OVERVIEW
The Spectrum of Mitochondrial Disease
Robert K. Naviaux, MD, PhD

Mitochondrial biology is one of the fastest growing areas in genetics and medicine, connecting scientific disciplines ranging from embryology to cancer, to infectious disease. Indeed, disturbances in mitochondrial metabolism are now known to play a role not only in rare childhood diseases, but have also been implicated in many common diseases of aging, including heart disease, diabetes, Parkinson disease, and dementia. This article is a brief update on mitochondrial biology for primary care physicians, genetic counselors, and other health care professionals who may find themselves involved in the care of children with mitochondrial disease and their families.

A Different Mitochondrion for Every Tissue
Physicians, and most biologists, are taught that mitochondria are monomorphic little sausages in our cells that make adenosine triphosphate (ATP*). In reality, mitochondria take on many different shapes and subserve a great number of different metabolic functions. Each mitochondrion’s shape is characteristic of the specialized cell in which it resides. (See EXCEPTIONAL PARENT, June 1997, pp. 40-42 for slides of the various shapes of mitochondria.)

All told, there are about 250 different cell types in the human body. The genes expressed in each cell type are tailored to meet specialized needs by selective transcription. In the same way, each mitochondrion is tailored to meet the needs of the cell in which it resides. In effect, there are different mitochondria with specialized metabolic functions for many of the 250 different cell types in our body. Most of our body’s nucleated cells contain 500 to 2000 mitochondria. In the cone cell photoreceptors of the eye, mitochondria make up 80% of the intracellular volume. In extraocular muscles like the lateral rectus, they account for 60%, and in heart muscle they comprise 40% of the volume of the cell.

Some cell types have only a few mitochondria. Platelets, for example, have only two to six mitochondria. Red blood cells do not contain mitochondria, but their cellular precursor, the proerythroblast, is critically dependent on mitochondrial function as it differentiates into a mature red blood cell.

Mitochondria are the only cellular organelles known to have their own DNA* (mitochondrial DNA* or mtDNA), distinct from the nuclear DNA* (nDNA). Defects in nDNA can be inherited from either parent but, due to a quirk in the process of fertilization, defects in the genes of the mtDNA are maternally inherited.

Energy Factories and Much More
The conventional teaching in biology and medicine is that mitochondria function only as “energy factories” for the cell. This oversimplification is a mistake which has slowed our progress toward understanding the biology underlying mitochondrial disease.

It takes about 3000 genes to make a mitochondrion. Mitochondrial DNA encodes just 37 of these genes; the remaining genes are encoded in the cell nucleus and the resultant proteins are transported to the mitochondria. Only about 3% of the genes necessary to make a mitochondrion (100 of the 3000) are allocated for making ATP. More than 95% (2900 of 3000) are involved with other functions tied to the specialized duties of the differentiated cell in which it resides. These duties change as we develop from embryo to adult, and our tissues grow, mature, and adapt to the postnatal environment.

Some cell types contain 500 to 2000 mitochondria. In heart muscle they comprise 40% of the cell's volume. In extraocular muscles like the lateral rectus, they account for 60%, and in heart muscle they comprise 40% of the volume of the cell.

**TABLE 1**
The Protein Complexes of the Mitochondrial Electron Transport Chain

<table>
<thead>
<tr>
<th>Complex</th>
<th>Enzymatic Activity</th>
<th>Inhibitors</th>
<th>Mitochondrial Subunits</th>
<th>Nuclear Subunits</th>
<th>Tissue-Specific Isoforms</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>NADH:CoQ Oxidoreductase</td>
<td>Rotenone</td>
<td>7</td>
<td>43+</td>
<td>Yes</td>
</tr>
<tr>
<td>II</td>
<td>Succinate:CoQ Oxidoreductase</td>
<td>Malonate</td>
<td>0</td>
<td>4</td>
<td>Yes</td>
</tr>
<tr>
<td>III</td>
<td>CoQ:Cytochrome bc1 Oxidoreductase</td>
<td>Antimycin</td>
<td>1</td>
<td>10+</td>
<td>Yes</td>
</tr>
<tr>
<td>IV</td>
<td>Cytochrome c Oxidase</td>
<td>Cyanide, Azide, CO</td>
<td>3</td>
<td>10</td>
<td>Yes</td>
</tr>
<tr>
<td>V</td>
<td>ATP Synthase:Proton Translocator</td>
<td>Efrapentin, Oligomycin</td>
<td>2</td>
<td>14</td>
<td>Yes</td>
</tr>
<tr>
<td>DHO-QO</td>
<td>Dihydroorotate:CoQ Oxidoreductase</td>
<td></td>
<td>0</td>
<td>1</td>
<td>No</td>
</tr>
<tr>
<td>ETF-QO</td>
<td>Electron Transfer Flavoprotein:CoQ Oxidoreductase</td>
<td>0</td>
<td>1</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>ANT</td>
<td>Adenine Nucleotide Translocator</td>
<td></td>
<td>0</td>
<td>1</td>
<td>Yes</td>
</tr>
</tbody>
</table>
ammonia in the urea cycle. Mitochondria are also required for cholesterol metabolism, for estrogen and testosterone synthesis, for neurotransmitter metabolism, and for free radical production and detoxification. They do all this in addition to breaking down (oxidizing) the fat, protein, and carbohydrates we eat and drink.

**Mitochondrial DNA**

The standard sequence to which all human mtDNA is compared is called the “Cambridge Sequence.” It was sequenced from several different human mtDNAs by a Medical Research Council (MRC) laboratory based at Cambridge, UK, in 1981. Fred Sanger, the distinguished biochemist, received his second Nobel Prize in part for this work. The mitochondrial chromosome of the Cambridge Sequence is 16,569 bases in length and predominantly circular, although linear forms of the same length are also found. It encodes 13 proteins, 22 tRNAs, and 2 ribosomal RNAs.

In practice, when the mtDNA of any single person is sequenced, a number of variations from the Cambridge Sequence are noted. The vast majority of these differences are simply polymorphisms and are not clinically significant. In fact, one region of mtDNA, called the Control Region (previously known as the D-loop), is so polymorphic that it has become useful for forensic purposes in providing a “DNA fingerprint” of suspects in criminal investigations.

Fig. 1 is a map of the morbid anatomy of human mtDNA. It lists a few of the known pathological mutations and the diseases to which they may lead. Unlike nDNA, where inherited mutations are almost always present in the same number in every cell of the body (one copy for dominant and X-linked, and two for recessive disorders), the abundance of mtDNA mutations can vary dramatically from cell to cell, and even from tissue to tissue. The term heteroplasmacy refers to this coexistence of wild-type (naturally occurring, nonmutant) and mutant mtDNA within the same cell (intracellular heteroplasmacy), and between different cells (intercellular heteroplasmacy).

The presence of a mutation in some copies of the mtDNA does not lead inexorably to disease. For example, some people may have detectable amounts of the NARP mutation in their blood but remain symptom-free until very old age. Others with exactly the same mutation may die in the first two years of life. Such heteroplasmacy makes genetic counseling and prenatal diagnosis of mtDNA diseases extremely difficult. At present, we do not have a sufficient understanding of the

*Refer to Glossary on Page 20*
### TABLE 2

**The Spectrum of Mitochondrial Disease.**

This table presents just a sample of the many genetic and acquired disorders that can result in primary or secondary disturbances of mitochondrial function. It demonstrates the importance of the intergenic dialogue in contributing to the wide variety of disorders associated with mitochondrial dysfunction.

**Some disorders known to be associated with mtDNA mutations**
- MELAS
- MERRF
- NARP
- Myoneurogastrointestinal disorder and encephalopathy (MNGIE)
- Pearson Marrow syndrome
- Kearns-Sayre-CPEO
- Leber hereditary optic neuropathy (LHON)
- Aminoglycoside-associated deafness
- Diabetes with deafness

**Some mendelian (nDNA) disorders of mitochondrial function involving regulation of fuel homeostasis**
- Luft disease
- Leigh syndrome (Complex I, COX, PDH)
- Alpers Disease
- MCAD, SCAD, SCHAD, VLCAD, LCHAD
- Glutaric aciduria II
- Lethal infantile cardiomyopathy
- Friedreich ataxia
- Maturity onset diabetes of young
- Malignant hyperthermia
- Disorders of ketone utilization
- mtDNA depletion syndrome
- Reversible COX deficiency of infancy
- Various defects of the Krebs Cycle
- Pyruvate dehydrogenase deficiency
- Pyruvate carboxylase deficiency
- Fumarase deficiency
- Carnitine palmitoyl transferase deficiency

**Some mendelian (nDNA) disorders with secondary disturbances in mitochondrial function†**
- Hemochromatosis
- Wilson disease
- Batten disease
- Wolff-Parkinson-White††
- Huntington disease
- Menkes disease
- Lesch-Nyhan syndrome

† nDNA mutations affecting proteins that are not located in the mitochondria but which alter mitochondrial function.

†† WPW generally has a non-mitochondrial cause but is sometimes seen in conjunction with cases of Complex I deficiency.

**Some primary disorders of intramitochondrial enzymes**
- Methylmalonic acidemia
- Erythropoietic porphyria
- Propionic acidemia
- Acute intermittent porphyria
- Variegate porphyria
- Maple syrup urine disease
- Nonketotic hyperglycinemia
- Hereditary sideroblastic anemia
- OTC Deficiency
- CPS Deficiency

**Disorders Sometimes Associated with Mitochondrial Dysfunction.**

<table>
<thead>
<tr>
<th>Polycyclic and Genetotrophic</th>
<th>Autoimmune</th>
<th>Environmental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aging</td>
<td>Multiple sclerosis</td>
<td>AZT toxicity</td>
</tr>
<tr>
<td>Type II diabetes mellitus</td>
<td>Systemic lupus</td>
<td>FIAT toxicity</td>
</tr>
<tr>
<td>Atherosclerotic heart disease</td>
<td>erythematosis</td>
<td>Lead, cyanide and mercury poisoning</td>
</tr>
<tr>
<td>Parkinson disease</td>
<td>Rheumatoid arthritis</td>
<td>Ackee fruit toxic hypoglycemia</td>
</tr>
<tr>
<td>Alzheimer dementia</td>
<td>Thyrotoxicosis</td>
<td>Doxorubicin cardiotoxicity</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>Primary biliary cirrhosis</td>
<td>Aminoglycoside ototoxicity and nephrotoxicity</td>
</tr>
<tr>
<td>Maternally inherited migraine</td>
<td>Procainamide lupus</td>
<td>Amytal poisoning</td>
</tr>
<tr>
<td>Niacin-responsive hypercholesterolemia</td>
<td>Guillon-Barré syndrome</td>
<td>Carbon monoxide poisoning</td>
</tr>
<tr>
<td>Postpartum cardiomyopathy</td>
<td></td>
<td>Amphotericin nephrotoxicity</td>
</tr>
<tr>
<td>Alcoholic myopathy</td>
<td></td>
<td>MPTP Parkinsonism</td>
</tr>
<tr>
<td>Wernicke encephalopathy</td>
<td></td>
<td>Vitamin deficiencies such as pellagra, beriberi, rickets, and ICU axonal neuropathy and pernicious anemia</td>
</tr>
<tr>
<td>Reye syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burkitt lymphoma (BCL2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer metastasis (NM23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritable bowel syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastroparesis-GI dysmotility</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
pathogenesis and development of these diseases to make reliable predictions.

Bioenergetics and the Electron Transport Chain*
Mitochondria produce energy in the form of ATP through the concerted actions of about 100 proteins located in and on the inner mitochondrial membrane (Fig. 2). These proteins are collectively called the electron transport chain (ETC) or respiratory chain (RC). They function as a molecular bucket brigade, passing electrons down an energy gradient, while pumping hydrogen ions (protons) out of the mitochondrial matrix into the space between the inner and outer mitochondrial membranes. This space becomes positively charged and acidic relative to the mitochondrial matrix. The resulting gradient of hydrogen ions stores chemical energy in the form of a chemiosmotic potential. The mechanism by which the proton chemiosmotic potential is harnessed to generate the energy used to produce ATP was first elucidated in 1961 by the British biochemist Peter Mitchell, who received the Nobel Prize in 1978 for this work.

The ETC is conventionally said to consist of five complexes. Each complex is actually a collection of as many as dozens of proteins working together in a large macromolecular assembly to produce the catalytic reducing power that we measure with standard ETC assays. Only the first three complexes pass along electrons. The fourth complex (COX) uses the electrons it receives to reduce dissolved oxygen (O$_2$) to water (H$_2$O). The fifth complex is the ATP synthase itself.

In addition to the named complexes I through V, three other complexes are essential for the normal function of the ETC. These are dihydroorotate:CoQ-oxidoreductase (DHO-QO), electron transfer flavoprotein:CoQ oxidoreductase* (ETF-QO), and the adenine nucleotide translocator* (ANT). Their relative locations within the ETC are indicated in Fig. 2 and their enzymatic activities are listed in Table 1.

Reactive Oxygen Species and Apoptosis
Under normal circumstances, ATP synthesis is strictly coupled to oxygen consumption. However, during fever, in certain mitochondrial diseases, and in cancer, mitochondria become partially “uncoupled” and more oxygen is consumed than is actually used to make ATP. Under these circumstances, free radical production by the ETC is dramatically increased.

Free radicals are a subset of molecules known as reactive oxygen species. These molecules participate in signaling pathways, but may also react with many different molecules in the cell to produce oxidative damage. When mtDNA residues are oxidized, they become more difficult for the mitochondrial polymerase to copy accurately, resulting in deletions, rearrangements, and other mutations. Lipids in the mitochondrial and cellular membranes are peroxidized, becoming stiff and leaky. Proteins may be damaged and partially unfolded by oxidation.

There is growing evidence that the production of reactive oxygen species is controlled during infectious illness by cytokines and is involved in signaling pathways that sometimes lead to a kind of programmed cell death called apoptosis. This is a highly evolved and sophisticated process designed to sacrifice certain infected cells in the body by killing them, thereby limiting the spread of infection to neighboring cells. In a number of mitochondrial diseases, however, this process backfires and certain critical cells, like neurons in the brain, may suffer excessive losses by apoptosis, leading to the neurological setbacks associated with infections that are so common in mitochondrial diseases.

Defining Mitochondrial Disease
Mitochondrial diseases are the result of either inherited or spontaneous mutations in mtDNA or nDNA which lead to altered function of the proteins or RNA molecules that normally reside in mitochondria (Fig. 1). Problems with mitochondrial function, however, may only affect certain tissues as a result of factors occurring during development and growth that we do not yet understand. Even when tissue-specific isoforms of mitochondrial proteins are considered (Table 1), it is difficult to explain the variable patterns of affected organ systems in the mitochondrial disease syndromes seen clinically.

Genocopies of Mitochondrial Diseases
Because mitochondria perform so many different functions in different tissues, there are literally hundreds of different mitochondrial diseases. Each disorder produces a spectrum of abnormalities that can be confusing to both patients and physicians in the early stages of diagnosis. Because of the complex interplay between the hundreds of genes and cells that must cooperate to keep our metabolic machinery running smoothly, it is a hallmark of mitochondrial diseases that identical mtDNA mutations may not produce identical diseases. Genocopies are diseases that are caused by the same mutation but which may not look the same clinically.

Phenocopies of Mitochondrial Diseases
The converse is also true: different mutations in mtDNA and nDNA can lead to the same diseases. In genetics, these are known as phenocopies. A good example is
### TABLE 3
#### Atypical Presentations of Mitochondrial Disease

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Atypical Features</th>
<th>Mitochondrial Defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epilepsy</td>
<td>Abrupt onset at 1-8 years with or without infection, worse at night, nonfocal EEG</td>
<td>mtDNA deletions, rearrangements and point mutations</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Seizures</td>
<td>MELAS</td>
</tr>
<tr>
<td>Isolated language delay</td>
<td>Elevated blood lactate</td>
<td>MELAS</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td>Worse with infections</td>
<td>NARP, GAI</td>
</tr>
<tr>
<td>Type II diabetes</td>
<td>Asthenic, hearing loss</td>
<td>MELAS</td>
</tr>
<tr>
<td>Leukodystrophy</td>
<td>Hypotonia</td>
<td>mtDNA deletions and rearrangements</td>
</tr>
<tr>
<td>Autism</td>
<td>Seizures</td>
<td>mtDNA duplications and deletions</td>
</tr>
<tr>
<td>Sudden Infant Death Syndrome (SIDS)</td>
<td>Hypoglycemia</td>
<td>NARP, MCAD, LCHAD</td>
</tr>
<tr>
<td>Leukemia</td>
<td>Maternally inherited thrombocytopenia</td>
<td>mtDNA deletions and rearrangements</td>
</tr>
<tr>
<td>Migraines</td>
<td>Hearing loss, strokes, diabetes</td>
<td>MELAS</td>
</tr>
<tr>
<td>Early hearing loss</td>
<td>Age &lt; 40 years</td>
<td>MELAS, LCHAD</td>
</tr>
<tr>
<td>Refractory infantile reflux</td>
<td>Carnitine deficiency, fall-off in growth at 6 months</td>
<td>GAI, LCHAD, MELAS phenocopies</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>Seizures</td>
<td>mtDNA mutations</td>
</tr>
<tr>
<td>Liver failure</td>
<td>No known viruses or toxins, elevated lactate</td>
<td>Mitochondrial polymerase deficiency and/or mtDNA depletion</td>
</tr>
<tr>
<td>Blindness</td>
<td>Optic atrophy, dystonia</td>
<td>LHON</td>
</tr>
<tr>
<td>Renal tubular acidosis</td>
<td>Elevated lactic acid, hypotonia</td>
<td>Complex I deficiency, COX, mtDNA deletions</td>
</tr>
<tr>
<td>Heart failure</td>
<td>Nonvalvular hypertrophic cardiomyopathy before age 50</td>
<td>mtDNA deletions, rearrangements and point mutations</td>
</tr>
<tr>
<td>Chronic pancreatitis</td>
<td>Stroke-like episodes</td>
<td>MELAS</td>
</tr>
</tbody>
</table>

Leigh syndrome, which can be caused by about a dozen different gene defects. Leigh syndrome, originally a neuropathological description of the brain of one affected child, was described by Denis Leigh, the distinguished British physician, in 1951. Today we know it as one of the more deadly mitochondrial diseases, leading to characteristic bilaterally symmetrical MRI abnormalities in the brain stem, cerebellum, and basal ganglia, and often accompanied by elevated lactic acid levels in the blood or cerebrospinal fluid. The mortality rate is about 50% per year after diagnosis. Leigh syndrome may be caused by the NARP mutation, the MERRF* mutation, complex I deficiency, cytochrome oxidase* (COX) deficiency, pyruvate dehydrogenase (PDH) deficiency, and other unmapped DNA changes. Not all children with these DNA abnormalities will go on to develop Leigh syndrome, however. Fig. 3 is a Venn diagram that illustrates this point.

Mitochondrial diseases are even more complex in adults because detectable changes in mtDNA occur as we age and, conversely, the aging process itself may result from deteriorating mitochondrial function. There is a broad spectrum of metabolic, inherited and acquired disorders in adults in which abnormal mitochondrial function has been postulated or demonstrated (Table 2).

**Unexpected Presentations of Mitochondrial Disease**
The complex cellular specialization of mitochondria leads to a dizzying array of signs and symptoms that physicians at

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*REFER TO GLOSSARY ON PAGE 20*
specialized referral centers have come to recognize as characteristic of mitochondrial disease. Symptoms may range from clumsiness, to migraines, seizures, diabetes, or catastrophic metabolic disease, and yet be totally absent in healthy relatives who are silent carriers. Many combinations of symptoms are possible.

Fig. 4 emphasizes the variety of disorders that can result from defects in mitochondrial metabolism. Most patients in these categories do not have mitochondrial disease. Physicians encounter patients in each category, however, who are “atypical.” It is among these atypical cases that mitochondrial disease is more common. For example, a child who is diagnosed with leukodystrophy but is hypotonic is atypical because leukodystrophy usually produces progressive spasticity and hypertonia. Table 3 lists some of the atypical features that should raise the possibility of mitochondrial disease, along with some examples of causes that have been found in each category, although the actual prevalence of mitochondrial diseases, even among these abnormal cases, is unknown and probably quite low.

Many mitochondrial disorders are so new that they have not yet made it into the medical textbooks or, in some cases, the medical literature. Consequently, most physicians are not able to recognize them reliably. Even physicians working in highly specialized referral centers who see dozens cases of mitochondrial disease every year are struck by the great diversity of signs and symptoms of these diseases.

Moving Toward a Diagnosis
The primary care physician should remember this relatively simple rule of thumb: “When a common disease has features that set it apart from the pack, or involves 3 or more organ systems, think mitochondria.” Fig. 5 is a check-list used to help referring physicians collect the necessary medical records for evaluation of a suspected mitochondrial disease. Most of the tests listed are relatively noninvasive and serve to guide further diagnostic studies.

An EEG, brain MRI, and a specialized muscle biopsy are frequently required if the first few studies suggest mitochondrial disease. Although there is some controversy, many specialists believe that fresh, not frozen or fixed, muscle tissue for isolation of mitochondria is essential for a reliable diagnosis. Unfortunately, this technology is only available in a few centers.

If there is any hepatomegaly or splenomegaly, or if the brain MRI shows a leukodystrophy, white blood cells should be sent for enzyme assays to rule out lysosomal storage disease. Adrenal leukodystrophy (ALD) should be ruled out by blood analysis or very-long-chain fatty acids.

In general, after the first few noninvasive studies suggest the possibility of a mitochondrial or metabolic disease, the patient should be referred to a specialized medical center where more comprehensive evaluation and treatment can be performed. For more information on testing or specialized labs and centers, visit the Biochemical Tests List or contact the Council of Regional Networks for Genetics Services (CORN) (see Resources).
Dietary, Vitamin and Cofactor Therapy
No single drug, diet, or vitamin has emerged as a panacea for mitochondrial disease. Time and again, physicians working at specialized metabolic centers are reminded that every child is biochemically unique. Two children with precisely the same point mutation* in their DNA, nominally leading to the same disease, may respond to medication and nutritional interventions in different ways. No patient should receive a treatment simply because he or she is known to have a specific mutation in their mitochondrial or nuclear DNA.

If a measured deficiency in blood or muscle carnitine is found, or if an elevation in urinary carnitine esters is found, the muscle carnitine is found, or if an elevation or nuclear DNA.

specific mutation in their mitochondrial interventions in different ways. No nominally leading to the same disease, may respond to medication and nutritional interventions in different ways. No patient should receive a treatment simply because he or she is known to have a specific mutation in their mitochondrial or nuclear DNA.

If a measured deficiency in blood or muscle carnitine is found, or if an elevation in urinary carnitine esters is found, the primary cause for these abnormalities should be systematically sought (see Fig. 5). Premature institution of L-carnitine therapy without an adequate diagnostic work-up may lead to delays or failure in establishing an accurate diagnosis. In addition, the use of L-carnitine therapy alone remains controversial in certain long-chain fatty acid abnormalities (e.g., VLCAD and LCHAD) and organic acid abnormalities (e.g., certain forms of 3-methyl glutaric aciduria). In these specific disorders, glycine is used either alone, or in conjunction with a reduced dose of L-carnitine.

When in doubt, consultation with a metabolic specialist is advised.

Patients with a suspected mitochondrial disease who are referred to our center are often placed on a combination of coenzyme Q10*, vitamin E, a balanced B-vitamin supplement called “B50”; and, in some cases, carnitine when indicated. Carnitine and coenzyme Q10 can be made by the body, but may become depleted in a number of disease states and must be supplemented to avoid clinical symptoms. This procedure is not followed by all specialists in the field, however.

Because mitochondrial and metabolic disorders involve defects at an exceedingly fundamental level in cell function, no vitamin or cofactor therapy is curative except in very rare and specific disorders such as primary carnitine deficiency or primary coenzyme Q10 deficiency. We have sometimes seen significant improvements in quality of life with vitamin and cofactor therapy even when overall longevity is not substantially increased. Nevertheless, physicians are cautioned to remember that over-the-counter health food supplements are considered food products rather than medicine; their quality is not regulated by the FDA, nor is there any published, peer-reviewed research that has tested the efficacy of these supplements in patients with mitochondrial disease. There is a need for reputable sources for these products for our patients and for research that proves their effectiveness. Physicians should also carefully consider how supplementation may affect diagnostic assays before prescribing them. Parents and adult patients are cautioned not to start new vitamin, cofactor, or nutritional therapies without the advice and supervision of their physician. Specific therapeutic interventions should be guided by a metabolic specialist.

### TABLE 4
**Vitamin and Cofactors for the Treatment of Mitochondrial Disease**

<table>
<thead>
<tr>
<th>Name</th>
<th>Biochemical Function</th>
<th>Dose</th>
<th>Divided</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coenzyme Q10</td>
<td>Electron transport, free radical scavenger</td>
<td>4 mg/kg/d</td>
<td>qD or BID</td>
</tr>
<tr>
<td>“B50” Complex (1 tablet)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiamine (B1)</td>
<td>Decarboxylation, transketolase, memory</td>
<td>50 mg</td>
<td></td>
</tr>
<tr>
<td>Riboflavin (B2)</td>
<td>Fatty acid oxidation, flavoproteins</td>
<td>50 mg</td>
<td></td>
</tr>
<tr>
<td>Niacin (B3)</td>
<td>Electron transport, ADP-ribosylation, cholesterol</td>
<td>50 mg</td>
<td>qD for &lt;10 kg</td>
</tr>
<tr>
<td>B6</td>
<td>Amino acid, glycogen, steroid metabolism</td>
<td>50 mg</td>
<td>BID for &gt;10 kg</td>
</tr>
<tr>
<td>Folate</td>
<td>1-carbon metabolism, RNA/DNA, amino acids</td>
<td>0.4 mg</td>
<td></td>
</tr>
<tr>
<td>B12</td>
<td>Ile, Val, Thr, Met metabolism, Met synthesis</td>
<td>0.05 mg</td>
<td></td>
</tr>
<tr>
<td>Biotin</td>
<td>Carboxylation, gluconeogenesis, lipid metabolism</td>
<td>0.05 mg</td>
<td></td>
</tr>
<tr>
<td>Pantothenic acid</td>
<td>CoA synthesis, energy and lipid metabolism</td>
<td>50 mg</td>
<td></td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Free radical scavenger</td>
<td>200-400 mg</td>
<td>qD for &gt;10 kg</td>
</tr>
<tr>
<td>L-carnitine† (Carnitor®)</td>
<td>Fatty acid transport, metabolite excretion</td>
<td>100 mg/kg/d</td>
<td>TID</td>
</tr>
<tr>
<td>Intercurrent Illness Supplement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin C</td>
<td>Antioxidant, neurotransmitter synthesis</td>
<td>25 mg/kg/d</td>
<td>QID, or qD if sustained release</td>
</tr>
<tr>
<td>Zinc-picolinate</td>
<td>Superoxide dismutase, tissue repair</td>
<td>30 mg</td>
<td>BID for &gt;20 kg</td>
</tr>
<tr>
<td>Biotin</td>
<td>Carboxylation, gluconeogenesis, lipid metabolism</td>
<td>10 mg</td>
<td>qD for &gt;10 kg</td>
</tr>
<tr>
<td>α-lipoic acid</td>
<td>Antioxidant, NMDA protection, glutathione sparing</td>
<td>10 mg/kg/d</td>
<td>qD for &gt;10 kg</td>
</tr>
</tbody>
</table>

† When indicated, after excluding disorders where the use of carnitine is controversial.

The vitamins, cofactors, and doses indicated are those used by Dr. Naviaux and do not imply endorsement by the MMDC, EXCEPTIONAL PARENT magazine, or the advisory board for this Special Report, nor has this treatment been tested by clinical trials in patients with mitochondrial disorders or in peer-reviewed studies. All treatment should be implemented only with the advice and supervision of a physician.
In addition to any vitamin and cofactor therapy, each child should receive a comprehensive nutritional evaluation by a registered dietitian trained in the nutritional management of metabolic diseases. This is routinely performed as part of a comprehensive metabolic assessment at some, but not all, specialized medical centers.

Fasting hypoglycemia is a common, nonspecific finding in younger children with a number of mitochondrial diseases. If fasting hypoglycemia is found, the child may need to receive more frequent feedings. If this does not work, cornstarch may be used to provide a sustained-release source of glucose. In these cases, a disorder of fatty acid oxidation should be excluded. Renal tubular acidosis is also a relatively common, nonspecific finding in mitochondrial disease. Its recognition and treatment are essential to promote normal growth and bone development.

Children with mitochondrial disease are at risk for neurological setbacks either during, or in the first week after, an intercurrent infectious illness. Although no therapy is entirely protective under these circumstances, our center will sometimes place a child known to be at risk on a supplemental regimen of vitamin C, biotin, zinc, and α-lipoic acid for three to seven days, as well as prescribe any antibiotics or other measures that may be indicated for the specific infection. This regimen is stopped when the child returns to his or her baseline level of health.

From Diagnosis to Progress
Thoughtful physicians have long recognized that naming a disease can be a two-edged sword. While many mitochondrial, metabolic, and other chronic medical conditions have technical names that help physicians classify the diseases, these very terms can also blind them to alternative diagnoses and therapies. It is essential to remember that not every disease with the same name behaves in the same way, or has the same underlying cause. Often a medical term is used to describe a large collection of disorders. Just as “leukemia” describes not one, but dozens of disorders with different etiologies, so may many disorders have a variety causes and manifestations, including atypical ones.

The lesson to remember about mitochondrial diseases is that unless the pathogenesis for the “common disease” is known with confidence, the diagnosis is never really established. Progress starts by saying, “This disease is different.”

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