Other key parts of their therapy include antibiotic treatments and a variety of percussive techniques and medications to help remove tenacious mucous from the lungs.

In 1982, when I first started working at St. Luke’s/MeritCare/Sanford Medical Center, the life expectancy of children with CF was 14 years. That was up from 7 years just a few years earlier. This picture is much improved now because of more understanding of the many ways this condition can affect health ... and ways to get around it. I no longer even know what the “life expectancy” is for CF; I am thrilled to say that some of my “children” with CF are now in their thirties and forties.

Genetic Defects in Bone and/or Skin Construction

Ectodermal Displasia (2)
Epidermolysis Bullosa (1)
Ichthyosis (1) and
Osteopenia Imperfecta (3)

All of these need nutrition interventions to improve the outcome, including wound healing, vitamin D production, intestinal problems and many other issues even though they cannot correct the primary defect. For example, vitamin D inadequacy is quite common in all three, and correcting inadequacy does not correct the primary metabolic problem.

However, none of these children need an added burden of having over 200 vitamin D hormone receptors throughout the body with no vitamin D available to provide key hormonal messages. The overzealous removal of vitamin D from children’s nutrition program has the potential to induce dangerous vitamin D deficiency, negatively affecting the child’s immune system, muscle strength, bone pain, risk of developing autoimmune diseases and other systems.

For one memorable child with **epidermolysis bullosa** I asked his physician to check the child's vitamin D level because the condition requires sun avoidance plus almost constant skin bandaging. These would surely suggest that he was at increased risk of deficiency even if he DID have the ability to produce vitamin D normally in spite of his major skin production error ... which I have not seen studied. He also lived in the north and had severe nutritional problems related to eating difficulties from the effects of the disease on his mouth and tissues lining the gastrointestinal tract. His dietary intake of vitamin D was very low and no vitamin D supplements were part of his care plan.

I wanted the level checked because I suspected that a prescription therapeutic dose would be needed. The physician did not check the level because he felt that there was no need to do so nor was there a need to provide supplemental vitamin D or other nutrient supplementation recommended to support the boy's constant need for wound healing. End of story.

For a good example of the breadth and depth of nutrition issues in treating this kind of condition please see my handout "Nutrition for People with Epidermolysis Bullosa" from my presentation at the National DEBra Patient Care Conference in Nashville. (DEBra is the Dystrophic Epidermolysis Bullosa Research Association of America.)

Calcium and/or Vitamin D Metabolism Problems, including
Hydroxylation defects in vitamin D metabolism (4)
DiGeorge Syndrome (3)
Williams Syndrome, (3)

The individual with a **hydroxylation defect in vitamin D metabolism** is most often unable to adequately convert the storage form of vitamin D (25-hydroxy vitamin D) to the active hormonal form (1,25-dihydroxy vitamin D in the kidney.) As noted earlier, the hormonal form provides instructions for over 200 tissues by sending messages to the vitamin D receptors. [There are also some known genetic defects in vitamin D receptor function seen as well, but I have not worked with these conditions.]

People with impaired conversion of the vitamin have sometimes been found to have neurologic problems like unusual MS ("unusual" in that it is very rapidly progressing or appearing very early, etc.) Happily, once this problem is identified it is not hard to provide 1,25 dihydroxy vitamin D because it is already available at pharmacies and used for people with inadequate conversion of vitamin D because of kidney disease.

I have seen **four cases** of gradations of the hydroxylation defect ... one in a 24 year old woman who had **MS** but was already totally paralyzed. I was consulted and a 1,25 dihydroxy vitamin D was ordered. It was extremely low in spite of an adequate storage form of vitamin D. Unfortunately, she passed away the day after the labs came

back so there is no way to know if intervention would have been at all useful at that late stage in her medical condition.

One lady with a new diagnosis of MS was found to have generous vitamin D intake but very poor conversion to the hormone form. This lady had significant slowing of the progression of her MS with 1,25 dihydroxy vitamin D treatment. She was observed to need significantly more than the usual dose to maintain an appropriate level.

A young girl aged 10 had been diagnosed with MS, and she had already experienced loss of motor coordination that was affecting her ability to participate in sports. As she was very young to be diagnosed with MS, we obtained a 1,25 dihydroxy vitamin D level. It turned out to be quite low in spite of a normal amount of the storage form of vitamin D. Subsequent treatment with the hormonal form substantially slowed the rate of development of her MS symptoms.

There is misunderstandings about the role of vitamin D in the problem of the potential for hypercalcemic events in **Williams Syndrome**. I saw one little boy who had been fed an overtly vitamin D deficient diet for the first year of life (breast-fed exclusively without supplementation, and no milk products given as he diversified his food intake, and he lived in the north.) However, his physician would not approve my request to check his vitamin D level because “if it is low I would have to give him vitamin D but you can’t give any vitamin D to children with Williams Syndrome.” Supplementation even at RDA levels was also not approved. Another End of Story.

Interestingly, it appears that part of the calcium problem sometimes seen in Williams Syndrome is related to bone breakdown (not due to excessive vitamin D or excessive hydroxylation of the storage form) and it has been shown to be stopped in emergency rooms with the osteoclast inhibitors used as a tool to prevent bone breakdown in people battling osteoporosis. This makes inducing a lifetime of vitamin D deficiency even more unattractive as the primary way to prevent potential hypercalcemic episodes.

A Final Word About Plain Old Vitamin D Inadequacy (from the Vitamin D Queen)

When we check vitamin D levels, a large proportion of our entire IEM population has been found to have vitamin D deficiency regardless of their diagnosis.

This is primarily not because of the Inborn Metabolic Error. It is because THEY LIVE UP HERE. The incidence of poor vitamin D status is very high in this region, and a metabolic error does not confer immunity. Our patients do not need one more metabolic problem tripping them up. **This is one reason why we automatically check (and correct) the vitamin D status of all of the people attending our metabolic clinics**, in addition to whatever labs are required for their specific condition. I confess that I regularly nag any and all family members present as well. ☺

For more specific information on this issue, please see my handout “My Current Top Five Easy Ways to Improve Your Family’s Nutrition.”
