Ignorance, Uncertainties, and Controversies

Or

What have we learned in 50 years?
Where are we now?

- Dozens of disorders classified as organic acidemias/acidurias and fatty acid oxidation disorders.
- Most of the locations on the KNOWN metabolic map are named; but, there is still some *terra incognita*. 
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Natural History

- Originally—patients identified by illness. Investigated, treated, followed.
- Realization that there were mild, intermittent, late-onset forms of many disorders; realization that there might be more severe, dramatic forms that could be lethal in utero.
NOW....

- Expanded newborn screening—
  - Finding the ‘classical’ patients, treating them earlier, (hopefully) leading to improved outcomes.
  - Finding others—
    - Would they get ill eventually?
    - How many families will be unnecessarily panicked? When can they relax?
Some examples

- 3-MCC (3-methylcrotonyl-CoA carboxylase) deficiency
  - Occasional illness
  - Many never become ill—disorder discovered by newborn screening of infant leading to recognition of asymptomatic condition in mother.
Examples--2

- **Biotinidase deficiency**—
  - Severe form absolutely needs treatment
  - What about milder forms? Treatment is safe, convenient, inexpensive—no reason not to “play it safe”

- **SCAD deficiency**—
  - How can there be such uncertainty?
    - Innocent bystander? Only part of the story?
Examples--3

- Mild forms of nearly everything else
  - VLCAD, LCHAD, MSUD, citrullinemia, hypermethioninemia (S-adenosylmethionine synthase deficiency), etc.
What makes them mild?

- Signals to transcribe the DNA (gene)
- Regulation of translation (enzyme/protein synthesis)
- Intrinsic activity of the molecule
- Increased numbers of abnormal molecules (increased synthesis, decreased recycling)
- Modifiers of the molecule—vitamin co-factors, small helper molecules, response to temperature (fever)
Alternative ways of thinking

- Recognition that many disorders are similar to toxins—accumulation of substrates, insufficiency of products, production of new substances
- Recognition that many FOD/OAA disorders have a lot in common with disorders of energy production (mitochondrial OXidative PHOSphorylation disorders).
Alternative Ways of Thinking--2

- Therefore think about addressing the problems according to what we know about the other conditions.
- i.e., Besides thinking about altering diets because of limitations, think directly about measuring and improving mitochondrial function. Exercise? Diet? Supplements?
Mitochondrial digression

IN GENERAL, increased frequency of feeding, high-carb diet, certain supplements (to meet RDA; some/lots more), avoiding drugs and other substances that can damage mito function. Will this help OA/FOD patients?
After diagnosis—then what?

- Long-term issues/late complications
Some Assumptions

- Everyone eats what is best, or at least adequate for them.
- Likewise for fluid intake.
If you are already compromised, these assumptions may cause you to overlook problems.

- Kidney problems in MMA—normal creatinine level (reassuring regarding kidney function), may actually be high (based on body muscle mass)

- Fluid intake may be inadequate—slight dehydration can lead to limited ability to excrete toxic by-products
Brain problems

- Organic acidurias can lead to brain problems—
  - Poor executive function
  - Poor learning
  - ADHD behaviors
  - Emotional lability/mood problems
  - Autism spectrum
- What’s the connection? Can we learn from children without OAs who have similar problems?
Organ Recital
Organ Recital--1

- Brain—stroke, stroke-like episodes
- Eye—retina, lens, cornea
- Ear
- Gut
- Heart
- Skeletal muscle
- Smooth muscle
Organ Recital--2

- Kidneys
- Bone (osteoporosis)
- Bone marrow (blood cell production)
- Immune function
- Endocrine glands—thyroid, adrenals, pancreas, parathyroids, ovaries, testes.
Care—by whom?

- Infants and children—access to specialists.
  - Direct
  - Telemedicine, internet, Dr. Wiki
  - Parent support groups
- Adults—
  - Even bigger shortage of trained physicians
  - Transition clinics—just beginning in US.
    Some experience elsewhere—UK, Australia, etc.
Education

- Common/standardized education—vocabulary, familiarity, etc.
  - Newborn Screening ACT sheets, websites.
  - North American Metabolic Academy (NAMA)
- What about
  - North American Parents’ Academy (NAPA)?
  - To provide background for this meeting. How does the New England (Yale—Dr. Seashore) fall meeting work?
TREATMENTS

- Carnitine (L-carnitine)
  - For deficiency—how defined?
    - Plasma vs muscle (tissue) levels
    - The first MCAD patients typically had low muscle carnitine levels, even if the plasma levels were normal (between episodes of hypoglycemia/illness).

- Carnitine for MCAD deficiency? All the time? Just when sick? What does age have to do with it?
  - Would acetylcarnitine (acetyl-L-carnitine) be better?
  - What about prescription vs OTC?
TREATMENTS--2

- Fasting –how long? Overnight at what age? Maximum interval when healthy?
  - For MCAD deficiency?
  - Long-chain defects?
  - Organic acidemias
- G-button—solution or problem?
- Indwelling catheter—”?”
How to provide fuel for long-chain FODs?

- How to limit use of long-chain fats—daily life, exercise, illness.
- Medium-chain triglycerides? Replaces (sort of) what is missing; will be used quickly, not stored.
- Triheptanoin (yields acetyl-CoA and propionyl-CoA) vs
  - Hydroxybutyrate (a ketone body)—as an acid? (yuck factor); as a sodium salt? (high sodium intake).
How to provide fuel for OAs?

- All all calories equivalent?
- “Standard” fat vs less? Can diet composition be optimized? Are all meals the same? How much leeway is there?
- Snacks before exercise? Afterwards? During? Simple carbs? Any benefit to natural foods vs synthetic?
INFLAMMATION IS EVERYWHERE

- Coronary artery disease, Alzheimer disease, diabetes, obesity...
- So what about the OAs/FODs?
  - Why not? If so, what?
- Does this connect with oxidative stress?
  - Probably.
- What about mitochondrial dysfunction?
  - Probably.
ABNORMAL LAB RESULTS

- Problem? Or Response?
- Low carnitine—problem or the body’s defensive response?
  - Consider fever—
- High glycine in PA, MMA—probably not a problem.
  - No evidence that glycine is increased in the brain in these disorders, unlike NON-ketotic hyperglycinemia.
MITO “COCKTAIL”

Every metabolic mixologist has his/her own favorite ingredients—
- Alpha lipoic acid (ALA)
- Coenzyme Q10 (many forms, not necessarily equivalent for efficacy, tolerance, etc.)
- Creatine (how much? How often?—Dr. Harding); precursor of creatinine (work for the kidneys)
- Riboflavin?
Cocktails—another round

- Pantothenic acid (or pantothenol?)—starting point for Coenzyme A synthesis
  - (Should we try to enhance CoA availability, or does the body limit it for reasons we don’t understand?).
- A digression—oxygen—friend or foe?
  - Depends on where you are and who you ask.
- Thiamine
- Folate (can it get where it’s needed? What about into the brain? What form is best?)
- Vitamin B12—what form?
WHOSE METABOLISM IS IT, ANYWAY?

- Lots of pathways. We pay attention to ours. What about our companions?
- Our FLORA.
  - They outnumber us.
  - How many genomes are we talking about?
  - How many different combinations are there?
  - How do they react to being in a body with PA, MMA, etc.?
The company we keep

- Just starting—
  - Production of propionate by gut flora. From?
    - What we eat?
    - What we shed/secrete?
  - What to do about it?
- Production of trimethylamine from carnitine. Or choline.
- Production of ammonia—from protein/amino acids. Don’t forget constipation as a factor/variable. Menstruation also.
More company

- Viruses—altering immune function. (If you’ve had mono, you probably haven’t forgotten it).
- Bacteria—Strep. Rheumatic fever. Sydenham’s chorea. And now PANDAS.
  - Watch out for sudden changes in behavior—better or worse. PITANDS.
- Chronic infections? Any reason to think they might be a problem for the kind of immune deficiency seen in OAs (PA, etc.)?
WHERE HAVE WE BEEN?

- Ignorance—still lots, but maybe a little less than a few years ago.
- Uncertainty—even more, because we know lots more, but the picture is still fuzzy in many ways.
- Controversy—plenty, but less than in the past, and not so intense.

Stay tuned for more.