



Metametrix Handbook

Clinical Reference Manual

Metametrix
Clinical Laboratories
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Comments:

0091 Organix™ Comprehensive Profile

This report is not intended for the diagnosis of medical or non-medical entities of metabolism.

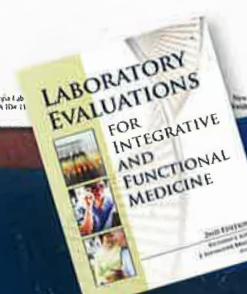
Ranges are for ages 13 and over

NUTRIENT MARKERS

Fatty Acid Metabolism (Carnitine & β-2)

Results: ug/mg creatinine

	Percentile Ranking by Quintile					
	1st	2nd	3rd	4th	5th	
1. Adipate	4.9	11	●	7.3		≤ 11.7
2. Bubrate	1.5	1	1	2.0		≤ 3.7
3. Palmitoleate	4.2	H	3.5			≤ 6.3
4. α-Linoleate	2.3	11	●	4.2		≤ 7.1
5. Isocitrate	5	1	1	2.7		≤ 4.7
6. β-Hydroxybutyrate	H	11	1	2.7		≤ 9.7
7. Citrate	350	1	●	622		≤ 1,032
8. Cr-Aconitate	25	1	1	54		≤ 98
9. Isocitrate	85	1	●	106		≤ 157
10. α-Ketoglutarate	15	11	1	22		≤ 38
11. Succinate	13.5	H	12.5			≤ 25.7
12. Fumarate	1.80	H	0.50			≤ 1.69
13. Malate	1.4	1	1	1.4		≤ 3.2
14. Hydroxymethylglutarate	5.1	H	4.2			≤ 8.0



A practical and succinct guide for personalized medicine from the publishers of LABORATORY EVALUATIONS FOR INTEGRATIVE AND FUNCTIONAL MEDICINE

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The Metametrix Mission

Much of the healthcare industry is focused on treating symptoms rather than investigating underlying causes of disease. At Metametrix, our mission is to improve health worldwide by providing clinical laboratory services in the areas of nutrients, toxicants, hormonal balance, biotransformation and detoxification, gastrointestinal function, and the microbiome. Physicians use our services to custom tailor nutritional therapies, detoxification programs, and other lifestyle changes for the prevention, mitigation, and treatment of complex chronic disease.

Common Abbreviations

α -AAA	alpha amino adipic acid
α -ANB	alpha amino n-butyric acid
α -ANB/LEU	α -amino-n-butyrate/leucine ratio
5-HIAA	5-hydroxyindoleacetic acid
5-HTP	5-hydroxytryptophan
AA	arachidonic acid
ACE	angiotensin-converting enzyme
ACTH	adrenocorticotrophic hormone
ADMA	asymmetric dimethylarginine
AGA	anti gliadin antibody
ALD	adrenoleukodystrophy
AMN	adrenomyeloneuropathy
ATP	adenosine triphosphate
BAL	British anti-Lewisite
BCAA	branched chain amino acid
BH4	tetrahydrobiopterin
BID	twice a day
BPA	bisphenol A
CAC	citric acid cycle (also referred to as the tricarboxylic acid cycle or Kreb's cycle)
CBD	chronic beryllium disease
CFS	chronic fatigue syndrome
CFU	colony forming units
CHF	congestive heart failure
CLA	conjugated linoleic acid
COPD	chronic obstructive pulmonary disease
CVD	cardiovascular disease
CYP	cytochrome P
D2	ergocalciferol
D3	cholecalciferol
DEXA	Dual energy x-ray absorptiometry
DGL	deglycrrhizinated licorice
DGLA	dihomogamma linolenic acid
DHA	docosahexaenoic acid
DHEA	dehydroepiandrosterone
DHEA-s	dehydroepiandrosterone sulfate
DMSA	dimercaptosuccinic acid
EFA	essential fatty acid
EPA	eicosapentaenoic acid
ETOH	ethanol
FAD	flavin adenine dinucleotide
FIGLU	formiminoglutamic acid
FOS	fructooligosaccharide
GABA	γ -aminobutyric acid
GERD	gastroesophageal reflux disease
GH	growth hormone
GLU/GLN	glutamine/glutamate ratio
GTP	guanosine triphosphate
HDL	high density lipoprotein
HMG	hydroxymethylglutarate
hs-CRP	high sensitivity c-reactive protein
HTN	hypertension
HVA	homovanillate

Table continues inside back cover...

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Clinical Laboratory
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Patient: Sample Report
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0091 Organix™ Comprehensive Profile
This report is not intended for the diagnosis of metabolic
abnormalities or metabolites.

Ranges are for ages 13 and over.

NUTRIENT MARKERS

	Results	Percentile Ranking by Quintile	95% Reference Interval
Fatty Acid Metabolism (Creatinine & R2)	Results mg/mmol creatinine	1st 20% 2nd 40% 3rd 60% 4th 80%	
1. Adipate	4.9	● 2.3	<= 11.2
2. Suberate	1.5	● 2.0	<= 3.7
3. Phytanoyl	4.2 H	● 3.5	<= 6.3
4. Citrate Metabolism (Lipid Acid, CoQ10)	2.3	● 4.2	<= 7.1
5. Acetoacetate	3	● 14	3 - 47
6. β -Hydroxybutyrate	<0.1	● 2.7	<= 0.7
Energy Production (Citric Acid Cycle) (B: citrate, CoQ10, Amino acids, Mg)			
7. Citrate	350	● 622	44 - 1,032
8. Cit-Acetate	25	● 54	16 - 88
9. Isocitrate	85	● 105	43 - 157
10. α -Ketoglutarate	15	● 22	<= 38
11. Succinate	13.5 H	● 17.3	<= 25.7
12. Fumarate	1.80 H	● 6.69	<= 1.69
13. Malate	1.4	● 7.4	<= 3.2
14. Hydroxymethylglutamate	5.1 H	● 4.2	<= 8.5

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Disclaimer: Clinical laboratory science and application is a complex and evolving field. No publication can be assumed to encompass the full scope of information that an individual practitioner brings to his or her practice and, therefore, this book is not intended to be used as a clinical manual recommending specific tests and/or treatments for individual patients. It is intended for use as an educational tool, to broaden the knowledge and perspective of the practitioner. It is the responsibility of the healthcare practitioner to make his or her own determination of the usefulness and applicability of any information contained therein. If medical advice is required, the services of a competent professional should be sought. The final decision to engage in any medical treatment should be made jointly by the patient and his or her healthcare practitioner. Neither the publisher, the editors, authors, nor reviewers assume any liability for any errors or omissions or for any injury and/or damage to persons or property arising from the use of information to be found in this publication.

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Preface

In 2005 Metametrix published the *ION Handbook* as a practical, succinct guide to the ION (Individualized Optimal Nutrition) Profile*, designed to fit into a clinician's pocket for easy reference and everyday use. It was the brainchild of Molly Roberts, MD, a clinician who used the ION Profile extensively in practice. Her primary resource was the textbook, *Laboratory Evaluations in Molecular Medicine: Nutrients, Toxicants, and Cell Regulators* (Bralley and Lord, 2001). Although she found the textbook to be a treasure trove of information, it was not conducive to finding quick answers in the middle of a patient consultation. She wanted something that was very clear and crisp that would give the most important clinically relevant information in an easy-to-use format, so she created a quick-reference guide, refining it over several months and sharing it with her colleagues. As more doctors got wind of this guide and wanted to use it in their practices, Dr. Roberts collaborated with Dr. Richard Lord at Metametrix to expand and edit the content and publish it in book format. Hence, the *ION Handbook*, a resource that today resides in offices of thousands of practitioners around the world, was born.

At the time of publication, the *ION Handbook* covered the majority of profiles offered by Metametrix. Since then we have added a number of new tests and wanted to create a broader, more inclusive resource to support all current Metametrix profiles. The analytes and pattern analyses contained in the original book are included and have been updated based upon new clinical and scientific evidence. Entire new sections have been added and the number of analytes, ratios and patterns has nearly doubled. Each analyte is presented separately with causes, symptoms and conditions, and treatments relating to high and low levels; physiological functions, food sources and other details are included as appropriate to the test category.

The *Metametrix Handbook* is a companion to the new *Laboratory Evaluations in Integrative and Functional Medicine* textbook (Lord & Bralley, 2008), which is a revision, update and expansion of the original textbook. Both the handbook and textbook cover tests to evaluate nutrients, toxicants, detoxification and biotransformation ability, adverse food responses and gastrointestinal and hormonal functions. The handbook's quick-reference format complements the textbook's in-depth discussions and nearly 3800 literature citations.

Our thanks to Molly Roberts for her vision in creating the *ION Handbook* that forms the core of this new work, and to Richard Lord for his tremendous contributions to both that work and the *Metametrix Handbook*. We also want to acknowledge

*A combination profile including amino, fatty, and organic acid profiles, antioxidant vitamins, and nutrient and toxic elements.

the talented Metametrix staff who contributed to the updates of the original text and the creation of the new sections of the book: Kara N. Fitzgerald, ND; Eve E. Bralley, PhD; Elizabeth H. Redmond, PhD; Terry A. Pollock, MS; and Cass Nelson-Dooley, MS. We are also grateful to Todd LePine, MD, for his content editing and suggestions, to Cathy Morris for copy review and to Philip Gómez for graphic layout and design. We are all deeply indebted to the clinicians who have used Metametrix testing over the years to improve the health and well-being of their patients and have given us feedback to help us improve our testing services.

We hope you enjoy this new handbook. As always, your feedback is both welcomed and appreciated.

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Amino Acids

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S ome amino acids appear in more than one category on the Metametrix test report and in this handbook because of their different roles. In the "Contents" list above, the first use of the amino acid appears in black font; a gray font indicates it is reappearing in an additional category.	
If chronic dietary protein deficiency is ruled out and many essential amino acids are low, consider malabsorption or maldigestion, especially hypochlorhydria. When replenishing with amino acid supplements, use a balanced or individualized formulation with all the essential L-amino acids in order to avoid induced deficiencies of the other amino acids.	

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Lysine

Common clinical presentations indicating need for amino acid assessment:

- ◆ History:
 - » Post surgery
 - » Weight control by severe diet restrictions
 - » Uninformed vegetarianism
 - » Antacid use
 - » Any digestive impairment
 - » Failure to thrive
 - » Chronic degenerative diseases affecting appetite, digestion or assimilation
- ◆ Symptoms/Conditions:
 - » Chronic fatigue
 - » Depression
 - » Hypertension
 - » Failure to thrive
 - » Autism spectrum disorders
 - » Rapid weight loss
 - » Dyspepsia
 - » Behavioral disorders

NOTES

Essential Limiting Amino Acids

Even if other amino acids are present in sufficient quantities, low levels of limiting amino acids can cause restriction of protein synthesis.

Lysine

- ◆ Essential amino acid required for carnitine formation
- ◆ Required for biosynthesis of all enzymes, receptor and transport proteins, and structural proteins
- ◆ Found in great quantities in muscle tissues—stabilizes collagen
- ◆ Excessive use of supplement may lead to kidney pathology due to increased total body nitrogen load, challenging ammonia clearance capacity.
- ◆ Used in treatment of:
 - » Osteoporosis by reducing calcium loss
 - » Cardiovascular disease
 - » Herpes infection—competitive inhibition with lysine residues on the surface of the viral particles—need plasma levels above 165 µmol/L
 - » Lead toxicity
- ◆ Stimulates:
 - » Calcium absorption
 - » Carnitine synthesis and fatty acid metabolism
 - » Growth and repair of muscle tissue



- » Development and regulation of:
 - Collagen
 - Antibodies
 - Hormones and enzymes
 - ◆ Decreases:
 - » Serum triglycerides
 - ◆ Food sources:
 - » Fish, eggs, dairy, lima beans, beef, soy, yeast, potatoes
- IF LYSINE HIGH:**
- ◆ Causes:
 - » High levels are rare
 - » Lysine supplementation
 - » Impaired metabolism of lysine due to genetic polymorphisms or toxicant effects
 - » Urea cycle abnormalities causing high arginine, which increases lysine spilling in *urine* through competitive transport mechanisms
 - ◆ Symptoms/Conditions:
 - » May be an indication of bone loss (turnover of collagen from bone resorption)
 - ◆ Treatments:
 - » Stop supplementation
 - » α-Ketoglutarate, 600 mg BID
 - » Vitamin B₃ (niacin), 50 mg/d
 - » Vitamin B₆ (pyridoxine), 100 mg/d
 - » Vitamin C, 1000–5000 mg/d
 - » Iron, 15 mg/d
- IF LYSINE LOW:**
- ◆ Causes:
 - » Prolonged stress
 - » Excessive arginine or

histidine supplementation competing for absorption

» Carnitine deficiency

- ◆ Symptoms/Conditions:
 - » Hypertriglyceridemia—due to decreased fatty acid transport from low carnitine levels
 - » Muscle weakness
 - » Easy fatigability
 - » Anemia
- ◆ Treatments:
 - » Balanced mix of amino acids
 - » L-Lysine, 12 mg/kg/d
 - » Carnitine, 1–2 g/d

Methionine

- ◆ Essential sulfur-containing amino acid
- ◆ Required for biosynthesis of all enzymes, receptor and transport proteins, and structural proteins
- ◆ Required for the formation of body tissues and glutathione
- ◆ Essential precursor to the amino acids cysteine and taurine
- ◆ Methyl group donor essential to genetic expression, muscle metabolism, adrenal catecholamine balance, and formation of choline and acetylcholine
- ◆ Food sources:
 - » Fish, eggs, dairy, beans, beef, garlic, onion, lentils, soybeans

Methionine; Tryptophan**IF METHIONINE HIGH:**

- ◆ Causes:
 - » Impaired hepatic function like cirrhosis
 - » Supplementation of methionine
 - » Reduced excretion:
 - Gastric resection
 - Ileocecal resection
 - Abnormal gut flora
- ◆ Symptoms/Conditions:
 - » Elevated homocysteine level
- ◆ Treatments:
 - » Stop supplementation
 - » Clear homocysteine from body
 - Folic acid, 800 µg/d
 - Vitamin B₆ (pyridoxine), 100 mg/d
 - Vitamin B₁₂ (cobalamin), 1000 µg/d
 - α-Ketoglutarate, 600 mg BID
 - Magnesium, 200 mg BID
 - SAMe, 200 mg BID

IF METHIONINE LOW:

- ◆ Causes:
 - » Low-quality protein diet
 - » High tannin intake
 - » Increased excretion
- ◆ Symptoms/Conditions:
 - » Allergic chemical sensitivities
 - » Headaches
 - » Eyestrain
 - » Muscle weakness
 - » Brittle hair
 - » Hair loss

- » Myopia
- » Mild myopathy
- » Osteoporosis
- » Cardiovascular symptoms
- » Slowed growth
- » Cirrhotic patients have decreased amounts of methionine derivatives, such as cysteine, glutathione, and albumin
- ◆ Treatments:
 - » Balanced mix of amino acids
 - » L-Methionine, 13 mg/kg/d
 - » Assure recovery from homocysteine
 - Vitamin B₆ (pyridoxine), 100 mg/d
 - Vitamin B₁₂ (cobalamin), 1000 µg/d
 - Folic acid, 800 µg/d

Tryptophan

- ◆ Essential, aromatic amino acid
- ◆ Required for biosynthesis of all enzymes, receptor and transport proteins, and structural proteins
- ◆ Precursor to serotonin and melatonin via the indolamine pathway
- ◆ Precursor to niacin production via the kynurenine pathway
- ◆ Indirect marker of changes in brain serotonin synthesis
- ◆ Regulates gut motility
- ◆ Plays a role in mood, sleep, emesis, sexuality and appetite
- ◆ Induces:
 - » Sleep in insomniacs

- » Therapeutic effect of tricyclic antidepressants
- ◆ Decreases:
 - » Used to treat depression (usually as 5-HTP)—levels in depressed patients may not rise with supplementation due to high rates of utilization
- ◆ Food sources:
 - » Dairy, beef, poultry/turkey, barley, brown rice, fish, soybeans, peanuts, bananas, lentils, and eggs

IF TRYPTOPHAN HIGH:

- ◆ Causes:
 - » Supplementation of tryptophan
 - » Poor metabolic utilization
 - » Sleep deprivation—decreased utilization
- ◆ Symptoms/Conditions:
 - » Risk for serotonin syndrome if patient is on a selective serotonin reuptake inhibitor
- ◆ Treatment:
 - » Stop L-Tryptophan supplements
 - » Vitamin B₃ (niacin), 50 mg/d
 - » Vitamin B₆ (pyridoxine), 100 mg BID
 - » L-Tryptophan, 3.5 mg/kg/d

NOTES**IF TRYPTOPHAN LOW:**

- ◆ Causes:
 - » Diet low in dairy or meat
 - » High utilization of tryptophan
 - » Inflammation causing increased flow of tryptophan through the kynurenine pathway to make quinolinate
 - » Elevated total body serotonin synthesis—depletes tryptophan
- ◆ Symptoms/Conditions:
 - » Low serotonin has been implicated in neuropsychiatric disorders such as depression, migraine, bipolar disorders and anxiety
 - » Insomnia

Essential Branched-Chain Amino Acids (BCAA)

BCAA are particularly needed for growth and maintenance of skeletal muscle. Their catabolic intermediates are critical for metabolic pathways such as the citric acid cycle.

Isoleucine, Leucine and Valine

- ◆ Essential, branched side-chain alpha-amino acids
- ◆ Abundant in muscle tissue
- ◆ Required for biosynthesis of all enzymes, receptor and transport proteins, and structural proteins
- ◆ Does not serve as precursor to neurotransmitters or bile acids like other amino acids
- ◆ Involved in control mechanisms for neurotransmitters
- ◆ Used for recovery from surgery, trauma, sepsis, and diabetic regulation—due to nitrogen-sparing and tissue-rebuilding effects
- ◆ During strenuous muscle activity, serves as source of energy regulation
- ◆ Hematopoiesis
- ◆ Cannot substitute for glucose in the fasting state, but can be converted into ketone bodies for an alternate source of energy
- ◆ Stimulates:
 - » Growth and repair of muscle tissue
 - » Wound healing
 - » Energy regulation
 - » Carbohydrate and fat metabolism
 - » Peptide and protein synthesis
 - » Rate of lean body mass increase in response to exercise

- » Respiration
- » Food intake to help return of normal eating in patients on total parenteral nutrition (TPN)
- » Digestion of proteins by suppressing gastric emptying to allow longer residence in acid milieu of the stomach
- ◆ Prevents:
 - » Stress-induced decrease of muscle protein synthesis
 - » Sleep apnea
- ◆ Food sources:
 - » Eggs, mushrooms, nuts, poultry, beef, soy, grain, dairy

IF ISOLEUCINE, LEUCINE, VALINE HIGH:

- ◆ Causes:
 - » Vitamin B₆ deficiency
 - » Excessive supplementation, particularly with athletes
 - » Insulin insensitivity/diabetes
- ◆ Symptoms/Conditions:
 - » May cause diabetic microangiopathy
 - » Increased urination
 - » Hypoglycemia
 - » Dizziness
 - » Headaches
 - » Fatigue
 - » Depression
 - » Confusion
 - » Irritability
 - » Loss of muscle mass
 - » Inability to build muscle
 - » Alopecia



- » Confusion
- » Irritability
- ◆ Treatments:
 - » Stop BCAA supplements
 - » Vitamin B₆ (pyridoxine), 100 mg/d—needed to offset high amino acid intake
 - » Zinc, 30 mg/d
 - » Vitamin B₅ (pantothenic acid), 50 mg/d
 - » Vitamin B₁ (thiamine), 50 mg/d
 - » Vitamin B₂ (riboflavin), 50 mg/d
 - » Vitamin B₃ (niacin), 50 mg/d
 - » Lipoic acid, 200 mg/d

IF ISOLEUCINE, LEUCINE, VALINE LOW:

- ◆ Causes:
 - » Chronic depletion from low protein intake, poor digestion, or increased utilization or renal loss
- ◆ Symptoms/Conditions:
 - » Hypoglycemia
 - » Dizziness
 - » Headaches
 - » Fatigue
 - » Depression
 - » Confusion
 - » Irritability
 - » Loss of muscle mass
 - » Inability to build muscle
 - » Alopecia
- ◆ Treatments:
 - » Balanced mix of amino acids
 - » Vitamin B₃ (niacin), 50 mg/d
 - » L-Isoleucine, 10 mg/kg/d

Other Essential Amino Acids

Phenylalanine

- ◆ Essential, aromatic amino acid
- ◆ Required for biosynthesis of all enzymes, receptor and transport proteins, and structural proteins
- ◆ Precursor for:
 - » Tyrosine
 - » Catecholamine synthesis (dopamine, epinephrine and norepinephrine)
- ◆ If tyrosine is low, conversion of phenylalanine to the catecholamines and/or thyroid hormone is compromised, mimicking low phenylalanine levels
- ◆ Stimulates:
 - » Pain relief
- ◆ Decreases:
 - » Appetite
 - » Depression
- ◆ Food sources:
 - » Dairy, almonds, avocados, lima beans, peanuts, seeds

IF PHENYLALANINE HIGH:

- ◆ Causes:
 - » Phenylketonuria
 - » Excessive protein intake
 - » Metabolic block in conversion of phenylalanine to tyrosine

Phenylalanine; Histidine

- ◆ Symptoms/Conditions:
 - » Decreased/increased blood pressure
 - » Headaches
 - » In infants:
 - Vomiting
 - Irritability
 - Eczema-like skin reactions
 - Increased muscle tone
 - Epilepsy
 - Mental retardation
 - Musty odor
- ◆ Treatment:
 - » Iron, 30 mg/d (if deficient)
 - » Vitamin C, 1 gm TID
 - » Vitamin B₃ (niacin), 50 mg/d
 - » Tetrahydrobiopterin (BH₄)
 - » Folic acid, 800 µg/d
 - » Low phenylalanine diet

IF PHENYLALANINE LOW:

- ◆ Causes:
 - » Stressful lifestyle
 - » Chronic deficiency
- ◆ Symptoms/Conditions:
 - » Hypothyroidism
 - » Chronic fatigue
 - » Learning, memory, or behavioral disorders
 - » Depression
 - » Autonomic dysfunction
 - » Slowed growth
 - » Lethargy
- ◆ Treatment:
 - » Reduce lifestyle stressors

- » Balanced mix of amino acids
- » L-Phenylalanine, 14 mg/kg/d

Histidine

- ◆ Essential amino acid
- ◆ Required for biosynthesis of all enzymes, receptor and transport proteins, and structural proteins
- ◆ Can indicate the status of protein metabolism
- ◆ Forms histamine
- ◆ Stimulates:
 - » Growth
 - » Tissue repair
 - » Dominant amino acid in urine due to low renal threshold
- ◆ Food sources:
 - » Pork, poultry, rice, wheat, cheese

IF HISTIDINE HIGH:

- ◆ Because of low renal threshold, urinary histidine more sensitively reveals elevated levels
- ◆ Causes:
 - » Excessive protein intake or histidine supplementation
 - » Skeletal muscle breakdown
 - » Renal failure can produce elevated plasma histidine
- ◆ Symptoms/Conditions:
 - » Stress
 - » Anxiety disorders
- ◆ Treatments:
 - » Decrease protein intake

IF HISTIDINE LOW:

- ◆ Causes:
 - » Poor dietary protein
 - » Malabsorption
 - » Folic acid deficiency—leads to increased catabolism of histidine
 - » Increased formation of histamine
 - » Salicylates and steroids—decrease histidine levels
 - » Excessive lysine or arginine supplementation competing for absorption
- ◆ Symptoms/Conditions:
 - » Rheumatoid arthritis
 - » Poor histamine response
- ◆ Treatments:
 - » Balanced mixture of amino acids
 - » L-Histidine, 500 mg TID to 4000 mg/d (take caution if low histidine is due to chronic histamine response)
 - » Folic acid, 800 µg/d

Threonine

- ◆ Required for biosynthesis of all enzymes, receptor and transport proteins, and structural proteins
- ◆ The only essential amino acid that can be converted into glycine and serine for biosynthesis and detoxification support
- ◆ Second or third limiting amino acid in vegetarian diets following methionine and lysine
- ◆ Uniquely stable in contrast to most other essential amino

acids in the early stages of dietary protein deficiency

- ◆ Stimulates:
 - » Growth of thymus gland—immune system stimulant
- ◆ Decreases:
 - » Spasms in leg muscles
 - » Detoxification demands, especially glutathione
 - » Plasma phenylalanine
 - » Spasticity in multiple sclerosis patients
- ◆ Food sources:
 - » Dairy, beef, poultry, eggs, beans, nuts, seeds

IF THREONINE HIGH:

- ◆ Causes:
 - » Supplementation
 - » Inadequate conversion to glycine (B₆-dependent)
 - » Vitamin B₆ deficiency
- ◆ Symptoms/Conditions:
 - » If other essential amino acids are low, suspect inadequate assimilation of dietary protein
- ◆ Treatment:
 - » Stop supplementation
 - » Vitamin B₆ (pyridoxine), 100 mg/d
 - » Zinc, 30 mg/d

IF THREONINE LOW:

- ◆ Causes:
 - » Low threonine in the face of normal levels of other amino acids is due to factors other than dietary inadequacies.

Threonine; Arginine

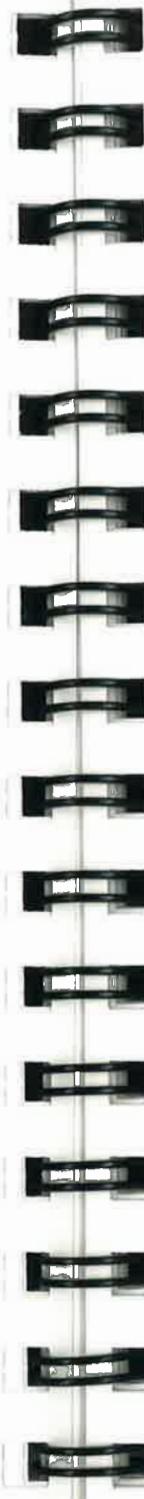
- » Increased glutathione demands
- » Catabolic processes like increased cortisol
- » Impaired:
 - Detoxification
 - Tissue repair
 - Gluconeogenesis
- ◆ Symptoms/Conditions:
 - » Hypoglycemia:
 - Fatigue
 - Headache
 - Anxiety
 - Shakiness between meals
- ◆ Treatment:
 - » Balanced mix of amino acids
 - » Glycine, 1000 mg TID
 - » L-Threonine, 7.5 grams/day between meals

Conditionally Essential Amino Acids

These amino acids are not normally required in the diet but must be supplied to specific populations that do not synthesize them in adequate amounts.

Arginine

- ◆ Conditionally essential amino acid
- ◆ Essential for maintenance of nitrogen status
- ◆ Required for biosynthesis of all body proteins
- ◆ Aids in ammonia clearance as a part of urea cycle
- ◆ Vital for muscle metabolism and liver function
- ◆ Precursor to nitric oxide (NO):
 - » Cell regulation
 - » Neurotransmission
 - » Endothelial relaxation
 - » Gastric mucosa protection
 - » Inflammatory signaling
- ◆ Used to treat liver disorders
- ◆ Stimulates:
 - » Growth hormone
 - » Immune system
 - » Muscle growth
 - » Fat metabolism
 - » Wound healing—improves macrophage function and decreases IL-6
 - » Collagen deposition via proline biosynthesis
 - » Muscle relaxation
 - » Penile erection (through NO function)—especially when given with ornithine to spare utilization for urea cycle function
 - » May stimulate tumor growth
- ◆ May cause decreased:
 - » Intimal thickness and vascular reactivity in atherosclerosis
 - » Platelet clumping and clot formation within arterial walls
 - » Cholesterol
 - » Post-surgical intraperitoneal adhesion formation
- ◆ Food sources:
 - » Legumes, whole grains, nuts, seeds,



peanuts, brown rice, popcorn, soy, raisins, chocolate, carob

- ◆ See "Vascular Function" on page 15 and "Urea Cycle and Ammonia Detoxification" on page 21

IF ARGININE HIGH:

- ◆ Causes:
 - » Genetic disorder (arginase deficiency)
 - » Functional block in urea cycle
- ◆ Symptoms/Conditions:
 - » Ammonia toxicity
 - » Confusion
 - » Disorientation
 - » Elevated urinary citrate
 - » Hypertension
 - » Weakness
 - » Diarrhea
 - » Nausea
 - » May increase the activity of some viruses and/or *H. pylori*
- ◆ Treatments:
 - » Manganese, 15 mg/d
 - » Magnesium, 200 mg BID
 - » Zinc, 30 mg/d
 - » Low protein diet
 - » Reduce nitrogen load
 - » Avoidance of high-arginine foods:
 - Nuts
 - Meat
 - Dairy products
 - » Decrease excess intracellular ammonia:
 - Vitamin B₆ (pyridoxine), 100 mg/d
- ◆ Treatments:
 - » Balanced mixture of amino acids
 - » L-Arginine, 1000 mg TID

Taurine

- ◆ Sulfur-containing amino acid
- ◆ Neurotransmitter with anticonvulsant properties
- ◆ Antioxidant
- ◆ Stabilizes platelets against aggregation
- ◆ Synthesized from cysteine
- ◆ Found in high concentrations in heart muscle and white blood cells

- α-Ketoglutarate, 600 mg BID

IF ARGININE LOW:

- ◆ Causes:
 - » Poor digestion of protein
 - » Increased demands for detoxification
 - » Calorie restriction diets
 - » Excessive lysine or histidine supplementation (competes for absorption)

- ◆ Symptoms/Conditions:
 - » Hyperammonemia—failure of ammonia removal
 - » Chronic inflammatory disorders
 - » Coronary artery disease
 - » Angina
 - » Hypertension
 - » Impaired insulin production
 - » Possible hair loss
 - » Decreased gastric mucosal protection

- ◆ Treatments:
 - » Balanced mixture of amino acids
 - » L-Arginine, 1000 mg TID

Taurine

- ◆ Required for bile formation (taurocholic acid)
- ◆ Stimulates:
 - » Bile acid, enhances cholesterol excretion
 - » Insulin release
- ◆ Decreases:
 - » Heart disease & hypertension
 - » Congestive heart failure
 - » Epilepsy
- ◆ Food source:
 - » Made by the body from methionine or cysteine
 - » Not found in animal proteins

IF TAURINE HIGH:

- ◆ Causes:
 - » Various stress reactions—mediated by release of various interleukins
 - » Supplementation with taurine
 - » Supplementation with serine in serine-responsive patients
 - » May indicate acute myocardial ischemia
- ◆ Symptoms/Conditions:
 - » Episodic acute psychosis characterized by sensory perceptual distortions (oral loading in such patients with serine or glycine can induce psychedelic symptoms)
 - » Major depression—high levels normalize with treatment
- ◆ Treatment:
 - » Stop serine and taurine supplementation
 - » Vitamin E, 800 IU/d

- » Vitamin C, 1 gm TID
- » β-Carotene, 25,000 IU/d
- » CoQ10, 30 mg/d
- » Lipoic acid, 200 mg/d

IF TAURINE LOW:

- ◆ Causes:
 - » Vegetarian diet
 - » Fat maldigestion
 - » Detoxification impairment
 - » Fat-soluble vitamin deficiencies
 - » Beta-agonist drugs
 - » Short gut syndrome
 - » Cirrhotic patients on a mixed foods or total parenteral diet
- ◆ Symptoms/Conditions:
 - » Excessive oxidative damage
 - » Formation of aldehydes
 - » Allergies
 - » Chemical sensitivities
 - » Congestive heart failure
 - » Night blindness
 - » Arrhythmia
 - » Angina
 - » Hypercholesterolemia
 - » Atherosclerosis
 - » Epilepsy
 - » Platelet clotting
- ◆ Treatment:
 - » Balanced mix of amino acids
 - » Vitamin B₆ (pyridoxine), 100 mg/d
 - » Choline, 425–550 mg/d
 - » Taurine, 300 mg BID
 - » N-Acetylcysteine (NAC), 250–1500 mg/d

Glycine

- ◆ Can be depleted due to increased needs for detoxification
- ◆ Required for biosynthesis of all enzymes, receptor and transport proteins, and structural proteins
- ◆ Precursor to the glycine cleavage system essential for enhancing the capacity for maintaining the single carbon pool for biosynthesis and methylation reactions
- ◆ Required for synthesis of collagen, hemoglobin, creatine, DNA and RNA
- ◆ Highly variable demands for hepatic glutathione synthesis, glycine conjugation and bile (glycocholic acid)
- ◆ Involved in maintaining blood sugar levels—can be used directly as an energy source or for synthesis of glucose
- ◆ Acts as an inhibitory neurotransmitter at glycineergic receptors
- ◆ Also able to co-agonize (with glutamate) glutamatergic NMDA excitatory receptors
- ◆ Precursor to serine for the membrane components, phosphoethanolamine and phosphoserine
- ◆ Stimulates:
 - » Cellular energy flow
 - » Detoxification
 - » Brain function
 - » Synthesis of glutathione, bile acids and detoxification
 - » Phase II conjugation reactions

IF GLYCINE HIGH:

- ◆ Causes:
 - » Enzyme polymorphisms that decrease activity of the glycine cleavage system resulting in nonketotic hyperglycinemia
 - » Glycine supplementation
- ◆ Symptoms/Conditions:
 - » Deficits in brain chemistry associated with behavioral or emotional disturbances
 - » Neuronal activity is overstimulated leading to neuromotor problems
 - » Early myoclonic encephalopathy
 - » Seizures
- ◆ Treatment:
 - » Stop supplementation
 - » NMDA receptor antagonists
 - » Sodium benzoate 250–750 mg/kg/d to deplete glycine via hepatic conjugation
 - » Folic acid, 800 µg/d
 - » Vitamin B₆ (pyridoxine), 100 mg/d
 - » Vitamin B₅ (pantothenic acid), 50 mg/d

IF GLYCINE LOW:

- ◆ Causes:
 - » Impaired:

Glycine; α -AAA; α -ANB; GABA

- Detoxification
- Tissue repair
- Gluconeogenesis
- » Toxicity from chemicals
- » Benzoic acid (a food preservative and natural ingredient), and many other food components and pharmaceuticals require glycine conjugation
- ◆ Symptoms/Conditions:
 - » Hypoglycemia-like symptoms
 - » Psychotic manifestations
 - » Depression
 - » Neuronal activity is underactivated
- ◆ Treatment:
 - » Balanced mix of amino acids enriched with threonine
 - » Glycine or combinations of glycine and serine, 1000 mg TID

Vitamin B₆ Status Markers

α -Aminoadipic Acid (α -AAA)

- ◆ A metabolite of lysine
- IF α -AMINOACIDIC ACID HIGH:
 - ◆ Causes:
 - » High dietary intake of lysine
 - » Inhibition of lysine metabolism due to functional vitamin B₆ deficiency
 - ◆ Symptoms/Conditions:
 - » Risk factor for heart disease

- ◆ Treatment:
 - » Vitamin B₆ (pyridoxine), 100 mg/d
 - » α -Ketoglutarate, 600 mg BID

α -Amino-N-Butyric Acid (α -ANB)

- ◆ Neurotransmitter derived from glutamine
- IF α -AMINO-N-BUTYRIC ACID HIGH:
 - ◆ Causes:
 - » Chronic alcohol intake if leucine and alanine are also elevated
 - » Vitamin B₆ deficiency
 - ◆ Treatment:
 - » Vitamin B₆ (pyridoxine), 100 mg/d
 - » α -Ketoglutarate, 600 mg BID
 - » Pyruvate and B₂ if excessive alcohol intake

γ -Aminobutyric Acid (GABA)

- ◆ An inhibitory neurotransmitter in the central nervous system
- ◆ Regulates neuronal excitability throughout the central nervous system and muscle tone
- ◆ GABAergic neuronal defects are thought to be involved in the etiology of epilepsy
- ◆ Produced from glutamate
- IF γ -AMINOBUTYRIC ACID HIGH:
 - ◆ Causes:
 - » Low conversion to succinic acid (a vitamin B₆-dependent reaction) for utilization by the citric acid cycle



- » Genetic polymorphisms in the succinic semialdehyde dehydrogenase enzyme

- ◆ Symptoms/Conditions:
 - » Retardation of language development
 - » Autism
- ◆ Treatment:
 - » Vitamin B₆ (pyridoxine), 100 mg/d
 - » α -Ketoglutarate, 600 mg BID

γ -Aminobutyric Acid LOW:

- ◆ Causes:
 - » Huntington disease
 - » Vitamin B₆ deficiency impairs GABA formation
- ◆ Symptoms/Conditions:
 - » Depression
- ◆ Treatment:
 - » Vitamin B₆ (pyridoxine), 100 mg/d

Cystathione

- ◆ The product of the conjugation of serine and homocysteine via the action of cystathione- β -synthase, a vitamin B₆ dependent enzyme deficient in hyperhomocysteinemia
- ◆ Cystathione conversion to cysteine catalyzed by another vitamin B₆-dependent enzyme, cystathione- γ -lyase

IF CYSTATHIONINE HIGH:

- ◆ Causes:
 - » Vitamin B₆ deficiency

GABA; Cystathione; Arginine; Taurine; α -AAA

- ◆ Symptoms/Conditions:
 - » Hyperhomocysteinemia
- ◆ Treatment:
 - » Vitamin B₆, 100mg

IF LOW:

- ◆ Causes:
 - » Increased glutathione demand due to oxidative stress or detoxification
- ◆ Symptoms/Conditions:
 - » Increased aging/cancer risks
- ◆ Treatment:
 - » N-Acetylcysteine (NAC), 500 mg BID

Vascular Function

Arginine

See "Arginine" on page 10

Taurine

See "Taurine" on page 11

α -Aminoadipic Acid (α -AAA)

See " α -Aminoadipic Acid (α -AAA)" on page 14

Phenylalanine; Tyrosine

Neurotransmitters and Precursors

Phenylalanine

See "Phenylalanine" on page 7

Tyrosine

- ◆ Produced from phenylalanine
- ◆ Required for biosynthesis of all enzymes, receptor and transport proteins, and structural proteins
- ◆ Catecholamine synthesis
- ◆ Precursor for thyroid hormone
- ◆ Precursor for melanin
- ◆ Used to maintain mitochondrial function (citric acid cycle intermediates)
- ◆ Induces:
 - » Catecholamine synthesis
 - » Mood regulation
 - » Memory and alertness
- ◆ Suppresses:
 - » Chronic fatigue
 - » Appetite
 - » Blood pressure
- ◆ Food sources:
 - » Almonds, avocados, bananas, beef, dairy, eggs, fish, lima beans, pumpkin seeds, sesame seeds, soy

IF TYROSINE HIGH:

- ◆ Causes:
 - » Tyrosine or phenylalanine supplementation

- » Functional metabolic block in thyroid, catecholamine or melanin pathways
- » Inability to utilize tyrosine properly, possibly from low levels of copper, iron, iodine, vitamin C, vitamin B₆

- ◆ Symptoms/Conditions:
 - » Excessive production of catecholamines
 - » Interacts with MAO inhibitors
- ◆ Treatment:
 - » Stop supplementation
 - » Copper, 3 mg/d
 - » Iron, 30 mg/d (if deficient)
 - » Vitamin C, 1 gm TID
 - » Vitamin B₆ (pyridoxine), 100 mg BID
 - » Iodine, 200 µg/d

IF TYROSINE LOW:

- ◆ Causes:
 - » Deficiency of iron, tetrahydrobiopterin or NAD
- ◆ Symptoms/Conditions:
 - » Conversion of phenylalanine to the catecholamines and/or thyroid hormone is compromised, mimicking low phenylalanine levels
 - » Hypothyroidism
 - » Chronic fatigue
 - » Learning, memory, or behavioral disorders
 - » Depression
 - » Autonomic dysfunction—blood pressure disorders



- » Stunted growth
- » Apathy
- » Edema
- » Weakness
- » Liver damage
- » Loss of muscle
- » Skin lesions
- ◆ Treatment:
 - » Vitamin B₃ (niacin), 50 mg/d
 - » L-Tyrosine, 500 mg TID

Tryptophan

See "Tryptophan" on page 4

Glutamic Acid

- ◆ Required for biosynthesis of all body proteins
- ◆ Principal excitatory neurotransmitter in the brain via NMDA (N-methyl-D-aspartic acid) receptor activation
- ◆ Precursor to the inhibitory neurotransmitter GABA
- ◆ Involved in acid-base balance
- ◆ Transports nitrogen out of brain and muscle
- ◆ Controls gastric function
- ◆ Food sources:
 - » Meats, poultry, fish, eggs, dairy, kombu

IF GLUTAMIC ACID IS HIGH:

- ◆ Causes:
 - » Supplementation
 - » Specimen degradation due to

Tyrosine; Tryptophan; Glutamic Acid

- extended time before or high temperature transit to laboratory
- » If glutamate is High and glutamine is Low, see "Glu/Gln" on page 33

◆ Symptoms/Conditions:

- » Headaches
- » Decreased gastric motility
- » Stroke
- » Epilepsy
- » Amyotrophic lateral sclerosis
- » Huntington chorea
- » Alzheimer disease
- » Mental retardation
- » Immunopathology of different diseases like AIDS

◆ Treatment:

- » Stop supplementation
- » Vitamin B₃ (Niacin), 50 mg/d
- » Vitamin B₆ (Pyridoxine), 100 mg BID

IF GLUTAMIC ACID LOW:

- ◆ Rules out specimen degradation as cause of low glutamine (see "Glu/Gln" on page 33)
- ◆ Causes:
 - » High protein diet
- ◆ Symptoms/Conditions:
 - » Decreased CNS function
 - » Mild hyperammonemia: headache, irritability, fatigue, mental confusion, poor concentration
 - » Food intolerance reactions, particularly to high protein food
 - » Depression

Glutamic Acid; Taurine; Methionine; Cystathione; Homocystine

- ◆ Treatment:
 - » Branched-chain amino acids
 - » Low protein, high complex carbohydrate diet
 - » α-Ketoglutaric acid, 600 mg TID
 - » Vitamin B₆ (pyridoxine), 100 mg/d
- ◆ Increased risk of stroke or a problem with blood flow

IF HOMOCYSTINE HIGH:

- ◆ Causes:
 - » Impaired function of cystathione β-synthetase for conversion to cystathione
 - » Smoking
 - » Menopause
 - » Drugs, alcohol
 - » Toxins
 - » Renal failure
 - » Hereditary predisposition
 - » Deficiency of B vitamins or folate
 - » Elevations of homocysteine, methylmalonate and formiminoglutamate (FIGLU) are the most sensitive indicators for megaloblastic anemia

◆ Symptoms/Conditions:

- » Increased risk of:
 - Atherosclerosis, particularly in smokers
 - Cardiovascular disease
 - Ocular abnormalities
 - Neurological abnormalities
 - Musculoskeletal abnormalities
 - Joint abnormalities
 - Placental thrombosis, abruption and miscarriage
- » CNS problems:
 - Mental retardation
 - Seizures
 - Stroke
- » Osteoporosis—impaired cross-linking of collagen

Taurine

See "Taurine" on page 11

**Sulfur Amino Acids
(Glutathione-Related)****Methionine**

See "Methionine" on page 3

Cystathione

See "Cystathione" on page 15

Homocystine

- ◆ An intermediate of methionine breakdown
- ◆ Produced from the oxidation of homocysteine
- ◆ Accumulation leads to endothelial dysfunction
- ◆ Causes cholesterol to change to oxidized LDL, irritating blood vessel linings
- ◆ Increased blood clotting



- ◆ Treatment:
 - » Stop precipitating causes (smoking, alcohol, etc.)
 - » Betaine, 1–2 gm TID
 - » Magnesium, 200 mg BID
 - » If xanthurene also elevated:
 - Vitamin B₆ (pyridoxine), 100 mg/d
 - » If FIGLU also elevated:
 - Folic acid, 800 µg/d or
 - 5-methyltetrahydrofolate if level remains high

Note: While a number of studies show a decreased risk for certain cancers with folate supplementation, recent data showed increased breast and colon cancer with doses >400 µg. It is recommended that folate supplementation be monitored. High-dose, long term supplementation is indicated only with demonstrated need. Genetic testing of MTHFR may be prudent with refractory homocysteine elevation.

- » If methylmalonate also elevated:
 - Vitamin B₁₂ (cobalamin), 1000 µg/d

Cystine

- ◆ Cystine is required for protein synthesis
- ◆ Produced from the oxidation of cysteine
- ◆ Hepatic cholesterol biosynthesis is modulated by dietary cystine

Homocystine; Cystine; Homocysteine**IF CYSTINE HIGH:**

- ◆ Causes:
 - » Intake of high sulfur foods such as eggs and legumes
 - » Impaired metabolism of cystine
- ◆ Symptoms/Conditions:
 - » Impaired detoxification
- ◆ Treatment:
 - » Vitamin B₆, 100 mg
 - » Folic Acid, 400 µg

IF CYSTINE LOW:

- ◆ Causes:
 - » May reflect a dietary deficiency of methionine and/or cysteine
 - » High dietary intake of condensed tannins
 - » Increased demand to make glutathione due to oxidative stress
 - » Cystine degrades easily after specimen collection, so prompt handling is required
- ◆ Symptoms/Conditions:
 - » Impaired synthesis of taurine, in which case plasma taurine will also be low
- ◆ Treatment:
 - » N-Acetylcysteine or cysteine, 500 mg

Homocysteine

- ◆ Homocysteine is the de-methylated form of methionine
- ◆ Precursor to cysteine and glutathione
- ◆ Associated with pathophysiology of atherosclerosis

Homocysteine**IF HOMOCYSTEINE HIGH:**

- ◆ Causes:
 - » Impaired function of cystathione β -synthetase for conversion to cystathione
 - » Smoking
 - » Menopause
 - » Drugs, alcohol
 - » Toxins
 - » Renal failure
 - » Hereditary predisposition
 - » Deficiency of B vitamins or folate
 - » Elevations of homocysteine, methylmalonate and formiminoglutamate (FIGLU) are the most sensitive indicators for megaloblastic anemia
- ◆ Symptoms/Conditions:
 - » Increased risk of:
 - Atherosclerosis, particularly in smokers
 - Cardiovascular disease
 - Ocular abnormalities
 - Neurological abnormalities
 - Musculoskeletal abnormalities
 - Joint abnormalities
 - Placental thrombosis, abruption and miscarriage
 - » CNS problems:
 - Mental retardation
 - Seizures
 - Stroke
 - » Osteoporosis—impaired cross-linking of collagen

Treatment:

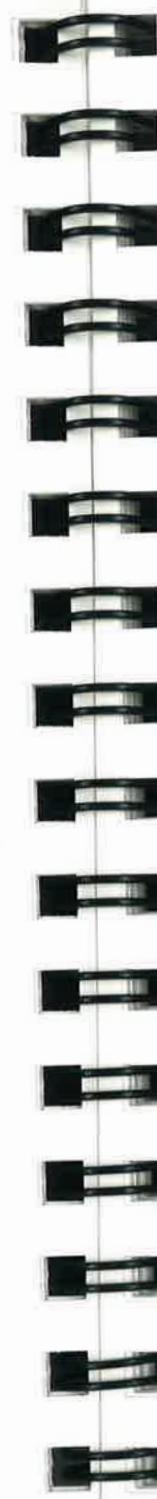
- » Stop precipitating causes (smoking, alcohol, etc.)
- » Betaine, 1–2 gm TID
- » Magnesium, 200 mg BID
- » If xanthurene also elevated:
 - Vitamin B₆ (Pyridoxine), 100 mg/d
- » If FIGLU also elevated:
 - Folic acid, 800 μ g/d or
 - 5-methyltetrahydrofolate if level remains high

Note: While a number of studies show a decreased risk for certain cancers with folate supplementation, recent data showed increased breast and colon cancer with doses >400 μ g. It is recommended that folate supplementation be monitored. High-dose, long term supplementation is indicated only with demonstrated need. Genetic testing of MTHFR may be prudent with refractory homocysteine elevation

- » If methylmalonate also elevated:
 - Vitamin B₁₂ (Cobalamin), 1000 μ g/d

IF HOMOCYSTEINE LOW:

- ◆ Causes:
 - » Depletion of sulfur amino acid pools
 - » Elevated toxicant or oxidant challenge leading to glutathione depletion
- ◆ Symptoms/Conditions:
 - » Heightened sensitivity to drugs and toxicants
 - » Impaired methylation capacity



- » Frequently found in autistic patients

- ◆ Treatments:
 - » N-Acetylcysteine or cysteine, 500 mg

Taurine

See "Taurine" on page 11

Urea Cycle and Ammonia Detoxification**Arginine**

See "Arginine" on page 10

Citrulline

- ◆ Urea cycle intermediate
- ◆ Precursor for renal biosynthesis and export of arginine
- ◆ Product of nitric oxide formation from arginine
- ◆ Food sources:
 - » No especially rich food sources

IF CITRULLINE HIGH:

- ◆ Causes:
 - » Genetic disorder or functional block in the argininosuccinate synthetase enzyme, leading to buildup of excess ammonia in the system
 - » Postoperative intestinal failure

AMINO ACIDS | 21

Homocysteine; Taurine; Arginine; Citrulline

Symptoms/Conditions:

- » Potential for buildup of toxic ammonia
- » Confusion
- » Disorientation
- » Weakness
- » Diarrhea
- » Nausea
- » Hypertension

Treatment:

- » Low protein diet
- » Magnesium, 200 mg BID
- » Aspartic acid, 1 mg BID

IF CITRULLINE LOW:**Causes:**

- » Inactivation of nitric oxide synthetase—signals low nitric oxide
- » Arginine-free diet
- » Protein restriction
- » Poor digestion of proteins

Symptoms/Conditions:

- » Low nitric oxide effects
- » Impotence or sexual dysfunction
- » Elevated blood pressure
- » Digestive disturbances
- » Increased susceptibility to infection
- » Possible increased risk for cancer

Treatment:

- » Balanced mix of amino acids
- » L-Arginine, 500 mg BID

Ornithine; Glutamine

Ornithine

- ◆ Urea cycle intermediate
- ◆ Can stimulate release of growth hormone
- ◆ Important for building body tissue
- ◆ Food sources:
 - » None—formed through urea cycle pathways

IF ORNITHINE HIGH:

- ◆ Causes:
 - » Higher body burden of ammonia
 - » Blockage of urea cycle
 - » Hepatic failure
 - » Intestinal bacterial overgrowth—large ammonia output
- ◆ Symptoms/Conditions:
 - » Abnormal growth rates in children
- ◆ Treatment:
 - » Magnesium, 200 mg BID
 - » α -Ketoglutarate, 600 mg BID
 - » Vitamin B₆ (pyridoxine), 100 mg/d
 - » Low protein diet

IF ORNITHINE LOW:

- ◆ Causes:
 - » Rare deficiency
- ◆ Symptoms/Conditions:
 - » Decreased cellular metabolism
- ◆ Treatments:
 - » Balanced mix of amino acids
 - » L-Arginine, 500 mg BID

Glutamine

- ◆ The most dominant free amino acid in plasma
- ◆ Important source of energy for many tissues as a gluconeogenic substrate
- ◆ Primary route of ammonia removal from skeletal muscle activity
- ◆ Primary energy and nitrogen source for enterocytes—supplementation improves gut mucosal integrity
- ◆ Acts as both a precursor and inhibitor of nitric oxide production
- ◆ Amino group transport (especially from muscle)
- ◆ Involved in acid-base balance—see “Glu/Gln” on page 33
- ◆ Can help curb sugar cravings
- ◆ Alternate source of fuel for the brain
- ◆ Provides nitrogen for synthesis of amino acids, purines, pyrimidines and nucleotides
- ◆ Stimulates:
 - » Digestion
 - » Protein synthesis
 - » Muscle growth and repair
 - » Mental function
- ◆ Food sources:
 - » Found abundantly in foods, esp. beef, chicken, fish, eggs, milk, dairy products, wheat, cabbage, beets, beans, spinach, and parsley

IF GLUTAMINE HIGH:

- ◆ Causes:
 - » In chronic dietary protein deficiency, endogenous glutamine production increases to supply



- amino groups for biosynthetic process, so plasma levels rise as essential amino acid levels fall
- » Vitamin B₆ deficiency
 - » Rarely elevated by oral glutamine supplementation due to high rate of consumption by enterocytes and hepatic clearance
 - ◆ Symptoms/Conditions:
 - » If glutamate is concurrently low suspect mild hyperammonemia:
 - Headache, irritability, fatigue, mental confusion, poor concentration
 - » Food intolerance reactions, particularly to high protein food
 - » May interfere with acid-base balance in the body
 - ◆ Treatment:
 - » α -Ketoglutarate, 600 mg BID
 - » Vitamin B₆ (pyridoxine), 100 mg/d
 - » Branched-chain amino acids
 - » Low protein, high complex carbohydrate diet if glutamate is low

IF GLUTAMINE LOW:

- ◆ Causes:
 - » If glutamate is high, suspect specimen degradation
 - » Ammonia detoxification problems
 - » Protein catabolic states:
 - Starvation
 - Injury
 - Sepsis
 - Patients with cancer or

Glutamine; Asparagine

HIV—increased skeletal muscle catabolism

- ◆ High protein diet decreases release of glutamine from muscle
- ◆ Symptoms/Conditions:
 - » Muscle wasting
 - » Depression
 - » Hyperammonemia
 - » Decreased gut function
- ◆ Treatment:
 - » Balanced free form amino acid mixture
 - » Oral L-glutamine has little effect on plasma levels due to high rate of consumption by enterocytes and hepatic clearance

Asparagine

- ◆ Required for urea cycle function
- ◆ Closely related to aspartic acid
- ◆ Required for protein synthesis
- ◆ Serves a special function for attachment of carbohydrate residues to membrane proteins by which cells are identified
- ◆ Food sources:
 - » Dairy, beef, poultry, eggs, asparagus

IF ASPARAGINE HIGH:

- ◆ Causes:
 - » Supplementation
- ◆ Symptoms/Conditions:
 - » None known
- ◆ Treatment:
 - » Stop supplementation

Asparagine; Aspartic Acid**IF ASPARAGINE LOW:**

- ◆ Causes:
 - » Specimen degradation due to extended time before or high temperature transit to the laboratory if aspartic acid is elevated
 - » Treatment of acute lymphoblastic leukemia with L-asparaginase
- ◆ Symptoms/Conditions:
 - » None known
 - » Protein synthesis taken over by other amino acids
- ◆ Treatment:
 - » Magnesium, 200 mg BID

Aspartic Acid

- ◆ Required for biosynthesis of all body proteins
- ◆ Pivotal in amino acid metabolism
- ◆ Required for urea cycle function
- ◆ Required for renal arginine synthesis and export
- ◆ Excitatory neurotransmitter
- ◆ Precursor of nucleic acids in DNA and RNA
- ◆ Used as an energy source
- ◆ Can enter the citric acid cycle
- ◆ Stimulates:
 - » Aids in detoxification of ammonia in urea cycle
 - » Increases stamina and resistance to fatigue
 - » Used to increase neurostimulatory amino acids in brain when given with arginine

Glycine; Serine**Glycine, Serine and Related Amino Acids****Glycine**

See "Glycine" on page 13

Serine

- ◆ Required for biosynthesis of all enzymes, receptor and transport proteins, and structural proteins
- ◆ Precursor to phosphoethanolamine, and phosphatidylcholine, important cellular membrane components
- ◆ Precursor to acetylcholine, a central nervous system neurotransmitter used in memory function and mediator of parasympathetic activity
- ◆ Precursor to cysteine—one of the three amino acids needed for glutathione synthesis
- ◆ Required for the proper metabolism of methionine
- ◆ Food sources:
 - » Dairy, beef, poultry, wheat gluten, peanuts, soy
- ◆ **IF SERINE HIGH:**
 - ◆ Causes:
 - » Supplementation
 - » Hemodialysis
 - ◆ Symptoms/Conditions:
 - » Possible depressed immune system
 - » Acute psychosis
 - » Depression
 - ◆ Treatment:
 - » Stop supplementation

- » Hemodialysis patients—Erythropoietin therapy normalizes levels

IF SERINE LOW:

- ◆ Causes:
 - » Increased demand for glutathione synthesis
- ◆ Impaired:
 - Detoxification
 - Tissue repair
 - Gluconeogenesis
- » Disordered methionine metabolism and methionine intolerance
- » Homocysteinuria patients on folate therapy
- » Renal transplant patients with mild elevations of creatinine
- ◆ Symptoms/Conditions:
 - » Memory problems
 - » Decreased parasympathetic response
 - » Problems with methionine metabolism
 - » High homocysteine levels

- ◆ Treatment:
 - » Balanced mix of amino acids
 - » Combinations of glycine and serine, 1000 mg TID
 - » Vitamin B₆ (pyridoxine), 100 mg/d
 - » Vitamin B₁₂ (cobalamin), 1000 µg/d
 - » Folic acid, 800 µg/d

Serine; Sarcosine; Phosphoserine; Ethanolamine

- » Betaine, 1000 mg/d
- » Manganese, 15 mg/d
- » Magnesium, 200 mg BID

Sarcosine

- ◆ Acts as buffer in the methyl-group supply system (SAMe formation)
- ◆ Utilization requires methyl group transfer to folate
- ◆ Adjunct therapy for schizophrenia by delivery of glycine to brain
- ◆ Stimulates:
 - » Gene expression regulation
 - » Detoxification
 - » Neurotransmitter formation

IF SARCOSINE HIGH:

- ◆ Causes:
 - » Polymorphisms of sarcosine dehydrogenase
 - » Folate deficiency
- ◆ Symptoms/Conditions:
 - » Parkinson disease
- ◆ Treatment:
 - » Folic acid, 800 µg/d
 - » SAMe, 200 mg BID

Phosphoserine

- ◆ Metabolite of serine

IF PHOSPHOSERINE HIGH:

- ◆ Causes:
 - » Elevated in Parkinson disease patients
 - » Vitamin B₆ deficiency

Ethanolamine; Phosphoethanolamine; Alanine**Alanine**

- ◆ Required for biosynthesis of all enzymes, receptor and transport proteins, and structural proteins
- ◆ Major carrier of amino acid nitrogen from muscle to liver where its carbon skeleton is converted to glucose (via gluconeogenesis)
- ◆ Carrier role significant because the metabolism of amino acids in skeletal muscle is a major contributor to overall protein metabolism

IF ALANINE HIGH:

- ◆ Causes:
 - » Possible vitamin B₆ deficiency required for its metabolism
 - » Exercise prior to blood draw
- ◆ Symptoms/Conditions:
 - » Hypoglycemia
 - » Chronic use of alanine for energy can lead to muscle wasting
- ◆ Treatment:
 - » Vitamin B₆ (pyridoxine), 100 mg/d
 - » α-Ketoglutarate, 600 mg BID

IF ALANINE LOW:

- ◆ Causes:
 - » Common when other amino acids are low
 - » Reflects low or impaired flow of nitrogen from muscle to liver
- ◆ Symptoms/Conditions:
 - » Hypoglycemia
 - » Easy fatigability between meals

Alanine; Proline; Hydroxyproline

- ◆ Treatment:
 - » Alanine, 500 mg BID
 - » Branched chain amino acids (leucine, isoleucine, valine)
 - » Vitamin B₆ (pyridoxine), 100 mg/d

Collagen-Related Amino Acids

Proline

- ◆ Found in virtually every dietary protein except lactalbumin
- ◆ Required for biosynthesis of all enzymes, receptor and transport proteins, and structural proteins
- ◆ Major constituent of collagen
- ◆ Metabolized to α-ketoglutaric acid
- ◆ Required for protein synthesis
- ◆ Metabolized to hydroxyproline, an important component of connective tissue

IF PROLINE HIGH:

- ◆ Causes:
 - » Inadequate connective tissue synthesis
 - » Collagen breakdown
 - » Genetic disorders characterized by renal and CNS dysfunction
- ◆ Symptoms/Conditions:
 - » Alport-like nephropathy
 - » Seizures
 - » Mental retardation

IF PROLINE LOW:

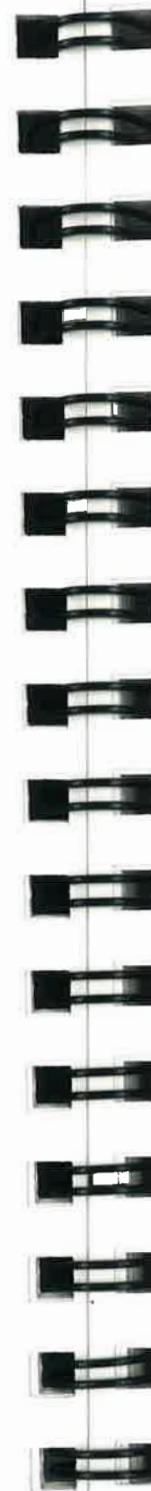
- ◆ Causes:
 - » Increased demand for connective tissue synthesis
 - » Dietary protein deficiency
- ◆ Symptoms:
 - » Essential amino acid deficiency symptoms
- ◆ Treatments:
 - » Balanced mix of amino acids

Hydroxyproline

- ◆ A component of collagen
- ◆ Synthesized from proline using vitamin C and iron as cofactors
- ◆ Urinary proline/hydroxyproline ratio reflects bone turnover, see "Pro/Hypro" on page 34

IF HYDROXYPROLINE HIGH:

- ◆ Causes:
 - » High rate of bone turnover—highly correlated with serum alkaline phosphatase
 - » Increased bone turnover associated with bone loss
 - Especially when Pro/Hypro ratio in urine is low
- ◆ Treatment:
 - » Vitamin C, 1000 mg 1-2/d
 - » Iron as needed to normalize iron status



Lysine

See "Lysine" on page 2

Hydroxylysine

- ◆ Modification of lysine in collagen
- ◆ Rising levels of urinary hydroxylysine indicate successful growth hormone therapy in GH-deficient children.

IF HYDROXYLYSINE HIGH:

- ◆ Causes:
 - » Marker for bone loss due to the turnover of collagen during bone resorption
 - » Can indicate liver disease
 - » Connective tissue breakdown
 - » Intake of dietary collagen
- ◆ Treatment:
 - » Support with the cofactors important in collagen synthesis: iron, α-ketoglutaric acid and vitamin C

β-Amino Acids and Derivatives

β-Alanine

- ◆ Released from skeletal muscles during strenuous exercise
- ◆ Part of dietary carnosine (β-alanylhistidine) and anserine (β-alanyl-1-methylhistidine), from which it is released on action of carnosinase

Lysine; Hydroxylysine; β-Alanine; Histidine; Carnosine

- ◆ Catabolism of cytosine and uracil from DNA and RNA forms β-alanine
- ◆ Intestinal bacteria and *Candida albicans* produce β-alanine
- ◆ Decreases:
 - » Renal tubular resorption of a variety of amino acids, including taurine, increasing losses in urine

IF β-ALANINE HIGH:

- ◆ Causes:
 - » High red meat intake
 - » Intestinal microbial overgrowth
 - » High turnover of muscle tissue
 - » Excessive taurine supplementation (taurine competes for transport into cells)
 - » Epileptics on vigabatrin that blocks β-alanine breakdown
- ◆ Symptoms/Conditions:
 - » Muscle weakness
- ◆ Treatment:
 - » Vitamin B₆ (pyridoxine), 100 mg
 - » Evaluate other dysbiosis markers
 - » Probiotics
 - » Prebiotics
 - » Decrease taurine supplementation (if high)

Histidine

See "Histidine" on page 8

Carnosine

- ◆ β-Alanylhistidine

Carnosine; 1-Methylhistidine; Anserine

- ◆ Involved in muscle function through the regulation of muscle phosphorylase activity
- ◆ Formed in skeletal muscle from histidine and β -alanine
- ◆ Hydrolyzed in tissues releasing histidine and β -alanine
- ◆ Forms a tight complex with zinc and assists in its absorption
- ◆ Testosterone increases synthesis
- ◆ Acts as an antioxidant in ischemia and ethanol-induced injury
- ◆ Can rescue neurons from zinc- and copper-mediated neurotoxicity
- ◆ Increases the respiratory burst and IL-1 β production in neutrophils
- ◆ Can modulate the immune response
- ◆ Food Sources:
 - » Meat, especially pork

IF CARNOSINE HIGH:

- ◆ Causes:
 - » Ingestion of meat, especially pork
 - » Supplementation with carnosine salts (e.g. zinc carnosine)
 - » Deficiency of enzyme carnosinase or its cofactor, zinc
- ◆ Symptoms/Conditions:
 - » Neurological development problems
 - » Mental retardation
 - » Sensory polyneuropathy
 - » Parkinson and multiple sclerosis
- ◆ Treatment:
 - » Zinc 30–60 mg/d
 - » Reduce meat intake, especially pork

1-Methylhistidine

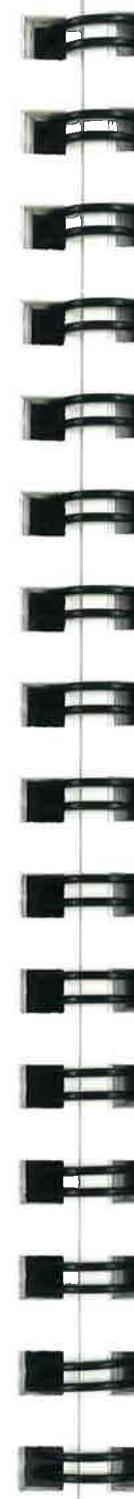
- ◆ Derived from the hydrolysis of anserine
- ◆ Urinary excretion can be used as a marker to distinguish a meat-eating individual from vegetarians
- ◆ May be associated with skeletal muscle breakdown, particularly when coupled with vitamin E deficiency

IF 1-METHYLHISTIDINE HIGH:

- ◆ Causes:
 - » High dietary meat intake, especially poultry
 - » Skeletal muscle breakdown
- ◆ Symptoms/Conditions:
 - » When associated with vitamin E deficiency, can increase oxidative effects in skeletal muscle
- ◆ Treatment:
 - » Vitamin E (as mixed tocopherols), 200–1600 mg/d
 - » Antioxidants

Anserine

- ◆ β -Alanyl-1-methylhistidine
- ◆ Involved in muscle function through the regulation of muscle phosphorylase activity
- ◆ Formed in skeletal muscle
- ◆ Hydrolyzed to 1-methylhistidine and β -alanine
- ◆ Increases with age
- ◆ Activates calcium uptake in mitochondria



- ◆ Increases respiratory burst and IL-1 β production in neutrophils
- ◆ Modulates the immune response
- ◆ Food Sources:
 - » Meat, especially poultry

IF ANSERINE HIGH:

- ◆ Causes:
 - » Deficiency of enzyme carnosinase or its cofactor, zinc
 - » High dietary intake of meat, especially poultry
- ◆ Symptoms/Conditions:
 - » None known
- ◆ Treatment:
 - » Zinc, 30 mg/d
 - » Reduce animal protein intake

Muscle-Specific Amino Acids**3-Methylhistidine**

- ◆ Catabolite of skeletal muscle proteins
- ◆ 24-hour urinary excretion can estimate skeletal muscle mass in healthy adults on a meat-free diet

IF 3-METHYLHISTIDINE HIGH:

- ◆ Causes:
 - » Active catabolism of muscle
 - » Marker of skeletal muscle breakdown as in strenuous exercise
 - » Urinary excretion rises with cortisol and falls with testosterone
 - » Ratio of urinary 3-methylhistidine

Anserine; 3-Methylhistidine; Phe/Tyr (Plasma)

to creatinine is increased in severe injury, thyrotoxicosis, neoplastic disease, prednisone administration and sometimes Duchenne muscular dystrophy

» Intake of dietary meat (confirm by elevated 1-Methylhistidine)

» Hypervitaminosis A

- ◆ Symptoms/Conditions:
 - » Excessive muscle tissue breakdown
 - » Oxidative stress

- ◆ Treatment:
 - » Antioxidants
 - » Branched-chain amino acids to prevent muscle proteolysis

Ratios**Phe/Tyr (Plasma)**

- ◆ Useful for monitoring ability to convert phenylalanine to tyrosine
- ◆ Conversion enzyme is phenylalanine hydroxylase (PAH) that requires tetrahydrobiopterin (BH4), niacin (B_3) and iron as cofactors
- ◆ Over 400 mutations in the genes encoding PAH, and many others cause lowered activity of the enzyme that initiates synthesis of BH4, GTP cyclohydrolase

Note: Individuals with mild forms of the enzyme polymorphisms may manifest only post prandial signs and symptoms when insulin is accelerating the metabolism of amino acids. Failure of Phe \rightarrow Tyr conversion produces a transient tyrosine insufficiency for biosynthesis

Phe/Tyr (Plasma); Trp/LNAA

of products such as proteins, catecholamines and thyroglobulin.

IF PHE/TYR HIGH:

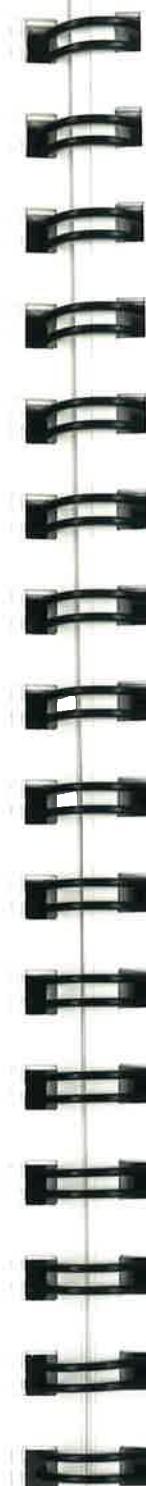
- ◆ Causes:
 - » Phenylketonuria (PKU) or non-PKU hyperphenylalaninemia due to:
 - Phenylalanine hydroxylase deficiency
 - GTP cyclohydrolase deficiency → BH₄ deficiency
 - Iron deficiency
 - Niacin deficiency
- ◆ Symptoms/Conditions:
 - » Neonatal:
 - Musty odor to the skin, hair, and urine
 - Vomiting and diarrhea, leading to weight loss
 - Irritability
 - Skin problems, such as dry skin, or itchy skin rashes (eczema)
 - Sensitivity to light (photosensitivity)
 - ◆ Children (untreated):
 - » Mental retardation
 - » Behavioral or social problems
 - » Seizures, tremors or jerking movements in the arms and legs
 - » Rocking
 - » Hyperactivity
 - » Stunted growth
 - ◆ Adults with milder forms of PKU (untreated):
 - » Poor academic performance (low IQ)

- » Poor socialization
- » Increased risk of mental illness and psychological disorders
- » Motor neuron damage
- » Multisystem neuropathology
- ◆ Treatments:
 - » Phenylalanine-restricted diet
 - » Tyrosine supplemented low-phenylalanine diet powder, 10–15% (10–15 g/100 g protein equivalent)
 - » Discontinue if plasma tyrosine becomes elevated, esp. in pregnant women
 - » BH₄, up to 10 mg/kg, titrate to normal Phe/Tyr ratio
 - » Folic or folinic acid (especially if BH₄ is unavailable)
 - » Niacin, 50mg BID
 - » Vitamin C, 1000 mg 1–2/d
 - » Iron as needed to normalize iron status

Trp/LNAA

- ◆ Tryptophan is a large, neutral amino acid (LNAA) that must compete with other LNAs, including leucine, isoleucine, valine, phenylalanine, and threonine for a single transporter to gain entry across the blood-brain barrier
- ◆ The ratio of tryptophan to the other LNAs governs the amount of tryptophan that enters serotonergic neurons to allow serotonin synthesis

CFS - 70% B6

**IF Trp/LNAA HIGH**

- ◆ Symptoms/Conditions:
 - » Chronic elevation of tryptophan in relation to the LNAA can increase manic tendencies by promoting elevated serotonin production
- ◆ Treatments
 - » Reduce use of L-Tryptophan supplements

IF Trp/LNAA LOW

- ◆ Symptoms/Conditions:
 - » The LNAA block passage of tryptophan across the blood-brain barrier, increasing the potential for inadequate production of serotonin with consequences of depressive conditions.
- ◆ Treatments
 - » L-Tryptophan, 250 mg BID with meals

Glu/Gln

- ◆ Can identify specimen handling issues that cause spontaneous degradation of glutamine to glutamate
- ◆ Can reveal origin of difficulty maintaining systemic pH balance
- ◆ Abnormalities may affect neurotransmitter role of glutamic acid
- ◆ Low ratio levels enhance glutamate outflow from brain neurons, contributing to development of major depression

IF GLU/GLN HIGH:

- ◆ Causes:
 - » Specimen delay or exposure to elevated temperatures
 - » Polymorphisms in SN1/SN2 transporter systems in liver and brain

Note: See "Laboratory Evaluations for Integrative and Functional Medicine" by Lord and Bralley for discussion of the SN1/SN2 transporter system.

- ◆ Symptoms/Conditions (assuming good specimen integrity):
 - Depressed gastric motility
 - Neurodegenerative disorders (i.e. ALS, Huntington chorea)
 - Exacerbation of neuronal glutamate toxicity that is potentiated by quinolinate (see "Quinolinate" on page 112)
 - Suppressed lymphocyte activity and low T4 (CD4) lymphocyte levels
- ◆ Treatments:
 - » Frequent, small meals of moderate protein content

IF GLU/GLN LOW:

- ◆ Causes:
 - » Positive evidence of good specimen integrity
 - » Defective pH responses of hepatic SN1/SN2 transporter system
- ◆ Symptoms/Conditions:
 - » Tendency for post-prandial systemic acidosis
 - » Ammonemic encephalopathy
 - » Trazadone antidepressant therapy

Glu/Gln; Pro/Hypro; α -ANB/Leu

- » Increased risk of major depression

◆ Treatments:

- » Smaller, more frequent meals
- » Normalization of systemic pH
- » Correct elevated organic acids (B-vitamins, CoQ10 as needed—see “Organic Acids in Urine” on page 95)
- » Correct ammonemia (arginine, citrulline supplementation)
- » Normalize small bowel bacterial overgrowth

Pro/Hypro

- ◆ Proline occurs in many proteins, but hydroxyproline is specific to collagen

IF PRO/HYPRO HIGH:

- ◆ Causes:
 - » Increased collagen turnover due to increased bone resorption
 - » Vitamin C deficiency
 - » Iron deficiency
- ◆ Symptoms/Conditions:
 - » Osteoporosis
 - » Inherited collagen synthesis defect
- ◆ Treatments:
 - » Enhance osteogenesis (Ca, Mg, Vit D, Vit K)
 - » Vitamin C, 1000–5000 mg/d
 - » Evaluate need for iron
 - » Reduce bone resorption
 - » Increase exercise

 α -ANB/Leu

- ◆ α -Amino-N-butyrate specifically elevated by high blood alcohol
- ◆ Dividing by leucine normalizes for other conditions of general elevation of blood amino acids

IF α -ANB/LEU HIGH:

- ◆ Causes:
 - » Recent alcohol intake
- ◆ Symptoms/Conditions:
 - » Alcoholism
- ◆ Treatments:
 - » Detoxification and rehabilitation

**2****Nutrient and Toxic Elements****Contents**

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Calcium; Magnesium; Potassium; Sodium; Phosphorus			
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Reducing Body Burdens; Chelation Procedures; Causes of High Toxic Elements in Blood, Hair or Urine			

Table of Specimen Differences

	Nutrient Elements	Toxic Elements
Erythrocytes	Levels reflect cellular uptake in erythropoiesis	Detects recent acute or long-term chronic exposure
Whole blood, Serum or Plasma	Levels represent availability and transport issues	Most commonly used specimen; good for detecting recent, acute exposure; low sensitivity for chronic low level exposure
Hair	Long term status (~3 month)	High sensitivity for chronic exposure
Urine	Short term intake (~ 2 days), depending on renal metallothionein	Sensitivity improved by challenge with complexing agent such as DMSA

Nutrient (Essential) Elements

Across all demographic strata in industrialized nations, nutrient element deficiencies are recognized as being involved in the pathogenesis of many health conditions, including heart disease, hypertension and cancer. Populations such as the elderly, pregnant women, small children, and immunocompromised patients are particularly vulnerable to essential element deficiencies.

Common Causes of Low Nutrient Elements

- ◆ Decreased intake:
 - » Low levels in diet due to soil depletion, poor food choices, or refined foods
 - » Failure to adequately fortify during total parenteral nutrition (TPN)
- ◆ Intestinal pathologies (including hypochlorhydria, maldigestion, malabsorption, or small intestinal bacterial overgrowth)
- ◆ Increased physiological demands and turnover (i.e. pregnancy, adolescence, childhood)

NOTES

- ◆ Genetic polymorphisms of transport proteins

Major Elements

Calcium

- ◆ Essential for:
 - » Bones and teeth
 - » Heart
 - » Nerves
 - » Muscle cells (smooth, cardiac and skeletal)
 - » Blood clotting
 - » Signal transduction, including:
 - Neuronal excitation
 - Neurotransmitter release
 - » Innate immunity
 - » Hormonal secretion
- ◆ Food sources:
 - » Dark green vegetables, whole grains, nuts, milk

Note: The significance of calcium abnormalities varies greatly, depending on the specimen submitted for analysis. The tabular format on the following section is used to clearly display these differences.



IF CALCIUM HIGH

Causes (Calcium High)

Erythrocyte	Hair	Urine (Unprovoked)
Glutathione insufficiency	Negative calcium balance	Hyperparathyroidism
		Sarcoidosis
		High calcium intake
		Vitamin D toxicity
		Hyperthyroidism
		Diabetes mellitus
		Immobility
		Steroid therapy
		Paget disease
		Primary (idiopathic) hypercalcioria
		Potassium insufficiency

Symptoms/Conditions (Calcium High)

Erythrocyte	Hair	Urine (Unprovoked)
Arrhythmias	Hyperparathyroid sequelae	Kidney stones
Pre-menstrual syndrome	Osteoporosis	Osteoporosis
Hypertension		
Renal failure		
Uremia		
Calcium channel disruption		
Oxidative stress		

Calcium

Treatment (Calcium High)

Erythrocyte	Hair	Urine (Unprovoked)
Glutathione support	Calcium, 800–1300 mg/d	Fresh fruits & vegetables Potassium, 150–300 mg/d
Essential fatty acids	Magnesium, 300–700 mg/day	Address underlying causes
Antioxidants	Restrict dietary phosphorus	
	Other tests: Bone loss markers, vitamin D	

IF CALCIUM LOW:

Causes (Calcium Low)

Erythrocyte	Hair	Urine (Unprovoked)
N.A.	Arteriosclerosis (adults) N.A. (children)	Dietary deficiency of calcium See, "Common Causes of Low Nutrient Elements" on page 36

Symptoms/Conditions (Calcium Low)

Erythrocyte	Hair	Urine (Unprovoked)
	Vascular occlusion diseases	Familial hypocalciuric hypercalcemia
		Thiazide diuretics
		Renal osteodystrophy
		Vitamin D deficiency
		Hypoparathyroidism
		Pre-eclampsia

Treatment (Calcium Low)

Erythrocyte	Hair	Urine (Unprovoked)
N.A.	Assess heart disease risk factors	Calcium, 800–1000 mg/day
		Vitamin D, 2000 IU/day
		Magnesium, 300–700 mg/day



Note: Evaluate other associated nutrient biomarkers including: magnesium (RBC, hair), vitamin K (ucOC), vitamin D, phosphorus (serum), deoxypyridinoline, parathyroid hormone and alkaline phosphatase.

Magnesium

- ◆ Stabilizes phosphate in ATP
- ◆ Affects all tissues due to ubiquitous energy (ATP) demands
- ◆ Muscle and nerve action
- ◆ Coenzyme for carbohydrates
- ◆ Protein metabolism
- ◆ Increases the absorption of calcium
- ◆ Activates vitamin D
- ◆ Aids in parathyroid function (decreases bone catabolism)
- ◆ Helps calcitonin function (increases absorption of calcium)
- ◆ Low RBC magnesium is associated with poor glutathione status
- ◆ Food sources:
 - » Whole grains, nuts, legumes, molasses, brewer's yeast

IF MAGNESIUM HIGH:

- ◆ Causes:
 - » Supplementation
 - » Addison disease (reduced aldosterone)
 - » Hypothyroidism
 - » Renal failure
 - » Medications
- ◆ Symptoms/Conditions:
 - » Diarrhea
- ◆ Treatment:
 - » Magnesium, 300–700 mg/d
 - » NAC, 500 mg/ BID

- » Nausea
- » Vomiting
- ◆ Treatment:
 - » Stop supplementation
 - » Address underlying causes

IF MAGNESIUM LOW:

- ◆ Causes:
 - » See "Common Causes of Low Nutrient Elements" on page 36
 - » Alcoholism
 - » Hyperaldosteronism
 - » Hypercalcemia
 - » Hyperthyroidism
 - » Pancreatitis
 - » Renal disease (renal tubular leak)
 - » Medications
- ◆ Symptoms/Conditions:
 - » Muscular twitching and cramping
 - » Depression
 - » Constipation
 - » Arrhythmias
 - » Irritability
 - » Hypertension
 - » Refractory hypokalemia (may mask Mg insufficiency)
 - » Diabetes type II
 - » Cardiovascular disease
 - » Myocardial infarction
 - » Convulsions
 - » Poor growth

Magnesium; Potassium**IF MAGNESIUM HIGH IN HAIR:**

- ◆ Causes:
 - » Bone loss
 - » Hyperparathyroidism
- ◆ Symptoms/Conditions:
 - » Osteopenia
 - » Osteoporosis
- ◆ Treatment:
 - » Magnesium, 300–700 mg/d

Potassium

- ◆ Neuromuscular function
- ◆ Intracellular fluid control
- ◆ Energy metabolism
- ◆ Food sources:
 - » Most fruits and vegetables; avocado, banana, mango, corn on the cob, dried beans, potatoes, tomatoes

IF POTASSIUM HIGH IN RBC OR URINE:

- ◆ Causes:
 - » Supplementation
 - » Acidosis or alkalosis
 - » Diabetes
 - » Hypoadosteronism
 - » Adrenal insufficiency
 - » Renal failure
 - » Tissue damage
 - » Medications—e.g. aldosterone-inhibiting diuretics, ACE inhibitors
- ◆ Symptoms/Conditions:
 - » Confusion
 - » Weakness

- » Nausea
- » Diarrhea
- » Paresthesia
- » Weakness
- » Cardiac depression/arrest
- » ECG findings:
 - Peaked T waves
 - Widened QRS complex
 - Depressed ST segment
- ◆ Treatment:
 - » Address underlying causes
 - » Stop supplementation

IF POTASSIUM LOW IN RBC OR URINE:

- ◆ Causes:
 - » See “Common Causes of Low Nutrient Elements” on page 36
- » Losses from vomiting or diarrhea
- » Renal losses
- » Cardiac failure
- » Alkalosis or acidosis
- » Diabetes
- » Cushing syndrome
- » Excessive licorice (aldosterone-like effect)
- » Excessive sweating
- » Hypothermia
- » Increased urination
- » Bartter syndrome
- » Medications—e.g. diuretics
- ◆ Symptoms/Conditions:
 - » Muscle weakness
 - » Hyporeflexia
 - » Arrhythmia



- » Neurological complaints

- » GERD
- » Hypertension
- » Stroke
- » Cardiac dysfunction
- » ECG:
 - Flattened T waves
 - Prominent U waves

- ◆ Treatment:
 - » Fresh fruits and vegetables
 - » Potassium, 150–300 mg/d

Sodium

Sodium is a monovalent element that is weakly bound in hair. Elevated hair sodium may indicate impaired electrolyte balance, adrenal and/or renal function. Low hair sodium has been found in breast cancer patients, and in children with electrolyte imbalances.

Phosphorus

Phosphorus is present in hair as negatively charged phosphate ions that do not form strong complexes with the cysteine residues, like positively charged divalent metal ions. Little is known about abnormal hair levels, although imbalances may be associated with calcium and magnesium imbalances. Consider follow-up testing using blood or urine, or evaluate bone turn-over using deoxypyridinoline (DPD).

Trace Elements**Iron (Serum Ferritin)**

- ◆ Major storage form of iron
- ◆ Most sensitive marker of iron deficiency anemia
- ◆ Acute phase reactant protein; may not accurately reflect iron status during inflammation
- ◆ Food sources (of iron):
 - » Organ meats, brewer's yeast, wheat germ, egg yolk, oyster, dried beans, and some fruits
 - » Phytates found in beans decrease iron absorption
 - » Vitamin C increases iron absorption

IF FERRITIN HIGH:

- ◆ Causes:
 - » Hemochromatosis
 - » Megaloblastic anemia
 - » Hemolytic anemia
 - » Inflammatory states
 - » Advanced cancers
 - » Anemia of chronic disease: cirrhosis, leukemia, collagen vascular diseases
 - » Supplementation with iron
- ◆ Symptoms/Conditions:
 - » Vomiting
 - » Abdominal pain
 - » Shock
 - » Lethargy
 - » Dyspnea

Iron; Zinc

- » Accelerated aging
- » Cataracts
- » Cirrhosis
- » Cardiac failure
- » Increased cardiotoxicity of anthracycline antibiotics
- ◆ Treatment:
 - » Decrease or remove iron supplements, alcohol, red meat
 - » Phlebotomy
 - » Increase dietary whole grains (phytates)
 - » IV chelation (desferroxamine)

IF FERRITIN LOW:

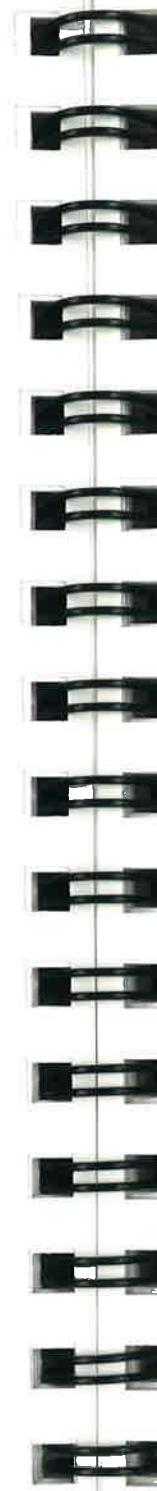
- ◆ Causes:
 - » See "Common Causes of Low Nutrient Elements" on page 36
 - » Dietary iron deficiency
 - » Copper deficiency (see "Copper" on page 43)
 - » Vitamin C deficiency
 - » Increased physiological demands (i.e. pregnancy or sudden growth in children)
 - » Blood loss
 - » Malabsorption (esp. post surgical)
 - » Protein deficiency
 - » Medications e.g. proton pump inhibitors
- ◆ Symptoms/Conditions:
 - » Iron deficiency anemia
 - » Fatigue
 - » Delay in growth or cognitive development
 - » Weakness

Zinc

- ◆ Necessary for growth and development of all life forms
- ◆ Cofactor for numerous enzymes
- ◆ Vital for wound healing
- ◆ Food sources:
 - » Red meat, shellfish, whole grains
- ◆ Causes:
 - » Supplementation
 - » Cancer metastasis
 - » Renal failure
- ◆ Symptoms/Conditions:
 - » GI irritation
 - » Copper deficiency

IF ZINC HIGH:

- ◆ Causes:
 - » Supplementation
 - » Cancer metastasis
 - » Renal failure
- ◆ Symptoms/Conditions:
 - » GI irritation
 - » Copper deficiency



- » Anemia due to copper deficiency
- ◆ Treatment:
 - » Stop supplementation
 - » Evaluate copper levels

IF ZINC LOW:

- ◆ Causes:
 - » See "Common Causes of Low Nutrient Elements" on page 36
 - » Diarrhea
 - » Sickle cell disease
 - » Corticosteroids
 - » Oral contraceptives
 - » Endogenous gonadal hormones of pregnancy
- ◆ Symptoms/Conditions:
 - » Lethargy
 - » Altered taste
 - » Diarrhea
 - » Chronic skin disorder—rashes
 - » Slow wound healing
 - » Acrodermatitis enteropathica
 - » Alopecia
 - » Poor immune function
 - » Depressed growth
 - » Photophobia and night blindness
 - » Reproductive dysfunction
 - » Decreased alkaline phosphatase
 - » Cystic fibrosis
 - » Anorexia
- ◆ Treatment:
 - » Zinc, 15–65 mg/d

Copper

- ◆ Cofactor for:
 - » Lipid metabolism
 - » Neurotransmitter synthesis
 - » Erythrocyte superoxide dismutase

- ◆ Important in:
 - » Thyroid function
 - » Melanin production
 - » Myelin, bone and connective tissue production
 - » Immune function
 - » Hematopoiesis
- ◆ Food sources:
 - » Liver, cashews, black-eyed peas, sunflower seeds

IF COPPER HIGH:

Note: If high in hair, exogenous sources of copper must be ruled out (i.e., copper in the water supply)

- ◆ Causes:
 - » Supplementation
 - » Exposure from copper piping or copper cookware
 - » Wilson disease
 - » Aging
 - » Liver and/or gall bladder disease
 - » Infection
 - » Inflammation
 - » Pregnancy
 - » Anemia
 - » Cancer
 - » Renal disease
 - » Rheumatoid arthritis
 - » SLE

Copper; Manganese

- » Thyroid disease
- » Medications
- ◆ Symptoms/Conditions:
 - » Nausea
 - » Vomiting and diarrhea
 - » Hepatic cirrhosis
 - » Neurodegenerative conditions
 - » Heart disease
 - » Retinal degeneration
 - » Elevated systolic blood pressure
 - » Learning and other mental disorders including Autism Spectrum Disorders
- ◆ Treatment:
 - » Zinc, 15–65 mg/d
 - » Stop supplementation with copper
 - » Decrease exposure (copper piping, cookware)
 - » Methionine, 250 mg TID

IF COPPER LOW:

- ◆ Causes:
 - » See, "Common Causes of Low Nutrient Elements" on page 36
 - » Nephrotic syndrome
 - » Menke disease
 - » Wilson disease (with lower levels of serum ceruloplasmin, elevated urinary copper and tissue copper levels) see link:
 - digestive.niddk.nih.gov/ddiseases/pubs/wilson/
 - » Laboratory tests measure the amount of copper in the blood, urine, and liver tissue. Most people with Wilson disease will have a lower than normal level
- ◆ Symptoms/Conditions:
 - » Refractory anemia
 - » Depigmentation
 - » Impaired glucose tolerance
 - » Elevated cholesterol
 - » Neutropenia
 - » Thrombocytopenia
 - » Neurological disorders
 - » Bone loss
 - » Accelerated aging/increased oxidative stress
 - » Cardiovascular degeneration:
 - Aortic fissures
 - Coronary artery thrombosis
 - Myocardial infarction
- ◆ Treatment:
 - » Copper, 2–10 mg/d

Manganese

- ◆ Cofactor for amino acid, lipid, and carbohydrate metabolism
- ◆ Immune function
- ◆ Regulation of blood sugar and cellular energy
- ◆ Reproduction

of copper in the blood and a lower level of corresponding ceruloplasmin, a protein that carries copper in the bloodstream. In cases of acute liver failure caused by Wilson disease, the level of blood copper is often higher than normal. A 24-hour urine collection will show increased copper in the urine in most patients who display symptoms.

◆ Symptoms/Conditions:

- » Refractory anemia
- » Depigmentation
- » Impaired glucose tolerance
- » Elevated cholesterol
- » Neutropenia
- » Thrombocytopenia
- » Neurological disorders
- » Bone loss
- » Accelerated aging/increased oxidative stress
- » Cardiovascular degeneration:

- Aortic fissures
- Coronary artery thrombosis
- Myocardial infarction

◆ Treatment:

- » Copper, 2–10 mg/d

- ◆ Digestion
- ◆ Repairs bones and connective tissue
- ◆ Protective against free radicals
- ◆ Food sources:
 - » Tea, whole grains, legumes, nuts, green vegetables

IF MANGANESE HIGH:

- ◆ Causes:
 - » Industrial exposure: welding or steel alloy
 - » Water
 - » Supplementation
- ◆ Symptoms/Conditions:
 - » "Manganese madness"
 - » Compulsions, violence
 - » Emotional instability
 - » Hallucinations
 - » Neurotoxicity
 - » Parkinsonism
 - » Schizophrenia with nervous disorders resembling Parkinson disease
 - » Fatigue and sexual dysfunction
- ◆ Treatment:
 - » Avoidance
 - » Stop supplementation
 - » EDTA chelation

IF MANGANESE LOW:

- ◆ Causes:
 - » See "Common Causes of Low Nutrient Elements" on page 36
 - » Excessive calcium supplementation

- ◆ Symptoms/Conditions:
 - » Skin rashes
 - » Premenstrual syndrome
 - » Reduced antioxidant protection
 - » Defects in lipid and carbohydrate metabolism
 - » Impaired ammonia clearance
 - » Impaired reproductive function
 - » Impaired growth
 - » Skeletal abnormalities
- ◆ Treatment:
 - » Manganese, 5–13 mg/d

Selenium

- ◆ Selenium is a primary antioxidant element
- ◆ Cofactor for redox enzymes including glutathione peroxidase and thyroxine oxidase
- ◆ Involved in:
 - » Endocrine and reproductive system
 - » Hepatic system
 - » Cardiovascular system
 - » Immune system
 - » Gastrointestinal system
 - » Musculoskeletal system
 - » Cancer prevention and treatment
- ◆ Food sources:
 - » Garlic, onions, broccoli, Brazil nuts, brewer's yeast
- ◆ Causes:
 - » Supplementation

IF SELENIUM HIGH:

- ◆ Causes:
 - » Supplementation

Selenium; Molybdenum

- » Excessive dietary intake
- ◆ Symptoms/Conditions:
 - » Garlic breath odor
 - » Brittle fingernails and hair
 - » Neurological complaints such as numbness, convulsions, or paralysis
 - » Swollen red skin of hands and feet
 - » Hair loss
- ◆ Treatment:
 - » Stop supplementation
 - » Decrease exposure, especially foods grown in selenium-rich soil
 - » Vitamins B₁₂, B₆, folic acid and SAMe

IF SELENIUM LOW:

- ◆ Causes:
 - » See "Common Causes of Low Nutrient Elements" on page 36
 - » Mercury and arsenic toxicity
- ◆ Symptoms/Conditions:
 - » Asthma
 - » Compromised immunity
 - » Reproductive system dysfunction
 - » Cardiovascular dysfunction
 - » Inflammation
 - » Abnormal thyroid hormone activity
 - » Increased risk for certain cancers
 - » Oxidative stress
 - » Cardiomyopathy
 - » Increased toxic responses to mercury
- ◆ Treatment:
 - » Selenium, 55–400 µg/d

Molybdenum

- ◆ Cofactor for sulfite oxidase, xanthine oxidase and aldehyde dehydrogenase
- ◆ Food Sources:
 - » Beans, nuts, grains, green leafy vegetables

IF MOYBDENUM HIGH:

- ◆ Causes:
 - » Environmental exposure
 - » Excessive supplementation
- ◆ Symptoms/Conditions:
 - » Gout
 - » Oxidative stress
 - » Increased copper excretion
- ◆ Treatment:
 - » Antioxidants
 - » Reduce intake

IF MOYBDENUM LOW:

- ◆ Causes:
 - » See "Common Causes of Low Nutrient Elements" on page 36
- ◆ Symptoms/Conditions:
 - » Sulfite sensitivity:
 - Asthma
 - Shortness of breath
 - Edema
 - Dermatitis
 - Anaphylaxis
 - » Copper toxicity
 - » Mental disturbance and coma
 - » Motor disabilities
- ◆ Treatment:
 - » Molybdenum, 50–400 µg/d

Chromium

- ◆ Found in the liver
- ◆ Increases insulin sensitivity via potentiating insulin receptor activity
- ◆ Sugar metabolism improved by 80% in those with slight glucose intolerance by supplementing with 200 µg/d of chromium
- ◆ Aids in lowering LDL cholesterol and raising HDL cholesterol
- ◆ Trivalent chromium is used in biological systems and is largely non-toxic
- ◆ Hexavalent chromium is found in industry, and is highly toxic
- ◆ Food sources:
 - » Whole grains, legumes, nuts, yeast, meats

IF CHROMIUM HIGH:

- ◆ Causes:
 - » Supplementation
 - » Industrial exposure: paint, metals, cement, detergents, chemicals
- ◆ Symptoms/Conditions:
 - » Dermatitis
 - » Cancer
- ◆ Treatment:
 - » Stop supplementation
 - » Balance gastrointestinal microflora
 - » Increase dietary phytates

Note: High urine chromium indicates frequent blood sugar peaks

IF CHROMIUM LOW:

- ◆ Causes:
 - » See "Common Causes of Low Nutrient Elements" on page 36
- ◆ Symptoms/Conditions:
 - » Glucose insensitivity
 - » Elevated blood glucose and insulin
 - » Cholesterol imbalances
 - » May increase risk of Type 2 diabetes
- ◆ Treatment:
 - » Address underlying causes
 - » Chromium, 200–1000 µg/d

Cobalt

- ◆ Food sources:
 - » Organ meats, nuts, yeast extract

IF COBALT HIGH:

- ◆ Causes:
 - » Vitamin B₁₂ supplementation (over 30 mg/day)
- ◆ Symptoms/Conditions:
 - » Goiter
 - » Hypothyroidism
- ◆ Treatment:
 - » Decrease exposure
 - » Decrease supplementation

IF COBALT LOW:

- ◆ Causes:
 - » See "Common Causes of Low Nutrient Elements" on page 36
 - » Vitamin B₁₂ deficiency

Cobalt; Boron; Lithium

- ◆ Symptoms/Conditions:
 - » Fatigue
 - » Peripheral neuropathy
 - » Dementia
 - » Pernicious anemia
 - » Macrocytic anemia
 - » May be associated with abnormal estrogen metabolism
- ◆ Treatment:
 - » Vitamin B₁₂, 1,000–5,000 µg/day, with adequate folic acid

Elements of Unknown Human Requirement

Boron

- ◆ Involved in steroid hormone modulation and bone health
- ◆ Food sources:
 - » Apples, soy, grapes, nuts

IF BORON HIGH:

- ◆ Causes:
 - » Supplementation
 - » Note regarding hair: exogenous sources may deposit in hair
- ◆ Symptoms/Conditions:
 - » Testicular atrophy
 - » Decreased seminal volume
 - » Decreased sexual activity
 - » Stunted growth
- ◆ Treatment:
 - » See "Managing Patients with Metal Toxicities" on page 59

IF BORON LOW:

- ◆ Causes:
 - » See "Common Causes of Low Nutrient Elements" on page 36
- ◆ Symptoms/Conditions:
 - » Osteoporosis
 - » Decreased plasma steroid hormones
 - » Arthritis
- ◆ Treatment:
 - » Boron, 1–12 mg/d

Lithium

- ◆ Involved in regulating genes associated with circadian rhythm
- ◆ Food sources:
 - » Vegetables, grains

IF LITHIUM HIGH:

- ◆ Causes:
 - » Pharmacological dosages
- ◆ Symptoms/Conditions:
 - » Thyroid suppression
 - » Alopecia
 - » Persistent cognitive and neurological impairment
 - » Life threatening
- ◆ Treatment:
 - » Reduce dose
 - Serum lithium must be monitored closely when taking pharmacological dosages of lithium
 - » Avoidance



IF LITHIUM LOW:

- ◆ Causes:
 - » See "Common Causes of Low Nutrient Elements" on page 36
 - » Unknown, likely insufficient intake or poor absorption
- ◆ Symptoms/Conditions:
 - » Neurosis
 - » Schizophrenia
 - » Psychosis
 - » Homicide
 - » Learning disabilities
 - » Heart disease
 - » Autism
 - » Circadian imbalances
- ◆ Treatment:
 - » Lithium, 400–1,000 µg/day

Note: Urine has been used to establish lithium deficiency

Nickel

- ◆ Food sources:
 - » Foods cooked in stainless steel cookware

Note: Hair may be the best specimen to measure past nickel exposure because it is rapidly cleared from blood and urine.

IF NICKEL HIGH:

- ◆ Causes:
 - » Stainless steel
 - » Tobacco smoke
 - » Industrial exhaust fumes
 - » Batteries
 - » Nickel jewelry

- ◆ Symptoms/Conditions:
 - » Dermatitis
 - » Asthma
 - » Rhinitis
 - » Sinusitis
 - » Cancer, if inhaled
- ◆ Treatment:
 - » See "Managing Patients with Metal Toxicities" on page 59
- ◆ Causes:
 - » See "Common Causes of Low Nutrient Elements" on page 36
 - » Unknown, likely insufficient intake or poor absorption
- ◆ Symptoms/Conditions:
 - » Poor growth and reproductive function in animals
 - » Unknown clinical symptoms in humans
- ◆ Treatment:
 - » Nickel, < 5 µg/d

Strontium

- ◆ 98% of total body strontium resides in bone
- ◆ Strontium therapy can falsely attenuate DEXA scans. Concurrent assessment of bone turnover marker deoxypyridinoline is indicated to ensure treatment efficacy.
- ◆ High dose strontium may inhibit vitamin D formation; supplementation of both is indicated

Strontium; Vanadium

- ◆ Food sources:
 - » Green leafy vegetables, Brazil nuts

IF STRONTIUM HIGH:

- ◆ Causes:
 - » Supplementation
 - » Environmental exposure (nuclear waste)
- ◆ Symptoms/Conditions:
 - » Cancer (if radioactive strontium)
- ◆ Treatment:
 - » Avoidance

Note: High levels in hair can indicate negative calcium balance and bone loss

IF STRONTIUM LOW:

- ◆ Causes:
 - » See "Common Causes of Low Nutrient Elements" on page 36
 - » Unknown, likely insufficient intake or poor absorption
- ◆ Symptoms/Conditions:
 - » Osteopenia
 - » Osteoporosis
- ◆ Treatment:
 - » Strontium, 125–680 mg
 - » Vitamin D, 800–2000 IU/day
 - » Calcium and strontium compete for absorption. Take separately

Vanadium

- ◆ Apparent role in insulin release and action
- ◆ Cholesterol, triglyceride reduction
- ◆ May be needed for thyroid function

Food sources:

- » Buckwheat, parsley, soybeans, safflower oil

Note: High urinary vanadium is the traditional test for occupational exposure.

IF VANADIUM HIGH:

- ◆ Causes:
 - » Supplementation
 - » Occupational exposure
 - » Living near vanadium plants
- ◆ Symptoms/Conditions:
 - » Respiratory disorders
 - » Neurological impairment
 - » Green tongue
 - » GI upset
- ◆ Treatment:
 - » See "Managing Patients with Metal Toxicities" on page 59

IF VANADIUM LOW:

- ◆ Causes:
 - » See "Common Causes of Low Nutrient Elements" on page 36
 - » Deficiency syndrome undefined in humans
- ◆ Symptoms/Conditions:
 - » Metabolic syndrome
 - » Type 2 diabetes
 - » Possible blood lipid elevation, insulin resistance, and bone growth impairment
 - » Hypertension
- ◆ Treatment:
 - » Vanadium (as vanadyl sulfate), 9 µg/d–125 µg/d

Toxic Elements**Aluminum**

- ◆ Renal failure decreases elimination and so increases toxicity
- ◆ Dialysis not effective at removing aluminum and can even add it through dialysate
- ◆ Can cause encephalopathy
- ◆ Accumulates in brain and bone
- ◆ Replaces calcium in bone and interrupts calcium exchange
- ◆ Primarily excreted in bile and secondarily in urine

IF ALUMINUM HIGH:

- ◆ Sources:
 - » Drinking water (aluminum used as bactericide; acid rain contamination)
 - » Aluminum cookware, cans, or foil
 - » Deodorants/antiperspirants
 - » Tobacco and cannabis smoke
 - » Toothpaste
 - » Baking powder/soda (aluminum sulfate)
 - » Antacids (certain brands, check labels)
 - » Medicinal products that contain phosphate binders
 - » Milk and milk products (from equipment)
 - » Aluminum in pickled foods (check labels)
 - » Some nasal sprays
 - » Some cat litter
- ◆ Symptoms/Conditions:
 - » Abnormal speech
 - » Myoclonic jerks
 - » Convulsions
 - » Osteomalacia—predisposition to fractures
 - » Anemia
 - » Impaired parathyroid function
 - » Progressive encephalopathy
 - » Alzheimer disease
 - » Parkinson disease
 - » Multiple Sclerosis
- ◆ Treatment:
 - » See "Managing Patients with Metal Toxicities" on page 59
 - » Make sure ferritin levels are normal

- » Infant formula, cow milk and soy products
- » Ceramics (made from AL 203 clay)
- » Dental amalgams
- » Cigarette filters and tobacco smoke
- » Automotive exhausts
- » Pesticides
- » FD&C color additives
- » Vanilla powder
- » Table salt, seasonings
- » Bleached flour
- » American cheese
- » Medications containing kaolin (aluminum silicate)
- » Sutures with wound-healing coatings
- » Rat poisons

Aluminum; Arsenic; Cadmium

- » Glycine—mobilizes aluminum
- » Check aluminum levels in drinking water

Arsenic**IF ARSENIC HIGH:**

Note: High arsenic in blood indicates recent exposure (six to ten hours)

- ◆ Sources:
 - » Metal foundry
 - » Drinking water
 - » Seafood (non-toxic arsenic source)
 - » Chicken
 - » Glues
 - » Industrial exposure
 - » Contaminated wine
 - » Contaminated herbal supplements
 - » Cigarette smoke
 - » Arsenic-treated wood (outdoor decks, playground equipment, etc.)
 - » Paint pigments
 - » Microelectronics industry
 - » Pesticides, herbicides
 - » Fungicides
- ◆ Symptoms/Conditions:
 - » Peripheral arteriosclerosis ("blackfoot disease")
 - » Peripheral neuropathy
 - » "Rice-water" stools
 - » Proteinuria
 - » Hyperkeratosis
 - » Hyperpigmentation
 - » Garlic breath odor
 - » Stomatitis

- » Cancers (skin, bladder, lung)
- » Diabetes
- » Neurological dysfunction
- » Dermatosis
- » Abnormal RBC counts
- » Acute:
 - Hemorrhagic gastroenteritis

Treatment:

- » See "Managing Patients with Metal Toxicities" on page 59
- » Assure adequate selenium status
- » *Emblica officinalis*

Cadmium

- ◆ Competes with zinc at all cellular binding sites—results in loss of enzyme activity
- ◆ Kidney and lung are affected primarily
- ◆ Chronic exposure can result in slow onset of renal dysfunction with proteinuria

IF CADMIUM HIGH:

- ◆ Sources:
 - » Tobacco smoke, tobacco products
 - » Industry
 - » Paint pigments
 - » Spray painting without a face mask is most common cause of chronic exposure
 - » Plants grown in cadmium-rich soil
 - » Engine exhaust emissions (auto mechanics at particular risk)
 - » Drinking water
 - » Soft water (from galvanized pipes)



- ◆ Treatment:
 - » See "Managing Patients with Metal Toxicities" on page 59
 - » Zinc, 50 mg/d—competes for cadmium binding sites
 - » Assure adequate iron
 - » Assure adequate vitamin D status
 - » Black cumin seeds

Lead

- ◆ Exposure from ingestion, inhalation, dermal exposure or infants in lactation
- ◆ Absorption increased in patients with compromised gastrointestinal integrity and low dietary intakes of calcium, magnesium, iron, vitamins C & D
- ◆ Nervous system is very sensitive to even low levels of lead
- ◆ Whole-blood lead is defined by the Centers for Disease Control as the preferred test for detecting lead exposure.

IF LEAD HIGH:

- ◆ Sources:
 - » Some red lipsticks
 - » Painted toys
 - » Lead pipes
 - » Old paint, artist pigments
 - » Paint intended for non-domestic use
 - » Old cars
 - » Soil around old cars, old homes or highways

- » Automobile exhaust (not as much since lead-free fuels)
- » Drinking water from lead plumbing
- » Vegetables grown in lead-contaminated soil
- » Canned fruits and vegetables
- » Wine or fruit juice that has been in lead-infused containers
- » Certain Chinese and Ayurvedic herbal preparations
- » Boxed wines
- » Canned evaporated milk
- » Milk from animals grazing on lead-contaminated land
- » Bone meal
- » Organ meats such as liver
- » Lead-arsenate pesticides
- » Leaded caps on wine bottles
- » Rainwater and snow
- » Improperly glazed pottery
- » Mexican pottery
- » Painted glassware
- » Crystal glassware
- » Painted pencils
- » Toothpaste
- » Newsprint
- » Colored printed materials
- » Eating utensils
- » Curtain weights
- » Putty
- » Car batteries
- » Cigarette ash, tobacco
- » Lead shot, firing ranges

- » Other chemicals using lead for processing
- ◆ Symptoms/Conditions:
 - » Anemias seen in lead poisoning:
 - Normocytic
 - Sideroblastic
 - Microcytic, hypochromic
 - » Possible basophilic stippling of RBCs
 - » Fatigue
 - » Bone resorption, releasing lead into blood
 - » Metallic taste
 - » Anorexia
 - » Renal dysfunction
 - » Epigastric pain and nausea
 - » Reproductive failure
 - » Insomnia
 - » Anxiety
 - » Irritability
 - » Reduced performance on visual intelligence and visual-motor coordination tests
 - » Learning disabilities
 - » Short-term memory deficits
 - » Impaired concentration
 - » Hyperactivity or decreased play activity
 - » Hypertension
 - » Muscle discomfort
 - » Constipation
 - » Central nervous system effects of lead:
 - Sensory, visual, auditory, and cerebellar (coordination) functions



- Paralysis and pain in the extremities
- ◆ Treatment:
 - » See "Managing Patients with Metal Toxicities" on page 59
 - » Calcium, 1000 mg/d—lowers intestinal absorption of lead
 - » Magnesium, 500 mg/d
 - » Assure adequate iron, 10–30 mg/d
 - » Vitamin D, 1000 IU/d
 - » Carotenoids
 - » Zinc
 - » Taurine
 - » Selenium
 - » Ca-EDTA chelation—IV or suppository

Mercury

- ◆ "Mad as a hatter"—from mercury used to make felt-brimmed hats
- ◆ Pervasive toxic tissue effects due to non-specific enzyme poisoning
- ◆ Blood and hair levels correlate with the severity of toxicity symptoms
 - » Low hair levels are seen in some children with autism

IF MERCURY HIGH:

- ◆ Sources:
 - » Dental amalgams
 - » Predator fish, certain lake fish
 - » Thimerosal (preservative) in vaccinations
 - » Broken thermometers and barometers

- » Grain seeds treated with methylmercury fungicide
- » Mercuric chloride
- » Calomel (body powder, talc, laxatives)
- » Latex and solvent-thinned paints
- » Hemorrhoid suppositories
- » Mercurochrome, merthiolate
- » Fabric softeners
- » Floor waxes and polishes
- » Air conditioner filters
- » Wood preservatives
- » Certain batteries
- » Fungicides for lawns and shrubs
- » Leather tanning products
- » Felt
- » Adhesives
- » Skin-lightening creams
- » Certain ointments to treat psoriasis
- » Photoengraving
- » Tattooing
- » Sewage sludge used as fertilizer
- » Electrical switches
- » Electrolysis
- ◆ Symptoms/Conditions:
 - » Mental symptoms:
 - Irritability
 - Insomnia
 - Fatigue
 - Poor short-term memory and concentration
 - Excitability
 - Sensitivity to stimulation
 - Depression

Mercury; Antimony

- Autism Spectrum Disorders
 - Dementia
 - ADHD
 - » Increased susceptibility to Parkinson disease
 - » Tremor & defects in psychomotor performance
 - » Peripheral neuropathy
 - » Bundle branch block
 - » Yeast overgrowth
 - » Stomatitis
 - » Gingivitis
 - » GI and renal disturbances
 - » Autoimmune conditions
 - » Decreased immunity
 - » Increased antibiotic-resistant strains of oral and intestinal bacteria
 - » Pain in joints and limbs
 - » Weight loss
 - » Metallic taste in mouth
 - » Hypertension
- ◆ Treatment:
- » Selenium, 200–400 µg/d (protects against cellular toxic effects of mercury)
 - » Manganese, 15 mg/d
 - » Molybdenum, 75–250 µg/d
 - » Zinc, 50 mg/d
 - » See "Managing Patients with Metal Toxicities" on page 59

Elements of Potential Toxicity

These elements have no known function in human physiology, although they are present in the environment as airborne particles or in water and foods. There are various reports of toxic effects when these elements accumulate, especially in the presence of specific disorders.

- ◆ If high levels suggest toxic status, see "Managing Patients with Metal Toxicities" on page 59

Antimony

- ◆ Urine has shown good correlation with acute antimony exposure.

IF ANTIMONY HIGH:

- ◆ Sources:
- » Flame-retardant materials:
 - Draperies
 - Wall coverings
 - Carpet
 - » Cosmetics
 - » Alloys
 - » Ceramics
 - » Glass
 - » Plastic
 - » Synthetic fabrics
- ◆ Symptoms/Conditions:
- » Nausea
 - » Vomiting
 - » Abdominal pain
 - » Hematuria



- » Hemolytic anemia
- » Renal failure
- » Disputed association with SIDS

◆ Treatment:

- » BAL (British anti-Lewisite)
- » DMSA
- » Glutathione or N-acetyl cysteine (antimony is conjugated with glutathione)

Barium

IF BARIUM HIGH:

◆ Sources:

- » X-Ray contrast media
- » Enema salts
- » Low levels in foods

◆ Symptoms/Conditions:

- » Gastrointestinal symptoms
- » Muscle weakness
- » Facial numbness
- » Hypotension

◆ Treatment:

- » Oral sodium sulfate
- » Assess and treat hypokalemia



Thallium

IF THALLIUM HIGH:

◆ Sources:

- » Intentional food poisoning
- » Exposure to soil contaminated with thallium-containing pesticides (banned since 1972)


Antimony; Barium; Thallium; Tin

◆ Symptoms/Conditions:

- » Nausea
- » Vomiting
- » Diarrhea
- » Severe, painful neurological and gastrointestinal symptoms
- » Alopecia with black pigment at the hair root

◆ Treatment:

- » Prussian blue
- » DMSA: doesn't cross blood brain barrier
- » Activated charcoal for ingested thallium
- » BAL, D-penicillamine and EDTA are contraindicated

Tin

IF TIN HIGH:

◆ Sources:

- » PVC
- » Glass coverings
- » Silicone and wood preservative
- » Paints
- » Biocides and pesticides
- » Medicines, including Ayurvedic treatments

◆ Symptoms/Conditions:

- » Possibly:
 - Neurotoxic
 - Immunogenic
 - Carcinogenic

◆ Treatment:

- » Selenium, 200–400 µg/day

Uranium; Beryllium; Bismuth; Titanium; Tungsten; Zirconium

Uranium

IF URANIUM HIGH:

- ◆ Sources:
 - » Military exposure
 - » Industrial contamination
- ◆ Symptoms/Conditions:
 - » Renal damage
 - » Lung cancer, if inhaled
- ◆ Treatment:
 - » IV sodium bicarbonate 1.4%
 - » Inositol hexaphosphate has been used in animal studies

Beryllium

Inhalation is associated with a pneumonia-like condition, called chronic beryllium disease (CBD). Increased rates of lung cancer and CHF have also been reported. Hair is not a sensitive specimen for bismuth toxicity; blood and urine are most commonly used.

Bismuth

Bismuth is generally non-toxic, although very high levels may cause nausea, vomiting and diarrhea. Renal, neurological and hematological problems have been associated with bismuth toxicity. Hair is not a sensitive specimen for bismuth toxicity; blood and urine are most commonly used.

Titanium

Implants alloyed with titanium may be associated with inflammation. Inhaled titanium has been associated with lung fibrosis. Only very high-dose injections of titanium compounds were shown to be carcinogenic in animal studies. Hair and serum have been shown to correlate with exposure.

Tungsten

Inhaled tungsten has been associated with pulmonary fibrosis, lung cancer and neurosensory and cognitive deficits. Oral exposure is suspected to cause reproductive, neurological and developmental effects. Hair and nails have been used to identify toxicity. Blood, urine and stool are also used for assessment.

Zirconium

Topical and inhaled exposures have been associated with skin and pulmonic granulomas, respectively. Hair has been used to assess exposure.



Managing Patients with Metal Toxicities

Reducing Body Burdens

1. Identify and avoid exposure to the toxic element
 - » Test water
 - » Evaluate cooking utensils
 - » Evaluate building materials in the home
 - » Diet: eat organic fruits and vegetables, consider seafood as a source of toxic elements
 - » Evaluate source of herbal supplements for contamination
2. Increase elimination by improving GI, liver, and kidney function
 - » Methionine, 3,000 mg/d, vitamin B₁₂, 1,000 µg/d and folate, 800 µg/d
 - » N-Acetylcysteine at 3–4 g/day (high doses have been associated with pulmonary hypertension)
 - » Sauna
 - » Reduce intestinal absorption
 - Total dietary fiber intake to 30–40 g/day
 - Bentonite
 - Beans, cooked vegetables, whole grain breads
 - Whole grain cereals, especially oatmeal
 - Fresh fruits, especially apples
3. Protect against damage
 - » Anti-oxidants including

Managing Patients with Metal Toxicities

vitamin C at 3 g/day or more; lipoic acid 200 mg TID

» Give protective agents such as nutrient elements or elements that compete for binding sites

4. Consider oral or intravenous chelation if warranted by clinical symptoms and test data

Chelation Procedures

ORAL DMSA CHALLENGE PROCEDURE

- ◆ 10–30 mg/kg or 500–1000 mg in a single dose (or taken at the beginning and middle of an 8 hour collection period) for most adult patients. Then collect urine for 8 hours or 24 hours thereafter.
- ◆ DMPS (10–30 mg/kg for adults) may be used instead of DMSA. It has a higher yield than DMSA for some metals, but it is not FDA approved for oral use.

INTRAVENOUS CHELATION

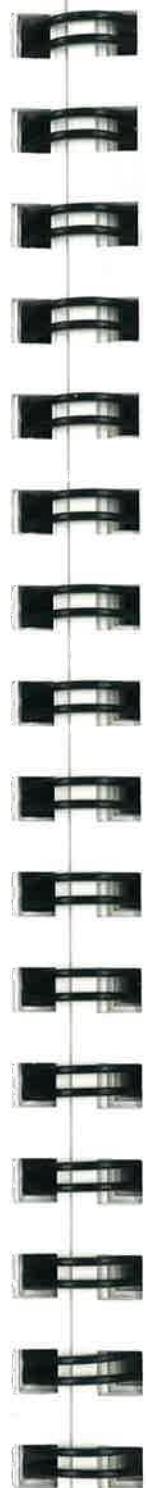
- ◆ Check kidney function (creatinine clearance) before instituting any treatment
- ◆ Benefits not yet fully established—use with caution and discretion
- ◆ Hold meds/vitamins that day—can take essential meds in the evening
- ◆ Avoid zinc and copper that day
- ◆ Give fiber/flax, etc. to help bowels move
- ◆ Check with urine challenge test every 6 weeks
- ◆ Regularly test essential elements

Managing Patients with Metal Toxicities

and supplement accordingly to avoid depletion from chelation

Causes of High Toxic Elements in Blood, Hair or Urine

- ◆ Environmental food, water or airborne particulate exposure
- ◆ Work-related exposure
- ◆ Use of toxic element-containing products
- ◆ Increased intestinal uptake (exacerbated with essential element deficiencies)
- ◆ Poor elimination (gut, liver, kidney function)
- ◆ Exogenous contamination (hair)

NOTES

3

Fat-Soluble Vitamins

Contents

Vitamin A	61	Vitamin K	65
Retinol; β-Carotene		Undercarboxylated Osteocalcin (ucOC)	
Vitamin E	63	Coenzyme Q10 (Ubiquinone)	66
α- and γ-Tocopherol		Markers of Oxidative Damage	68
Vitamin D	64	Lipid Peroxides; 8-Hydroxy-2'-deoxyguanosine (8-OHdG)	
25-Hydroxyvitamin D			

Serum levels of the fat-soluble vitamins A, D and E (alpha and gamma tocopherol), beta-carotene and coenzyme Q10 are measures of total body status of these antioxidant nutrients. Vitamin K is a required coenzyme for the addition of carboxyl groups to the ubiquitous bone-forming protein osteocalcin. Under-carboxylation of osteocalcin (ucOC) serves as a marker for deficiency of vitamin K. Oxidation of polyunsaturated fatty acids and DNA results in increased excretion of oxidation products, lipid peroxides and 8-hydroxy-2'-deoxyguanosine, respectively, which are measures of total antioxidant status.

Vitamin A

Retinol

- ◆ Part of the super-family of transcription regulators which also include steroid and thyroid hormones, and 1,25-dihydroxycholecalciferol
- ◆ Reproduction
- ◆ Skin health
- ◆ Vision
- ◆ Maintenance roles for vision, bone growth, cancer, cataracts, skin integrity, atherosclerosis, macular degeneration, and spermatogenesis
- ◆ Cell membrane protection and sub-cellular membrane function
- ◆ Mucopolysaccharide synthesis
- ◆ Cell differentiation
- ◆ Abnormal vitamin A levels may be associated with thyroid dysfunction:
 - » Both high and low levels have been found in hypothyroidism

Retinol; β-Carotene

- » Low levels have been found in hyperthyroidism
- ◆ Food sources:
 - » Orange and yellow fruits and vegetables as beta-carotene—carrots, parsley, spinach, yams
 - » Animal fats as vitamin A—liver, egg yolks

IF RETINOL HIGH:

- ◆ Causes:
 - » Overconsumption of supplements
 - » Retin A treatment for acne
 - » Ingestion of large amounts of liver
 - » Hypothyroidism
- ◆ Symptoms/Conditions:
 - » Hypothyroidism
 - » Teratogenic effects—particularly dangerous for fetuses
- ◆ Treatment:
 - » Address underlying causes
 - » Decrease supplements or food sources

IF RETINOL LOW:

- ◆ Causes:
 - » Poor diet
 - » Fat maldigestion
 - » Thyroid imbalance
 - » Alcoholism
 - » Liver disease
- ◆ Symptoms/Conditions:
 - » Hypothyroidism
 - » Hyperthyroidism
 - » Acne and other skin problems
 - » Poor night vision

β-Carotene

- ◆ Vitamin A precursor
- ◆ Significant antioxidant
- ◆ Food sources:
 - » Carrots and other yellow vegetables

IF β-CAROTENE HIGH:

- ◆ Causes:
 - » Supplementation
 - » Poor conversion to vitamin A in hypothyroidism
- ◆ Symptoms/Conditions:
 - » No major toxicities
 - » May have orange skin and palms—unlike in jaundice, the sclera is spared in carotenemia
- ◆ Treatment:
 - » Decrease supplements
 - » Evaluate and treat thyroid
 - » Check serum vitamin A to ensure conversion

IF β-CAROTENE LOW:

- ◆ Causes:
 - » Insufficient consumption



of β-carotene containing fruits and vegetables

- ◆ Symptoms/Conditions:
 - » Acne and other skin problems
 - » Poor night vision
 - » Acute infections
 - » Xerophthalmia—most common cause of blindness in young children
- ◆ Treatment:
 - » β-Carotene, 10,000–50,000 IU/d; mixed carotenoids
 - » Increase vegetable and fruit intake

Vitamin E**α- and γ-Tocopherol**

There are four tocopherol isomers: alpha, beta, gamma and delta.

The isomers differ with regard to the number of methyl groups at the chroman ring. α-Tocopherol is the dominant isomer *in vivo* and has the highest biological activity. γ-Tocopherol is the dominant isomer in western diets. *In vivo*, it possesses unique anti-inflammatory properties.

α-Tocopherol supplementation may result in significantly lower circulating γ-tocopherol levels. Laboratory assessment can ensure appropriate levels of both isomers have been achieved.

- ◆ Physiological functions:
 - » Membrane and plasma lipoprotein antioxidant—most important in body

β-Carotene; α- and γ-Tocopherol

- » Defense against age-producing oxygen free radical attacks
- » Supports immune function
- » Protects sexual and reproductive organs
- » Used to protect cardiovascular, neurological and respiratory systems
- ◆ May protect against:
 - » Cancer
 - » Dementia
 - » Cataracts
- ◆ Food sources of vitamin E:
 - » Vegetable oils, nuts, seeds, dark green leafy vegetables, whole grains
 - » α-Tocopherol:
 - Almonds, hazelnuts, sunflower oil, avocado
 - » γ-Tocopherol:
 - Soy, corn and canola oil

IF α- OR γ-TOCOPHEROL HIGH:

- ◆ Causes:
 - » Supplementation
- ◆ Symptoms/Conditions:
 - » Toxicity very uncommon
 - » Usually none
- ◆ Treatment:
 - » Decrease supplements

IF α- OR γ-TOCOPHEROL LOW:

- ◆ Causes:
 - » Poor diet (for many, it may be difficult to achieve repletion from diet alone)
 - » Fat maldigestion

α - and γ -Tocopherol; 25-Hydroxyvitamin D

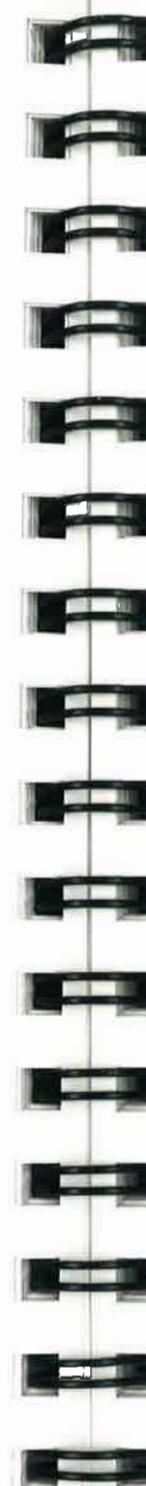
- ◆ Symptoms/Conditions:
 - » Increased free radical damage from environmental (pesticides, inhaled toxins, etc.) and food chemical exposure
 - » Increased inflammation
 - » Cancer
 - » Heart disease
 - » Hemolytic anemia
 - » Neurological disease—including ataxia
 - » Neuropathies
 - » Sexual problems
- ◆ Treatment:
 - » Address underlying causes
 - » Vitamin E, 200–800 IU/d mixed tocopherols preferred
 - » To replete vitamin E, it is best to take it with other antioxidants, including alpha lipoic acid, vitamin C and selenium.

Vitamin D**25-Hydroxyvitamin D**

- ◆ Part of superfamily of transcription regulators which also include steroid and thyroid hormones, and vitamin A
- ◆ Principle circulating derivative of vitamin D—there are two forms, D3 (cholecalciferol) is produced in the skin upon UVB exposure, and D2 (ergocalciferol) which is similarly produced in plants. D3 is considered to be the more active form. Both are available as supplements.

IF 25-HYDROXYVITAMIN D HIGH:

- ◆ Causes:
 - » Excessive supplementation of vitamin D
 - » Excessive intake of foods with very high vitamin D content (some wild game organ meats)
 - » Hyperparathyroidism secondary to chronic kidney disease



- ◆ Symptoms/Conditions:
 - » Arterial and other soft tissue calcification (especially with insufficient vitamin K intake)
 - » Low PTH and calcitonin
- ◆ Treatment:
 - » Address underlying causes
 - » Suspend supplementation of vitamin D

IF 25-HYDROXYVITAMIN D LOW:

- ◆ Causes:
 - » Inadequate exposure to sunlight:
 - Excessive sunscreen
 - Northern latitude
 - Darker skin tone
 - Clothing
 - » Dietary deficiency due to insufficient intake of D-containing foods
 - » Elderly individuals may have decreased ability to synthesize vitamin D
 - » Fat maldigestion
 - » Fat malabsorption
 - » Cystic fibrosis
 - » Pancreatic insufficiency
 - » Renal diseases
 - » Antiepileptic drug-induced hypocalcemia
 - » Excessive calcium intake
 - » Excessive animal protein intake
 - » Defective CYP2R1 gene for 25-hydroxylase

- ◆ Symptoms/Conditions:
 - » Depression

25-Hydroxyvitamin D; ucOC

- » Seasonal Affective Disorder
- » Inflammatory Bowel Disease
- » Cancer (e.g. colorectal, breast, prostate)
- » Cognitive impairment
- » Autism
- » Rickets
- » Osteomalacia
- » Secondary hyperparathyroidism
- » Periodontal disease
- » Increased risk of insulin resistance and the metabolic syndrome
- ◆ Treatment:
 - » Ensure adequate sunlight exposure
 - » Vitamin D, 700–10,000 IU/d
 - » Calcium, 800–1000 mg/d
 - » Evaluate other associated nutrient biomarkers including: Magnesium (RBC, hair), vitamin K (ucOC), calcium (hair), phosphorus (serum), deoxypyridinoline, parathyroid hormone and alkaline phosphatase

Vitamin K**Undercarboxylated Osteocalcin (ucOC)**

- ◆ Functional marker of vitamin K deficiency
- ◆ Vitamin K catalyzes gamma-glutamyl carboxylation of proteins, including parathyroid hormone and clotting enzymes
- ◆ Absence of vitamin K allows for the

ucOC; CoQ10

- » accumulation of undercarboxylated osteocalcin (ucOC)
- ◆ Vitamin K1 is also known as phylloquinone and is synthesized by plants
- ◆ Vitamin K2 is also known as menaquinone, and is synthesized by bacteria and some animal tissues. K2 may be more bioavailable than K1. There are a number of different menaquinones (e.g. MK-4, MK-7), which are differentiated by the number of unsaturated isoprenyl groups.
- ◆ Vitamin K3, menadione, is the synthetic form.
- ◆ Food sources of vitamin K1:
 - » Green vegetables (esp. kale, spinach and collard greens)
- ◆ Food sources of vitamin K2:
 - » Dairy, eggs, meat and fermented foods including sauerkraut and natto (fermented soybeans)

IF ucOC HIGH:

- ◆ Causes:
 - » Dietary deficiency of vitamin K
 - » Fat malabsorption
 - » Pancreatic insufficiency
 - » Biliary stasis
 - » Celiac disease
 - » High-dose vitamin E
- ◆ Symptoms/Conditions:
 - » Soft tissue calcification (including arteriosclerosis)
 - » Bleeding disorders
 - » Increased prothrombin time

- » Osteopenia/osteoporosis/retarded bone growth
- ◆ Treatment:
 - » Address underlying causes
 - » Vitamin K, 200–4000 µg/d. K2 may be preferred for arteriosclerosis and osteocalcin, although mixed supplementation with K1 and K2 forms may also be desirable (up to 100 µg/d usually does not interfere with oral warfarin therapy)

Coenzyme Q10 (Ubiquinone)

- ◆ Mitochondrial energy production throughout the body (ubiquitous)
- ◆ Delivers electrons to oxygen in the mitochondrial membrane electron transport chain for energy production (ATP)
- ◆ Powerful antioxidant
- ◆ Most prominently in the heart, kidney, muscle and brain
- ◆ A conditionally essential nutrient
- ◆ Cancer-fighting substance
- ◆ Regulates immune processes
- ◆ Enhances energy
- ◆ Protects against diabetes
- ◆ Regulates cardiac function
- ◆ Protects against arrhythmia, cardiomyopathy, congestive heart failure and hypertension
- ◆ Declines with age
- ◆ Treatment for:
 - » Tinnitus



- » Senility
- » Alzheimer disease
- » Parkinsonism
- » Male infertility and low sperm counts
- » General fatigue
- » Periodontal disease
- » Protects against drug-induced toxicity of some chemotherapeutic and anti-hypertensive medications
- ◆ Food sources:
 - » Found in small amounts in many nutrient-dense foods

IF COENZYME Q10 HIGH:

- ◆ Causes:
 - » Supplementation
- ◆ Symptoms/Conditions:
 - » None
- ◆ Treatment:
 - » Decrease supplements

IF COENZYME Q10 LOW:

- ◆ Causes:
 - » HMG-CoA reductase inhibitors—Lipitor, Lescol, Mevacor, Pravachol, Zocor (blocks body's ability to make CoQ10)
 - » Anti-diabetic sulfonylureas—Diabeta, Glynnase, Tolinsase, Micronase, Dymelor (competitive inhibition of NADH-oxidase enzyme)
 - » Beta-blockers—Inderal, Lopressor, Tenormin, Pindolol (antagonizes synthesis of CoQ10)
 - » Tricyclic antidepressants—Elavil,

CoQ10

Pamelor, Tofranil, Norpramin, Etrafon, Sinequan

- » Major Tranquilizers—Thorazine, Navane, Mellaril, Prolixin (inhibit absorption of CoQ10)
- » Malnutrition
- » Low carbohydrate diet (higher glucagon inhibits HMG-CoA reductase)

- ◆ Increased need if:
 - » Heart disease, CHF
 - » Muscle cramping
 - » Mitochondrial dysfunction

- ◆ Symptoms/Conditions:
 - » Fatigue
 - » Myalgia
 - » Heart and blood pressure problems
 - » Periodontal disease
 - » Immune system related problems
 - » Mitochondrial myopathy
 - » Elevation of CoQ10 functional biomarkers: urinary lactate, succinate, malate, fumarate and pyruvate

- ◆ Treatment:
 - » Address underlying causes
 - » CoQ10, 30–3000 mg/d
 - » May interfere with anticoagulant medications
 - » Take with nuts or nut butters (peanut butter) for better absorption

Lipid Peroxides; 8-OHdG

Markers of Oxidative Damage

Lipid Peroxides

- ◆ Membrane oxidative damage
- ◆ A product of the chemical damage done by oxygen free radicals to the polyunsaturated fatty acid component of cell membranes
- ◆ Reflects whole-body cell membrane free radical activity
- ◆ Also known as TBARS test (thiobarbituric acid reactive substance)
- ◆ The HPLC method measures the specific malondialdehyde TBARS derivative, removing most interferences

IF LIPID PEROXIDES HIGH:

- ◆ Causes:
 - » Smoking
 - » High polyunsaturated fat intake with inadequate antioxidant support
 - » Chronic inflammation and inflammatory conditions including:
 - Diabetes
 - Occlusive arterial disease
 - Pre-eclampsia
 - Autoimmune conditions
 - » Irradiation
 - » Thermal injury
 - » Toxicity induced by certain metals, solvents, pesticides, and drugs
 - » Chronic psychological stress

- » Antioxidant insufficiency or imbalance
- » Helicobacter pylori infection
- ◆ Symptoms/Conditions:
 - » Accelerated aging
 - » Stroke
 - » Heart disease
 - » Cancer
 - » DNA damage leading to cell aging
- ◆ Treatment:
 - » Treat underlying cause
 - » If excessive, reduce PUFA intake
 - » Vitamin E, 200–1600 mg/d (mixed tocopherols)
 - » Vitamin A, 5,000–10,000 IU/d
 - » Vitamin C, 1,000–5,000 mg/d
 - » Glutathione, 300–1000 mg/d (questionable bioavailability with oral form) or NAC, 500–1000 mg/d
 - » CoQ10, 30–3000 mg/d
 - » Selenium, 200 µg/d
 - » Zinc, 15–65 mg/d
 - » Manganese, 5–13 mg/d
 - » Copper, 2–10 mg/d
 - » Lipoic acid, 100–1,800 mg/d
 - » Green tea (epigallocatechin sources)
 - » Red wine, grapes, berries, colorful vegetables, etc (flavonoid sources)

8-Hydroxy-2'-deoxyguanosine (8-OHdG)

- ◆ Normal product of DNA oxidative damage and repair



- ◆ A repair product of the highly mutagenic oxidation of guanine in DNA or the cellular pool of GTP
- ◆ Reflects whole-body cytosolic and nuclear free radical activity

IF 8-OHDG HIGH:

- ◆ Causes:
 - » Oxidative damage to DNA (oxidative stress)
 - » Chronic psychological stress/ perceived overwork
 - » Smoking
 - » Hypercholesterolemia
 - » Chronic inflammation
 - » Chronic liver disease
 - » Hypertension
 - » Antioxidant deficiencies/ imbalance in antioxidant levels
 - » Atherosclerosis
 - » Diabetes
 - » Air pollution
 - » Irradiation
 - » Thermal injury
 - » Toxicity induced by certain metals, solvents, pesticides, and drugs
- ◆ Symptoms/Conditions:
 - » Cancer
 - » Accelerated aging
 - » Chronic liver disease and hepatocarcinoma
 - » Worsened atherosclerosis
 - » Tubulointerstitial injury in patients with diabetic nephropathy
- ◆ Treatment:
 - » Treat underlying cause

- » Vitamin E, 200–1600 mg/d (mixed tocopherols)
- » Vitamin A, 5,000–10,000 IU/d
- » Vitamin C, 1,000–5,000 mg/d
- » Glutathione, 300–1000 mg/d (questionable bioavailability with oral form) or NAC, 500–1000 mg/d
- » CoQ10, 30–3000 mg/d
- » Selenium, 200 µg/d
- » Zinc, 15–65 mg/d
- » Manganese, 5–13 mg/d
- » Copper, 2–10 mg/d
- » Lipoic acid, 100–1,800 mg/d
- » Green tea (epigallocatechin sources)
- » Red wine, grapes, berries, colorful vegetables, etc (flavonoid sources)
- » Avoid excessive alcohol consumption

NOTES



Fatty Acids

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General Comments on Specimen Types

Specimen	Factors Bearing on Interpretation of Results
Fasting plasma	Fatty acid composition of circulating lipoproteins (mainly LDL) that represents recent dietary intake and hepatic synthesis and export
Erythrocyte	Fatty acid composition of cell membranes that represents lipoprotein supply and metabolism during erythropoiesis
Fasting plasma & erythrocyte	Reported as absolute concentrations
Blood Spot	Results show a composite view of ~60% plasma and 40% RBC + WBC Analytes reported as % of total fatty acids

Differentiation of Fatty Acid Deficiency Signs and Symptoms

Symptom	Cause	Treatment
Emaciation, weakness, disorientation	Caloric deprivation	Balanced dietary fat, protein, & carbohydrate
Reduced growth, renal dysplasia, reproductive deficiency, scaly skin	Classic essential fatty acid deficiency and excess <i>trans</i> -fats	Good quality fats and oils and avoid commercially hydrogenated oils
Eczema-like skin eruptions, loss of hair, liver degeneration, behavioral disturbances, kidney degeneration, increased thirst, frequent infections, poor wound healing, sterility (m) or miscarriage (f), arthralgia, cardiovascular disease, growth retardation	LA insufficiency	Sunflower or safflower oils
Growth retardation, weakness, impairment of vision, learning disability, poor coordination, tingling in arms/legs, behavioral changes, mental disturbances, low metabolic rate, high blood pressure, immune dysfunction	ALA and GLA insufficiency	Flax, primrose, or black currant oils
Depression, anxiety, learning/behavioral/visual development, cardiovascular disease	Long-chain PUFA-dependent neuromembrane function, prostanoid balance	Fish oils and avoid hydrogenated oils
Rheumatoid Arthritis	Low GLA & DGLA Low omega-3 fats	Primrose oil Fish oil
Myelinated nerve degeneration	Increased very long chain fatty acids	High-erucate canola (rape seed) or mustard oils
Fatty liver	Saturated and omega-9 accumulation in liver	Restrict alcohol, add lecithin, & increase methionine

NOTES

Polyunsaturated Omega-3 Fatty Acids

Alpha Linolenic Acid (ALA)

- ◆ Treatment:
 - » Decrease supplementation
 - » Increase antioxidants
- IF ALA LOW:
 - ◆ Causes:
 - » Essential fatty acid dietary deficiency
 - » Fat malabsorption
 - ◆ Symptoms/Conditions:
 - » Hypertension/CVD
 - » Emaciation
 - » Slow growth and brain development disorders in children
 - » Behavioral/mood/coordination disorders
 - » Reproduction problems
 - » Dry hair/skin eruptions, dryness
 - ◆ Treatment:
 - » Treat causes of malabsorption
 - » Flax seeds, 1–6 tablespoons/d
 - » Fish oil, 2–3 gm/d (with food for best absorption)

IF ALA HIGH:

- ◆ Causes:
 - » Supplementation
 - » Excessive intake of food sources
- ◆ Symptoms/Conditions:
 - » Diarrhea
 - » Oily hair/skin
 - » Poor wound healing
 - » Gastrointestinal disorders
 - » Hormonal abnormalities
 - » Enhanced oxidative stress

Eicosapentaenoic Acid (EPA)

- ◆ Long chain, polyunsaturated fatty acid (20:5n3)
- ◆ Substrate for anti-inflammatory eicosanoid production (3-series prostaglandins, 3-series thromboxanes and 5-series leukotrienes)
- ◆ Deficiency prevalent in Western society
- ◆ Antagonizes arachidonic acid eicosanoids—Inflammation may decrease within days

EPA; DPA

- ◆ Decreases total cholesterol and HTN
- ◆ Can improve heart health
- ◆ Sources:
 - » Marine fish (salmon, trout, cod, halibut, sardines, etc.), breast milk, endogenous synthesis from ALA

IF EPA HIGH:

- ◆ Causes:
 - » Supplementation
 - » Excessive fish intake
- ◆ Symptoms/Conditions:
 - » Diarrhea
 - » Oily skin and hair
 - » Possible oxidative damage if not on antioxidants
 - » Potential excessive bleeding
 - » Potential increased risk of infection
- ◆ Treatment:
 - » Decrease supplementation
 - » Increase antioxidants to reduce oxidative stress

IF EPA LOW:

- ◆ Causes:
 - » Insufficient intake—most common fatty acid deficiency
 - » Insufficiency or malabsorption of fats
 - » Low ALA intake
 - » Deficiency of cofactors (see treatments below)
 - » Slowed conversion of ALA to EPA due to high levels of:
 - Saturated fats
 - Monounsaturated fats

- Trans-fatty acids
- Cholesterol
- » Symptoms/Conditions:
 - Dry hair/skin/skin eruptions
 - Behavioral/mood/developmental disorders
 - Depression
 - Aging
 - Exacerbated inflammatory response (as in osteoarthritis)
 - Heart disease
 - Cardiac arrhythmias
 - Metabolic syndrome
 - Gastrointestinal disorders
 - Slow growth
 - Reproduction problems
- ◆ Treatment:
 - » Treat causes of malabsorption
 - » Marine fish (salmon, trout, cod, halibut, sardines, etc.)
 - » Fish oil, 2–3 gm/d
 - » Flax seeds, 1–6 tablespoons/d
 - » Take with food for best absorption
 - » Can be produced from ALA—cofactors:
 - Zinc, 30 mg/d
 - Magnesium, 200 mg BID
 - Vitamin B₃, (niacin), 50 mg/d
 - Vitamin B₆, (pyridoxine), 100 mg/d
 - Vitamin C, 1 gm BID

Docosapentaenoic Acid (DPA)

- ◆ Very long chain, highly unsaturated fatty acid (22:5n3)



- ◆ Nerve membrane function
- ◆ Retinal cells
- ◆ Neurological development
- ◆ Food sources:
 - » Fish
 - » Breast milk

IF DPA HIGH:

- ◆ Causes:
 - » Supplementation of omega-3 oils
 - » Excessive intake of fish
 - » Symptoms/Conditions:
 - » Diarrhea
 - » Oily skin and hair
 - » Oxidative damage if not on antioxidants
- ◆ Treatment:
 - » Decrease supplementation of omega-3 oils
 - » Decrease fish intake
 - » Increase antioxidants

IF DPA LOW:

- ◆ Causes:
 - » Inadequate fish intake
 - » Fat malabsorption
- ◆ Symptoms/Conditions:
 - » Attention deficit disorder
 - » Failure in development of visual system
- ◆ Treatment:
 - » Marine fish (salmon, trout, cod, halibut, sardines, etc.)
 - » Fish oil, 2–3 gm/d
 - » Treat causes of malabsorption

Docosahexaenoic Acid (DHA)

- ◆ Very long chain, highly unsaturated fatty acid (22:6n3)
- ◆ Neurological development
- ◆ Retinal function
- ◆ Final synthesis from ALA is peroxisome-dependent
- ◆ Prevalent fatty acid deficiency in Western society
- ◆ Food sources:
 - » Marine fish (salmon, trout, cod, halibut, sardines, etc.)
 - » Breast milk—rich source if mother eating fish

IF DHA HIGH:

- ◆ Causes:
 - » Supplementation of omega-3 oils
 - » Excessive intake of fish
- ◆ Symptoms/Conditions:
 - » Oxidative damage if not on an antioxidant
 - » Diarrhea
 - » Oily skin and hair
- ◆ Treatment:
 - » Decrease supplementation of omega-3 oils
 - » Decrease fish intake
 - » Increase antioxidants

IF DHA LOW:

- ◆ Causes:
 - » Inadequate intake
 - » Fat malabsorption
 - » Inadequate conversion from ALA (although ALA conversion to

DHA; LA

DHA is generally minimal—supplementation (or fish intake) is required in most individuals)

◆ Symptoms/Conditions:

- » Retinitis pigmentosa
- » ADHD
- » Failure in development of the CNS/visual system
- » Slow growth
- » Behavioral/mood disorders
- » Reproduction problems
- » Dry hair/skin/skin eruptions

◆ Treatment:

- » Marine fish (salmon, trout, cod, halibut, sardines, etc.)
- » Fish oil, 2–3 gm/d

Polyunsaturated Omega-6 Fatty Acids

Linoleic Acid (LA)

- ◆ Long chain polyunsaturated essential fatty acid (18:2n6)
- ◆ Precursor for DGLA and AA endogenous synthesis
- ◆ Aids in structural integrity of cells
- ◆ Most abundant polyunsaturated fatty acid in human tissues and most foods
- ◆ Food sources (in order of percent amounts in oil):
 - » Safflower (75), primrose (72), grape (71), sunflower (65), hemp (60), corn (59), walnut (58), soybean (50), wheat germ (50), cottonseed (50),

black currant seed (46), pumpkin seed (45), chia (40), borage (39), rape (canola) (30), peanut (29), Brazil (24), almond (17), flax (linseed) (14), avocado (10), macadamia (10), olive (8), cashew (6), coconut (3), palm kernel (2)

IF LA HIGH:

◆ Causes:

- » High amounts of corn and seed oils in diet
- » Poor conversion to GLA (poor desaturase activity)

◆ Symptoms/Conditions:

- » Pro-inflammatory effects

◆ Treatment:

- » Decrease omega-6 dietary intake

IF LA LOW:

◆ Causes:

- » Essential fatty acid deficiency
- » Malabsorption
- » Dietary insufficiency

◆ Symptoms/Conditions:

- » Eczema-like skin eruptions
- » Loss of hair
- » Degeneration of liver, kidney
- » Behavioral disturbances
- » Increased thirst
- » Frequent infections
- » Poor wound healing
- » Sterility (m) or miscarriage (f)
- » Arthralgia
- » Cardiovascular disease
- » Growth retardation



- » High blood pressure

◆ Treatment:

- » Dietary—fresh, raw nuts and seeds, seed oils

Gamma Linolenic Acid (GLA)

- ◆ Long chain fatty acid (18:3n6)
- ◆ DGLA (and AA) precursor
- ◆ Can be produced from linoleic acid
- ◆ Supplementation corrects most zinc deficiency symptoms—shows central role of zinc in fatty acid metabolism
- ◆ Prevents drying and atrophy of lacrimal and salivary glands (Sjogren syndrome)
- ◆ Food sources (in order of percent amounts in oil):
 - » Borage (24), black currant (17), evening primrose (9), rape (canola) (7), hemp (2)

IF GLA HIGH:

◆ Causes:

- » Excessive supplementation

◆ Symptoms/Conditions:

- » Possible enhanced tumorigenesis
- » Gastrointestinal disorders
- » Poor wound healing
- » Hormonal abnormalities

◆ Treatment:

- » Decrease supplementation
- » Supplement omega-3 fatty acids to balance GLA

Eicosadienoic Acid

- ◆ Long chain (20-carbon) fatty acid (20:2n6)
- ◆ DGLA precursor

Eicosadienoic Acid; DGLA

- ◆ Desaturase inhibition

- IF EICOSADIENOIC ACID HIGH:**
- ◆ Causes:
 - » May be associated with low total fat intake causing increased rates of desaturation
- ◆ Symptoms/Conditions:
 - » None reported
- ◆ Treatment:
 - » Zinc, 30 mg/d

IF EICOSADIENOIC ACID LOW:

- ◆ Causes:
 - » Low linoleic acid intake or zinc deficiency
- ◆ Symptoms/Conditions:
 - » None reported if DGLA is normal
- ◆ Treatment:
 - » Omega-6-rich oils:
 - Evening primrose, black currant seed, borage
 - » Decrease corn oil intake

Dihomogamma Linolenic Acid (DGLA)

- ◆ Long chain fatty acid (20:3n6)
- ◆ Substrate in the production of class 1 (anti-inflammatory) prostaglandins, thromboxanes, and leukotrienes
- ◆ Critical for a large number of tissue controls
- ◆ Antagonizes pro-inflammatory effects of arachidonic acid

- ◆ Food sources:
 - » Evening primrose, black currant, borage oils

IF DGLA HIGH:

- ◆ Causes:
 - » Supplementation with linoleic or gamma linolenic sources
- ◆ Symptoms/Conditions:
 - » Elevated insulin promotes conversion to AA
- ◆ Treatment:
 - » Decrease LA sources (usually corn oil)

IF DGLA LOW:

- ◆ Causes:
 - » Result from diets low LA or GLA sources
 - » Slowed conversion of GLA to DGLA due to high levels of:
 - Saturated fats
 - Monounsaturated fats
 - Trans-fatty acids
 - Cholesterol
- ◆ Symptoms/Conditions:
 - » Hypertension
 - » Cardiovascular disease
 - » Rheumatoid arthritis
 - » Hormonal abnormalities
 - » Immune dysfunction
 - » Chronic inflammatory disorders
 - » Gastrointestinal disorders
 - » Depression/behavioral disorders
 - » Brain development problems
 - » Reproductive problems



- » Dry hair/skin
- » Poor wound healing
- » Heart disease
- » Slow growth
- » Decreased 1-series prostanooids and leukotrienes—impairs a wide range of cellular functions and tissue responses

- ◆ Treatment:
 - » Zinc, 30 mg/d
 - » Evening primrose oil, 2–8 g/d
 - » Black currant oil (if patient has a history of tumor formation), 2–8 g/d
 - » Borage oil, 1–4 g/d

Arachidonic Acid (AA)

- ◆ Long chain, polyunsaturated, essential fatty acid (20:4n6)
- ◆ Substrate for production of class 2 prostaglandins, thromboxanes, and leukotrienes
- ◆ Insulin stimulates production of AA
- ◆ Pro-inflammatory
- ◆ Blood clotting activity
- ◆ Infrequently found insufficient
- ◆ Food sources:
 - » Corn and corn oil (precursor sources), flesh from corn-fed cattle, chicken and hogs, corn-fed chicken eggs

IF AA HIGH:

- ◆ Causes:
 - » Dysinsulinemia
 - » High intake of food sources

- ◆ Symptoms/Conditions:
 - » Brittle hair, flaking dry skin
 - » Gallstone formation
 - » Blood clotting
 - » Heart disease
 - » Depression
 - » Chronic inflammatory disorders
 - » Cancers—breast, prostate, colon
- ◆ Treatment:
 - » Reduce/normalize insulin levels
 - » Reduce red meats and corn products

IF AA LOW:

- ◆ Causes:
 - » General essential fatty acid deficiency
 - » Omega-3 dominance due to excessive supplementation with EPA or ALA
- ◆ Symptoms/Conditions:
 - » Impaired membrane fluidity
 - » Sleep disturbances
 - » Poor immune response
 - » Low insulin (poorly managed type 1 diabetes)
- ◆ Treatment:
 - » Zinc, 30 mg/d
 - » Evening primrose oil, 2–6 g/d
 - » Black currant oil (if patient has a history of tumor formation), 2–6 g/d
 - » Borage oil, 1–4 g/d

Docosadienoic Acid; DTA

- ◆ Very long chain, polyunsaturated fatty acid (22:2n6)
- ◆ Elongation product of DGLA
- ◆ Peroxisomal activation
- ◆ Weight gain
- ◆ Food sources:
 - » None—an intermediate in metabolism of omega-6 fats

IF DOCOSADIENOIC ACID HIGH:

- ◆ Causes:
 - » Copper deficiency
 - » Omega-6 fatty acid-rich diet
- ◆ Symptoms/Conditions:
 - » Insulin insensitivity
 - » Fat gain, obesity
- ◆ Treatment:
 - » Copper citrate, 6 mg/d
 - » Dietary fat restriction

IF DOCOSADIENOIC ACID LOW:

- ◆ Causes:
 - » Fat-restricted diet
 - » Essential fatty acid deprivation
- ◆ Symptoms/Conditions:
 - » See "Differentiation of Fatty Acid Deficiency Signs and Symptoms" on page 72
- ◆ Treatment:
 - » Increase essential fatty acids in diet

Docosatetraenoic Acid (DTA)

- ◆ Very long chain, polyunsaturated fatty acid (22:4n6)

**Polyunsaturated Omega-9 Fatty Acids****Mead Acid**

- ◆ Long chain fatty acid (20:3n9)
- ◆ Can serve as a membrane structural component in place of the normal polyunsaturated fatty acids derived from essential precursors
- ◆ Cannot serve in the critical role of precursor to eicosanoid cell regulators
- ◆ When polyunsaturated fatty acids are plentiful, there is little conversion of oleic acid to mead acid
- ◆ Food sources:
 - » None—produced in human tissue by conversion from oleic acid

IF MEAD ACID HIGH:

- ◆ Causes:
 - » Long-term essential fatty acid deficiency—causes production of mead to maintain membrane fluidity
 - » Confirmatory findings: elevated palmitoleic acid and elevated triene/tetraene ratio
 - » If mead and triene/tetraene ratio are high with normal AA, there is evidence of recent intake of AA sources with long-term deficiency of other essential fatty acids
 - » Long-term supplemental EFA can stimulate peroxisomal proliferation, increasing mead formation with normal triene/tetraene ratio

tetraene ratio (false positive for EFA deficiency)

- ◆ Symptoms/Conditions:
 - » Symptoms of essential PUFA deficiencies
 - » Fatty liver
- ◆ Treatment:
 - » Essential fatty acids

Monounsaturated Fatty Acids (MUFA)

Endogenous production of monounsaturates from saturates is catalyzed by delta 9 desaturase (D9D), which is stimulated by insulin and inhibited by glucagon.

The fatty acids most likely to reflect D9D activity are palmitic and stearic saturates being converted to palmitoleic and oleic acids, respectively.

Long-standing hyperinsulinemia will generally show evidence of many PUFA (omega-6), MUFA and SFA elevations. When such a pattern is evident, triglycerides and cholesterol levels are likely elevated as well.

The saturation index (SI) compares the level of saturated fats to monounsaturated fats in erythrocyte membrane. It has long been used to evaluate the upregulation of D9D by cancer cells. The SI has also been shown to correlate with hyperinsulinemia. Increased production of MUFA by cancer cells has been shown to be associated with proliferation and metastases.

Myristoleic Acid; Palmitoleic Acid**Myristoleic Acid**

- ◆ Medium chain monounsaturated fatty acid (14:1n5)
- ◆ Desaturation product of myristic acid
- ◆ Increases membrane fluidity
- ◆ Food sources:
 - » None are rich sources
 - » Beef and dairy products
 - » Coconut oil provides the saturated precursor, myristic acid

IF MYRISTOLEIC ACID HIGH:

- ◆ Causes:
 - » Essential fatty acid deficiency
 - » Dairy intake—accumulates in adipose tissue
 - » Hyperinsulinemia
 - » Coconut oil intake
- ◆ Symptoms/Conditions:
 - » Correlates with levels of conjugated linoleic acid (CLA)—also found in dairy products—CLA may have anti-carcinogenic properties
- ◆ Treatment:
 - » Essential fatty acids
 - » Reduce dairy intake

Palmitoleic Acid

- ◆ Long chain monounsaturated fatty acid (16:1n7)
- ◆ Desaturation product of palmitic acid
- ◆ Food sources:
 - » None are rich sources

IF PALMITOLEIC ACID HIGH:

- ◆ Causes:
 - » Essential fatty acid deficiency
 - » If palmitic and palmitoleic acids are greatly elevated while others in this class are normal, look for hyperinsulinemia (causing stimulation of hepatic fatty acid synthase and delta 9 desaturase activity). As discussed above, this pattern may apply to other MUFA.
- ◆ Symptoms/Conditions:
 - » See “Differentiation of Fatty Acid Deficiency Signs and Symptoms” on page 72
 - » Hyperinsulinemia
 - » Hypercortisolemia
 - » Peptic ulcers
 - » Osteoporosis
 - » Nausea/vomiting
 - » Edema
 - » Headache
 - » Dizziness
 - » Mood swings/anxiety
 - » Insomnia
 - » Hypertension
 - » Hyperglycemia
 - » Menstrual irregularities
 - » Acne
 - » Impaired wound healing
- ◆ Treatment:
 - » Treat hormonal abnormalities
 - » Evaluate serum triglyceride levels
 - » Essential fatty acids

**Vaccenic Acid**

- ◆ Long chain monounsaturated fatty acid (18:1n7)
- ◆ Membrane fluidity
- ◆ Positional isomer of oleic acid
- ◆ Inhibition of tumor growth in cell culture
- ◆ Food sources:
 - » See sources for Oleic acid below

IF VACCENIC ACID HIGH:

- ◆ Cause:
 - » High oleic acid consumption
- ◆ Symptoms/Conditions:
 - » Inhibition of tumor growth
- ◆ Treatment:
 - » No treatment needed

IF VACCENIC ACID LOW:

- ◆ Cause:
 - » Biotin deficiency
- ◆ Symptoms/Conditions:
 - » Impaired processing of other fatty acids
- ◆ Treatment:
 - » Biotin, 500 µg BID
 - » Olive oil

Oleic Acid

- ◆ Long chain monoenoic fatty acid (18:1n9)
- ◆ Membrane fluidity
- ◆ Major dietary and tissue monounsaturated fatty acid
- ◆ Influences multiple cell responses

and cell-cell interactions due to cell and organelle membrane fluidity modulation

- ◆ Easily produced by fatty acid synthetic pathways in hepatocytes
- ◆ Normally constitutes 15% of fatty acids in erythrocyte membranes
- ◆ Reduces foam cell accumulation rates on arterial walls, lowering risk of atherosclerosis
- ◆ May be formed by desaturation of stearic acid

- ◆ Inhibits growth of *Helicobacter pylori*—associated with gastric ulcer
- ◆ Anti-cancer properties (especially in oleic-rich extra virgin olive oil)
- ◆ Food sources (in order of percent amounts in oil):

» Almond (78), olive (76), macadamia (71), avocado (70), cashew (70), rape (canola) (54), peanut (49), Brazil (48), pumpkin (34), soybean (26), wheat germ (25), corn (24), sunflower (23), cottonseed (21), flax (linseed) (19), walnut (18), grape (17), borage (17), safflower (13), palm kernel (13), hemp (12), black currant (12), coconut (5), primrose (2)

IF OLEIC ACID HIGH:

- ◆ Cause:
 - » High consumption of food sources (esp. olive oil)
- ◆ Hyperinsulinemia will result in increased endogenous oleic acid from stearic acid via D9D

Oleic Acid; 11-Eicosenoic Acid; Erucic Acid

- ◆ Symptoms/Conditions:
 - » No symptoms if elevation is from exogenous sources
 - » If other MUFA and SFA are elevated, may be a result of hyperinsulinemia
 - » See Stearic/Oleic ratio
- ◆ Treatment:
 - » No treatment needed—consider decreasing consumption of food sources
 - » Evaluate and treat hyperinsulinemia

IF OLEIC ACID LOW:

- ◆ Cause:
 - » Inadequate intake
 - » Deficiencies are uncommon
- ◆ Symptoms/Conditions:
 - » Reduced membrane fluidity
 - » May increase risk of gastric ulcer
- ◆ Treatment:
 - » Olive oil

11-Eicosenoic Acid

- ◆ Long chain monoenoic fatty acid (20:1n9)
- ◆ Desaturation product of arachidic acid
- ◆ Membrane fluidity
- ◆ Food sources:
 - » Rape (canola) and mustard seed oils

IF 11-EICOSENOIC ACID HIGH:

- ◆ Cause:
 - » Caloric restriction—apparent stimulation of desaturation
- ◆ Symptoms/Conditions:
 - » None reported
- ◆ Treatment:
 - » Increase caloric intake

IF 11-EICOSENOIC ACID LOW:

- ◆ Cause:
 - » Essential fatty acid deficiency causes increased conversion to mead acid
- ◆ Symptoms/Conditions:
 - » See specific omega-3 and -6 fatty acid status and symptoms
- ◆ Treatment:
 - » Essential fatty acids

Erucic Acid

- ◆ Very long chain monounsaturated fatty acid (22:1n9)
- ◆ Nerve membrane function
- ◆ Used to treat adrenoleukodystrophy (ALD) and adrenomyeloneuropathy (AMN)—very long chain fatty acid disorders
- ◆ Food Sources:
 - » Rape seed oil (canola)
 - » Wallflower oil
 - » Argentine avocados

IF ERUCIC ACID HIGH:

- ◆ Causes:
 - » High intake of rape seed oil



- » Treatment with Lorenzo's oil (4:1 mixture of oleic and erucic acids)
- » Zellweger syndrome—peroxisomes are absent

- ◆ Symptoms/Conditions:
 - » Side effects of Lorenzo's oil:
 - Increases in liver enzymes
 - Thrombocytopenia
 - Gastrointestinal complaints
 - Gingivitis
- ◆ Treatment:
 - » If erucic acid given as treatment, side effects may need to be tolerated

Nervonic Acid

- ◆ Very long chain monounsaturated fatty acid (24:1n9)
- ◆ Nerve membrane function
- ◆ Neurological development
- ◆ Myelin sheath rich in nervonic acid
- ◆ Food sources:
 - » Salmon
 - » Yellow mustard (238 mg/200 cal serving)

IF NERVONIC ACID HIGH:

- ◆ Causes:
 - » Genetic defects in fatty acid metabolism
 - » May be seen in non-ALD demyelination disorders, such as multiple sclerosis
- ◆ Symptoms/Conditions:
 - » ALD
 - » Nerve disorders

Erucic Acid; Nervonic Acid; Capric Acid

- ◆ Treatment:
 - » Conjugated linoleic acid (CLA), 1–3 gm/d

IF NERVONIC ACID LOW:

- ◆ Causes:
 - » Endogenous desaturation impaired by factors discussed in "MUFA" on page 81
- ◆ Symptoms/Conditions:
 - » Demyelization
 - » Multiple sclerosis
 - » See specific omega-3 and -6 fatty acid status and symptoms
- ◆ Treatment:
 - » Erucic acid, found in canola oil (organic)—erucic acid is converted (elongated) to nervonic acid in the tissues

Saturated Fatty Acids (SFA)**Capric Acid**

- ◆ Medium chain saturated fatty acid (10:0)
- ◆ Medium-chain fatty acyl carnitine transferase required for mitochondrial oxidation
- ◆ Food sources:
 - » Most vegetables, coconut oil, palm kernel oil, butter

IF CAPRIC ACID HIGH:

- ◆ Causes:
 - » Exogenous intake

Capric Acid; Lauric Acid; Myristic Acid

- » Medium chain acyl-coenzyme A dehydrogenase deficiency (MAD)
- ◆ Symptoms/Conditions:
 - » Hypertriglyceridemia
 - » Hyperinsulinemia
- ◆ Treatment:
 - » Treat underlying cause
 - » Vitamin B₂ (riboflavin), 50 mg TID
 - » Carnitine, 1–2 gm/d
 - » Vitamin B₃ (niacin), 50 mg/d

IF CAPRIC ACID LOW:

- ◆ Causes:
 - » Deficiencies not of concern
- ◆ Symptoms/Conditions:
 - » None
- ◆ Treatment:
 - » No treatment needed

Lauric Acid

- ◆ Medium chain saturated fatty acid (12:0)
- ◆ Medium-chain fatty acyl carnitine transferase required for mitochondrial oxidation
- ◆ Food sources:
 - » Palm kernel oil, coconut oil, butter

IF LAURIC ACID HIGH:

- ◆ Causes:
 - » Exogenous intake
 - » Medium chain acyl-coenzyme A dehydrogenase deficiency (MAD)
- ◆ Symptoms/Conditions:
 - » Hypertriglyceridemia

- » Hyperinsulinemia
- ◆ Treatment:
 - » Treat underlying cause
 - » Vitamin B₂ (riboflavin), 50 mg TID
 - » Carnitine, 1–2 g/d
 - » Vitamin B₃ (niacin), 50 mg/d

IF LAURIC ACID LOW:

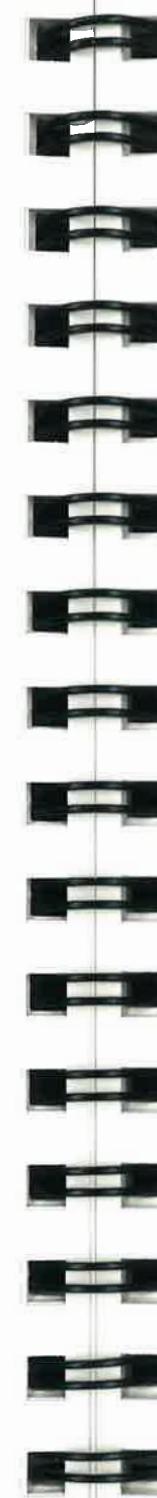
- ◆ Causes:
 - » Deficiencies not of concern
- ◆ Symptoms/Conditions:
 - » None
- ◆ Treatment:
 - » No treatment needed

Myristic Acid

- ◆ Medium chain saturated fatty acid (14:0)
- ◆ Medium-chain fatty acyl carnitine transferase required for mitochondrial oxidation
- ◆ Food sources: nutmeg, palm kernel oil, coconut oil

IF MYRISTIC ACID HIGH:

- ◆ Causes:
 - » Exogenous intake
 - » Medium chain acyl-CoA dehydrogenase deficiency (MAD)
- ◆ Symptoms/Conditions:
 - » Hypertriglyceridemia
 - » Hyperinsulinemia
- ◆ Treatment:
 - » Vitamin B₂ (riboflavin), 50 mg TID



- » Carnitine, 1–2 g/d
- » Vitamin B₃ (niacin), 50 mg/d
- » Lipid lowering agents

IF MYRISTIC ACID LOW:

- ◆ Causes:
 - » Deficiencies not of concern
- ◆ Symptoms/Conditions:
 - » None
- ◆ Treatment:
 - » No treatment needed

Palmitic Acid

- ◆ Long chain saturated fatty acid (16:0)
- ◆ Preferentially utilized fatty acid for energy during strenuous exercise
- ◆ Long chain fatty acyl carnitine transferase required for mitochondrial oxidation
- ◆ Food sources (in order of percent amounts in oil):
 - » Palm oil (45), coco butter (25), butter fat (12)

IF PALMITIC ACID HIGH:

- ◆ Causes:
 - » Hyperinsulinemia
 - » Diet high in simple carbohydrates/sugars
 - » Poor quality dietary fat
 - » Mitochondrial dysfunction
 - » If palmitic and palmitoleic acids are greatly elevated, look for chronic hyperinsulinemia, hypercortisolemia (stimulation of hepatic fatty acid synthase activity and delta 9 desaturase)

Myristic Acid; Palmitic Acid

- ◆ Symptoms/Conditions:
 - » Hypertriglyceridemia
 - » Hyperinsulinemia
 - » Mitochondrial dysfunction
 - » Hypercholesterolemia
 - » Atherosclerosis
 - » Cardiovascular disease
 - » Stroke
 - » Depression
 - » Chronic inflammatory disorder
- ◆ Treatment:
 - » Lipid lowering agents including omega-3 fats
 - » Reduce simple carbohydrates/sugars
 - » Treat hyperinsulinemia
 - » Reduce saturated fats if intake is high
 - » Vitamin B₃ (niacin), 500 mg/d
 - » Exercise

IF PALMITIC ACID LOW:

- ◆ Causes:
 - » Ketosis (fasting, starvation, poorly controlled diabetes, low carbohydrate diet)
 - » Excessive or strenuous exercise
 - » Deficiencies uncommon
- ◆ Symptoms/Conditions:
 - » Low triglyceride levels
- ◆ Treatment:
 - » None needed

Stearic Acid; Arachidic Acid

Stearic Acid

- ◆ Long chain saturated fatty acid (18:0)
- ◆ A major saturated fatty acid in the diet and in the body
- ◆ Preferentially utilized fatty acid for energy during strenuous exercise
- ◆ Long chain fatty acyl carnitine transferase required for mitochondrial oxidation
- ◆ Food sources (in order of percent amounts in oil):
 - » Coco butter (38), butter fat (12) almond (5), flax (linseed) (4)

IF STEARIC ACID HIGH:

- ◆ Causes:
 - » Hyperinsulinemia
 - » Diet high in simple carbohydrates/sugars
 - » Poor quality dietary fat
- ◆ Symptoms/Conditions:
 - » Hypertriglyceridemia
 - » Hyperinsulinemia
 - » Mitochondrial dysfunction
- ◆ Treatment:
 - » Lipid lowering agents including omega-3 fats
 - » Reduce simple carbohydrates/sugars
 - » Vitamin B₃ (niacin), 500 mg/d
 - » Exercise

IF STEARIC ACID LOW:

- ◆ Causes:
 - » Ketosis (fasting, starvation, poorly controlled diabetes, low carbohydrate diet)

- » Exercise
- » Deficiencies are uncommon
- ◆ Symptoms/Conditions:
 - » Increased membrane fluidity that has been associated with active tumor proliferation and hyperinsulinemia (see "Erythrocyte Stearic/Oleic" ratio on page 94)
 - » Cancer marker
- ◆ Treatment:
 - » Increase food sources
 - » Treat ketosis if indicated

Arachidic Acid

- ◆ Long chain saturated fatty acid (20:0)
- ◆ Can be used as an energy source or to build membrane phospholipids
- ◆ Long chain fatty acyl carnitine transferase required for mitochondrial oxidation
- ◆ Food sources:
 - » Peanuts (arachis)

IF ARACHIDIC ACID HIGH:

- ◆ Causes:
 - » Exogenous intake
 - » Impaired peroxisomal oxidation
 - » Increased lipogenesis
- ◆ Symptoms/Conditions:
 - » See palmitic and stearic acids above
- ◆ Treatment:
 - » Check eicosanoid ratios
 - » Lipid lowering agents
 - » Reduce exogenous intake

**IF ARACHIDIC ACID LOW:**

- ◆ Causes:
 - » Suppressed lipogenesis
 - » Low exogenous intake
 - » Ketosis
- ◆ Symptoms/Conditions:
 - » None
- ◆ Treatment:
 - » No treatment needed
 - » Treat ketosis if indicated

Behenic Acid

- ◆ Very long chain saturated fatty acid (22:0)
- ◆ Peroxisomal activity required for oxidation
- ◆ Used to build sphingolipids of nerve membranes
- ◆ Used in neonatal screening for peroxisomal disorders
- ◆ Food sources:
 - » Nuts, seeds

IF BEHENIC ACID HIGH:

- ◆ Causes:
 - » Exogenous intake
 - » Increased lipogenesis
 - » Degenerative diseases of the central nervous system
- ◆ Symptoms/Conditions:
 - » Adrenoleukodystrophy (ALD)—X-linked disease, childhood variant
 - » Adrenomyeloneuropathy (AMN)—X-linked disease, adult variant

FATTY ACIDS | 89

Arachidic Acid; Behenic Acid; Lignoceric Acid

- ◆ Symptoms/Conditions:
 - » Impaired peroxisomal oxidation
 - » Several genetic disorders involve accumulation of sphingolipids containing behenic acid, usually due to a lack of the enzymes necessary to maintain the turnover of membrane components
- ◆ Treatment:
 - » Lipid lowering agents
 - » Reduce exogenous intake
 - » Lorenzo's oil (4:1 mixture of oleic and erucic acids)

IF BEHENIC ACID LOW:

- ◆ Causes:
 - » Impaired lipogenesis
- ◆ Symptoms/Conditions:
 - » See "Palmitic Acid" on page 87
- ◆ Treatment:
 - » No treatment needed

Lignoceric Acid

- ◆ Very long chain saturated fatty acid (24:0)
- ◆ Peroxisomal activity required for oxidation
- ◆ Used to build sphingolipids of nerve membranes
- ◆ Nerve membrane function
- ◆ Used in neonatal screening
- ◆ Food sources:
 - » Brazil nuts, peanuts

Lignoceric Acid; Hexacosanoic Acid

IF LIGNOCERIC ACID HIGH:

- ◆ Causes:
 - » Degenerative diseases of the central nervous system
 - » Adrenoleukodystrophy (ALD)—X-linked disease, childhood variant
 - » Adrenomyeloneuropathy (AMN)—X-linked disease, adult variant
- ◆ Symptoms/Conditions:
 - » Several genetic disorders involve accumulation of sphingolipids, usually due to a lack of the enzymes necessary to maintain the turnover of membrane components
 - » Excess consumption of Brazil nuts and peanuts
- ◆ Treatment:
 - » Decrease consumption of Brazil nuts and peanuts
 - » Rape (canola) or mustard seed oils
 - » Lorenzo's oil (4:1 mixture of oleic and erucic acids)

IF LIGNOCERIC ACID LOW:

- ◆ Causes:
 - » Deficiencies not of concern
- ◆ Symptoms/Conditions:
 - » None
- ◆ Treatment:
 - » No treatment needed

Hexacosanoic Acid

- ◆ Very long chain saturated fatty acid (26:0)
- ◆ Peroxisomal activity required for oxidation
- ◆ Elongation stimulation
- ◆ Used to build sphingolipids of nerve membranes
- ◆ Used in neonatal screening

IF HEXACOSANOIC ACID HIGH:

- ◆ Causes:
 - » Degenerative diseases of the central nervous system
 - » Adrenoleukodystrophy (ALD)—X-linked disease, childhood variant
 - » Adrenomyeloneuropathy (AMN)—X-linked disease, adult variant
- ◆ Symptoms/Conditions:
 - » Several genetic disorders involve accumulation of sphingolipids, usually due to a lack of the enzymes necessary to maintain the turnover of membrane components
- ◆ Treatment:
 - » Rape (canola) or mustard seed oils
 - » Lorenzo's oil (4:1 mixture of oleic and erucic acids)

**Odd Chain Fatty Acids****Pentadecanoic, Heptadecanoic, Nonadecanoic, Heneicosanoic, and Tricosanoic Acids**

These fatty acids are produced when the 3-carbon precursor, propionic acid is elongated successively by 2-carbons to produce odd-numbered chain lengths. Propionic acid can accumulate due to deficiency of vitamin B₁₂ or biotin. Propionate clearance is dependent on vitamin B₁₂, and propionate formation is enhanced when biotin is inadequate. Overgrowth of certain intestinal bacteria that produce propionate can also be a source of odd-chain fatty acid elevations.

- » Decrease gastrointestinal bacterial overgrowth

Note: When very long-chain odd chain fatty acids are elevated as part of an overall pattern of very long-chain fatty acid elevation, it may be due to impaired peroxisomal oxidation.

Trans-Fatty Acids**Palmitelaidic Acid**

- ◆ Long chain (16-carbon) fatty acid (16:1n7t)
- ◆ *Trans*-isomer of palmitic acid
- ◆ Formed during hydrogenation of oils
- ◆ Food sources:
 - » Partially hydrogenated oils in:
 - Margarines
 - Bakery products—breads, rolls, cookies, crackers, pies and cakes
 - Peanut butter
 - Food labels indicating

Palmitelaidic Acid; Total C:18 Trans-Isomers; LA/DGLA

- “vegetable oil” or “partially hydrogenated vegetable oil”
- Oils used in many restaurants

IF PALMITELAIDIC ACID HIGH:

- ◆ Causes:
 - » Intake of processed foods
 - » Toxic exposure
 - » Certain GI bacteria may produce *trans*-isomers from *cis*-fatty acids
- ◆ Symptoms/Conditions:
 - » Eicosanoid interference
 - » Increased risk for:
 - Heart disease
 - Increased LDL cholesterol and decreased HDL cholesterol
 - Cancer
 - Diabetes
 - Degenerative diseases related to fat metabolism
- ◆ Treatment:
 - » Eliminate hydrogenated oils—takes several months to decrease levels in the cell membranes of major organs

Total C:18 Trans-Isomers

- ◆ Group of 18-carbon fatty acids made up of elaidic acid (*trans*-isomers of oleic acid) and two positional isomers of elaidic acid
- ◆ Formed during hydrogenation of oils
- ◆ Food sources:
 - » Partially hydrogenated oils in:
 - Margarines

- Bakery products—breads, rolls, cookies, crackers, pies and cakes
- Peanut butter
- Product labels indicating “vegetable oil” or “partially hydrogenated vegetable oil”
- Oils used in many restaurants

IF TOTAL C:18 TRANS-ISOMERS HIGH:

- ◆ Causes:
 - » Excessive food sources
- ◆ Symptoms/Conditions:
 - » Eicosanoid interference
- ◆ Treatment:
 - » Eliminate hydrogenated oils—takes several months to decrease levels in the cell membranes of major organs

Fatty Acid Ratios**LA/DGLA**

- ◆ Primary marker of functional zinc insufficiency
- ◆ Zinc-dependent omega-6 desaturase enzyme activity required for conversion of LA into DGLA

IF LA/DGLA HIGH:

- ◆ Causes:
 - » Failure to convert LA into DGLA fast enough
 - » Zinc deficiency
 - » Excess saturated, monoenoic or *trans*-fatty acids



- ◆ Symptoms/Conditions:
 - » See relevant symptoms above
- ◆ Treatment:
 - » Black currant oil, 2–8 g/d
 - » Evening primrose oil, 2–8 g/d
 - » Borage oil, 1–4 g/d
 - » Zinc, 30 mg/d
 - » Increase sources of EPA, DHA and AA as indicated

EPA/DGLA

- ◆ Ratio of series 3 to series 1 eicosanoid precursors
- ◆ Omega-3 to omega-6 balance important for eicosanoid regulation of tissue responses
- ◆ Refer to individual fatty acids for more information

IF EPA/DGLA HIGH:

- ◆ Causes:
 - » Excessive fish oil supplementation
 - » Insufficient GLA dietary intake
- ◆ Symptoms/Conditions:
 - » See relevant symptoms at the beginning of this chapter
- ◆ Treatment:
 - » Black currant oil, 2–8 g/d
 - » Evening primrose oil, 2–8 g/d
 - » Borage oil, 1–4 g/d

IF EPA/DGLA LOW:

- ◆ Causes:
 - » Insufficient intake of omega-3 oils
 - » Excessive intake of omega-6 oils

LA/DGLA; EPA/DGLA; AA/EPA

- ◆ Symptoms/Conditions:
 - » See relevant symptoms at the beginning of this chapter
- ◆ Treatment:
 - » Fish oil, 2–3 g/d

AA/EPA (Omega-6/Omega-3)

- ◆ Ratio of series 2 to series 1 eicosanoid precursors
- ◆ Omega-3 to omega-6 balance important for eicosanoid regulation of tissue responses
- ◆ Refer to individual fatty acids for more information

IF AA/EPA HIGH:

- ◆ Causes:
 - » Hyperinsulinemia
 - » Diet high in corn-fed red meats, eggs and corn oil-rich foods

- ◆ Symptoms/Conditions:
 - » Inflammatory disorders
 - » Cancers—breast, colon, prostate
 - » Dry, itching skin that worsens with cold weather

- ◆ Treatment:
 - » Fish oil—may need several weeks of supplementation
 - » Reduce dietary intake of AA sources
 - » Treat hyperinsulinemia

IF AA/EPA LOW:

- ◆ Causes:
 - » Eicosanoid imbalance
 - » Excessive fish oil intake

AA/EPA; Mead/AA; Erythrocyte; Stearic/Oleic

- ◆ Symptoms/Conditions:
 - » Reduced immune system responsiveness
- ◆ Treatment:
 - » Decrease fish oil,
 - » Increase omega-6 oils

Triene (Mead)/Tetraene (AA)

- ◆ General essential fatty acid deficiency marker
- ◆ Becomes elevated when essential fatty acid substrates (LA and ALA) are not available, (mead is produced in greater quantity)
- ◆ Remains within normal limits when mead formation rises due to up-regulated desaturase activity (frequently due to elevated ALA and EPA)

IF TRIENE/TETRAENE HIGH:

- ◆ Causes:
 - » Essential fatty acid deficiency
 - » Sensitive marker of the combined effect of non-essential fatty acid desaturation and essential fatty acid deficiency
- ◆ Symptoms/Conditions:
 - » See "Differentiation of Fatty Acid Deficiency Signs and Symptoms" on page 72
- ◆ Treatment:
 - » Evaluate erythrocyte Stearic/Oleic acid
 - » Marker for therapeutic success against several forms of neoplastic disease

Erythrocyte Stearic/Oleic

- ◆ Used to monitor effectiveness of cancer therapy
- ◆ Ratio for erythrocyte specimen only
- ◆ < 1.1 associated with malignancy

IF STEARIC/OLEIC LOW:

- ◆ May indicate presence of malignant tissue:
 - » Increased membrane fluidity, allowing in rapid movement of nutrients and waste products, increasing metabolic rate of tumor cells
 - » Low ratio found in breast, prostate, liver, pancreas, colon, lung and gallbladder cancers
- ◆ Treatment:
 - » Evaluate for cancers or cancer treatment as indicated
 - » An improved ratio may indicate successful tumor regression

Organic Acids

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The *Organix™ Comprehensive Profile* provides a view into the several metabolic processes and the efficiency of metabolic function. Identifying metabolic blocks that can be treated nutritionally allows individual tailoring of interventions that maximize patient responses and lead to improved patient outcomes.

Organic acids are metabolic intermediates that are produced in pathways of central energy production, detoxification and biotransformation, neurotransmitter breakdown, or intestinal microbial activity. Marked accumulation of specific organic acids detected in urine often signals a metabolic inhibition or blockage. The abnormality may be due to a nutrient deficiency, an inherited enzyme deficit, toxic interference, or

Adipate; Suberate

drug effect. Several analytes provide insight into gastrointestinal bacterial or fungal imbalance.

- ◆ Elevations in any organic acids can contribute to metabolic acidosis
- ◆ Symptoms from mild, chronic acidurias may not manifest until adulthood
- ◆ **The mitochondrial function markers include:**
 - » Fatty Acid Metabolism
 - » Carbohydrate Metabolism
 - » Citric Acid Cycle Intermediates

Fatty Acid Metabolism

- ◆ Needed for energy
- ◆ Supplements:
 - » Carnitine, a metabolic cofactor synthesized from L-lysine and L-methionine (as SAMe)
 - Conditionally essential nutrient
 - Fatty acid transport carrier from cytosol into mitochondria for beta-oxidation
 - » Vitamin B₂ (riboflavin)
 - Aids oxidative metabolism of fats within the mitochondria

Adipate (Adipic Acid), and Suberate (Suberic Acid)

- ◆ Functional markers of carnitine insufficiency
- ◆ Six and eight carbon dicarboxylic acids, respectively
- ◆ Treatment:
 - » L-Carnitine, 500–1000 mg TID
 - » May be contraindicated in certain patients on thyroid medications

- ◆ Products of peroxisomal fatty acid oxidation
- ◆ Increased when carnitine insufficiency limits long chain fatty acid entry into mitochondria

IF ADIPATE AND SUBERATE HIGH:

- ◆ Causes:
 - » Incomplete fatty acid oxidation
 - » Carnitine deficiency
 - » Environmental toxin exposure—alters lipid metabolism
 - » Adipate elevation alone: consider exogenous adipate ingestion (gelling and flavoring agent)
- ◆ Symptoms/Conditions:
 - » Periodic mild weakness
 - » Mitochondrial dysfunction
 - » Nausea
 - » Fatigue
 - » Hypoglycemia
 - » Recurrent infections
 - » “Sweaty feet” odor
 - » Attention deficit in children (association noted)
 - » Metabolic acidosis
 - » Reye syndrome (inhibition of fatty acid oxidation likely caused by aspirin in presence of a genetic mutation given for viral infection—viral toxins also implicated)
- ◆ Treatment:
 - » L-Carnitine, 500–1000 mg TID
 - » May be contraindicated in certain patients on thyroid medications



- » Vitamin B₂ (riboflavin), 100 mg BID
- » L-Lysine (if low), 1000 mg QD-TID—a precursor for carnitine

- » Other nutrients involved in carnitine synthesis include SAMe, B₆, magnesium, ascorbate, iron, niacin
- » Ensure optimal protein intake, digestion and absorption

**Ethylmalonate
(Ethylmalonic Acid)**

- ◆ Five carbon branched dicarboxylic acid formed in isoleucine catabolism
- ◆ Functional marker of carnitine insufficiency
- ◆ May be formed when short chain fatty acid oxidation is compromised, which causes an elevation of butyrate, some of which is converted to ethylmalonate
- ◆ Oxidation dependent on formation of acylcarnitine

IF ETHYLMALONATE HIGH:

- ◆ Causes:
 - » Carnitine deficiency
 - » Riboflavin deficiency
 - » Failure in formation or oxidation of butyrylcarnitine
 - » Genetic mutations (short-chain acyl-CoA dehydrogenase, multiple acyl-CoA dehydrogenase)
 - » Isoleucine loading
- ◆ Symptoms/Conditions:
 - » See above: Adipate and Suberate

Adipate; Suberate; Ethylmalonate; Pyruvate

- ◆ Treatment:
 - » Same as above for Adipate and Suberate
 - » Also:
 - Glycine, 250 mg/kg/day
 - Avoid medium chain fatty acids such as coconut oil

Carbohydrate Metabolism**Pyruvate**

- ◆ Three carbon keto-acid (α -ketopropionate)
- ◆ Breakdown product of glucose oxidation—energy production
- ◆ Under aerobic conditions, oxidized to acetyl-CoA
- ◆ Under anaerobic conditions, reduced to lactate (skeletal muscle)
- ◆ Stimulates gluconeogenesis and inhibits fatty acid synthesis
- ◆ Substrate of pyruvate dehydrogenase complex (PDC) that requires coenzymes produced from vitamins B₁, B₂, B₃, B₅, and lipoic acid

IF PYRUVATE HIGH:

- ◆ Causes:
 - » Vitamin B deficiencies, especially B₁ and B₅
 - » Lipoic acid insufficiency
 - » Under eating
- ◆ Symptoms/Conditions:
 - » Thiamine-deficiency encephalopathy associated

L-Lactate

- » with alcohol use (Wernicke-Korsakoff syndrome)
- » Fatty liver associated with alcohol use
- » Metabolic acidosis
- ◆ Treatment:
 - » Vitamin B₁ (thiamine), up to 100 mg TID with B complex support; for concurrent L-lactate elevation: lipoic acid, 500 mg TID

L-Lactate (L-Lactic Acid)

- ◆ Chiral center of lactic acid generates 2 enantiomers, D and L
- ◆ Human metabolic product is always L-lactate (D-lactate is discussed under "intestinal dysbiosis")
- ◆ Three carbon hydroxy acid
- ◆ Anaerobic energy production
- ◆ Principal product of glucose oxidation in skeletal muscle
- ◆ Gluconeogenesis substrate
- ◆ NADH-dependent oxidation to pyruvate prior to mitochondrial entry

IF L-LACTATE HIGH:

- ◆ Causes:
 - » Block in final oxidative phosphorylation stage of energy production—inactivation of citric acid cycle
 - » Coenzyme Q10 deficiency
 - » Biotin deficiency
 - » Lipoic acid deficiency
 - » Temporary increase due to alcohol consumption

- » Metabolic acidosis from:
 - Hypoxia
 - Poor perfusion, induced by various shock states
 - Overwhelming infection
- » Medicinal and toxic causes:
 - Acetaminophen
 - Alcohols and glycols (ethanol, ethylene glycol, methanol, propylene glycol)
 - Antiretroviral nucleoside analogs (zidovudine, delavirdine, didanosine, lamivudine, stavudine, zalcitabine)
 - Beta-adrenergic agents (e.g., epinephrine, ritodrine, terbutaline), biguanides (phenformin, metformin)
 - Cocaine
 - Cyanogenic compounds (e.g., cyanide, aliphatic nitriles, nitroprusside)
 - Diethyl ether
 - 5-fluorouracil
 - Halothane
 - Isoniazid
 - Nalidixic acid
 - Propofol
 - Sugars and sugar alcohols (fructose, sorbitol, and xylitol)
 - Salicylates (e.g., Reye syndrome)
 - Strychnine
 - SulfaSalazine
 - Valproic acid



- » Underlying disease (mechanism may be occult tissue hypoperfusion):
 - Diabetes mellitus (concurrent diabetic ketoacidosis)
 - Severe iron-deficiency anemia
 - Liver diseases
 - Alcoholic ketoacidosis
 - Pancreatitis
 - Malignancy (e.g., leukemias, lymphomas, lung cancer)
 - Alkalosis
 - Infections (malaria, cholera)
 - Renal failure
 - Pheochromocytoma
 - Thiamine deficiency
 - Short gut syndrome
 - Other carbohydrate malabsorption syndromes (e.g., D-lactic acidosis)
 - Milk protein intolerance
- » Inborn errors of metabolism:
 - Glucose-6-phosphatase deficiency (von Gierke disease)
 - Fructose-1, 6-diphosphatase deficiency
 - Pyruvate carboxylase deficiency
 - Pyruvate dehydrogenase deficiency
 - Oxidative phosphorylation deficiency
 - Methylmalonic aciduria
- ◆ Symptoms/Conditions:
 - » If acidosis significant, cardiovascular compromise
 - » Cyanosis

L-Lactate; β-Hydroxybutyrate

- » Cold extremities
- » Tachycardia
- » Hypotension
- » Signs of dehydration
- » Hyperventilation or dyspnea
- » Vomiting and/or abdominal pain
- » Lethargy, stupor or coma
- » MELAS syndrome (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes)
- Caused by a point mutation in mitochondrial DNA
- Associated with valproate use
- Occurs in pregnancy and childhood
- ◆ Treatment:
 - » Identify and address underlying cause
 - » CoQ10, 60–300 mg/d
 - » Vitamin B₁ (thiamine), up to 100 mg TID with B complex support; for concurrent L-lactate elevation: lipoic acid 500 mg TID
 - » Biotin, up to 5 mg/day

β-Hydroxybutyrate

- ◆ Four carbon hydroxy acid (3-hydroxybutyrate)
- ◆ Ketone body produced in proportion to dependence on fatty acid oxidation for ATP, most often due to restricted carbohydrate oxidation

IF β-HYDROXYBUTYRATE HIGH:

- ◆ Causes:
 - » Fasting

β-Hydroxybutyrate; Citrate, *cis*-Aconitate & Isocitrate

- » Low carbohydrate diet
- » Diabetes/impaired glucose metabolism (metabolic syndrome)
- » Insufficient cellular glucose uptake stimulates oxidation of free fatty acids, creating acetyl-CoA which is converted to ketone bodies β-hydroxybutyrate and acetone
- » Defects in cytochrome oxidase enzymes—electron transport chain
- ◆ Symptoms/Conditions:
 - » May be asymptomatic
 - » Metabolic acidosis—Type I Diabetes (i.e. in diabetic ketoacidosis where insufficient insulin is present)
 - » Excess fatigue on exertion
- ◆ Treatment:
 - » If due to metabolic syndrome or diabetes:
 - Chromium picolinate, 500 µg BID
 - Vanadium, 500 µg BID
 - Lipoic acid, 600 mg/d
 - General glucose regulation approaches
 - » If due to cytochrome oxidase defect:
 - CoQ10 up to 3000 mg/day
 - Carnitine may also be helpful

Citric Acid Cycle (CAC) Intermediates

- ◆ Serves both anabolic and catabolic functions
- ◆ Final common pathway of energy

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- release from catabolism of fats, proteins, and carbohydrates
- ◆ Source of basic structural molecules that are drawn away from the cycle to support organ maintenance and neurological function—anabolic processes
- ◆ Crossroads of food conversion and utilization
- ◆ Spillage of intermediates in urine may indicate mitochondrial inefficiencies in energy production
- ◆ A block in any step may cause a build-up of compounds that precede this step
- ◆ Amino acids supply carbon skeletons for maintaining mitochondrial concentrations

Citrate, *cis*-Aconitate and Isocitrate

- ◆ Six carbon tricarboxylic acid (TCA) intermediates of the citric acid cycle
- ◆ Aerobic energy production
- ◆ Counter-ions for renal ammonia clearance ((NH₃)₃-TCAs passed in urine)
- ◆ Different binding positions on the enzyme aconitase are responsible for the conversion of citrate to isocitrate followed by *cis*-aconitate. Aconitase has an iron-sulfur catalytic center.

IF CITRATE, *CIS*-ACONITATE AND ISOCITRATE HIGH:

- ◆ Causes:
 - » May be due to ammonia toxicity



- » When citrate, *cis*-aconitate and isocitrate are high (renal ammonia clearance), check orotate (hepatic urea cycle disposal of ammonia). Elevated orotate indicates need for urea cycle stimulation by arginine or citrulline (manganese cofactor).
- » If orotate is not high, check for elevations of organic acid markers of intestinal microbial overgrowth which may be a source of ammonia challenge to renal clearance capacity.
- » When any of the TCAs, including malate, fumarate and α-ketoglutarate are concurrently high, suspect cytochrome C oxidase deficiency and inefficient oxidation of NADH (the primary product of the CAC) and reduced mitochondrial energy (ATP) production.
- » Mitochondrial dysfunction
- » Gentamicin toxicity
- » Excessive supplementation of citrate complex (e.g. magnesium citrate)
- ◆ Symptoms/Conditions:
 - » Fatigue
 - » Weakness
 - » Confusion and poor memory
 - » Behavioral abnormalities
- ◆ Treatment:
 - » Arginine or citrulline, 1–3 gm/day
 - » Lipoic acid, 25 mg/kg/d—esp. for Gentamicin toxicity
 - » Magnesium, 200 mg BID—esp. for Gentamicin toxicity

IF CITRATE, *CIS*-ACONITATE AND ISOCITRATE LOW:

- ◆ Causes:
 - » Amino acid deficiencies (their catabolic products allow mitochondrial refilling of CAC intermediates)
 - » Insufficient digestion and assimilation functions
- ◆ Symptoms/Conditions:
 - » Fatigue due to impairment of CAC
 - » Childhood developmental retardation
- ◆ Treatment:
 - » Amino acid mixtures
 - » Magnesium citrate, 500 mg
 - » L-Aspartic acid, 1500 mg
 - » Increase dietary protein (good nutrition and digestion stimulates the flow of amino acids)
 - » Digestive enzymes

IF ONLY *CIS*-ACONITATE OR ISOCITRATE HIGH:

- ◆ The conversion of citrate to *cis*-aconitate and then to isocitrate is mediated by the enzyme aconitase that is highly susceptible to oxidative damage and mitochondrial iron excess (hemochromatosis) or deficiency (anemia).
- ◆ Causes:
 - » Genetic polymorphisms of aconitase
 - » Poisoning or oxidative damage of aconitase from toxic heavy metals or mitochondrial oxidative stress

Citrate; cis-Aconitate & Isocitrate; α -Ketoglutarate; Succinate

- ◆ Symptoms/Conditions:
 - » Fatigue
 - » Weakness
 - » Freidrich ataxia
 - » Accelerated aging
- ◆ Treatment:
 - » Evaluate/treat iron deficiency or iron overload
 - » Reduce oxidative stress
 - » Reduce heavy metal body burden

 α -Ketoglutarate

- ◆ Five carbon 2-keto (oxo) dicarboxylic acid citric acid cycle intermediate
- ◆ Aerobic energy production
- ◆ Feedback regulation of urea cycle
- ◆ Substrate of keto acid dehydrogenase complex that requires co-enzymes produced from vitamins B₁, B₂, B₃, B₅, and lipoic acid

IF α -KETOGLUARATE HIGH:

- ◆ Causes:
 - » Under eating
 - » Mitochondrial dysfunction
 - » B-complex deficiencies
 - » Catabolic breakdown product of glutamic acid, histidine, arginine, proline and glutamine
 - » When α -ketoglutarate, succinate, fumarate and malate are high, suspect insufficiency of coenzyme Q10 or cytochrome C oxidase and inefficient utilization of NADH, the primary product of the CAC

Succinate

- ◆ Four carbon dicarboxylic acid
- ◆ Mitochondrial oxidation utilizing FAD
- ◆ Produced in catabolism of leucine and isoleucine

IF SUCCINATE HIGH:

- ◆ Causes:
 - » Coenzyme Q10 deficiency
 - » Riboflavin deficiency

IF α -KETOGLUTARATE LOW:

- ◆ Causes:
 - » Amino acid insufficiency
 - » Up-regulated fatty acid synthesis
 - » Increased palmitic acid in plasma and cell membranes
- ◆ Symptoms/Conditions:
 - » Fatigue
 - » Increased serum triglycerides
- ◆ Treatment:
 - » α -Ketoglutaric acid, 500 mg BID—particularly helpful if taken 30 minutes before and after exercise



- » Mitochondrial dysfunction
- » When succinate, fumarate and malate are high, suspect insufficiency of coenzyme Q10 or cytochrome C oxidase and inefficient utilization of NADH, the primary product of the CAC

- ◆ Symptoms/Conditions:
 - » Fatigue
 - » Lassitude
 - » Myocardial degeneration
 - » Neurological degeneration
- ◆ Treatment:
 - » Coenzyme Q10, 60–300 mg/d
 - » Vitamin B₂ (riboflavin), 50 mg/d
 - » Magnesium, 500 mg/d

IF SUCCINATE LOW:

- ◆ Causes:
 - » Failure to refill Citric Acid Cycle (CAC) intermediates
- ◆ Treatment:
 - » L-Leucine, 1000 mg TID
 - » L-Isoleucine, 1000 mg TID
 - » Check for B₁₂ deficiency

Fumarate

- ◆ Four carbon unsaturated dicarboxylic acid
- ◆ Mitochondrial oxidation
- ◆ Produced in catabolism of phenylalanine and tyrosine

IF FUMARATE HIGH:

- ◆ Causes:
 - » Coenzyme Q10 deficiency

Succinate; Fumarate; Malate

- » Mitochondrial dysfunction
- » When succinate, fumarate and malate are high, suspect insufficiency of coenzyme Q10 or cytochrome C oxidase and inefficient utilization of NADH, the primary product of the CAC

- ◆ Symptoms/Conditions:
 - » Fatigue
 - » Weakness
- ◆ Treatment:
 - » Coenzyme Q10, 60–300 mg/d

IF FUMARATE LOW:

- ◆ Causes:
 - » Failure to refill Citric Acid Cycle (CAC) intermediates
- ◆ Symptoms/Conditions:
 - » Fatigue
- ◆ Treatment:
 - » Balanced mix of amino acids
 - » L-Tyrosine, 500 mg TID
 - » L-Phenylalanine, 14 mg/kg/d

Malate

- ◆ Four carbon hydroxy dicarboxylic acid
- ◆ Mitochondrial oxidation

IF MALATE HIGH:

- ◆ Causes:
 - » Coenzyme Q10 deficiency
 - » Mitochondrial dysfunction
 - » Fatty acid synthesis inhibits malate dehydrogenase enzyme—seen in patients on low fat, high carbohydrate diets or

Malate; HMG

- ◆ those with hyperinsulinism (metabolic syndrome)
- » When malate, fumarate and α-ketoglutarate are high, suspect cytochrome C oxidase deficiency and inefficient utilization of NADH, the primary product of the CAC
- ◆ Symptoms/Conditions:
 - » Fatigue
 - » Weakness
- ◆ Treatment:
 - » Coenzyme Q10, 60–300 mg/d

IF MALATE LOW:

- ◆ Causes:
 - » Failure to refill Citric Acid Cycle (CAC) intermediates
- ◆ Symptoms/Conditions:
 - » Fatigue—relieved by protein intake
- ◆ Treatment:
 - » Balanced mix of amino acids

Hydroxymethylglutarate (HMG)

- ◆ Substrate of HMG-CoA reductase
- ◆ Metabolic precursor of cholesterol and Coenzyme Q10

IF HMG HIGH:

- ◆ Causes:
 - » Inhibition of HMG-CoA reductase
 - » Statin drug use
 - » Mitochondrial dysfunction
 - » Insulin stimulates and glucagon inhibits HMG-CoA reductase

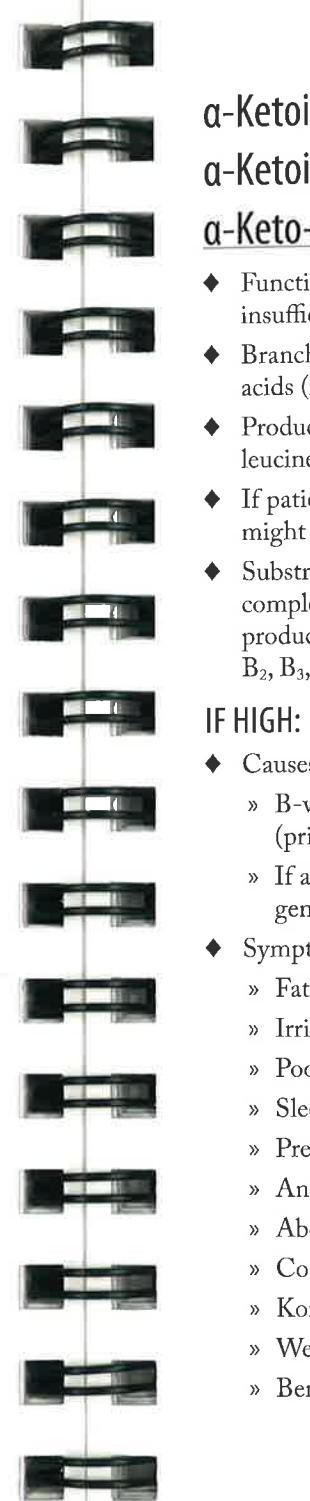
- ◆ Symptoms/Conditions:
 - » Fatigue
 - » Weakness
 - » Myalgia
 - » Myopathy
 - » Myoglobinuria
 - » May contribute to rhabdomyolysis
- ◆ Treatment:
 - » Coenzyme Q10, 60–300 mg/d—especially if CAC intermediates are high and serum CoQ10 is low

IF HMG LOW:

- ◆ Causes:
 - » Inhibition cholesterologenesis prior to HMG-CoA step
 - » Slow rate of CoQ10 production
- ◆ Symptoms/Conditions:
 - » Fatigue—relieved by protein intake
- ◆ Treatment:
 - » Coenzyme Q10, 60–300 mg/d—recheck for effectiveness

B-Complex Vitamin Status Markers

- ◆ All compounds in this category are metabolic intermediates in the degradation of amino acids—B vitamin deficiencies result in slower reaction rates
- ◆ B₆ >15mg/day can block absorption of the Parkinson medication levodopa

**α-Ketoisovalerate, α-Ketoisocaproate & α-Keto-β-Methylvalerate; Xanthurene**

- ◆ Treatment:
 - » Thiamine up to 100 mg TID with B-complex support
 - » Lipoic acid, 100–600 mg/day

Xanthurene

- ◆ Functional marker of pyridoxine insufficiency
- ◆ Tryptophan catabolism (hepatic kynurenin pathway)
- ◆ L-Tryptophan challenge test—give 3–5 grams tryptophan and then evaluate xanthurene for vitamin B₆ deficiency

IF XANTHURENE HIGH:

- ◆ Causes:
 - » Vitamin B₆ deficiency
 - » Excess L-tryptophan due to a high protein diet or L-tryptophan supplementation
- ◆ Symptoms/Conditions:
 - » Seborrheic dermatitis
 - » Depression
 - » Premenstrual syndrome
 - » Fatigue
 - » High homocysteine
 - » Glossitis
 - » Cheilosis
 - » Peripheral neuropathy
 - » Lymphopenia
 - » Convulsions (infants)
 - » Anemia (adults—usually normocytic but occasionally microcytic)

Xanthurenone; β-Hydroxyisovalerate; MMA

- ◆ Treatment:
 - » Vitamin B₆ (pyridoxine), 100 mg/d
 - » Pyridoxine-5-phosphate, 30 mg/d

β-Hydroxyisovalerate

- ◆ Functional marker of biotin insufficiency
- ◆ Isoleucine catabolism
- ◆ Gluconeogenesis and other anabolic pathways

IF β-HYDROXYISOVALERATE HIGH:

- ◆ Causes:
 - » Biotin deficiency—due to lack of biotin-rich foods or genetic variations in enzymes that cycle biotin
 - » Antibiotic overuse—decreases intestinal bacteria that produce biotin
 - » Dysbiosis or lack of beneficial bacteria
 - » Use of avidin—a biotin binding protein found in raw egg white
 - » Pregnancy
 - » Anticonvulsant therapy (specifically: phenytoin [Dilantin], primidone [Mysoline], carbamazepine [Tegretol], phenobarbital [Solfoton], and possibly valproic acid)
- ◆ Symptoms/Conditions:
 - » Alopecia
 - » Skin rash
 - » Candida dermatitis
 - » Seborrheic dermatitis
 - » Blood sugar dysregulation

Methylation Cofactor Markers

Methylmalonate (MMA)

- ◆ Functional marker of vitamin B₁₂ insufficiency
- ◆ Odd-chain fatty acid catabolism
- ◆ Intermediate in the catabolism of valine

IF MMA HIGH:

- ◆ Vitamin B₁₂ deficiency caused by:
 - » Alcohol abuse



- » Immune deficiencies
- » Muscle weakness
- » Multiple carboxylase deficiency—an inherited disorder
- » Developmental delay
- » Truncal ataxia
- » Convulsions
- » Tremors
- » Loss of language development
- » Leiner disease (desquamative erythroderma)
- ◆ Treatment:
 - » Biotin, 5 mg/day; magnesium, 100 mg BID
 - » Biotin-rich foods—eggs, fish, milk and milk products, whole grain cereals, legumes, yeast, cruciferous vegetables, white and sweet potatoes, lean beef
 - » B-complex vitamins
 - » Pre- and probiotics

- ◆ Symptoms/Conditions:
 - » Fatigue
 - » Peripheral neuropathy
 - » Depression
 - » Hyperreflexia
 - » Upper respiratory infections
 - » Gastrointestinal disorders
 - » Anemia (masked by folic acid)
 - » Ischemic heart disease
 - » Stroke
 - » Deep vein thrombosis
- ◆ Treatment:
 - » Vitamin B₁₂ (cobalamin), 1000–5000 µg/d—oral if adequate intrinsic factor
 - » Vitamin B₁₂—sublingual or IM if oral doses are ineffective
 - » Stop alcohol
 - » Treat dysbiosis

MMA; FIGLU

Formiminoglutamate (FIGLU)

- ◆ Functional marker of folic acid insufficiency
- ◆ Catabolism of histidine to glutamic acid—FIGLU is an intermediate requiring folic acid (not methyl folate)
- ◆ Sensitivity of testing increased by bedtime challenge of L-histidine (10–15 gm)
- ◆ FIGLU excretion has been used to measure the influence of drugs or alcohol on functional folate status

IF FIGLU HIGH:

- ◆ Causes:
 - » Folate deficiency—FIGLU elevation can appear about 90 days prior to anemia from folate deficiency
 - » Poor dietary intake of folate-rich foods
 - » Excessive intake of processed foods
 - » Impaired absorption
 - » Inadequate utilization due to a metabolic block
 - » Increased folate demands
 - » Increased folate excretion
 - » Increased folate degradation
 - » Methotrexate use
 - » Oral contraceptive use
 - » Phenytoin (Dilantin) use
 - » Vitamin C deficiency—oxidative destruction of folate
 - » Genetic enzyme defects
 - » Cigarette smoking

FIGLU;VMA

- » Pregnancy
- » Alcoholism:
 - Impairs folate coenzymes
 - Possible malabsorption of folate
 - Vitamin B₁₂ deficiency (5-methyltetrahydrofolate trap)
 - Reduced folate uptake across enterocytes and other cell membranes
 - Reduced cell retention
- ◆ Symptoms/Conditions:
 - » Fatigue
 - » Depression
 - » Inhibition of DNA synthesis
 - » Impaired cell division
 - » Alterations in protein synthesis
 - » Hypersegmentation of polymorphonuclear leukocytes
 - » Heart disease
 - » Infertility
 - » Neural tube defects
 - » Megaloblastic anemia
 - » Colon cancer
 - » Pancreatic cancer
 - » Breast cancer (53% higher risk with folate deficiency)

Note: Excess folate supplementation has also been associated with increased risk of cancers. Thus, monitoring markers associated with folate status is important.

- » Thrombosis
- » Elevated homocysteine—but not necessarily high due to differences in binding affinity and forms of folate (homocysteine clearance requires

5-methyltetrahydrofolate while FIGLU clearance requires only folic acid)

- » Ischemic heart disease
- » Stroke
- » Deep vein thrombosis

◆ Treatment:

- » Stop alcohol
- » Folic acid, 400–800 µg/d
- » Consider using 5-methyltetrahydrofolate, 800 µg/d, if homocysteine is refractory to therapy. Genetic testing of the enzyme MTHFR may also be indicated

Neurotransmitter Metabolism Markers

The first three of these compounds are catabolic end products of neurotransmitters formed in brain or other tissues. Their urinary excretion represents total body turnover of the respective neurotransmitters. The last three compounds are active forms that are released into circulation from brain or hepatic kynurenin pathway activities.

Vanilmandelate (VMA)

- ◆ Epinephrine and norepinephrine catabolism
- ◆ Marker of metabolic fitness and stress management



IF VMA HIGH:

- ◆ Causes:
 - » Chronic stress response
 - » Synergism of pituitary adrenocorticotrophic hormone and adrenal cortisol
 - » Heightened sympathetic reactions to stress
 - » Increased rate of catecholamine synthesis and degradation in normal tissue
- » Pharmacologic causes:
 - Ephedra (Ma Huang)
 - Caffeine
 - Pseudoephedrine
- » Abnormal production by tumor tissue (particularly neuroblastomas or pheochromocytomas)—Incidence of elevated values increases as a function of tumor size—small tumors may not result in high VMA
- » Myocardial injury—especially if cardiac troponin I is also high
- » Chronic elevation can deplete tyrosine
- » Symptoms/Conditions relating to sympathetic arousal:
 - Hypertension
 - Headaches
 - Muscle aches
 - GI disturbances
 - Decreased immunity
 - Cold hands
 - Anxiety
 - Sleep disturbances
 - Fatigue (consider:

IF VMA LOW:

- ◆ Causes:
 - » Low levels of epinephrine or norepinephrine
 - » Adrenal insufficiency (stress “burnout”)
 - » Phenylalanine—tyrosine insufficiency
- ◆ Symptoms/Conditions:
 - » Depression
 - » Sleep disturbances
 - » Anxiety
 - » Fatigue
- ◆ Treatment:
 - » Treatments to improve protein digestion:
 - Pancreatic enzymes
 - Balanced mix of essential amino acids
 - Treat gastrointestinal dysbiosis
 - » L-Tyrosine, 500 mg TID
 - » **Cofactors involved in synthesis** include: folate, BH4, niacin, B₆, magnesium, copper and vitamin C

adrenal insufficiency, fibromyalgia syndrome)

VMA; HVA; 5-HIA

- » Decrease stress (cortisol)—emotional and physical
- » Adrenal support

Homovanillate (HVA)

- » Dopamine catabolism
- » Indicator of metabolic fitness

IF HVA HIGH:

- ◆ Causes:
 - » Increased rate of synthesis and degradation in normal tissue
 - » Essential amino acid deficiency
 - » Medication for Parkinson disease (L-dopa)
 - » Copper deficiency (especially if VMA is low)
 - » Cocaine use
 - » Amphetamine use
 - » Rare: pheochromocytoma

Symptoms/Conditions:

- » Agitation
- » ADD/ADHD
- » Delirium
- » Psychosis
- » Chronic elevation can deplete tyrosine

- ◆ Treatment:
 - » Essential amino acids
 - » Stop related drug use
 - » Evaluate copper need

IF HVA LOW:

- ◆ Causes:
 - » Chronic stress
 - » Anti-psychotic medication

- » Phenylalanine—tyrosine insufficiency

◆ Symptoms/Conditions:

- » Depression
- » Sleep disturbances
- » Anxiety
- » Fatigue
- » Parkinson symptoms
- » ADD/ADHD

◆ Treatment:

- » Correct metabolic stress due to nutrient insufficiencies
- » L-Dopa
- » L-Tyrosine 1000 mg BID–TID between meals
- » Cofactors involved in synthesis include: folate, BH4, niacin, B₆, magnesium.
- » Antidepressants (Wellbutrin)
- » Decrease stress (cortisol)—emotional and physical

5-Hydroxyindoleacetate (5-HIA)

- ◆ Serotonin turnover in gut and brain
- ◆ Indicator of metabolic fitness

IF 5-HIA HIGH:

- » Catabolic breakdown of serotonin
- » Serotonin-specific re-uptake inhibitor antidepressants (SSRI's)
- » High intake of tryptophan or 5-hydroxytryptophan
- » Increased release of serotonin from three specific sites:
 - Central nervous system
 - Intestinal enterochromaffin cells



- Platelets

- » Carcinoid tumors composed of serotonin-producing enterochromaffin tissue

◆ Symptoms/Conditions:

- » Chronic elevation can deplete tryptophan
- » Depression
- » Stunted growth
- » Osteoporosis
- » Colonic motility issues (IBS)

◆ Treatment:

- » Address underlying metabolic abnormality
- » Essential amino acids

IF 5-HIA LOW:

- ◆ Causes:
 - » Lowered production of serotonin
 - » Tryptophan deficiency
 - » Cofactor deficiency
 - » Alcohol consumption
 - » Catecholamine excess

◆ Symptoms/Conditions:

- » Colonic motility issues (IBS)
- » Depression
- » Fatigue
- » Insomnia
- » Suicide
- » ADD/ADHD
- » Behavioral disorders

◆ Treatment:

- » Evaluate underlying metabolic imbalance
- » Increase consumption of foods high in tryptophan:

- Turkey

- Bananas

- Low fat milk

- Lentils

- Eggs

- » 5-HTP, 150–300 mg/d or L-tryptophan, 3.5 mg/kg/d (use with caution if SSRI therapy is ongoing)

- » Cofactors involved in the synthesis of serotonin: folate, BH4, B₆, magnesium, niacin
- » Balanced mix of amino acids

Kynureneate

- ◆ Tryptophan catabolism (hepatic kynurenin pathway)
- ◆ Precursor to quinolinate (macrophage kynurenin pathway)
- ◆ Involved in host defenses against pathogens
- ◆ Endogenous ligand that antagonizes ionotropic glutamate receptors
- ◆ Has preferential affinity for the glycine-binding site of the N-methyl-D-aspartate (NMDA) receptor—antagonizes NMDA activation and so is neuroprotective; competes with neurotoxic (NMDA agonist) quinolinate at NMDA receptors
- ◆ In inflammatory diseases, a high quinolinate:kynureneate (QUIN:KYNA) ratio increases risk of neurotoxicity
- ◆ Involved in pain perception
- ◆ Has anticonvulsant properties
- ◆ May be mechanism of action

Kynureneate; Quinolate

for Vitamin B₆'s beneficial neurological effects

IF KYNURENATE HIGH:

- ◆ Causes:
 - » Host defense against intracellular pathogens—via the kynurenin pathway in interferon-gamma stimulated macrophages
 - » Inflammatory disorders
 - » Vitamin B₆ deficiency
 - » Excess L-tryptophan due to a high-protein diet or L-tryptophan supplementation
- ◆ Symptoms/Conditions:
 - » Increased pain perception
 - » Relapsing-onset multiple sclerosis—high levels of kynureneate indicate active disease
 - » Schizophrenia has been associated with high CSF and urinary kynureneate
- ◆ Treatment:
 - » Vitamin B₆ (pyridoxine), 100 mg/d
 - » Magnesium, 500 mg/d
 - » Resolve inflammatory stimulation

Quinolate

- ◆ Produced from L-tryptophan in interferon-gamma (IFN-γ)—stimulated macrophages via the kynurenin pathway (TH1-driven response)
- ◆ No significant production as end product of hepatic kynurenin pathway
- ◆ Functions in immune system modulation of brain activity

- ◆ Quinolate is a powerful agonist of the NMDA receptors, ultimately leading to glutamate toxicity
- ◆ In inflammatory diseases, a high quinolate:kynureneate (QUIN/KYNA) ratio increases risk of neurotoxicity
- ◆ May be elevated by L-tryptophan, but not by 5-hydroxytryptophan loading

IF QUINOLINATE HIGH:

- ◆ Causes:
 - » Disordered tryptophan metabolism
 - » Chronic stimulation of the immune response:
 - Causes release of INF-γ by macrophages
 - Results in tryptophan conversion to quinolate by astrocytes and microglia in CNS
 - » Bacterial infection, recent or chronic
 - » Meningitis
 - » Fungal and parasitic infections
 - » Viral infection, recent or chronic
 - » Gastrointestinal microbial overgrowth
 - » HIV-related neurological dysfunction:
 - Due to overstimulation by quinolate of the NMDA receptors
 - Causes subsequent neurological degeneration with permanent loss of brain function
 - » Autoimmune diseases
 - » Septicemia



- » Chronic hyperammonemia
- » Inflammatory bowel diseases
- ◆ Symptoms/Conditions:
 - » Viral infection
 - » Irritable bowel disease—common site of inflammation via INF-γ
 - » Neurodegenerative conditions (e.g. ALS, Parkinson)
 - » Memory deficits
 - » Insomnia
 - » Learning difficulties in children
 - » Neurotoxic effects on hippocampus
 - » Chronic fatigue syndrome (immune mediated form aids in differentiating causes of CFS)
 - » Involved in pain syndromes via stimulation of nociception
- ◆ Treatment:
 - » Antioxidants (vitamin C, vitamin E, lipoic acid)
 - » Magnesium, 500 mg/d
 - » Glycine, 500 mg TID
 - » Resolve inflammatory stimulation
 - » NMDA antagonists

Picolinate

- ◆ Hepatic kynurenin pathway metabolite of tryptophan
- ◆ Isomer of nicotinic acid
- ◆ Activator of Th1-associated inflammatory chemokines
- ◆ Regulates leukocyte recruitment
- ◆ May augment *C. albicans* growth
- ◆ May inhibit retroviral transfer

- ◆ Antitumor activity
- ◆ Dietary proteins and fats modulate genetic expression of enzyme that controls production
- ◆ High protein intake may stimulate production
- ◆ Polyunsaturated fats (especially omega-3's) may inhibit production
- ◆ Dietary and pancreatic picolinate may assist in absorption of essential elements

IF PICOLINATE IS HIGH

- ◆ Causes:
 - » Inflammation/immune stimulation
 - » Rule out exogenous supplementation with picolinate salts
 - » Excess protein intake
 - » Excess supplemental amino acid intake
- ◆ Treatment:
 - » Identify and treat inflammatory/immune processes stimulating picolinate production
 - » Reduce protein intake if applicable
 - » Reduce supplemental amino acid intake, including tryptophan
 - » Reduce intake of picolinate salts

IF PICOLINATE IS LOW:

- ◆ Causes:
 - » Protein insufficiency
 - » Protein maldigestion
 - » Evaluate excess polyunsaturated fatty acid intake inhibiting picolinate production

Picolinate;JPLA;8-OHdG

- ◆ Symptoms/Conditions:
 - » Acrodermatitis enteropathica
 - » Essential element deficiency symptoms
 - » Poor immune response
- ◆ Treatment:
 - » Increase amino acid intake, including tryptophan
 - » Increase protein intake
 - » Essential element picolinate salts
 - » If intake is excessive, reduce polyunsaturated fatty acid intake

Oxidative Damage (Antioxidant Status) Markers

Antioxidant status can be challenged by toxicants, impaired detoxification or by anything that causes stimulation of normal oxidative pathways. Chronic antioxidant insufficiency allows for increased production of oxidized products that serve as markers of oxidative damage status.

p-Hydroxyphenyllactate (HPLA)

- ◆ Increased cell proliferation and pro-oxidant production
- ◆ Associated with carcinogenesis
- ◆ Binds to nuclear estrogen receptor
- ◆ Metabolite of tyrosine
- ◆ A marker for the depletion of methyl-p-hydroxyphenyllactate (MeHPLA), an important cell growth-inhibiting agent

IF HPLA HIGH:

- ◆ Causes:
 - » Increased level of oxidative challenge
 - » Increased tissue growth response
 - » Associated with cancer or normal tissue growth
 - » Inborn errors of metabolism
 - » Hepatic cirrhosis
- ◆ Symptoms/Conditions:
 - » Early onset of aging-related effects
 - » Tumor growth
 - » Leukemia
 - » Breast cancer
 - » Hepatic encephalopathy
 - » High HPLA results in dramatically decreased vitamin C concentration in the liver, adrenal glands and blood
- ◆ Treatment:
 - » Vitamin C—gram quantities (100 mg/kg body weight daily or to bowel tolerance)
 - » Other antioxidants (e.g. vitamin E, lipoic acid)
 - » CoQ10, 60–300 mg/d

8-Hydroxy-2'-deoxyguanosine (8-OHdG)

- ◆ Normal product of DNA oxidative damage and repair
- ◆ A repair product of the highly mutagenic oxidation of guanine in DNA or the cellular pool of GTP

IF 8-OHDG HIGH:

- ◆ Causes:
 - » Oxidative damage to DNA (oxidative stress)
 - » Chronic psychological stress
 - » Perceived overwork
 - » Smoking
 - » Hypercholesterolemia
 - » Chronic inflammation
 - » Chronic liver disease
 - » Low levels of antioxidants
 - » Hypertension
 - » Antioxidant deficiencies
 - » Atherosclerosis
 - » Diabetes
 - » Air pollution
 - » High polyunsaturated fat intake with inadequate vitamin E
 - » Irradiation
 - » Thermal injury
 - » Toxicity induced by certain metals, solvents, pesticides, and drugs
- ◆ Symptoms/Conditions
 - » Cancer
 - » Increased aging
 - » Chronic liver disease and hepatocarcinoma
 - » Atherosclerosis pathogenesis
 - » Tubulointerstitial injury in patients with diabetic nephropathy
- ◆ Treatment:
 - » Treat underlying cause of oxidative stress
 - » Vitamin E, 200–1600 mg/d (mixed tocopherols)

8-OHdG; 2-Methylhippurate

- » Vitamin A, 5,000–10,000 IU/d
- » Vitamin C, 1,000–5,000 mg/d
- » Glutathione, 300–1000 mg/d (questionable bioavailability with oral form) or NAC, 500–1000 mg/d
- » CoQ10, 60–300 mg/d
- » Selenium, 200 µg/d
- » Zinc, 15–65 mg/d
- » Manganese, 5–13 mg/d
- » Copper, 2–10 mg/d
- » Lipoic acid, 100–1,800 mg/d
- » Green tea (epigallochatechin sources)
- » Red wine, grapes, berries, colorful vegetables, etc (flavonoid sources)
- » If excessive, reduce alcohol consumption

Toxicants and Detoxification

2-Methylhippurate

- ◆ Specific product of detoxification of xylene from environmental exposure
- ◆ Hepatic Phase I oxidation of xylene to 2-methylbenzoate and Phase II conjugation with glycine
- ◆ Constituent of petroleum and coal tar

IF 2-METHYLHIPPURATE HIGH:

- ◆ Causes:
 - » Xylene exposure:
 - Cigarette smoke
 - New paint, spray paint

2-Methylhippurate; Orotate; Glucarate

- New carpet
- New cars
- Dry cleaning fluid
- Cleaning solvents
- Paint thinners
- Building products
- Fuel and exhaust fumes
- Industrial degreasers and solvents
- ◆ Symptoms/Conditions:
 - » Increased oxidative stress
- ◆ Treatment:
 - » Avoidance of xylene sources
 - » Glycine, 2–5 gm/d
 - » Pantothenic acid, 500 mg/d

Orotate

- ◆ Metabolic intermediate in pyrimidine synthesis
- ◆ Urea cycle overload causes increased orotate synthesis and spillage as a secondary ammonia detoxification pathway

IF OROTATE HIGH:

- ◆ See "Citrate, *cis*-Aconitate and Isocitrate" on page 100 regarding renal ammonia clearance status
- ◆ Causes:
 - » Orotate is very sensitive to anything that increases ammonia loading, including heavy protein intake or dysbiosis (intestinal bacterial ammonia production)
 - » Sensitive indicator of arginine deficiency

Glucarate

- ◆ Detoxification, liver P450 enzyme induction—Phase I detoxification
- ◆ Marker for glucuronidation—Phase II biotransformation
- ◆ Cytochrome P450 oxidation of glucose to glucuronic acid to glucarate



- » Magnesium deficiency
- » Long-term oral glutamine supplementation above 10 gm/day
- ◆ Symptoms/Conditions:
 - » Hyperammonemia (possibly mild, intermittent form)
 - » Poor growth
 - » Poor coordination
 - » Tachypnea
 - » Ataxia
 - » Lethargy
 - » Behavioral changes
 - » Intellectual impairment
 - » Seizures (may be due to NMDA excitotoxicity)
 - » Headaches
- ◆ Treatment:
 - » Decrease protein or amino acid intake
 - » Treat gut dysbiosis
 - » Arginine, 1–3 gm/day
 - » α -Ketoglutarate, 300 mg TID
 - » Aspartic Acid, 500 mg BID
 - » Magnesium, 300 mg/day
 - » Manganese, 40 mg/day

IF GLUCARATE HIGH:

- ◆ Causes:
 - » Intestinal dysbiosis (microbial toxins)
 - » Food components
 - » Exposure to:
 - Pesticides
 - Herbicides
 - Fungicides
 - Petrochemicals
 - Alcohol
 - » Drugs, including:
 - Salicylates
 - Acetaminophen
 - Morphine
 - Meprobamate
 - Benzodiazepines
 - Clofibrate acid
 - Naproxen
 - Digoxin
 - Phenylbutazone
 - Valproic acid
- ◆ Converts fat-soluble substances to water-soluble forms for elimination
- ◆ Indicator of overall hepatic detoxification function
- ◆ Part of many degradation pathways:
 - » Bile
 - » Drugs
 - » Food components
 - » Products of gut microbial metabolism
- ◆ This marker should not be used to assess the cancer-protective role of oral glucarate salts.
- » Polycyclic aromatic hydrocarbons:
 - Benzo(a)pyrene
 - Benzanthracene
 - Naphthalene
- » Various nitrosamines:
 - Cured meats
 - Tobacco products
 - Rubber products
 - Pesticides
- » Fungal toxins:
 - Aflatoxin
- » Steroid hormones:
 - Estrogen
 - Testosterone
- » Heterocyclic amines:
 - Well-done meats
 - Fried foods
 - Barbecued meats
- » Pharmaceutical drugs:
 - Aspirin
 - Lorazepam
 - Digoxin
 - Morphine
- » Vitamins:
 - Vitamin A
 - Vitamin D
 - Vitamin E
 - Vitamin K

Glucarate; AHB

- ◆ Symptoms/Conditions:
 - » Oxidative stress
 - » High levels of P450 activity
 - » Reduced capacity for Phase II conjugation reactions
 - » Fatigue
 - » Headaches
 - » Muscle pain
 - » Mood disorders
 - » Poor exercise tolerance
 - » Chronic fatigue syndrome
 - » Multiple chemical sensitivity
- ◆ Treatment:
 - » Glycine, 2–5 gm/day
 - » N-acetylcysteine, 500 mg BID
 - » General liver detoxification support
 - » Treat dysbiosis
 - » Toxicant (xenobiotic) avoidance and removal
 - » Reduce excessive vitamin use

 α -Hydroxybutyrate (AHB)

- ◆ Also known as 2-Oxobutyrate
- ◆ Marker of hepatic glutathione synthesis rate
- ◆ By-product of the final step in the hepatic pathway: methionine → homocysteine → cystathionine → cysteine
- ◆ Threonine catabolic product
- ◆ α -Hydroxybutyrate dehydrogenase (AHBD) enzyme very active in cardiac tissue
- ◆ AHBD activity assay used to estimate myocardial infarct size and reperfusion rate

IF AHB HIGH:

- ◆ Causes:
 - » Increased hepatic glutathione synthesis
 - » Oxidative stress causes reciprocal regulation so that homocysteine conversion to methionine is inhibited while conversion to cysteine (above) is stimulated
 - » Toxin-stimulated up-regulation of detoxification:
 - Glutathione conjugation (urinary mercaptans)
 - Intestinal microbial products
 - Xenobiotics
 - Pharmaceuticals—esp. acetaminophen
 - Sulfation
 - » Diseases that increase glutathione demand:
 - **Muscular dystrophy**
 - Macular degeneration
 - Diabetes
 - Emphysema (COPD)
 - Respiratory distress syndromes
 - Hepatic cirrhosis
 - Parkinson disease
 - Inflammatory Bowel Disease
 - Autism
 - Cachexia
 - Radiation poisoning
 - » Extreme endurance training



- ◆ Symptoms/Conditions:
 - » Any associated with the diseases listed above

- » Aging effects associated with chronic oxidative stress and toxin loading

Treatment:

- » IM or IV reduced glutathione—oral doses probably not absorbed
- » N-Acetylcysteine (NAC), 1500 mg/d
- » L-Methionine, 1000 mg/d (monitor homocysteine)
- » Taurine, 500 mg BID
- » Alpha-lipoic acid, 200 mg/d
- » Whey protein isolate, 0.8 g/kg/d

Pyroglutamate

- ◆ Product of the γ -glutamyl pathway required for renal amino acid recovery and small intestinal amino acid absorption (consume up to $\frac{1}{3}$ of circulating glutathione)
- ◆ Glutathione normally re-synthesized via ATP-consuming reactions
- ◆ The normally glutathione-conserving pathway results in glutathione wasting if the re-synthesis reactions are impeded by lack of ATP, toxicant effects, genetic polymorphisms of the cycle enzymes, or glutathione amino acid deficiencies

IF PYROGLUTAMATE HIGH:

- ◆ Causes:
 - » Glutathione wasting
 - » Inadequate methionine,

AHB; Pyroglutamate; Sulfate

cysteine and glycine for production of glutathione

» Acetaminophen toxicity

» **Mitochondrial inefficiency**

» See "Methylation Precursor Insufficiency" on page 195

» See "Glutathione Demand" on page 196

Symptoms/Conditions:

» See conditions and diseases associated with AHB elevation

Treatment:

» See glutathione repletion treatments under "AHB" on page 118

» Carnitine, CoQ10, or other nutrient factors needed for mitochondrial functional as indicated. See "mitochondrial function markers" starting on page 96

Sulfate

◆ Formed from cysteine in the hepatic PAPS (phosphoadenosylphosphosulfate) pathway

◆ Hepatic sulfation increases water solubility of hydrophobic compounds for excretion (Phase II liver detoxification) for biotransformation of:

- » Many drugs
- » Steroid hormones
- » Phenolic compounds
- » Other compounds

◆ See "Glutathione Demand" on

Sulfate; Intestinal Dysbiosis Markers

page 196 for relationships to other glutathione-related markers.

IF SULFATE HIGH:

- ◆ Causes:
 - » Early stages of:
 - Increased flow of sulfur compounds into hepatic glutathione synthesis
 - Increased sulfate production for specific detoxification demanding sulfation
 - » High intake of dietary sulfate
 - » Exposure to sulfate salts (e.g. glucosamine sulfate)
- ◆ Symptoms/Conditions:
 - » See "AHB" on page 118
- ◆ Treatment:
 - » If glutathione (or sulfation) demand increase is confirmed see "AHB" on page 118
 - » If glutathione demand is ruled out decrease exposure to inorganic sulfate

IF SULFATE LOW:

- ◆ Causes:
 - » Chronic high glutathione demand resulting in glutathione depletion
 - » Long term specific detoxification requiring sulfation
- ◆ Symptoms/Conditions:
 - » See "AHB" on page 118
- ◆ Treatment:
 - » See "AHB" on page 118 for glutathione repletion (treatments for low levels)
 - » Short term sulfate repletion

may be achieved by dietary inorganic sulfate sources such as glucosamine sulfate, 1500 mg/d

Intestinal Dysbiosis Markers

Definition: Abnormal overgrowth of unfavorable microflora in the small and large intestines.

- ◆ Flora may be different in the small and large intestines—different microenvironments and levels of competition
- ◆ Stool samples may not pick up on what is growing in the small intestines
- ◆ Microflora create distinct toxins and metabolic products that can be measured in the urine
- ◆ Often a chronic condition
- ◆ Toxic products can affect multiple organs
- ◆ The GI tract can become "leaky" due to inflammation and gut mucosal damage—intestinal hyperpermeability
- ◆ Inflammatory mediators from intestines can impact or initiate systemic inflammatory processes.
- ◆ Urinary markers have high predictive ability for dysbiosis
- ◆ Amino acids and sugars that are ingested can be used by the microflora for growth
- ◆ Can result in maldigestion and malabsorption of nutrients

Causes of General Dysbiosis

- ◆ Low levels of hydrochloric acid in the stomach, caused by:
 - » Widespread use of antacids
 - » Prescription drugs that block stomach acid production
 - » Aging
 - » Genetic causes—can be a common finding in children and adults
- ◆ Low levels of HCl can have the same symptoms as high levels
- ◆ Repeated use of antibiotics
- ◆ Carbohydrate malabsorption
- ◆ Food allergies and sensitivities
- ◆ Use of NSAIDs
- ◆ Alcohol abuse
- ◆ Corticosteroid use
- ◆ Pancreatic insufficiency
- ◆ Excessive stress
- ◆ Consumption of infected foods
- ◆ Gastrointestinal surgeries
- ◆ Immune deficiencies (HIV and others)
- ◆ Nutritional insufficiencies
- ◆ Improper fasting or dieting

Symptoms/Conditions:

- ◆ Small intestinal bacterial overgrowth
- ◆ Diarrhea
- ◆ Constipation
- ◆ Steatorrhea (fatty stools)
- ◆ Abdominal distention
- ◆ Abdominal pain
- ◆ Irritable Bowel Syndrome (IBS)

Causes of General Dysbiosis; Symptoms/Conditions

- ◆ Inflammatory Bowel Disease (IBD)
- ◆ Celiac disease
- ◆ Gastroesophageal reflux disorder (GERD)
- ◆ Pancreatic insufficiency leading to malabsorption
- ◆ Impaired immune defenses
- ◆ Hepatic damage
- ◆ Food sensitivities and intolerance
- ◆ Skin rashes
- ◆ Poor exercise tolerance
- ◆ Shortness of breath
- ◆ Cognitive deficits
- ◆ Generalized symptoms related to deficiencies in vitamins, minerals, amino acids, fatty acids, etc.
- ◆ Headaches
- ◆ Arthralgias
- ◆ Myalgias
- ◆ Fevers of unknown origin
- ◆ Allergies
- ◆ Fibromyalgia
- ◆ Fatigue
- ◆ Chronic fatigue syndrome
- ◆ Autoimmune disorders
- ◆ Recurrent sinusitis
- ◆ Recurrent vaginal yeast infections
- ◆ Recurrent bladder infections
- ◆ Infectious enterocolitis
- ◆ Cystic fibrosis
- ◆ Acne
- ◆ Eczema
- ◆ Psoriasis
- ◆ Urticaria
- ◆ Dermatitis herpetiformis

Symptoms/Conditions; Antibiotic Treatments

- ◆ Autism
- ◆ Childhood hyperactivity
- ◆ Spondyloarthropathies
- ◆ HIV infection exacerbations
- ◆ Neoplasia
- ◆ Environmental illness

Dietary Treatments

- ◆ Improve mealtime habits to provide time for digestive processes (chew food, "rest and digest")
- ◆ HCl and digestive enzyme support as needed
- ◆ Fasting:
 - » Starves out the harmful bacteria
 - » Bacteria need amino acids and carbohydrates to survive
- ◆ Vegetable broth-based diets
- ◆ Elemental diets
- ◆ General carbohydrate restriction
- ◆ Specific carbohydrate restricted (maltose sources)
- ◆ High fiber diet
- ◆ Effective prebiotic (growth substrate for favorable organisms)
- ◆ Remove mucosal irritants such as allergenic or IgG positive foods
- ◆ Stop alcohol use
- ◆ Stop NSAID use

Antibiotic Treatments

- ◆ In order of general effectiveness for most organisms:
- ◆ Small intestine bacterial overgrowth: Xifaxamin (Rifaximin) non-absorbed antibiotic

- ◆ For Microaerophilic Bacteria:
 - » Medications:
 - Trimethoprim-Sulfamethoxazol (Bactrim)—significant side effects
 - Amoxicillin-Clavulanic Acid (Augmentin)—frequent digestive intolerance
 - Cephalexin (Keflex)
 - Amoxicillin
 - Erythromycin
 - » Herbs:
 - Goldenseal and other berberine-containing herbs
 - Citrus seed extract
 - Garlic
 - Uva ursi
 - Aloe vera
 - Glycyrrhiza
 - Olive leaf extract
- ◆ For Clostridia and other anaerobic spp:
 - » Medications:
 - Metronidazole (Flagyl)
 - Vancomycin (Vancocin)
 - Amoxicillin-Clavulanic Acid (Augmentin)—frequent digestive intolerance
 - Amoxicillin
 - Erythromycin
 - Trimethoprim-Sulfamethoxazol (Bactrim)—significant side effects

**Antibiotic Treatments; Antifungal Treatments; Probiotics; Prebiotics; Mucosal Regeneration**

- » Herbs:
 - Goldenseal and other berberine-containing herbs
 - Citrus seed extract
 - Garlic
 - Uva ursi
 - Glycyrrhiza
 - Olive leaf extract
 - Oil of oregano
 - Undecylenic acid
- ◆ For D-lactate producing *Lactobacillus* species:
 - » Stop or decrease *Lactobacillus* probiotic use
 - » Medications:
 - Amoxicillin-Clavulanic Acid (Augmentin)—frequent digestive intolerance
 - Amoxicillin
 - Erythromycin

Antifungal Treatments

- ◆ May need a month or more of antifungal therapy
- » Medications:
 - Nystatin
 - Fluconazole (Diflucan)
 - Itraconazole (Sporanox)
 - Ketoconazole
- ◆ Check liver function regularly while on therapy with Ketoconazole, Diflucan or Sporanox
- » Herbs:
 - Tannins, Caprylic acid, Undecylenic acid

Mucosal Regeneration

- ◆ L-Glutamine, Aloe Vera
- ◆ Pantothenic acid

Mucosal Regeneration; Benzoate; Hippurate

- ◆ Deglycyrrhizinated licorice (DGL)
- ◆ Slippery elm
- ◆ Oligopeptide preparations
- ◆ Essential fatty acids
- ◆ Zinc
- ◆ Vitamin C

Further Treatment and Testing Options

- ◆ See “Gastrointestinal Function” on page 131

Markers of Intestinal Dysbiosis—Bacterial**Benzoate**

- ◆ Hepatic Phase II conjugation
- ◆ Bacterial deamination of the amino acid phenylalanine produces benzoate.

IF BENZOATE HIGH:

- ◆ Causes:
 - » Inadequate conversion to hippurate in the liver
 - » Glycine and pantothenic acid are the rate-limiting factors
 - » Should not be high if hepatic glycine conjugation is efficient because benzoate is rapidly converted to hippurate
 - » Intestinal bacterial overgrowth
 - » Confirmed by simultaneous elevation of other bacterial markers

Hippurate

- ◆ Hepatic Phase II glycine conjugation of benzoate
- ◆ Commonly one of the most abundant compounds in normal urine

IF HIPPURATE HIGH:

- ◆ Causes:
 - » When no other bacterial markers are high, only heavy dietary intake of benzoate is indicated (no clinical consequence)



- » Benzoate production from intestinal bacterial overgrowth
- » Confirm by examining other bacterial markers
- » Excess intake of exogenous sodium benzoate (preserved, packaged foods or cranberries)
- » Malabsorption of phenylalanine due to low HCl in stomach
- » Toluene exposure
- ◆ Symptoms/Conditions:
 - » See “Intestinal Dysbiosis Markers” on page 120
- ◆ Treatment:
 - » Glycine, 1000 mg TID
 - » Vitamin B₅ (pantothenic acid), 500 mg/d
 - » See “Intestinal Dysbiosis Markers” on page 120
 - » Reduce toluene exposure

Phenylacetate (PAA)

- ◆ Intestinal bacterial action on polyphenols, tyrosine or phenylalanine results in PAA
- ◆ Should only be present in background concentrations in healthy subjects
- ◆ Is trace product of endogenous phenylalanine, may accumulate in phenylketonuria (PKU)
- ◆ May accumulate in schizophrenia
- ◆ Elimination may be reduced in depression
- ◆ May modulate estrogen-mediated cancers

IF PHENYLACETATE HIGH:

- ◆ Causes:
 - » Intestinal bacterial overgrowth
 - » Polyphenol intake in the presence of PAA-producing bacteria
 - » Malabsorption of phenylalanine due to low HCl in stomach
 - » PKU
- ◆ Symptoms/Conditions:
 - » See “Intestinal Dysbiosis Markers” on page 120
 - » Rule out PKU
- ◆ Treatment:
 - » See “Intestinal Dysbiosis Markers” on page 120
 - » Decrease sugars and amino acids

Phenylpropionate (PPA)

- ◆ Intestinal bacterial (including *Clostridia* sp.) action on polyphenols and phenylalanine results in phenylpropionate
- ◆ Is metabolized by mitochondrial medium-chain acyl-CoA-dehydrogenase (MCAD), and is therefore not generally present in urine in significant amounts
- ◆ High urinary phenylpropionate suggests MCAD deficiency

IF PHENYLPROPIONATE HIGH:

- ◆ Causes:
 - » MCAD deficiency
 - » Intestinal bacterial overgrowth
 - » Polyphenol intake in the presence of PPA-producing bacteria

PPA; p-Hydroxybenzoate; HPA

Malabsorption of phenylalanine due to low HCl in stomach

◆ Symptoms/Conditions:

- » See "Intestinal Dysbiosis Markers" on page 120

◆ Treatment:

- » If very elevated, evaluate MCAD deficiency (see Fatty Acids)
- » See "Intestinal Dysbiosis Markers" on page 120

p-Hydroxybenzoate

◆ Derived from tyrosine and various polyphenols

◆ Not a significant product of normal human metabolism

IF P-HYDROXYBENZOATE HIGH:

◆ Causes:

- » Intestinal bacterial overgrowth
- » *Escherichia coli* (creates p-hydroxybenzoate from glucose)
- » Other bacteria
- » Malabsorption of tyrosine due to low HCl in stomach

◆ Symptoms/Conditions:

- » See "Intestinal Dysbiosis Markers" on page 120

◆ Treatment:

- » See "Intestinal Dysbiosis Markers" on page 120
- » Pre- and probiotics
- » Antibiotics more effective for *E. coli*:

 - Amoxicillin-Clavulanic Acid (frequent digestive intolerance)

- Cephalothin (Keflex)
- Amoxicillin
- » Decrease sugars and amino acids

p-Hydroxyphenylacetate (HPA)

- ◆ Derived from tyrosine
- ◆ Not a product of normal human metabolism

IF HPA HIGH:

◆ Causes:

- » Direct intestinal pathology or digestive organ failure
- » Malabsorption of tyrosine due to low HCl in stomach
- » Dysbiosis
 - *Proteus vulgaris*
 - *Clostridium difficile*
 - *Giardia lamblia* (protozoan)
 - *Anaerobic bacteria*
- » Jejunal web
- » Ileal resection with blind loop
- » Lactose intolerance
- » Low immunoglobulin
- » Ileo-colic intussusception
- » Use of antibiotics that act primarily against aerobic bacteria can encourage growth of protozoa and anaerobic bacteria, resulting in increased p-Hydroxyphenylacetate

◆ Symptoms/Conditions:

- » See "Intestinal Dysbiosis Markers" on page 120

◆ Treatment:

- » See "Intestinal Dysbiosis Markers" on page 120



» Antibiotics:

- Metronidazole if *Clostridia* or *Giardia* identified
- Trimethoprim-sulfamethoxazole if *Proteus* identified
- Erythromycin may not be as effective
- » Vitamin C, 1 gm BID
- » Decrease sugars and amino acids

Indican (indoxy1 sulfate)

- ◆ Derived from tryptophan
- ◆ Bacteria produce indole from tryptophan, which undergoes phase I and II biotransformation in the liver, first to indoxy1 and second to indoxy1 sulfate.
- ◆ Present in low levels in healthy subjects

IF INDICAN HIGH:

◆ Causes:

- » Upper bowel intestinal bacterial overgrowth
- » Celiac disease
- » Jejuno-ileal bypass surgery
- » Impaired protein digestion
- » Enteric protein loss
- » Aging – due to impaired protein absorption
- » In patients with steatorrhea (fatty stools) given pancreatic enzymes:
 - Those with pancreatic insufficiency will have increased indican levels
 - Those with biliary stasis or

- ◆ Symptoms/Conditions:
- » See "Intestinal Dysbiosis Markers" on page 120
 - » In patients with cirrhosis of the liver, tryptophan loading can cause neuropsychiatric symptoms due to intestinal bacterial production of tryptophan metabolites – antibiotics can reduce these symptoms
- ◆ Treatment:
- » See "Intestinal Dysbiosis Markers" on page 120
 - » Pre- and probiotics—*Lactobacillus* strains other than acidophilus
 - *Lactobacillus Rhamnosus GG*
 - *L. salivarius*
 - *L. plantarum*
 - *L. casei*
 - » Antibiotics—oral, unabsorbed antibiotics
 - » Decrease sugars and amino acids

Tricarballylate

- ◆ Tricarballylate has extremely high affinity for magnesium, preventing its absorption
- ◆ Ruminant animal herds can develop severe magnesium deficiency from overgrowth of specific strains of ruminal bacteria that produce tricarballylate
- ◆ The disease is caused by overfeeding high-carbohydrate herbage

normal subjects will have normal indican levels

Tricarballylate; D-Lactate**IF TRICARBALLYLATE HIGH:**

- ◆ Causes:
 - » Intestinal bacterial overgrowth
 - » Associated with high dietary carbohydrate
 - » Probably due to microaerophilic bacteria
- ◆ Symptoms/Conditions:
 - » See "Intestinal Dysbiosis Markers" on page 120
 - » Elements tightly bound by tricarballylate causing decreased intestinal absorption:
 - Magnesium
 - Calcium
 - Zinc
- ◆ Treatment:
 - » Magnesium, 400 mg/d
 - » Calcium, 800 mg/d
 - » Zinc, 40 mg/d
 - » See "Intestinal Dysbiosis Markers" on page 120
 - » Restricted carbohydrate diet

D-Lactate

- ◆ D-Lactate is neurotoxic at elevated concentrations
- ◆ *L. acidophilus* specifically grows well in carbohydrate-rich, acidic conditions induced by carbohydrate malabsorption, and can tolerate high levels of D-lactate, whereas other bacteria may not
- ◆ Intestinal resection and stomach stapling procedures induce carbohydrate malabsorption

- ◆ 80% of post-intestinal resection patients develop D-lactic acidemia-induced encephalopathy
- ◆ Several genus and species other than *L. acidophilus* produce D-lactate

IF D-LACTATE HIGH:

- ◆ Causes:
 - » Intestinal bacterial overgrowth
 - *Lactobacillus acidophilus*
 - *Lactobacillus plantarum*
 - *Lactobacillus delbrueckii*
 - » If multiple bacterial markers are high, suspect general bacterial overgrowth, not specific to *L. acidophilus*
 - » If no other bacterial markers are high, suspect *L. acidophilus* overgrowth due to:
 - Intestinal surgery
 - Jejunoileostomy patients
 - High dietary carbohydrate
 - Antibiotic use
 - Carbohydrate malabsorption
 - May elevate in celiac disease and ulcerative colitis
- ◆ Symptoms/Conditions:
 - » See "Intestinal Dysbiosis Markers" on page 120
 - » D-Lactic acidosis—sugar is turned into acid in the GI tract
 - » Encephalopathy
- ◆ Treatment:
 - » See "Intestinal Dysbiosis Markers" on page 120
 - » Antibiotics
 - » Pre- and probiotics



- Avoid all *Lactobacillus* probiotics if specific *L. acidophilus* overgrowth is indicated
- Other probiotic genus may be used
- » Decrease carbohydrates in diet
- » Stop alcohol
- » Decrease sugars and amino acids
- » See "Intestinal Dysbiosis due to Carbohydrate Malabsorption" on page 198

3, 4-Dihydroxyphenylpropionate (DHPP)

- ◆ Intestinal bacterial overgrowth

IF 3, 4-DHPP HIGH:

- ◆ Causes:
 - » *Clostridium* overgrowth (primarily *Clostridium coccoides*)
 - » Other organisms in lesser degree
- ◆ Symptoms/Conditions:
 - » See "Intestinal Dysbiosis Markers" on page 120
 - » Test for *Clostridium difficile* if symptoms warrant, including:
 - » Severe diarrhea
 - » Abdominal tenderness (rebound tenderness)
 - » Malaise
 - » Fever
 - » Dehydration
- ◆ Treatments:
 - » See "Intestinal Dysbiosis Markers" on page 120

D-Lactate; DHPP; D-Arabinitol

- » Pre- and probiotics:
 - *Saccharomyces boulardii*
 - *Lactobacillus rhamnosus*
- » Antibiotics:
 - Metronidazole (Flagyl)
 - Vancomycin (Vancocin)
- » Decrease sugars and amino acids

Marker of Intestinal Dysbiosis—Yeast/Fungal

- ◆ Candida infections are of widest clinical concern due to:
 - » Transmission by direct invasion of the GI and GU tracts
 - » Ability to rapidly overwhelm immune responses in hospitalized, immunocompromised patients, producing disseminated candidiasis
 - » Grow best on carbohydrate substrates
- ◆ Some degree of yeast growth is common in normal GI tract

D-Arabinitol

- ◆ Intestinal yeast overgrowth
- ◆ A metabolite of most pathogenic *Candida* species
- ◆ One of the most sensitive markers for invasive candidiasis
- ◆ Better indicator than blood cultures

■ Arabinitol

- ◆ Treatment with antifungals tends to normalize levels

IF D-ARABINITOL HIGH:

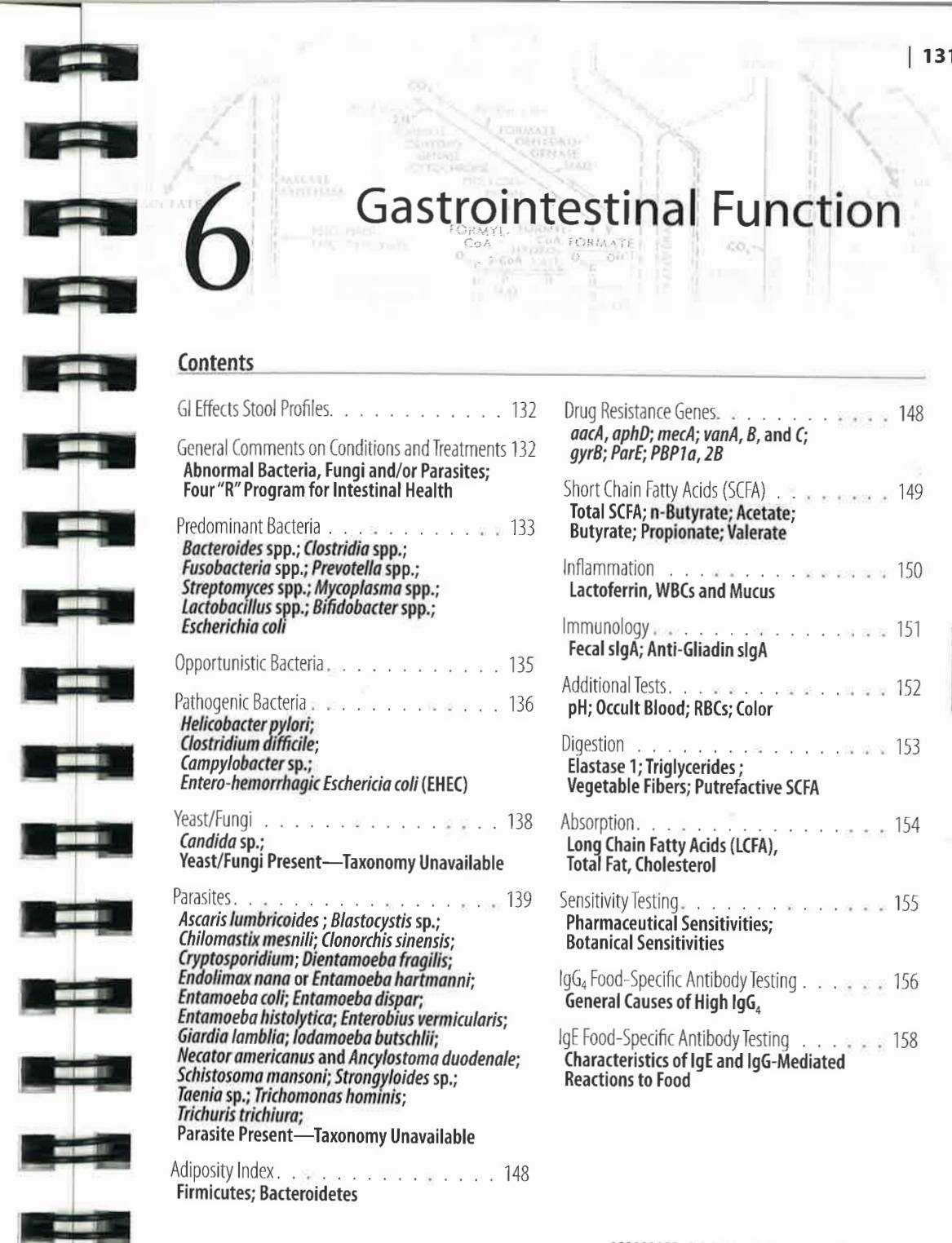
- ◆ Causes:
 - » Specific marker for *Candida* sp.
(most commonly *Candida albicans*)
 - » Signals invasive candidiasis in immunocompromised patients
 - ◆ Symptoms/Conditions:
 - » Chronic vaginal yeast infections
 - » Intolerance to carbohydrates and fiber in diet
 - » Chronic sinus infections
 - » Fatigue
 - » Diarrhea
 - » GI hypersensitivity

NOTES

- » Autism
 - » Mucocutaneous lesions
 - » Onychomycosis
 - » Fungal sinusitis

◆ Treatments:

 - » See treatments for fungal infections above
 - » Pre- and probiotics:
 - *Saccharomyces boulardii*
 - General probiotics
 - » Antifungals are usually necessary
 - » Stop alcohol
 - » Decrease sugars
 - » Avoid antibiotics



Gastrointestinal Function

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<i>Schistosoma mansoni</i> ; <i>Strongyloides</i> sp.;	
<i>Taenia</i> sp.; <i>Trichomonas hominis</i> ;	
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Abnormal Bacteria, Fungi and/or Parasites

GI Effects Stool Profiles

Proper gastrointestinal (GI) function is critical to adequate nutritional status and can impact all aspects of body function. The microbial population is measured using DNA analysis (PCR amplification) of the genetic material of each organism, allowing for sensitive detection, and the ability to detect and identify organisms that cannot be cultured or are extremely difficult to grow under laboratory conditions.

Results are reported as Colony Forming Units per gram of feces (CFU/gram). One CFU is equivalent to one microorganism.

Results are expressed in standard scientific notation: For example, *Bacteroides* spp. may be reported as 2.57 E7, or 2.5×10^7 , or 25,000,000 CFU/ gram, which is read as 25 million CFU per gram of feces.

The cutoff for clinical significance for predominant bacteria has been set at 1E7 (1×10^7), for opportunistic bacteria 1E5 (1×10^5), and for pathogens at 1E3 (1×10^3).

Stool profiles include sensitivity testing for opportunistic and fungal microbes. Pharmaceutical sensitivities are based on moderate dosing. Botanical sensitivities are done using concentrated active constituents, not whole plants. Depending on the degree of infection, when using botanicals, high-dose standardized combination products appear most efficacious.

For additional information on gastrointestinal microbial imbalances and treatments, refer to "Intestinal Dysbiosis Markers" on page 120.

For additional information on intestinal hyperpermeability ("leaky gut") and other antibody testing, refer to "IgG4 Food-Specific Antibody Testing" on page 156.

General Comments on Conditions and Treatments

Abnormal Bacteria, Fungi and/or Parasites

- ◆ Suspect:
 - » Inadequate physical and immune barrier functions
 - » Food sensitivities/leaky gut syndrome (elevated IgG)
 - » Low intestinal secretory IgA
 - » Gluten intolerance/celiac disease
 - » Inflammatory bowel disease
- ◆ Medication history
 - » Antibiotics
 - » NSAIDs
 - » Antacids, proton pump inhibitors, and acid-blockers
- ◆ Decreased colonic short-chain fatty acids



Bacteroides, Clostridia, Prevotella, Fusobacteria, Streptomyces, Mycoplasma & Lactobacillus spp.

bacteria, supplement with prebiotics such as inulin, xylooligosaccharides, larch arabinogalactans, beta glucan, and fiber.

Repair mucosal lining by giving support to healthy intestinal mucosal cells, goblet cells, and to the immune system. Consider L-glutamine, essential fatty acids, zinc, pantothenic acid and vitamin C.

Predominant Bacteria

- ◆ Produce short chain fatty acids (e.g. butyric acid) from undigested foodstuff
- ◆ Cell components act as immune system signals
- ◆ Modulate host caloric yield from foodstuff
- ◆ Provide colonization resistance against opportunistic and pathogenic organisms
- ◆ Produce vitamins (e.g. biotin, vitamin K)
- ◆ *Bacteroides* spp. and *Bifidobacter* spp. usually most abundant in healthy individuals
- ◆ Genus-level population counts are reported for:

- » Obligate anaerobes:
 - *Bacteroides* spp.
 - *Clostridia* spp.
 - *Prevotella* spp.
 - *Fusobacteria* spp.
 - *Streptomyces* spp.
 - *Mycoplasma* spp.
- » Facultative anaerobes:
 - *Lactobacillus* spp.

Treatment Using Four "R" Program for Intestinal Health

Remove offending foods, medications, and gluten (if sensitive) and reduce poor quality fats, refined carbohydrates, sugars, and fermented foods (if yeast is present). Consider antimicrobial, antifungal, and/or antiparasitic therapies in the case of opportunistic/pathogenic bacterial, yeast, and/or parasite overgrowth (see below for specific recommendations).

Replace what is needed for normal digestion and absorption such as betaine HCl, pancreatic enzymes, herbs that aid in digestion such as deglycrrhizinated licorice and marshmallow root, dietary fiber, and water.

Reinoculate with favorable microbes (probiotics such as *Lactobacillus* sp., *Bifidobacter* sp., and *Saccharomyces boulardii*). To enhance the growth of the favorable

Bifidobacter spp.; Escherichia coli

- *Bifidobacter* spp.
- » Obligate aerobes
- *Escherichia coli*

IF PREDOMINANT BACTERIA LOW

- ◆ Causes:
 - » Antibiotics
 - » Diarrhea
 - » Imbalanced diet
- ◆ Symptoms/Conditions:
 - » Irritable bowel syndrome
 - » Food intolerance
 - » Increased likelihood of acquiring opportunistic and pathogenic organisms
- ◆ Treatment:
 - » Probiotics 10–450 billion CFUs 1–5x/day depending on condition
 - Modulate *Lactobacillus* or *Bifidobacter* dosage according to need based on GI Effects results
 - » Prebiotics as directed, including: psyllium, oat bran, oligofructose, xylooligosaccharide, inulin, beta-glucan, and/or arabinogalactan
 - » Increase intake of fresh vegetables and fibers

IF PREDOMINANT BACTERIA DISPROPORTIONATELY HIGH

Healthy individuals consuming balanced diets with good levels of soluble and insoluble fiber generally have beneficial bacterial populations that are uniformly in the upper quintile ranges relative to the general population. Abnormal states are when only a few genera are very abundant, while others are in the first quintile.

- ◆ Causes:
 - » Constipation
 - » Dysbiosis
 - » Imbalanced diet
 - » Maldigestion/malabsorption
 - » Food intolerance
- ◆ Symptoms/Conditions:
 - » Gastrointestinal:
 - Constipation
 - Cramping
 - Bloating
 - Flatulence
 - » Blood infections of *Mycoplasma* sp. have been linked to chronic fatigue syndrome and fibromyalgia
 - » Severe overgrowth of *Lactobacillus* sp. with displacement of other genera produces D-lactic acidemia (commonly found in patients with short bowel syndrome) See "D-Lactate" on page 128 for further discussion of this situation.
 - » Overgrowth of certain *Clostridia* sp. clusters may play a role in certain cases of autism
 - » If the *Prevotella* spp. result is in the 5th quintile, suspect possible oral/throat infection
 - » Reactive arthritis has been associated with overgrowth of predominant bacterial genus *Prevotella* and *E. coli*
- ◆ Treatment:
 - » Balance flora using appropriate probiotics or antibiotics

***Klebsiella pneumoniae, Morganella morganii, Staphylococcus aureus, and Yersinia enterolytica***

- » For high *Lactobacillus* spp. results:
 - Restrict dietary carbohydrates (check urinary D-lactate see "D-Lactate" on page 128), and encourage intake of fresh vegetables. High fiber foods might exacerbate patient symptoms. Short courses of antibiotics against *Lactobacillus* sp. may be necessary if D-lactate encephalopathy is present.
- » For high *Clostridia* spp. results:
 - Supplement with *Saccharomyces boulardii* probiotic
 - » Consider anti-microbial (pharmaceutical and/or botanical) agents
 - » Address other GI Effects abnormalities
 - » Evaluate food sensitivities

IF OPPORTUNISTIC BACTERIA PRESENT

- ◆ Causes:
 - » Low predominant bacteria (see above)
 - » Pathogen or parasite infection
 - » Poor diet
 - » Antibiotic use
 - » Lowered gut immunity
- ◆ Symptoms/Conditions:
 - » Asymptomatic
 - » Diarrhea
 - » Constipation
 - » Bloating/gas
 - » Myalgia
 - » Fatigue
 - » Headaches
 - » Autoimmunity:
 - Reactive arthritis: *Salmonella* sp.; *Yersinia* sp.; *Klebsiella* sp.
 - General molecular mimicry mechanism: *Morganella*, *Proteus* and possibly *Pseudomonas*
 - Hashimoto thyroiditis and Grave disease: *Yersinia enterocolitica*
- ◆ Treatment:
 - » Probiotics 10–450 billion CFUs 1–5x/day depending on condition
 - » Modulate lactobacillus or bifidobacter dosage according to need based on GI Effects results
 - » Prebiotics as directed, including: psyllium, oat bran, oligofructose, xylooligosaccharide, inulin, beta-glucan, and/or arabinogalactan

Helicobacter pylori; Clostridium difficile

- » Do not use fructooligosaccharide (FOS) if *Klebsiella* sp. or *Citrobacter* sp. are present
- » Increase intake of fresh vegetables and fibers
- » Identify and treat food sensitivities
- » May need to use pharmaceutical or botanical anti-microbial agent(s)—refer to sensitivity testing on stool profile.
- » Visit www.emedicine.com to search for the pathology of the individual opportunistic bacteria and treatment options.
- » Address other GI Effects abnormalities

Pathogenic Bacteria

Helicobacter pylori

Helicobacter pylori (*H. pylori*) bacterium causes peptic ulcer disease and has been associated with increased gastric cancer risk. *H. pylori* is a Type I carcinogen. It is estimated that 50% of the world's population is infected with *H. pylori*.

- ◆ Causes:
 - » Oral to oral
 - » Fecal to oral
 - » Family inter-infection is common route of transmission
- ◆ Symptoms/Conditions:
 - » Asymptomatic
 - » Peptic ulcer disease
 - » Acute gastritis with abdominal

Clostridium difficile

- ◆ Causes:
 - » Suspect recent antibiotic use, especially the cephalosporins, ampicillin/amoxicillin, and clindamycin
 - » Nosocomial
 - » Advanced age
- » pain, nausea and vomiting, usually within two weeks of infection
- » Recurrent abdominal symptoms (non-ulcer dyspepsia)
- » Depletes mucosal glutathione
- » May induce mucosal atrophy and metaplastic changes
- » Stimulates autoantibodies to parietal cells

◆ Treatment:

- » Standard treatment for *H. pylori* consists of a combination of 3 or 4 drugs, including antibiotics and proton pump inhibitors for 7 to 14 days. Current recommendations can be found at www.acg.gi.org. Eradication does not generally exceed 80%.
- » Supplementation with lactoferrin (200 mg/d), prebiotics, and vitamin C (up to 5 grams), may improve treatment efficacy, while reducing adverse reactions.
- » Botanicals
- » Mastic (*Pistacia lentiscus*)
- » DGL (deglycyrrhizinated licorice)
- » Zinc-carnosine (PepZin-GI)
- » Vitamin C

***Clostridium difficile; Campylobacter sp.; Enterohemorrhagic Escherichia coli (EHEC)***

- » Fecal-oral colonization
- ◆ Symptoms/Conditions:
 - » Asymptomatic carrier
 - » Cramping, lower abdominal pain, fever and diarrhea usually decreases once antibiotics are stopped, though can continue for up to 4 weeks
 - » Pseudomembranous colitis
- ◆ Treatment:
 - » Do not treat if patient is asymptomatic
 - » Stop use of causative antibiotics
 - » In severe cases:
 - Vancomycin, 125 mg PO QID for 10–14d; Metronidazole, 500 mg PO TID, or 250 mg PO QID for 10–14d
 - » Herbal antibiotics such as berberine or oregano oil
 - » Replete beneficial microorganisms, esp. *S. boulardii* and *Bifidobacteria*

Campylobacter sp.

- ◆ Causes:
 - » Contaminated animal food sources (poultry and red meat)
 - » Dogs (infected by rodents) may infect humans
 - » Hydrochloric acid insufficiency
 - » Secretory IgA deficiency
- ◆ Symptoms/Conditions:
 - » Abrupt influenza-like symptoms are common, including headache and malaise

- » GI symptoms include abdominal pain, nausea and vomiting; diarrhea
- » Associated with reactive arthritis
- ◆ Treatment:
 - » Generally self-limiting infection not requiring treatment
 - » Support rehydration if diarrhea is present
 - » If infection persists treat with erythromycin: 500 mg erythromycin stearate, base, or estolate salts (or 400 mg ethylsuccinate) every 6h

Enterohemorrhagic Escherichia coli (EHEC)

Also referred to as Shiga toxin-producing *E. coli* (STEC).

- ◆ Causes:
 - » Contaminated food (undercooked meat, raw milk, unpasteurized apple juice, water, and lettuce)
- ◆ Symptoms:
 - » Severe abdominal cramping, watery or bloody diarrhea, and vomiting
 - » Hemorrhagic colitis (up to 10% of cases)
 - » Hemolytic uremic syndrome (up to 10% of cases)
- ◆ Treatment:
 - » Generally self-limiting
 - » Rehydrate if diarrhea (IV may be necessary)
 - » Antibiotic therapy can

Candida sp.

- » predispose to development of hemolytic uremia
- » Streptomycin, sulfonamides, and tetracycline have demonstrated resistance to many EHEC strains
- » Probiotic/prebiotic therapy
 - *L. acidophilus*
 - *Clostridium butyricum*

Yeast/Fungi

Commonly identified genera: *Candida*, *Rhodotorula*, *Geotrichum*, *Saccharomyces* and *Trichosporon*. *Candida* sp. are detailed below. If other commonly identified species are reported, consider patient symptoms and degree of infection to decide if anti-fungal therapy is warranted. *Saccharomyces* spp. may be reported if patient is supplementing with *S. boulardii*. Restore proper predominant microflora populations and address all other imbalances found on the GI Effects test report. May need to use pharmaceutical or botanical anti-microbial agent(s)—refer to sensitivity testing on stool profile.

***Candida* sp.**

Candida are normal inhabitants of the gastrointestinal tract and are present in 40–65% of the human population with no harmful effects. However, in conditions of overgrowth, various *Candida* sp. are most commonly found as the causal agents of opportunistic fungal infections. See “D-Arabinitol” on page 129.

◆ Causes:

- » Antibiotic use—main cause

- » High intake of sugar, milk, other dairy products and foods containing a high concentration of yeast or mold
- » Hypochlorhydria
- » Food allergies
- » Depressed immune system
- » Altered bowel flora
- ◆ Symptoms/Conditions:
 - » Gastric pain
 - » Nausea and vomiting
 - » Gas and bloating
 - » Altered fecal transit time
 - » Intestinal permeability
 - » Imbalance in gut microflora
 - » Opportunistic bacterial infection
 - » Esophagus is most common site of infection, followed by stomach then small and large bowel
 - » 15% develop systemic candidiasis
 - » May be associated with autistic spectrum disorders
- ◆ Extra-Intestinal Symptoms/Conditions:
 - » Chronic fatigue
 - » Vaginal yeast infection
 - » Frequent bladder infections
 - » Depression
 - » Irritability
 - » Chemical sensitivity
 - » Eczema, psoriasis
- ◆ Treatment:
 - » Reduce intake of refined carbohydrates and sugars
 - » May need to use pharmaceutical or botanical anti-fungal

*Candida* sp.; *Ascaris lumbricoides*

- » Address other abnormal results on the GI Effects test first, with the expectation that rare yeast/fungi will be crowded out when healthy conditions are restored

Parasites

Pharmaceutical recommendations for each parasite are from the 2007 publication in The Medical Letter, “Drugs for Parasitic Infections.” Parasites are listed in alphabetical order.

◆ Botanical Treatment:

- » Common botanical antiparasitic herbs used to treat each parasite listed include black walnut, quassia, garlic, berberine, grapefruit seed extract, oil of oregano, barberry, and artemesia. When treating parasites with botanicals, it is recommended to use a blend of several, to lengthen treatment duration, and to rotate antiparasitic agents. Retesting for the organism will help ensure treatment efficacy.
- » Also, see “Botanical Sensitivities” on page 155

Ascaris lumbricoides

Intestinal nematode infections are a fairly common finding worldwide, with *Ascaris lumbricoides* (“roundworm”) being the most prevalent. The other common nematodes, *Enterobium vermicularis* (“pinworm”) and *Trichuris trichiura* (“whipworm”) are discussed below. *Ascaris lumbricoides* is the largest nematode

Ascaris lumbricoides; Blastocystis sp.; Chilomastix mesnili

associated with human parasitosis, measuring up to 35 cm in length.

- ◆ Transmission:
 - » Fecal-oral
 - » Contaminated food and water
 - » Eggs penetrate intestinal walls, hatched larvae enter bloodstream and grow in the lung alveoli. Larvae are coughed, swallowed and returned to the small intestines, where the worms mature.
- ◆ Symptoms/Conditions:
 - » Early:
 - Asymptomatic
 - Pneumonitis
 - Cough
 - Fever
 - Eosinophilia
 - » Late:
 - » Abdominal pain and distention
 - » Vomiting
 - » Peritonitis
 - Intestinal obstruction
 - » Gallbladder and liver damage
- ◆ Treatment:
 - » Prevention with good personal hygiene and sanitary conditions
 - Reinfection is common, consider treating entire family.
 - » Albendazole, 400 mg PO once or Mebendazole, 100 mg BID PO x 3d or 500 mg once or Ivermectin, 150–200 µg/kg PO once
 - » Botanicals (see "Botanical Sensitivities" on page 155)

Blastocystis sp.

Seven subspecies have been identified and *Blastocystis* sp. 4 infection has been correlated with disease. *Blastocystis* sp. 2 is considered to be asymptomatic.

- ◆ Transmission:
 - » Fecal-oral
 - » Contaminated food or water
- ◆ Symptoms/Conditions:
 - » Asymptomatic (depending on species)
 - » Diarrhea
 - » Abdominal pain
 - » Nausea and vomiting
 - » Fever
 - » Fatigue—may be chronic
 - » Irritable bowel syndrome
 - » Infective arthritis
 - » Intestinal obstruction
- ◆ Treatment:
 - » Prevention with good personal hygiene and sanitary conditions
 - » Metronidazole, 750 mg PO TID x 10d or iodoquinol, 650 mg PO TID x 20d or trimethoprim/sulfamethoxazole, 1 DS tab PO bid x 7d have been reported to be effective
 - » Infection is difficult to get rid of—botanicals may not be strong enough

Chilomastix mesnili

While considered to be a non-pathogenic protozoan by authorities, some

Chilomastix mesnili; Clonorchis sinensis; Cryptosporidium

- » Diarrhea
- » Eosinophilia
- » Inflammation and intermittent obstruction of the biliary ducts
- ◆ Chronic infections associated with:
 - » Cholangitis
 - » Cholelithiasis
 - » Pancreatitis
 - » Cholangiocarcinoma
- ◆ Treatment:
 - » Praziquantel, 75 mg/kg/d in 3 doses x 2d
 - » Albendazole, 10 mg/kg/d x 7d
 - » Botanicals (see "Botanical Sensitivities" on page 155)

Cryptosporidium

- ◆ Transmission:
 - » Contaminated water, including swimming pools (crypto is resistant to chlorine)
 - » Raw milk
 - » Meat
 - » Likely cause of traveler's diarrhea
- ◆ Symptoms/Conditions:
 - » Watery diarrhea
 - » Dehydration
 - » Weight loss
 - » Abdominal pain
 - » Fever
 - » Nausea and vomiting
 - » May be severe in immunocompromised patients
- ◆ Treatment:
 - » Usually self-limiting in an

Cryptosporidium; Dientamoeba fragilis; Endolimax nana or Entamoeba bartmanni; Entamoeba coli

immunocompetent person, with symptoms lasting 1–2 weeks

- » If symptoms persist look for possible water contamination
- » Nitazoxanide, 500 mg PO BID x 3d for persistent infections
- » Botanicals (see “Botanical Sensitivities” on page 155)

Dientamoeba fragilis

- ◆ Transmission:
 - » Fecal-oral
 - » Water contamination
 - » Often accompanies pinworm
- ◆ Symptoms/Conditions:
 - » Asymptomatic
 - » Diarrhea
 - » Fatigue
 - » Abdominal bloating
 - » Chronic infections
 - » Abdominal tenderness
 - » Nausea
 - » Weight loss
- ◆ Treatment:
 - » Iodoquinol, 650 mg PO TID x 20d; Paromomycin, 25–35 mg/kg/d in 3 doses x 7d; Tetracycline, 500 mg PO QID x 10d or Metronidazole, 500–750 mg PO TID x 10d
 - » Botanicals (see “Botanical Sensitivities” on page 155)

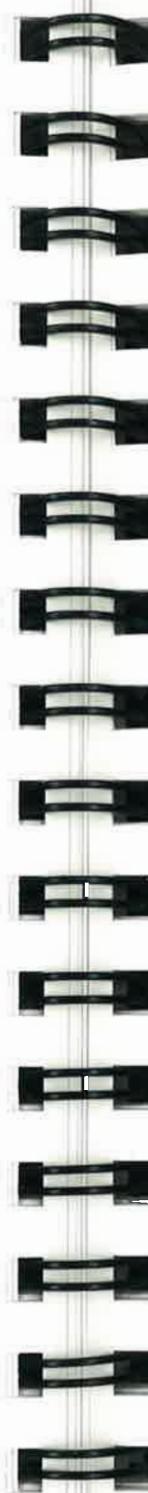
Endolimax nana or Entamoeba hartmanni

While considered to be non-pathogenic protozoa by authorities, some research has associated gastrointestinal complaints with *Endolimax nana* and *Entamoeba hartmanni*. The presence of these parasites may also be considered dysbiotic. Thus, when there is positive identification of this protozoan, conservative treatment may be indicated if clinical presentation is consistent with enteroparasitosis.

- ◆ Transmission:
 - » Fecal-oral
 - » Contaminated food or water
- ◆ Treatment:
 - » Prevention with good personal hygiene and sanitary conditions
 - » See “Treatment Using Four “R” Program for Intestinal Health” on page 133
 - » If presentation is consistent with parasite infestation, use a broad spectrum antiparasitic treatment followed by pre- and probiotics
 - » Botanicals (see “Botanical Sensitivities” on page 155)

Entamoeba coli

While considered to be a non-pathogenic protozoan by authorities, some research has associated gastrointestinal complaints with *Entamoeba coli*. The presence of this parasite may also be considered dysbiotic. Thus, when there is positive identification of this protozoan,



Entamoeba coli; Entamoeba dispar; Entamoeba histolytica

conservative treatment may be indicated if clinical presentation is consistent with enteroparasitosis.

- ◆ Transmission:
 - » Fecal-oral
 - » Contaminated food or water
- ◆ Treatment:
 - » Prevention with good personal hygiene and sanitary conditions
 - » See “Treatment Using Four “R” Program for Intestinal Health” on page 133
 - » If presentation is consistent with parasite infestation, use a broad spectrum antiparasitic treatment followed by pre- and probiotics
 - » Botanicals (see “Botanical Sensitivities” on page 155)

Entamoeba dispar

While considered to be a non-pathogenic protozoan by authorities, the presence of *Entamoeba dispar* may be considered dysbiotic. Thus, when there is positive identification of this parasite, conservative treatment for dysbiosis may be indicated.

- ◆ Transmission:
 - » Fecal-oral
 - » Contaminated food or water
- ◆ Treatment:
 - » Prevention with good personal hygiene and sanitary conditions
 - » See “Treatment Using Four “R” Program for Intestinal Health” on page 133
 - » If presentation is consistent with

parasite infestation, use a broad-spectrum antiparasitic treatment followed by pre- and probiotics

- » Botanicals (see “Botanical Sensitivities” on page 155)

Note: *Entamoeba dispar* is morphologically identical to the pathogenic protozoa, *Entamoeba histolytica* (discussed below). DNA analysis allows clear differentiation of these organisms despite their similarities.

Entamoeba histolytica

Entamoeba histolytica is considered to be a pathogenic protozoa

- ◆ Transmission:
 - » Contaminated food or water
 - » Pets
 - » Sexual contact
 - » Fecal-oral route
 - » Cysts are sensitive to chlorinated water
- ◆ Symptoms/Conditions:
 - » Asymptomatic
 - » Diarrhea
 - » Fulminating colitis (resembling ulcerative colitis)
 - » Dysentery
 - » Extraintestinal lesions on: liver, lung, brain, skin and other tissues
- ◆ Treatment:
 - » Asymptomatic carriers should be treated in order to avoid spread
 - » For asymptomatic patients:
 - Iodoquinol, 650 mg PO TID x 20d; Paromomycin,

Entamoeba histolytica; Enterobius vermicularis; Giardia lamblia

- » 25–35 mg/kg/d in 3 doses x 7d or Diloxanide furoate, 500 mg PO TID x 10d
- » For mild to moderate intestinal disease:
 - Metronidazole, 500–750 mg PO TID x 7–10d or Tinidazole, 2 g once daily x 3d followed by either Iodoquinol, 650 mg PO TID x 20d or Paromomycin, 25–35 mg/kg/d in 3 doses x 7d
- » For severe intestinal and extraintestinal disease:
 - Metronidazole, 750 mg PO TID x 7–10d or Tinidazole, 2 g once daily x 5d followed by either Iodoquinol, 650 mg PO TID x 20d or Paromomycin, 25–35 mg/kg/d in 3 doses x 7d
- » Botanicals (see "Botanical Sensitivities" on page 155)

***Enterobius vermicularis*
(Pinworm)**

- ◆ Transmission:
 - » Fecal-oral
 - » Females emerge from the anus and lay eggs on the perianal surface
 - » Eggs can survive on bed linens and fabrics for 2–3 weeks.
- ◆ Symptoms/Conditions:
 - » Nocturnal perianal pruritus
 - » Skin bacterial infection
 - » Abdominal pain
 - » Anorexia

- » May enter the vagina and cause cystitis
- ◆ Treatment:
 - » Mebendazole, 100 mg once, repeat in 2 weeks; Pyrantel pamoate, 11 mg/kg base once (max. 1 g), repeat in 2wks
 - » Albendazole, 400 mg once; repeat in 2wks
 - » Botanicals (see "Botanical Sensitivities" on page 155)

Giardia lamblia

Giardia lamblia is a flagellate considered to be a pathogen and the most common cause of diarrheal disease worldwide.

- ◆ Transmission:
 - » Contaminated water and food
 - » Fecal-oral transmission
 - » Symptoms/Conditions:
 - » Incubation period is 1–3 weeks
 - » Asymptomatic
 - » Acute diarrhea (generally self-limiting)
- ◆ Chronic infection (30–60% develop chronic giardiasis):
 - » Diarrhea
 - » Bloating
 - » Intestinal malabsorption
 - » Steatorrhea (possibly due to bile salt deconjugation)
 - » Weight loss
- ◆ Allergic manifestations:
 - » Urticaria
 - » Reactive arthritis

Giardia lamblia; Iodamoeba butschlii; Nector americanus and Ancylostoma duodenale

- » Biliary tract disease
- » May induce lactose intolerance
- » B₁₂ deficiency
- » Reduced sIgA
- ◆ Treatment:
 - » Metronidazole, 250 mg PO TID x 5–7d
 - » Avoid fatty foods as giardia feeds on bile salts
 - » Paromomycin, 25–35 mg/kg/d in 3 doses x 5–10d; or Furazolidone, 100 mg PO QID x 7–10d; or Quinacrine, 100 mg PO TID x 5d
 - » Botanicals (see "Botanical Sensitivities" on page 155)

Iodamoeba butschlii

While considered to be a non-pathogenic protozoan by authorities, some research has associated gastrointestinal complaints with *Iodamoeba butschlii*. The presence of this parasite may also be considered dysbiotic. Thus, when there is positive identification of this protozoan, conservative treatment may be indicated if clinical presentation is consistent with enteroparasitosis.

- ◆ Transmission:
 - » Fecal-oral
 - » Contaminated food or water
- ◆ Treatment:
 - » Prevention with good personal hygiene and sanitary conditions
 - » See "Treatment Using Four 'R' Program for Intestinal Health" on page 133
 - » If presentation is consistent with

- parasite infestation, use a broad-spectrum antiparasitic treatment followed by pre- and probiotics
- » Botanicals (see "Botanical Sensitivities" on page 155)

***Necator americanus and Ancylostoma duodenale*
(Hookworm)**

- ◆ Transmission:
 - » Skin contact with contaminated soil
 - » Oral ingestion of the larvae
 - » Worms can travel to the lungs or attach to the mucosa of the GI and suck blood
- ◆ Symptoms/Conditions:
 - » Itching and rash at the site of penetration
 - » Light infection may be asymptomatic
 - » Heavy infection:
 - Anemia
 - Abdominal pain
 - Diarrhea
 - Loss of appetite
 - Weight loss
 - Has been associated with reactive arthritis.
- ◆ Treatment:
 - » Albendazole, 400 mg once; Mebendazole, 100 mg PO BID x 3d or 500 mg once, or Pyrantel pamoate, 11 mg/kg (max. 1g) x 3d

Necator americanus and *Ancylostoma duodenale*; *Schistosoma mansoni*; *Strongyloides sp.*; *Taenia sp.*

- » Botanicals (see "Botanical Sensitivities" on page 155)

Schistosoma mansoni

- ◆ Transmission:
 - » Skin contact with contaminated water—parasite burrows through the skin
 - » Larvae can migrate to the lungs and liver and can live for 25–30 years
 - » Eggs secrete an enzymatic substance that destroys surrounding tissues.
- ◆ Symptoms/Conditions:
 - » Light infection may be asymptomatic
 - » Heavy infection:
 - Myalgias
 - Abdominal pain
 - Diarrhea
 - Cough
 - Tender liver
 - Ulceration of the intestinal mucosal layer
 - Infection has been linked with reactive arthritis and sacroilitis
- ◆ Treatment:
 - » Praziquantel, 40 mg/kg/d in 2 doses x 1d, or Oxamniquine, 15 mg/kg once
 - » Botanicals (see "Botanical Sensitivities" on page 155)

Strongyloides sp.

- ◆ Transmission:
 - » Skin contact with contaminated soil
 - » Oral ingestion of the larvae
 - » Larvae are carried to the lungs or are swallowed and mature in the small intestine
- ◆ Symptoms/Conditions:
 - » Itching and a rash at the site of penetration
 - » Light infection may be asymptomatic
 - » Heavy infection:
 - Epigastric pain
 - Nausea and vomiting
 - Gas
 - Alternating constipation and diarrhea
 - Infection has been associated with reactive arthritis
- ◆ Treatments:
 - » Thiabendazole, 50 mg/kg/d in two doses x 2d; Ivermectin, 200 µg/kg/d x 1–2d, or Albendazole, 400 mg/d x 3d
 - » Eradication may be difficult, recheck stool in 3 months
 - » Botanicals (see "Botanical Sensitivities" on page 155)

Taenia sp. (Tapeworm)

- ◆ Transmission:
 - » Undercooked, infected pork or beef

Taenia sp.; *Trichomonas hominis*; *Trichuris trichiura*

- » Maturation from cyst to worm takes 2 months

- » Can grow 4–8 meters long and live 25 years

◆ Symptoms/Conditions:

- » Asymptomatic
- » Abdominal pain
- » Anorexia
- » Weight loss
- » Malaise
- » Vitamin B₁₂ deficiency

◆ Treatment:

- » Praziquantel, 5–10 mg/kg once, Niclosamide, 2 g once
- » Botanicals (see "Botanical Sensitivities" on page 155)

Trichuris trichiura (Whipworm)

It is the most common helminth infection. *T. trichiura* can become embedded in the intestinal villi, feeds on tissue secretions and can cause eosinophilia. Larvae hatch in the small intestine and take up residence in the large intestine. Adult female lays eggs for up to five years.

◆ Transmission:

- » Fecal-oral
- » Contaminated soil
- » Under-washed vegetables

◆ Symptoms/Conditions:

- » Often asymptomatic and self-limiting

» Heavy infection:

- Bloody diarrhea
- Abdominal pain
- Nausea
- Anemia
- Eosinophilia

◆ Treatment:

- » Mebendazole, 100 mg PO BID x 3d or 500 mg once; Albendazole, 400 mg x 3d, or Ivermectin, 200 µg/kg daily x 3d

Trichuris trichiura; Parasite Present; Taxonomy Unavailable; Firmicutes Bacteroidetes Ratio

- » Botanicals (see “Botanical Sensitivities” on page 155)

Parasite Present— Taxonomy Unavailable

The DNA probe identified a parasite but genus and species probes for known human pathogens were negative. Suspect that the parasite identified is likely NOT a human pathogen, and probably a transient, non-colonizer of the human GI tract. Evaluate patient symptoms and inflammatory markers on the GI Effects test. If symptoms are consistent with a parasite infection, consider treatment.

- ◆ Treatment:
 - » Address other abnormal results in the GI Effects profile first, with the expectation that a rare parasite will be crowded out when healthy conditions are restored
 - » See “Treatment Using Four “R” Program for Intestinal Health” on page 133
 - » Consider exposures such as pets, sushi, camping, or foreign travel
 - » If presentation is consistent with parasite infestation, use a broad-spectrum antiparasitic treatment followed by pre- and probiotics
 - » Botanicals (see “Botanical Sensitivities” on page 155)

Adiposity Index

Research indicates that obesity has a microbial component that alters caloric yield from ingested food. Altering the

gut microbiota may also improve insulin sensitivity and oral glucose tolerance. Treatments for obesity that result in lowering the percentage of Firmicutes relative to the percent of Bacteroidetes may assist in weight control.

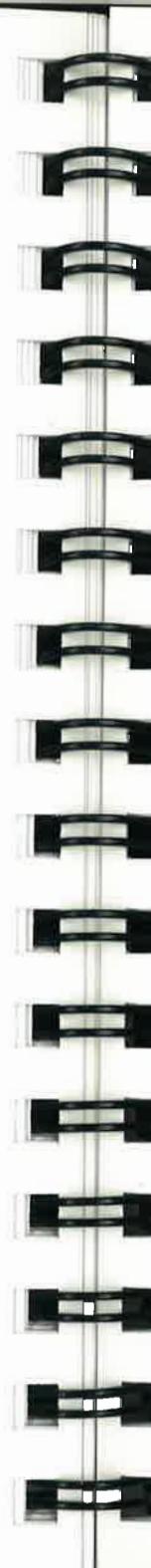
- ◆ The Firmicutes class includes the various species of *Clostridia*, *Streptomyces*, *Lactobacillus*, *Mycoplasma* and *Bacillus*.
- ◆ The Bacteroidetes class includes the various species of *Bacteroides* and *Prevotella*.
- ◆ See “Predominant Bacteria” on page 133.

IF HIGH FIRMICUTES: BACTEROIDETES RATIO

- ◆ Causes:
 - » Bacteria classes known to increase caloric extraction from food are present
 - » Dysbiosis
- ◆ Treatment:
 - » Balance predominant bacteria using 4R protocol
 - » Remove opportunistic bacteria, especially *Bacillus* spp.
 - » Supplement with *Bifidobacter* spp. and *S. boulardii*
 - » Reduce refined carbohydrates
 - » Address all GI Effects imbalances

Drug Resistance Genes

- ◆ Demonstrates unidentified bacterial resistance to antibiotic class
- ◆ Avoid using class of antibiotics for which patient has drug resistance gene



aacA, aphD; mecA; vanA, vanB, vanC; gyrB, ParE; PBP1a, PBP2B; SCFA; N-Butyrate

- ◆ Resistance genes may change over time, as bacterial population shifts

Drug Resistance Names and Antibiotics

- ◆ ***aacA, aphD***
 - » Antibiotic:
 - Gentamicin, Kanamycin, Tobramycin (aminoglycosides)
 - » Target organism:
 - Gram-positive bacteria (cocci), namely Enterococci
- ◆ ***mecA***
 - » Antibiotic:
 - Methicillin (Beta-Lactam)
 - » Target Organism:
 - Aerobic, Gram-negative
- ◆ ***vanA, vanB, vanC***
 - » Antibiotic:
 - Vancomycin and Teicoplanin (glycopeptides)
 - » Target organism:
 - Gram-positive bacteria, particularly beta-lactamase-producing organisms such as *Staphylococcus*
- ◆ ***gyrB, ParE***
 - » Antibiotic:
 - Ciprofloxacin and later generation quinolones
 - » Target organism:
 - Gram-positive and Gram-negative bacteria
- ◆ ***PBP1a, PBP2B***
 - » Antibiotic:

Short Chain Fatty Acids (SCFA)

IF TOTAL SCFA OR N-BUTYRATE LOW

- ◆ Colonic bacterial fermentation of carbohydrates (fiber, prebiotics) or amino acids
- ◆ SCFAs play important role in the maintenance of the intestinal barrier
- ◆ SCFAs, especially n-butyrate serve as the fuel for the colonocytes
- ◆ Butyrate has been shown to be protective against colon cancer
- ◆ Causes:
 - » Low anaerobic bacteria (see “Predominant Bacteria” on page 133)
 - » Antibiotic treatment
 - » Insufficient fiber intake/poor diet
 - » Slow transit time (more time for SCFA absorption)
- ◆ Treatment:
 - » Pre- and probiotic supplementation if the predominant bacteria are low
 - » Psyllium, oat bran, oligofructose, inulin xylooligosaccharide, beta-glucan, or arabinogalactan
 - » Increase dietary intake of fruits and vegetables
 - » In ulcerative colitis, Crohn’s or those at risk for colon

SCEA; N-Butyrate; Lactoferrin, WBCs & Mucus

- » cancer, consider butyrate enemas or enteric-coated butyrate supplements
- » Enemas are contraindicated for those with GI bleeds

IF TOTAL SCFA OR N-BUTYRATE HIGH

- ◆ High-normal levels likely mean optimal fiber intake and bacterial population. For extremely elevated SCFAs and n-butyrate—consider evaluation in conjunction with the other GI Effects markers. Values of 184 mM/g or greater are above the 95% confidence interval.
- ◆ Causes:
 - » Bacterial overgrowth
 - » Rapid transit time (less time for SCFA absorption)
 - » Malabsorption
 - » Pancreatic insufficiency resulting in carbohydrate maldigestion and increased bacterial fermentation
 - » Bacterial fermentation of blood
- ◆ Treatment:
 - » Address all GI imbalances
 - » Normalize transit time
 - » Pancreatic enzymes, betaine HCl, or digestive herbs

Inflammation**Lactoferrin, WBCs and Mucus**

- ◆ Lactoferrin is an iron-binding glycoprotein released from neutrophils during inflammation. It is a marker of leukocyte activity

Lactoferrin, WBCs & Mucus; sIgA; Anti-Gliadin Antibody

- » Stress reduction
- » Treat underlying causes
- » Support general immune function

IF FECAL sIgA HIGH

- ◆ Causes:
 - » Immune response to pathogenic organisms in GI tract
 - » Sensitivities to foods
- ◆ Treatments:
 - » Support immune function
 - » Remove pathogens, parasites, opportunistic bacteria, virus
 - » Rule out food sensitivities
 - » Elimination diet

Immunology**sIgA**

- ◆ Secretory IgA is the chief antibody in the membranes of the gastrointestinal and respiratory tracts

IF FECAL sIgA LOW

- ◆ Causes:
 - » Chronic stress
 - » Immunocompromised
 - » Dysbiosis
 - » Immuno-suppressing medication
- ◆ Treatment:
 - » Support gut mucosa:
 - Glutamine
 - Probiotics (*S. boulardii*, *Bifidobacterium*)
 - Colostrum
 - Immunoglobulins
 - Essential fatty acids
 - Zinc

Anti-Gliadin Antibody**IF ANTI-GLIADIN ANTIBODY HIGH**

- ◆ Causes:
 - » Gluten enteropathy or sensitivity in colon
- ◆ Treatments:
 - » Remove gluten
 - » Consider Celiac Profile
 - » Consider nutrients and herbs for mucosal healing (see “Inflammation” on page 150)

pH; Occult Blood

Additional Tests

pH

IF pH LOW

- ◆ Causes:
 - » Bacterial overgrowth
 - » Carbohydrate malabsorption
 - » Lipid malabsorption
 - » Rapid transit time
- ◆ Treatment:
 - » Support digestion and absorption
 - » Plant or pancreatic enzymes:
 - Betaine HCl
 - Disaccharidases
 - » Normalize transit time
 - » Address all GI Effects imbalances

IF pH HIGH

- ◆ Causes:
 - » Decreased SCFAs:
 - Insufficient or imbalanced flora
 - Low dietary fiber, insufficient water
 - Insufficient acid-producers such as *Lactobacillus* sp.
 - Hypochlorhydria
 - High meat diet
 - Slow transit time
 - High pH increases risk for colon cancer
- ◆ Treatment:
 - » Probiotics
 - » Treat dysbiosis
 - » Dietary fiber (esp. soluble)

- » Decrease meat intake
- » Water
- » Support digestion:
 - Betaine HCl
 - Ginger, peppermint, etc.
- » Address all GI Effects imbalances

Occult Blood

POSITIVE OCCULT BLOOD

- ◆ Causes:
 - » Upper GI bleed includes:
 - » Peptic ulcer
 - » Inflammatory bowel disease
 - » Parasite infection
 - » Colon cancer
 - » Hemorrhoids
 - » Rule out false positive from red meat
- ◆ Treatment:
 - » Repeat occult blood test on two more occasions
 - » Address all GI Effects imbalances
 - » Rule out iron deficiency anemia
 - » Consider esophagogastroduodenoscopy (EGD) or colonoscopy to identify source, treat accordingly
 - » Anti-inflammatory medical food
 - » Anti-inflammatory diet
 - » Food allergens



RBCs

POSITIVE RBCs

- ◆ Causes:
 - » Lower GI bleed includes:
 - Hemorrhoids
 - Intestinal polyps
 - Anal tears
 - » Those with compromised liver function are more likely to develop hemorrhoids
- ◆ Treatment:
 - » Treat constipation if present
 - » Consider colonoscopy to identify source, treat accordingly
 - » Assess liver function
 - » Soothe and repair gut mucosa
 - » Follow-up RBCs, occult blood test

Digestion

Elastase 1

IF ELASTASE 1 LOW

- ◆ Elastase 1 is a digestive enzyme excreted by the pancreas exclusively, and has a direct correlation with pancreatic function. Elastase 1 results are not affected by pancreatic enzyme replacement therapy.
- » Optimal levels are > 500 µg/mL

- ◆ Causes:
 - » Suppressed pancreatic function
 - » Gallstones or post-cholecystectomy

RBCs; Elastase 1; Vegetable Fibers; Triglycerides

- » Chronic pancreatitis
- » Diabetes
- » Hypochlorhydria
- » Cystic fibrosis
- ◆ Treatment:
 - » Support digestion:
 - Betaine HCl
 - Pepsin
 - Plant or pancreatic enzymes
 - Digestive herbs
 - Bile salts
 - Taurine
 - Cholagogues (esp. if high triglycerides and constipation)
 - Relax while eating and chew thoroughly
 - » Treat underlying causes

Vegetable Fibers

ELEVATED VEGETABLE FIBERS, TRIGLYCERIDES

- ◆ Causes:
 - » Malabsorption
 - » Hypochlorhydria
 - » Pancreatic insufficiency
 - » Bile salt insufficiency (if elevated triglycerides)
 - » Inadequate chewing (if elevated vegetable fibers)
- ◆ Treatment:
 - » Support digestion:
 - Betaine HCl
 - Pepsin
 - Plant or pancreatic enzymes

Vegetable Fibers; Triglycerides; Putrefactive SCFA; LCFA, Total Fat, Cholesterol

- Digestive herbs
- » Pancreatic insufficiency
- Bile salts
- » Malabsorption, esp. if elevated long chain fatty acids or cholesterol
- Taurine
- » Bacterial overgrowth of the small intestine
- Cholagogues (esp. if high triglycerides and constipation)
- ◆ Treatment:
- Relax while eating and chew thoroughly
- » Treat underlying causes
- » Support digestion:
 - Betaine HCl with pepsin
 - Plant or pancreatic enzymes
 - Digestive herbs
- » Treat underlying causes
- » Identify and remove food sensitivities

Putrefactive SCFA**IF PUTREFACTIVE SCFA HIGH**

- ◆ Causes:
 - » Protein maldigestion
 - » Hypochlorhydria

Absorption**Long Chain Fatty Acids (LCFA), Total Fat, Cholesterol****IF LCFA, TOTAL FAT, OR CHOLESTEROL HIGH**

- ◆ Causes:
 - » Malabsorption
 - Diarrhea
 - Intestinal dysbiosis
 - Parasites
 - Colitis
 - Gluten intolerance
 - Food allergy
 - Essential fatty acid deficiency
 - Pancreatic or bile salt insufficiency
 - Chronic NSAID usage

- » High dietary fat intake
- » Medications designed to bind and eliminate fats
- » If elevated cholesterol rule out increased mucosal cell turnover resulting from inflammation
- » Bacterial overgrowth of the small intestine (esp. if elevated SCFAs)
- » Bacterial enzymes can also impair micelle formation, resulting in lipid malabsorption

- ◆ Treatment:
 - » Support digestion
 - Betaine HCl
 - Pepsin

**GASTROINTESTINAL FUNCTION—GI EFFECTS STOOL PROFILES****LCFA, Total Fat, Cholesterol; Pharmaceutical Sensitivities; Botanical Sensitivities**

for which antibiotic resistance genes were found.

Botanical Sensitivities

When treating with botanicals, it is recommended to use a broad spectrum product. Treatment with botanicals might also require a longer duration than treatment with pharmaceuticals. Antimicrobial botanicals may be rotated and/or administered in a pulsatile fashion to improve efficacy. Listed below are the active ingredients tested for each botanical used in antimicrobial blends.

Botanicals and Their Active Ingredients

Botanical	Active Ingredient
Wormwood (Artemesia)	Artemisinin
Olive leaf	Oleuropein
Uva Ursi (Bearberry)	Arbutin
Garlic	Alliin
Undecylenic acid (from castor bean)	Undecylenic acid
Oil of thyme	Thymol
Oil of oregano	Carvacrol
Goldenseal	Berberine
Cat's Claw	Quinic acid
Black Walnut	5-hydroxy-1,4-naphthoquinone

Sensitivity Testing**Pharmaceutical Sensitivities**

Sensitivity testing using commonly employed antimicrobial agents is conducted for opportunistic and fungal findings. Refer to stool profile test results for findings.

To prevent further proliferation of resistant organisms, avoid the use of agents

IgG₄ Food-Specific Antibody Testing

- ◆ Performed on either serum or dried blood spot specimens
- ◆ The 4-type IgG subclass constitutes up to 5% of the major G class of circulating immunoglobulins.
- ◆ Formed in response to presentation of food antigens
- ◆ Unique protein structure results in failure to directly stimulate the complement cascade and very long 20 day half-life
- ◆ High IgG₄ levels are indicative of long-term sensitization to a specific food antigen due to chronic antigen presentations rather than temporary episodes that cause other IgG subclass elevations.
- ◆ Not to be confused with IgE-mediated food allergy, although IgG₄ does have a blocking, protective effect toward IgE
- ◆ Reveals food sensitivity reactions to foods commonly eaten
- ◆ Used to design custom elimination/rotation diets to reduce food-generated immune system stress

General Causes of High IgG₄

- ◆ Patterns of multiple elevated food-specific IgG₄ levels reveal small intestinal hyperpermeability (leaky gut)
- ◆ Hyperpermeability may arise from chronic stress, malnutrition, maldigestion, malabsorption or chronic inflammation of

intestinal mucosa. Alcohol and numerous medications such as NSAIDs also contribute to intestinal hyperpermeability.

IF FEW FOOD-SPECIFIC IgG₄ ELEVATIONS (< 5)

- ◆ Positive foods are generally those that are habitually and frequently consumed and/or are generating IgG₄ to block IgE reactions.
- ◆ Negative foods are being adequately digested and the intestinal immune and physical barriers are adequate to prevent excessive presentation of food antigens to the gut-associated lymphoid tissue.
- ◆ Immunosuppressant drugs (corticosteroids) inhibit production of IgG₄.
- ◆ Cause:
 - » Gut integrity sufficient to prevent buildup of many blocking antibodies
 - » Eating during stressful episodes
 - » Use of immunosuppressant drugs (corticosteroids)

IF MANY FOOD-SPECIFIC IgG₄ ELEVATIONS (≥ 5)

- ◆ Episodic physical, emotional or toxic stress can result in mild, transient increases of intestinal permeability leading to temporary IgG food reactions. If this state continues, IgG₄ class may elevate in response to frequently consumed foods as well. (hyperpermeability)



- ◆ Many food antigens are stimulating the formation of IgG antibodies that block full anaphylactic (IgE) reactions.
- ◆ Cause:
 - » Maldigestion or malnutrition
 - » Impaired gut integrity—intestinal hyperpermeability (see above):
 - Multiple blocking antibodies in circulation
 - Large antigen-antibody complexes deposit in tissues
 - Complement may be triggered by secondary mechanisms.
 - Increased susceptibility to infections
- ◆ Symptoms and Conditions:
 - » Myalgia
 - » Arthritis
 - » Headache
 - » Eczema
 - » Psoriasis
 - » Asthma
 - » Chronic URI
 - » Fatigue
 - » Brain fog
 - » These and many other symptoms are due to stages of immune activation or suppression, autoimmune reactions or direct food or bacterial toxin-mediated effects.
- ◆ Treatment:
 - » Restore the physical and immune barriers in the small intestines
 - » Reduce food antigenic load:
 - Remove foods that generate

high IgG₄ levels to reduce immune system stress

- Rotate other food classes to reduce chronic single antigen presentation
- Include a large variety of foods to achieve nutritional adequacy
- » Repair gut tissue integrity:
 - Glutamine, 5 g BID
 - α -Ketoglutarate, 250 mg TID
 - Pantothenic acid, 100 mg/d
- » Replace digestive factors
 - Gastric acid (Betaine HCl)
 - Pancreatic enzyme supplements
- ◆ Relationship to other test results:
 - » Zinc, biotin, B₁₂ and amino acid deficiencies
 - (Maldigestion and malabsorption causes multiple nutrient deficiencies. Chronically activated antibody production contributes to depletion of essential amino acids.)
 - » Fat-soluble vitamins
 - Intestinal degradation can lead to malabsorption
 - » Arachidonic acid elevation (esp. with EPA deficiency)
 - Exacerbates repair by stimulating inflammatory responses
 - » Small or large intestinal chronic dysbiosis
 - Immune stimulation by products from abnormal bacterial populations

IgE; IgE & IgG-Mediated Reactions to Food

IgE Food-Specific Antibody Testing

- ◆ The E class of circulating immunoglobulins constituting long-term memory of antigenic exposures
 - ◆ Antigen-antibody complexes trigger atopic (and anaphylactic) allergic reactions
- IF FOOD-SPECIFIC IgE ELEVATIONS**
- ◆ Causes:
 - » Exposure to antigenic food components that are not bound by IgG antibodies results in detection by antigen-presenting cells, stimulation of a specific clone of B-cells that have long-lasting ability to produce IgE antibodies to the food
 - » Re-exposure can result in the formation of IgE-antigen complexes that initiate the atopic response, including the release of histamine and other vasoactive amines from mast cells
 - ◆ Symptoms:
 - » Rhinitis, conjunctivitis, bronchoconstriction, urticaria, atopic eczema, vomiting, diarrhea, anaphylaxis
 - ◆ Treatments:
 - » Food elimination, desensitization therapies
 - » Anaphylaxis:
 - Subcutaneous or intramuscular epinephrine and intravenous fluids with adjunctive airway protection, antihistamines, steroids and beta agonists

Characteristics of IgE and IgG-Mediated Reactions to Food

IgE Mediated	IgG Mediated
Incidence is relatively low	Incidence is relatively high
Result from infrequent exposure	Result from frequent exposure
Very predictable short term symptoms	Chronic, variable symptoms
Offending food is usually obvious	Offending food frequently not suspected
Basophil/mast cell triggered anaphylaxis	Immune complex trigger
Histamine/leukotriene release	Inflammatory response
Patient aware of offending food	Patient rarely aware of offending food
Antibody persistent for years	Antibody declines within one month
In vitro testing for serum IgE for confirmation	In vitro testing for serum IgG shows food offenders and extent of gut permeability
Treatment: Permanent food avoidance and immunotherapy	Treatment: Eliminate then rotate food(s), heal gut, improve digestion

Toxicants

Contents

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Xenobiotics

Phthalates and Bisphenol-A (BPA)

- ◆ Compounds used in the production of plastics
 - » Phthalates are esters of 1,2-benzenedicarboxylic acid that are added to plastics to confer flexibility
 - » BPA is a monomer used in the production of polycarbonates, which are a group of plastics with the identification (recycling) code of 7—not all code 7 plastics contain BPA
 - ◆ Exposure is universal due to use of common plastics, cosmetics and other convenience items
 - ◆ Worldwide production of, roughly, a billion pounds of phthalates per year
 - ◆ Levels in blood or urine show relative exposure levels
- IF PHTHALATES HIGH:**
- ◆ Causes:
 - » Inhalation of aerosols containing phthalates
 - » Exposure to plastics, paints and cosmetic products or inhalation of air in rooms where such products are used
 - » Use of lotions, powders and shampoos containing phthalates
 - » Skin exposure can reach ~ 1000 mg/day
 - ◆ Symptoms/Conditions:
 - » Steroid hormone function disruptions
 - » Impaired male reproductive development

Phthalates & BPA

- » Endometriosis
- » Obesity
- » L-Tryptophan depletion and quinolinolate elevation due to altered hepatic kynurenine pathway activity
- » Oxidative stress (possibly due to PPAR stimulation)
- ◆ Treatments:
 - » Reduce exposures
 - » Increase strenuous exercise
 - » Sauna treatments
 - » Detoxification procedures (refer to Chapter 8 in *Laboratory Evaluations for Integrative and Functional Medicine*)
 - » Choose products labeled as "Phthalate-free"

Phthalates and Their Metabolites

Phthalate Name (CAS #)	Abbr	Urinary Metabolite (CAS #)	Abbr
Dimethyl phthalate (131-11-3)	DMP	Mono-methyl phthalate (4376-18-5)	MMP
Diethyl phthalate (84-66-2)	DEP	Mono-ethyl phthalate (2306-33-4)	MEP
Dibutyl phthalates (84-74-2)	DBP	Mono-n-butyl phthalate (131-70-4) Mono-isobutyl phthalate	MnBP
Benzylbutyl phthalate (85-68-7)	BzBP	Mono-benzyl phthalate (2528-16-7) (some mono-n-butyl phthalate)	MBzP
Dicyclohexyl phthalate (84-61-7)	DCHP	Mono-cyclohexyl phthalate (7517-36-4)	MCHP
Di-2-ethylhexyl phthalate (117-81-7)	DEHP	Mono-2-ethylhexyl phthalate (4376-20-9) Mono-(2-ethyl-5-oxohexyl) phthalate Mono-(2-ethyl-5-hydroxohexyl) phthalate	MEHP MEOHP MEHHP
Di-n-octyl phthalate (117-84-0)	DOP	Mono-n-octyl phthalate (5393-19-1) Mono-(3-carboxypropyl) phthalate	MOP MCPP
Di-isooctyl phthalate (28553-12-0)	DiNP	Mono-isooctyl phthalate	MiNP

Phthalates & BPA; Volatile Solvents; PCBs**Polychlorinated Biphenyls (PCBs)***

- ◆ PCB #118
(2,3',4,4',5-Pentachlorobiphenyl)
- ◆ PCB #126
(3,3',4,4',5-Pentachlorobiphenyl)
- ◆ PCB #153
(2,2',4,4',5,5'-Hexachlorobiphenyl)
- ◆ PCB #138
(2,2',3,4,4',5'-Hexachlorobiphenyl)
- ◆ PCB #169
(3,4,5,3',4',5'-Hexachlorobiphenyl)
- ◆ PCB #180
(2,2',3,4,4',5,5'-Heptachlorobiphenyl)

* All PCBs are considered to be Pesticide Action Network (PAN) Bad Actors due to their carcinogenicity, developmental or reproductive toxicity, and suspected endocrine disruptor status.

See "Chlorinated Pesticides" table on following page...

Volatile Solvents

- ◆ Benzene
- ◆ Toluene
- ◆ Ethylbenzene
- ◆ Xylenes (o,m,p)
- ◆ Styrene
- ◆ 2-Methylpentane
- ◆ 3-Methylpentane
- ◆ n-Hexane
- ◆ (See updated list at Metametrix.com and clicking on Test Menu for Toxic Effect Profiles)

NOTES

Chlorinated Pesticides

Chlorinated Pesticides

Xenobiotic	Characteristics	Toxicity Symptoms
Hexachlorobenzene	PAN* Bad Actor	Acute toxicity, carcinogen, developmental toxicity, and suspected endocrine disruptor
β -Hexachlorocyclohexane	PAN* Bad Actor	Carcinogen, suspected endocrine disruptor
Heptachlor epoxide	PAN* Bad Actor	Carcinogen, suspected endocrine disruptor
Oxychlordane	Organochlorine breakdown product	Suspected endocrine disruptor <ul style="list-style-type: none"> • Hypersensitivity to stimulation, headache, dizziness, nausea, vomiting, incoordination, tremor, mental confusion, hyperexcitable, convulsions, seizures, coma and respiratory depression • Cholinesterase inhibitor and probable endocrine disruptor
Trans-nonachlor	Organochlorine insecticide	
p,p'-DDE(Dichloro-diphenyl dichloroethylene)	Very stable in fat tissue, therefore poorly excreted	Endocrine disruptor
p,p'-DDT (Dichloro-diphenyl trichloroethane)	Highly efficient insect contact poison Opens sodium ion channels	Non-allergic asthma, diabetes, cancer (hepatic, renal, pancreatic, testicular, myeloma, lymphoma) <ul style="list-style-type: none"> • Immune, reproductive and nervous systems damage • Parkinson, breast cancer
Dieldrin	Developed as alternative to DDT; Extremely persistent and bioaccumulative	
Mirex	Fire ant control and flame retardant; Persistent and bioaccumulative	Crosses placenta and passes into breast milk

* Pesticide Action Network "most toxic" pesticides because of one of five characteristics: Known or probable carcinogen, reproductive or developmental toxicant, neurotoxic, groundwater contaminant, or high acute toxicity

NOTES

Porphyrins

Porphyrins appear elevated in urine when the cellular pathway for heme synthesis is blocked by natural or man-made toxicants or when genetic disorders that affect the enzymes of the porphyrin pathway are present.

Porphyrins are particularly well suited as biomarkers of toxic exposure for two reasons. First, the pathway is highly active, so any disturbance tends to cause rapid and relatively large accumulations of intermediates. Second, the enzymes of the porphyrin-producing pathway are widely distributed in human tissues and some of them are highly sensitive to the presence of various toxins.

The highly regulated heme pathway consists of eight enzyme-driven reactions. When porphyrinogens build up, they are easily oxidized to porphyrins that appear in urine. Toxicants like heavy metals and organic xenobiotics bind to one or more enzymes to produce patterns of urinary porphyrin elevation. Oxidized porphyrins are themselves damaging, and can accumulate in the body and cause some of the symptoms associated with porphyrias.

Finding abnormalities in urine porphyrin testing is not sufficient for diagnosis of hereditary porphyrias. DNA testing is considered the "gold standard" for the diagnosis of hereditary porphyrias.

- ◆ Elevated porphyrins can be a result of:
 - » Enzyme polymorphisms
 - » Heavy metal or organotoxin enzyme poisoning
 - » Pharmaceuticals that stimulate porphyrin synthesis or inhibit enzymes of the pathways
 - » Estrogenic stimulation
- ◆ Common clinical associations:
 - » Behavioral and learning disorders
 - » Immune dysfunctions
 - » Chronic fatigue
 - » Neurological and mental/emotional disorders
- ◆ Treatments:
 - » See "Managing Patients with Metal Toxicities" on page 59
 - » If weight loss is necessary ensure it is done slowly with adequate detoxification support, as adipose degradations may release stored toxins

Porphyrinurias

Environmental Toxin-Induced Porphyrinurias

	Heavy Metals				Organotoxins						
	Aluminum	Arsenic	Mercury	Lead	Hexachlorobenzene	Methylchloride	Dioxin	Polyvinylchloride	Polybrominated biphenyl	Alcohol (Chronic Hepatic Porphyria—early)	Alcohol (Chronic Hepatic Porphyria—late)
Porphyrinurias	+	+			+		+		+		++*
Analytes											
Heptacarboxyporphyrin	(+)				(+)	(+)	(+)		(+)		+
Hexacarboxyporphyrin	(+)				(+)	(+)	(+)		(+)		+
Pentacarboxyporphyrin	(+)	+									
Precoproporphyrin	++										
Coproporphyrin I					+		+		+	+	+
Coproporphyrin III	+	+	+		+		+		+	+	++
Precopro/Uro I & III											
Copro I/Copro III					+						

Note: The single plus symbols show the typical pattern of elevated porphyrins. The double plus symbols show dominant elevations. Plus symbols enclosed in parenthesis indicate alternate patterns that may appear. Calculated total porphyrins levels are generally elevated in the severe types of any condition that produce porphyrias. Aminolevulinic acid (ALA) and zinc protoporphyrin are other porphyrin pathway intermediates elevated in lead toxicity and iron deficiency, respectively. *Hepatic degeneration due to porphyrin accumulation in the liver is found in these conditions.

NOTES

Hepta-, Hexa-Carboxyporphyrin; Pentacarboxyporphyrin; Precoproporphyrin; Coproporphyrin I

- » Evaluate urine, challenged urine or whole blood to track toxic element status

IF PRECOPROPORPHYRIN HIGH:

- ◆ Causes:
 - » Mercury
 - (This is a primary mercury marker)
- ◆ Treatments:
 - » Identify exposure source
 - » NAC, 500 mg BID
 - » Vitamin B₁₂, 100–1,000 µg/day
 - » Folic acid, 200–800 µg/day
 - » Vitamin B₆, 50–200 mg/day

Note: See “Managing Patients with Metal Toxicities” on page 59

- » Evaluate urine, challenged urine or whole blood to track toxic element status

IF COPROPORPHYRIN I HIGH:

- ◆ Causes:
 - » Exposure to:
 - Arsenic
 - Lead
 - Methyl chloride
 - Polyvinylchloride
 - Polybrominated biphenyl
 - Chronic alcohol intake
- ◆ Treatments:
 - » Look for exposure

Note: See “Managing Patients with Metal Toxicities” on page 59 for specific treatment information



Hepta-, Hexa-Carboxyporphyrin; Pentacarboxyporphyrin; Precoproporphyrin; Coproporphyrin I

Decarboxylated Intermediates



The cytosolic enzyme, uroporphyrinogen decarboxylase, is susceptible to various poisoning effects by environmental toxins. The flow of the pathway may be interrupted in ways that cause one or more of the four decarboxylated intermediates to accumulate abnormally and spill into urine as carboxyporphyrins.



IF HEPTA- OR HEXA-CARBOXYPORPHYRIN HIGH:



- ◆ Causes:

- » Exposure to:
 - Arsenic
 - Hexachlorobenzene
 - Dioxin
 - Polybrominated biphenyl
 - Chronic alcohol intake



- ◆ Treatments:

- » Identify exposure source



Note: See “Managing Patients with Metal Toxicities” on page 59

- » Evaluate urine, challenged urine or whole blood to track toxic element status



IF PENTACARBOXYPORPHYRIN HIGH:



- ◆ Causes:

- » Exposure to:
 - Arsenic
 - Mercury



- ◆ Treatments:

- » Look for exposure



Note: See “Managing Patients with Metal Toxicities” on page 59 for specific treatment information



COPROPORPHYRIN I; COPROPORPHYRIN III; PRECOPROPORPHYRIN/URO I & III RATIO

- » Evaluate urine, challenged urine or whole blood to track toxic element status
- » Ensure adequate iron status with lead, avoid increased vitamin C intake since it may increase lead absorption.

IF COPROPORPHYRIN III HIGH:

- ◆ Causes:
 - » Exposure to:
 - Aluminum
 - Mercury
 - Lead
 - Methyl chloride
 - Polyvinylchloride
 - Polybromated biphenyl
 - Chronic alcohol intake
- ◆ Treatments:
 - » Look for exposure—See “Managing Patients with Metal Toxicities” on page 59 for specific treatment information
 - » Evaluate urine, challenged urine or whole blood to track toxic element status
 - » Aluminum inhibits some heme synthetic enzymes and has been implicated in causing porphyria in chronic hemodialysis patients, whom are often aluminum overloaded.
 - » Ensure adequate iron status with lead poisoning and avoid excessive vitamin C intake since it may increase lead absorption.

IF PRECOPROPORPHYRIN/URO I AND III RATIO HIGH:

- ◆ Causes:
 - » Exposure to:
 - Mercury
- ◆ Treatments:
 - » Look for exposure—See “Managing Patients with Metal Toxicities” on page 59 for specific treatment information
 - » Evaluate urine, challenged urine or whole blood to track toxic element status
 - » If precoproporphyrin is very high, then mercury effects are always suspected. Slight elevations, however, might be overlooked. High precoproporphyrin with lower Uro I & III will elevate the Precopro/Uro I & III ratio, drawing attention to a specific mercury effect. On the other hand, high Uro I & III with a normal Precopro/Uro I & III ratio is indicative of pathway stimulation rather than mercury specific effects.
 - » Mercury is cleared via glutathione. The sulfur in glutathione grabs mercury. Treatments includes ensuring adequate glutathione functions as well as ensuring pathways are adequate that lead up to glutathione, such as methylation (ensure adequate B₁₂ and folate) and transulfuration (ensure adequate B₆).



COPROPORPHYRIN I/COPROPORPHYRIN III RATIO; PATTERN OF PORPHYRIN ELEVATIONS

IF COPROPORPHYRIN I/COPROPORPHYRIN III RATIO HIGH:

- ◆ Causes:
 - » Exposure to:
 - Arsenic
- ◆ Treatments:
 - » Look for exposure—See “Managing Patients with Metal Toxicities” on page 59 for specific treatment information
 - » Evaluate urine, challenged urine or whole blood to track toxic element status
 - » Elevation of the Copro I/III ratio lets you spot the potential arsenic-specific effects. Arsenic causes a diversion away from the enzymatic product (Copro III) to the non-enzymatic one (Copro I). This effect is rarely dramatic, so the ratio is useful.

General Pattern of Porphyria Elevations

- ◆ Causes:
 - » Exposure to:
 - Aluminum
 - Arsenic
 - Hexachlorobenzene
 - Dioxin
 - Polybromated biphenyl
 - Chronic alcohol intake
- ◆ Treatments:
 - » See “Treatments” on page 160 for specific treatment information

- » Evaluate urine, challenged urine or whole blood to track toxic element status

» In increased alcohol intake hepatic degeneration due to porphyrin accumulation in the liver is found in these conditions.

» Aluminum inhibits some heme synthetic enzymes and has been implicated in causing porphyria in chronic hemodialysis patients, who may be aluminum overloaded.

» Acute porphyrias

- ◆ Primary complaints:
 - » Neurologic presentations due to porphyrin accumulation:
 - Acute abdominal pain
 - Nausea
 - Vomiting
 - Constipation
 - Seizures

- ◆ Conditions that may precipitate acute porphyrias:

- » Low carbohydrate diets (skipped meals)
- » Intake of alcoholic beverages
- » Medications, including sulfa drug antibiotics, barbiturates, estrogen, birth control pills
- » Exposure to toxic chemicals

Note: See “Managing Patients with Metal Toxicities” on page 59 for specific treatment information

- ◆ Non-acute porphyrias:

- » Primary complaint:
 - Cutaneous presentation (photosensitivity)

Pattern of Porphyrin Elevations

- Pigmentation
 - Changes in facial hair
 - Fragile skin
 - Rashes
 - Blistering
- ◆ Conditions exacerbated by non-acute porphyrias:
- » All of the above
 - » Skin symptoms made worse by exposure to sunlight—copper or brass jewelry exacerbates reaction

NOTES**8****Hormones****Contents**

Adrenal Stress	169	Urinary Estrogen Metabolites (Estronex)	174
Cortisol; DHEA; Patterns of Adaptive Responses; Stress Responses of Cortisol and DHEA; Total Secretory IgA; IgA Antigliadin Antibody (AGA)		2-OHE:16 α -OHE1 Ratio (2:16); 2-Methoxyestrogens (2-OMeE), 4-Hydroxyestrogens (4-OHE), & 4-Methoxyestrogens (4-OMeE)	

Adrenal Stress

- ◆ Salivary cortisol (4 timed specimens: morning, noon, afternoon, midnight)
- ◆ Salivary DHEA (average of two specimen readings)
 - » Salivary cortisol and DHEA concentrations closely correlate with plasma levels.
 - » Diurnal patterns of cortisol and daily DHEA levels exhibit patterns characteristic of adaptation to stress stages.
 - » Inability to generate cortisol rhythms can affect energy levels, emotional state, disease resistance, and general sense of well-being.
 - » Saliva testing measures the free-circulating, biologically active hormones.
 - » Cortisol elevation also dampens immune responses,

and may reduce immunoglobulin responses, such as secretory IgA (sIgA) and antigliadin antibody (AGA) production.

- » Adrenal hyper- or hypo-function has far-reaching effects on the endocrine system as a whole, including thyroid and sex hormone production.

Cortisol

- ◆ Adrenal cortex production stimulated by ACTH (adrenocorticotropic hormone)
- ◆ Derived from cholesterol via pregnenolone and progesterone
- ◆ Primary functions
 - » Mobilize glucose control
 - » Regulate blood pressure
 - » Modulate immune function and inflammatory responses

Cortisol

- ◆ Circadian rhythm of cortisol regulated by the sleep-wake cycle—characterized by a steep increase in the morning, peaking at approximately 8 a.m., followed by a gradual tapering off until about midnight, when circulating levels are at their lowest.
- ◆ Highest peak concentrations normally occur in February, March, and April
- ◆ Lowest concentrations usually occur in July and August
- ◆ Daily secretion ~ 6–8 mg/m² body surface area (can increase 10 fold in acute, severe stress)

IF CORTISOL HIGH:

- ◆ Cause:
 - » May identify chronic stress
 - » Initially DHEA will also rise; sIgA may decrease
 - » Hyperthyroidism
 - » Cushing syndrome (primarily iatrogenic)
 - » Cushing disease (ACTH-producing adenoma in the pituitary gland)
 - » Ectopic ACTH-producing tumors
- ◆ Symptoms/Conditions:
 - » Stress intolerance
 - » Insomnia
 - » Chronic fatigue
 - » Allergies
 - » Osteoporosis
 - » Dysglycemia / dysinsulinemia
 - » Weight gain
 - » Depression

- » Hypertension
- » Muscular weakness
- » Thinning skin
- » Easy bruising
- » Moon-like facies
- » Hyperpigmentation
- » High serum free amino acids
- » A higher cortisol will create a negative feedback, decreasing ACTH production and consequently lowering cortisol.

Treatment:

- » See “Guidelines for Potential Intervention” on page 171
- » Reduce stress levels
- » Supplementing with calming botanicals, vitamin B₆ and/or magnesium as needed
- » Slowly taper exogenous corticoids
- » Surgical intervention as indicated for tumor

IF CORTISOL LOW:

- ◆ Cause:
 - » May identify adrenal fatigue/exhaustion; DHEA will also be low
 - » Addison disease (usually autoimmune destruction of adrenal gland, infection or cancer)
 - » Hypopituitarism
- ◆ Symptoms/Conditions:
 - » Weakness
 - » Fatigue
 - » Weight loss
 - » Insomnia
 - » Anxiety/depression



- » Nausea
 - » Lack of appetite
 - » Postural hypotension
 - » Hyperpigmentation
 - » Hyponatremia
 - » Hyperkalemia
- ◆ Treatment:
- » See table below for treatment suggestions.
 - » Corticosteroids, fluid and electrolyte replacement

DHEA

DHEA is secreted by the adrenal gland. The pituitary gland secretes adrenocorticotropic hormone (ACTH), which travels through the bloodstream to the adrenal glands located atop the kidneys. ACTH signals the adrenal glands to convert cholesterol to both DHEA and cortisol. DHEA is released into the bloodstream primarily as DHEA-sulfate (DHEA-S). DHEA serves as the precursor to both androgens and estrogens.

Guidelines for Potential Intervention

Test Results (Noon-PM Averages)		Adrenal Support Protocols Using Hormones, Extracts, and B-Vitamins					
Total Cortisol	DHEA	Pregnenolone	DHEA	Ginseng ^o	Licorice Root ^o	B Vitamins [^]	
High	High				+		+
High	Normal			+	++		+
High	Low			++	+++		+
Normal	High				++		
Normal	Low	+		++	++		+
Normal	High				++		
Low	Normal			+		++	
Low	Low	+++	+++	+++	+++	+++	+

This table is provided as a guide to potential ways that have been found to be beneficial when abnormal hormone patterns are found. Nutritional support for the adrenal glands may include 2000–5000 mg vitamin C and essential elements, including 20 mg zinc, 200 mg magnesium, and 400 mg calcium. Adrenal glandular extract may be added to assure return to normalcy for some abnormal patterns.

[^] 50 mg B-complex with 1000 mg pantothenic acid and 200 mg biotin.

^o Licorice root contains glycyrrhizin, a substance which extends the half-life of cortisol. Chronic use may deplete potassium and increase blood pressure.

Siberian ginseng can help to normalize elevated output of DHEA and cortisol.

Relaxation techniques have also been shown to normalize cortisol and DHEA output.

DHEA; Cortisol & DHEA

In addition to production in the adrenal cortex, DHEA is also synthesized in the brain and skin.

IF DHEA LOW:

- ◆ DHEA is frequently the first to become limited.
- ◆ DHEA will decline with early-stage chronic stress, while cortisol remains elevated.
- ◆ Consider late-stage chronic stress if cortisol is also low.
- ◆ DHEA levels begin to decrease after age 30.
- ◆ DHEA may be low in some people with anorexia, end-stage kidney disease, type 2 diabetes (non-insulin dependent diabetes), AIDS.
- ◆ Several drugs may decrease DHEA; insulin, corticosteroids, opiates, and danazol.
- ◆ There is significant research to support the use of supplementing with DHEA in depression, obesity, lupus and adrenal insufficiency.

IF DHEA HIGH:

- ◆ DHEA may increase with supplementation—re-evaluate dose.
- ◆ Cushing syndrome will lead to a rise in DHEA.
- ◆ Chromium picolinate may increase blood DHEA levels.

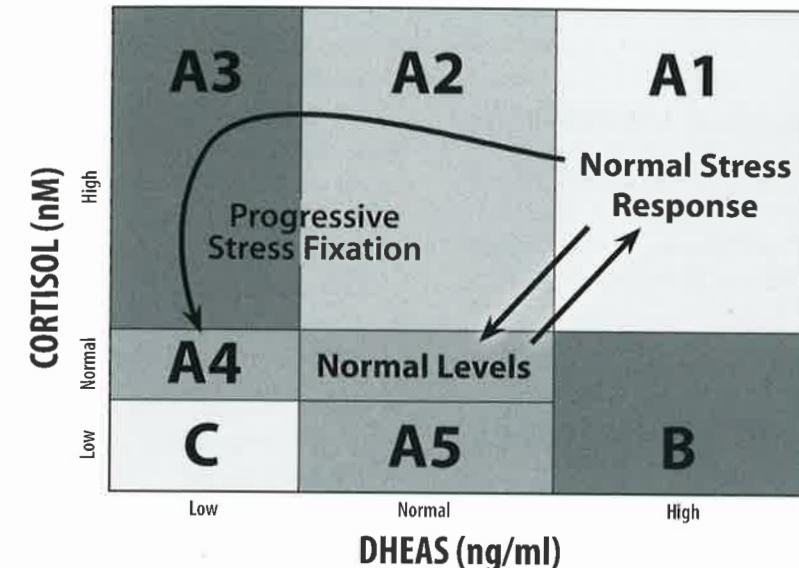
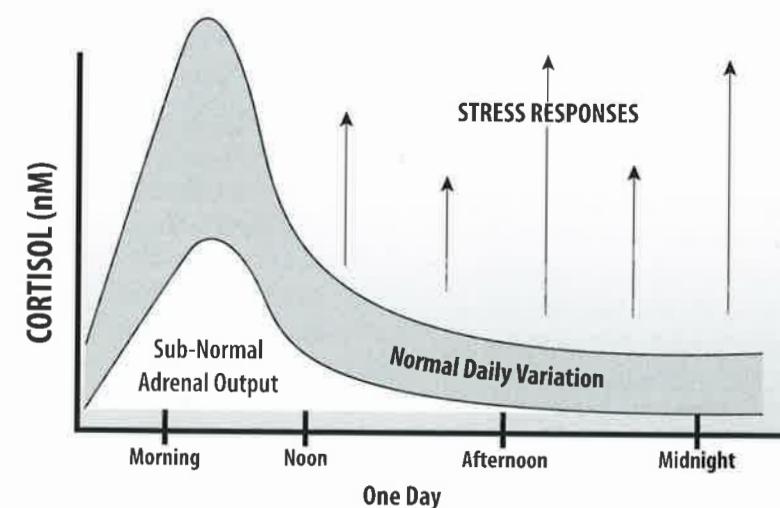
Patterns of Adaptive Responses

When forced to respond to continued, chronic stress the adrenal glands enter a compensated phase in which the production of the stress hormones is divergent. Because of the difference in response to ACTH, the production of DHEA falls as cortisol remains elevated. The process is shown graphically in the figure below where the initial stress response is labeled "A1." The negative feedback of cortisol on the hypothalamus is lost as higher cortisol is required to shut down adrenal responses and bring ACTH into the normal range.

Stress Responses of Cortisol and DHEA

Later phases of compensated response may go through the progression from "A2" to "A5." The progression has been called "stress fixation." Output of DHEA falls from high to normal to low followed by the same progression for cortisol. If the stress is prolonged, the production of both hormones falls into the sector labeled "C." Individuals affected with Addison disease, where the adrenals are unable to produce stress hormones, have values that fall into the "C" sector. The rare finding of elevated

DHEA with normal or low cortisol (Type "B") is genetically determined and these individuals should avoid high stress occupations.

Patterns of Cortisol and DHEA in Stages of Stress**Circadian Cortisol Rhythm**

Total Secretory IgA; IgA Antigliadin Antibody; 2-OHE:16 α -OHE1 Ratio

Total Secretory IgA

- ◆ See "Total Immunoglobulin A (IgA)" on page 186

Note: Total IgA and IgA AGA are part of the **Adrenal Stress Plus Profile**

IgA Antigliadin Antibody (AGA)

- ◆ See "Total Immunoglobulin A (IgA)" on page 186

Note: Total IgA and IgA AGA are part of the **Adrenal Stress Plus Profile**

Urinary Estrogen Metabolites (Estronex)

- ◆ Phase 1 estrogen metabolism occurs via a number of CYP450 pathways, including 1A1, 1B1 and 3A4, which yield 2-hydroxyestrogens (2-OHE), 4-hydroxyestrogens (4-OHE) and 16 α -hydroxyestrone (16 α -OHE1), respectively.
- ◆ 2-OHE and 4-OHE are further metabolized via catechol-O-methyltransferase (COMT) to the 2-methoxyestrogens (2-OMeE) and 4-methoxyestrogens (4-OMeE).
- ◆ 2-OMeE, 4-OMeE and 16 α -OHE1 metabolites may also be conjugated via sulfation and glucuronidation.
- ◆ Imbalances in the ratios of these compounds demonstrate compromised phase 1 and 2 detoxification and biotransformation and have been associated with an increased risk for certain cancers, including breast, prostate and colon.

2-OHE:16 α -OHE1 Ratio (2:16)

- ◆ The 2-OHE are associated with reduced cancer growth, and are referred to as "good" estrogen metabolites.
- ◆ 16 α -OHE1 is a powerful estrogen receptor agonist, shown to encourage tumor development.
- ◆ Ratio is stable over the menstrual cycle
- ◆ Influence of ratio on breast cancer risk may be different for pre- and post-menopausal women, although a low ratio has been shown as significant for both groups.

IF 2:16 RATIO LOW (BELOW 2.0)

- ◆ Increased risk of estrogen sensitive cancers:
 - » Uterine
 - » Ovarian
 - » Cervical
 - » Prostate
- ◆ Other cancer associations:
 - » Head and neck cancers
- ◆ Polycystic Ovarian Syndrome (PCOS)
- ◆ Treatment:
 - » Lower an elevated BMI
 - » Supplement with di-indolemethane (DIM) or indole-3-carbinol (I3C)
 - Stimulate hepatic P450-1A1 biosynthesis
 - » Increase cruciferous vegetables, including: broccoli, cabbage, and Brussels sprouts



- ◆ Natural sources of DIM and I3C
- » Increase ground flax seed or soy isoflavones
- » Increase intake of fish oils:
 - Omega-3 fatty acids
- » Supplement with dried organic Brussels sprouts and kale
- » Increase fruit and vegetable intake
- » Oral contraceptive users may have significantly lower 2:16 ratios.
- » Ensure adequate estrogen receptor functions:
 - Higher levels of inflammation can impact estrogen receptor reactivity.
 - Oxidative stress must be assessed to assure adequate hormone function.
- » Evaluate markers for oxidative stress, such as p-hydroxyphenyllactate, 8-hydroxy-2'-deoxyguanosine, and lipid peroxides
- » Ensure adequate estrogen detoxification
 - Hepatic Phase II sulfation, glucuronidation and methylation may be supported with sulfur-rich compounds, calcium and methyl donors such as SAMe, B₁₂, folic acid and B₆.
- » Supplement with D-glucarate to ensure adequate gut elimination by preventing bacterial deconjugation

IF 2:16 RATIO HIGH

- ◆ Most but not all epidemiological studies have found that women

2-OHE:16 α -OHE1 Ratio — 2-OMeE, 4-OHE; 4-OMeE

with a high urinary 2:16 ratio are at reduced risk for breast cancer.

However, excessive reduction of 16 α -hydroxyestrone may reduce bone formation because this metabolite acts to stimulate osteogenesis. There is also some evidence of increased oxidant stress.

- ◆ Check methylation activity (homocysteine, B₁₂, folic acid status). Since metabolism of 2OHE is dependent on SAMe, accumulation of 2OHE may demonstrate poor methylation activity.
- ◆ Treatment:
 - » Consider need to reduce therapies that enhance 2-hydroxylation (see above)
 - » Increase antioxidants

2-Methoxyestrogens (2-OMeE), 4-Hydroxyestrogens (4-OHE), & 4-Methoxyestrogens (4-OMeE)

- ◆ 2-OMeE
 - » Produced from 2-OHE via COMT
 - » Highly potent anticancer effects
 - » Lower amounts found in urine of breast cancer patients
- ◆ 4-OHE
 - » Produced by CYP1B1
 - » CYP1B1 is found in breast, prostate and other tissue
 - » Human breast cancer tissue produces higher 4-OHE than normal breast tissue.

—2-OMeE, 4-OHE; 4-OMeE

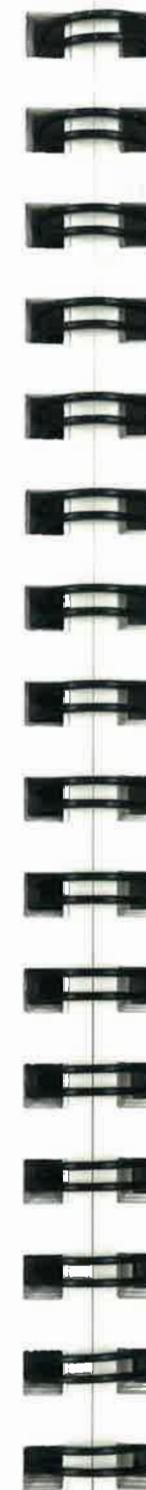
- » High activity CYP1B1 genetic polymorphism is associated with increased risk for estrogen-sensitive cancers.
- » Elevated in colorectal cancer biopsy tissue
- » Can be converted to DNA-damaging estrogen quinones, which are higher in urine of those with and those at high risk for breast and prostate cancer (2-OHE does not form significant amounts of estrogen quinones)
- » 4-OHE is deactivated via COMT to non-carcinogenic 4-OMeE.
- ◆ 4-OMeE
 - » Produced from 4-OHE via COMT
 - » Deactivated, non-carcinogenic metabolite
 - » Low 4-OMeE found in urine of high-risk and breast cancer patients
 - » High COMT activity associated with reduced risk for certain cancers

IF 2-OHE:2-OMeE RATIO HIGH

- ◆ Imbalanced estrogen metabolism
- ◆ Low activity COMT—impaired methylation
- ◆ Low 2-OMeE associated with pre-eclampsia
- ◆ Insufficient cancer-protective 2-OMeE
- ◆ Treatment:
 - » See methylation, COMT below

IF 4-OHE:4-OMeE RATIO HIGH

- ◆ Imbalanced estrogen metabolism
- ◆ Low activity COMT—impaired methylation
- ◆ High activity CYP1B1
- ◆ High urinary ratio may be found in those at high risk for breast cancer.
- ◆ Treatment:
 - » Evaluate methylation activity: homocysteine, B₁₂ and folic acid status
 - » Consider genetic testing for COMT and CYP1B1 activity, particularly if positive family history
 - » Reduce stress: COMT is involved in the metabolism of catecholamines, reducing availability for estrogen metabolism.
 - » B₁₂, 1000–5000 µg/d
 - » Folic acid, 400–800 µg/d
 - » SAMe, 200 mg BID
 - » B₆, 100 mg/d
 - » Glutathione (reduction of estrogen quinones), 300–1000 mg/d, or, NAC, 500–1500 mg/d
 - » Resveratrol (prevents estrogen quinone formation), 200–400 mg/d
 - » Selenium, 55–400 µg/d
 - » Zinc, 15–65 mg/d
 - » Magnesium, 300–700 mg/d
 - » See above treatment for 2:16 ratio (therapies will increase CYP1A1 and decrease CYP1B1 activity)



9

Disease Risk Profiles

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- Cardiovascular Disease Risk Markers 177
Total Cholesterol; LDL Cholesterol; HDL Cholesterol; Triglycerides; Lipoprotein (a); Ferritin; Fibrinogen; c-Reactive Protein; Insulin; Testosterone; Sex Hormone Binding Globulin and Free Androgen Index; RBC Magnesium; Homocysteine; Coenzyme Q10, Lipid Peroxides, and α-Tocopherol; ADMA

- Celiac Disease and Gluten Intolerance 186
GI Symptoms of Gluten Intolerance; Total Immunoglobulin A (IgA); IgA Transglutaminase Antibody (IgA tTG); Anti-gliadin IgA
- Bone Loss 189
Deoxypyridinoline (DPD)

Cardiovascular Disease Risk Markers

The following analytes, reported with the Cardiovascular Health profile and the CardioION profile, are used to evaluate risk of cardiovascular disease.

Total Cholesterol

- ◆ A steroid alcohol C27H45OH present in animal cells and body fluids that regulates membrane fluidity, functions as a precursor molecule in various metabolic pathways and as a constituent of LDL may contribute to arteriosclerosis
- ◆ Endogenous synthesis is stimulated by insulin; inhibited by glucagon
- ◆ As with most metabolic processes, genetics and environment influence cholesterol fractions and production

- ◆ Major dietary sources of cholesterol include cheese, egg yolks, beef, pork, poultry, and shrimp

IF CHOLESTEROL HIGH:

- ◆ Causes:
 - » Hyperinsulinemia
 - » Metabolic syndrome
 - » Type 2 Diabetes
 - » Excess carbohydrate intake
 - » Medications: aspirin, oral contraceptives, steroids, thiazides, some beta blockers and sulfonamides

Total Cholesterol; LDL Cholesterol; HDL Cholesterol

- » Stress
- ◆ Treatment:
 - » Garlic, 4 g fresh garlic or 8 mg of essential oil/d
 - » Niacin (B_3), 50–3,000 mg/d
 - » Vitamin C, 1,000–5,000 mg/d
 - » Vitamin E, 200–800 IU/d (mixed tocopherols)
 - » Fish oil, EPA, 1–3 g/d; DHA, 1–3 g/d

LDL Cholesterol

- ◆ A lipoprotein of blood plasma that is composed of a moderate proportion of protein with little triglyceride and a high proportion of cholesterol and that is associated with increased probability of developing atherosclerosis—also called “bad cholesterol”, beta-lipoprotein, low-density lipoprotein

IF LDL HIGH:

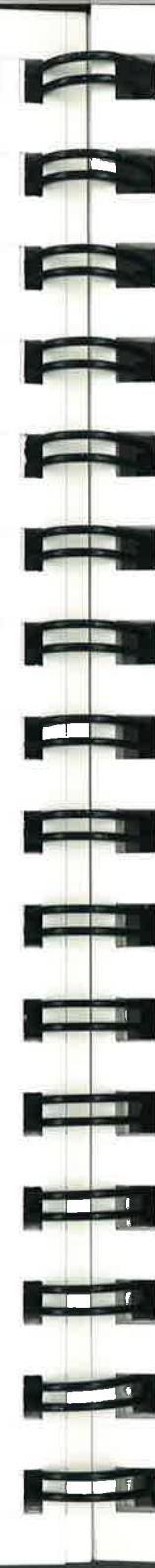
- ◆ Causes:
 - » See “If Cholesterol High:” on page 177
 - » Hypothyroidism
 - » Alcohol intake (excessive)
 - » Liver disease
 - » Cushing syndrome (hypercortisolism)
- ◆ Treatment:
 - » See “Treatment” under “If Cholesterol High” above

IF LDL LOW:

- ◆ Causes:
 - » Statin therapy
 - » Long term low carbohydrate diet
 - » Insufficient caloric intake
 - » Vegetarian diet
 - » Low LDL has been associated with dementia
 - » Hyperthyroidism
- ◆ Treatment:
 - » Consider statin reduction
 - » Increase carbohydrate intake
 - » Increase calorie intake
 - » Increase cholesterol-rich foods

HDL Cholesterol

- ◆ A lipoprotein of blood plasma that is composed of a high proportion of protein with little triglyceride and cholesterol
- ◆ HDL is associated with decreased probability of developing atherosclerosis—called also alpha-lipoprotein, “good cholesterol,” high-density lipoprotein
- ◆ Niacin reduces atherogenic apolipoprotein (Apo) β , increases anti-atherogenic Apo $\alpha 1$
- ◆ Pro-inflammatory eicosanoids decrease HDL
- ◆ Fish oil increases anti-inflammatory eicosanoids
- ◆ Vitamin C raises HDL and lowers triglycerides

**IF HDL LOW:**

- ◆ Causes:
 - » Insufficient exercise
 - » Dysinsulinemia
 - » Heart disease (HDL decreases for up to three months post-myocardial infarction)
 - » Smoking
 - » Alcohol intake (excessive)
 - » Liver disease
 - » Hypoproteinemia
- ◆ Treatment:
 - » Niacin (B_3), 50–3,000 mg/d
 - » Fish oil, EPA, 1–3 g/d; DHA, 1–3 g/d
 - » Vitamin C, 1,000–5,000 mg/d

Triglycerides

- ◆ Any of a group of lipids that are esters formed from one molecule of glycerol and three molecules of one or more fatty acids—are widespread in adipose tissue, and commonly circulate in the blood in the form of lipoprotein—also called neutral fat
- ◆ Elevated triglycerides are associated with metabolic syndrome, increased risk of coronary artery disease and stroke
- ◆ Carnitine increases oxidation of fatty acids
- ◆ Chromium potentiates insulin response, lowering triglyceride rich particles
- ◆ Fish oil activates PPARs, increasing fatty acid oxidation

HDL Cholesterol; Triglycerides

- ◆ Vitamin C increases the uptake of triglycerides into cells
- ◆ Food sources:
 - » Triglycerides in plasma are derived from fats eaten in foods or made in the liver from other energy sources like carbohydrates
 - Calories ingested in a meal and not used immediately by tissues are converted to triglycerides and transported to fat cells to be stored
 - Hormones regulate the release of triglycerides from fat tissue so they meet the body's needs for energy between meals.

IF TRIGLYCERIDES HIGH:

- ◆ Causes:
 - » Hyperinsulinemia
 - » Metabolic syndrome
 - » Type 2 diabetes
 - » Alcoholism
 - » Coronary artery disease
 - » Hypothyroidism
 - » Hyperlipidemia
 - » Pregnancy
 - » Medications: cholestyramine, estrogens, oral contraceptives
- ◆ Treatment:
 - » Carnitine, 250–1,000 mg/TID
 - » Chromium, 200–1,000 $\mu\text{g}/\text{d}$
 - » Fish oil, EPA, 1 g/d; DHA, 1 g/d
 - » Vitamin C, 1,000–5,000 mg/d
 - » Reduce carbohydrate intake

Lipoprotein (a); Ferritin; Fibrinogen

Lipoprotein (a)

- ◆ Like other lipoproteins, Lp(a) (pronounced lipoprotein little a") is comprised of cholesterol, fatty acids and protein.
- ◆ Studies have identified Lp(a) as a putative risk factor for atherosclerotic diseases such as coronary heart disease and stroke.
- ◆ Competing with plasminogen, Lp(a) binds to fibrin and to membrane proteins of endothelial cells and monocytes. It inhibits the binding of plasminogen and formation of plasmin, allowing fibrin and cholesterol to deposit at locations of vascular injury, leading to increased risk of cardiovascular disease
- ◆ Lp(a) elevation is primarily attributed to genetic polymorphisms

IF LIPOPROTEIN (A) HIGH:

- ◆ Causes:
 - » Genetic predisposition
- ◆ Treatment:
 - » Niacin, 50–3,000 mg/d (monitor liver enzymes)

Ferritin

- ◆ A crystalline iron-containing intracellular protein that functions in the storage of iron and is found especially in the liver and spleen

IF FERRITIN HIGH:

- ◆ Causes:
 - » Excess intake of iron supplements
 - » Inflammation—arthritis, etc.

- » Alcoholic liver disease
- » Hemochromatosis
- » Hemolytic anemia
- » Hodgkin lymphoma
- » Megaloblastic anemia
- » Infection
- » Vitamin C potentiates iron absorption

Treatment:

- » Reduce inflammation
- » Phlebotomy
- » Desferrioxamine
- » Black or green tea, coffee, phytates, calcium, soy

IF FERRITIN LOW:

- ◆ Causes:
 - » Long-term digestive tract bleeding
 - » Heavy menstrual bleeding
 - » Iron deficiency anemia
 - » Malabsorption e.g. celiac disease
- ◆ Treatment:
 - » Identify cause
 - » Iron, 30 mg TID (monitor ferritin levels)
 - » Vitamin C, 1–5 g/day
 - » Taurine, 1 g/day

Fibrinogen

- ◆ A plasma protein that is produced in the liver and is converted into fibrin during blood clot formation
- ◆ Elevated fibrinogen increases risk of developing blood clots.
- ◆ Fish oil reduces thrombin



formation and garlic inhibits platelet aggregation.

IF FIBRINOGEN HIGH:

- ◆ Causes:
 - » Acute infections
 - » Cancer
 - » Coronary heart disease
 - » Myocardial infarction
 - » Stroke
 - » Inflammatory disorders (like rheumatoid arthritis and glomerulonephritis)
 - » Trauma
- ◆ Treatment:
 - » Fish oil, EPA, 1–3 g/d; DHA, 1–3 g/d
 - » Garlic, 4 g fresh garlic or 8 mg of essential oil/d

c-Reactive Protein (hs-CRP)

- ◆ High sensitivity c-reactive protein is a test that measures the amount of a protein in the blood that signals acute inflammation.
- ◆ The major factors that promote atherogenesis—cigarette smoking, hypertension, atherogenic lipoproteins, and hyperglycemia can also cause stimuli that release chemicals and activate cells involved in the inflammatory process. These events are thought to contribute not only to the formation of plaque but may also contribute to its disruption resulting in the formation of a blood clot. Thus, virtually every step in atherogenesis is believed to involve

Fibrinogen; hs-CRP; Insulin

substances in the inflammatory response and cells that are characteristic of inflammation.

- ◆ Elevated hs-CRP levels increase the risk of myocardial infarction
- ◆ Fish oil produces anti-inflammatory eicosanoids and helps to reduce c-reactive protein

IF hs-CRP HIGH:

- ◆ Causes:
 - » Cancer
 - » Connective tissue disease
 - » Heart attack
 - » Infection (also stealth infection e.g. periodontal disease)
 - » Inflammatory bowel disease (IBS)
 - » Lupus
 - » Pneumococcal pneumonia
 - » Rheumatoid arthritis
 - » Tuberculosis
 - » General inflammation
- ◆ Treatment:
 - » Fish oil, EPA, 1–3 g/d; DHA, 1–3 g/d

Insulin

- ◆ Elevated fasting insulin is a hallmark of the metabolic syndrome in which poor insulin sensitivity is offset by progressively increasing insulin secretion in response to a standard glucose load.
- ◆ Chronic insulin elevation stimulates lipogenesis, leading to hypertriglyceridemia.

Insulin; Testosterone

- ◆ Insulin sensitivity may be improved by normalizing chromium
- ◆ Niacin can lower serum lipids and lipoic acid can enhance insulin sensitivity.

IF INSULIN HIGH:

- ◆ Causes:
 - » Excess carbohydrate intake
 - » Insulin resistance
 - » Obesity
 - » Cushing syndrome (hypercortisolism)
 - » Diabetes
 - » Fructose or galactose intolerance
 - » Medications: corticosteroids, levodopa, oral contraceptives
- ◆ Treatment:
 - » Chromium, 200–1,000 µg/d
 - » Niacin, 50–3,000 mg/d
 - » α-Lipoic acid, 200–1800 mg/d; or r-lipoic acid, 30–100 mg/d
 - » Cinnamon, ½ tsp/d
 - » Conjugated linoleic acid (CLA), 1 g TID

Testosterone

- ◆ Testosterone is negatively associated with all other risk factors for cardiovascular disease, and interventions that normalize low testosterone levels can help to reduce other risk factors.

IF TESTOSTERONE HIGH:

- ◆ Female:
 - » Polycystic ovarian syndrome
 - » Taking testosterone or DHEA supplement
- ◆ Male:
 - » Testosterone or DHEA supplementation
- ◆ Treatment:
 - » Discontinue or reduce supplementation

IF TESTOSTERONE LOW:

- ◆ Causes:
 - » Male:
 - Aging
 - Obesity
 - Hypothyroidism
 - Diabetes
 - » Female:
 - Menopause
- ◆ Symptoms/Conditions:
 - » Diminished libido
 - » Osteoporosis
 - » Anemia
 - » Depression
 - » Cognitive decline
 - » Myopathy



- ◆ Treatment:

- » Male:
 - Testosterone, 100 mg IM every 2 weeks
 - DHEA, 25–50 mg/d
 - Boron, 1–12 mg/d
 - Zinc, 15–65 mg/d

- » Female:
 - DHEA, 25–50 mg/d
 - Boron, 1–12 mg/d
 - Zinc, 15–65 mg/d

Sex Hormone Binding Globulin and Free Androgen Index

- ◆ Sex hormone-binding globulin (SHBG) is a serum glycoprotein that transports testosterone and estradiol.
- ◆ Only a small fraction of circulating sex hormones are unbound, or "free," and thus biologically active and able to enter a cell and activate its receptor.
- ◆ Elevated SHBG effectively lowers available hormone levels.
 - » As SHBG rises, calculated free androgen index (FAI=Total Testosterone / SHBG) falls

IF SHBG HIGH (FREE ANDROGEN INDEX LOW):

- ◆ Treatment:
 - » Urtica dioica, 4–6 g/d
 - » Arginine, 3–6 g/d (IV arginine has also been used)
 - » Vegetarian diet

Testosterone; SHBG; RBC Magnesium; Homocysteine

- » Correct insulin resistance and hypothyroidism if present
- » Exercise

RBC Magnesium

- ◆ See "Magnesium" on page 39

Homocysteine

- ◆ Homocysteine is the demethylated form of methionine
- ◆ Precursor to cysteine and glutathione
- ◆ Associated with pathophysiology of atherosclerosis

IF HOMOCYSTEINE HIGH:

- ◆ Causes:
 - » Impaired function of methylenetetrahydrofolate reductase for conversion to methionine
 - » Impaired function of cystathione β-synthase for conversion to cystathione
 - » Smoking
 - » Menopause
 - » Drugs, alcohol
 - » Toxins
 - » Renal failure
 - » Hereditary predisposition
 - » Deficiency of B vitamins or folate
 - » Elevations of homocysteine, methylmalonate and formiminoglutamate (FIGLU) are the most sensitive indicators for megaloblastic anemia.

Homocysteine; CoQ10; Lipid Peroxides; α -Tocopherol; ADMA

- ◆ Symptoms/Conditions:
 - » Increased risk of:
 - Atherosclerosis, particularly in smokers
 - Cardiovascular disease
 - Ocular abnormalities
 - Neurological abnormalities
 - Musculoskeletal abnormalities
 - Joint abnormalities
 - Placental thrombosis, abruption and miscarriage
 - » CNS problems:
 - Mental retardation
 - Seizures
 - Stroke
 - » Osteoporosis—impaired cross-linking of collagen
- ◆ Treatment:
 - » Stop precipitating causes (smoking, alcohol, etc.)
 - » Betaine, 1–2 gm TID
 - » Magnesium, 200 mg BID
- ◆ If xanthurene also elevated:
 - Vitamin B₆ (pyridoxine), 100 mg/d
- ◆ If FIGLU also elevated:
 - Folic acid, 800 μ g/d or
 - 5-methyltetrahydrofolate if level remains high
- ◆ If methylmalonate also elevated:
 - Vitamin B₁₂ (cobalamin), 1000 μ g/d

IF HOMOCYSTEINE LOW:

- ◆ Causes:
 - » Depletion of sulfur amino acid pools
 - » Elevated toxicant or oxidant challenge leading to glutathione depletion
- ◆ Symptoms/Conditions:
 - » Heightened sensitivity to drugs and toxicants
 - » Impaired methylation capacity
 - » Frequently found in autistic patients
- ◆ Treatment:
 - » See “ α -Hydroxybutyrate (AHB)” on page 118

Coenzyme Q10, Lipid Peroxides, and α -Tocopherol

- ◆ See “Fat-Soluble Vitamins” on page 61

ADMA

ADMA is included in this chapter, rather than the Amino Acids chapter, because it is frequently ordered with the **Cardiovascular Profile**.

- ◆ ADMA is an endogenous nitric oxide synthase (NOS) inhibitor.
- ◆ NOS produces nitric oxide (NO) and citrulline from arginine.
- ◆ Arginine stimulates NO synthesis to overcome the inhibitory effects of high ADMA.
- ◆ High levels of ADMA result



- in lower levels of NO and elevated plasma arginine.
- ◆ NO is a vasodilator without which normal blood pressure cannot be maintained.
- ◆ By inhibiting NO production, ADMA may impair blood flow, accelerate atherogenesis, and interfere with angiogenesis.
- ◆ ADMA degradation is inhibited by hypercholesterolemia, oxidized LDL, elevated homocysteine and hyperglycemia.
- ◆ ADMA is formed by the methylation of arginine residues of nuclear proteins. It may be increased by methionine loading.

IF ADMA HIGH:

- ◆ Causes:
 - » Cardiovascular disease
 - » Renal insufficiency or failure
 - » Hypertension
 - » Hypercholesterolemia (oxidized LDL)
 - » Preeclampsia
 - » Diabetes mellitus
 - » Tobacco use
 - » PCOS
 - » Aging
- ◆ Symptoms/Conditions:
 - » Erectile dysfunction
 - » Hypertension
 - » Preeclampsia
 - » Dysinsulinemia
 - » PCOS
 - » Independent CVD risk factor
- ◆ Treatment:
 - » Evaluate markers of inflammation:
 - hsCRP, fibrinogen, Lp(a); ferritin
 - » Vitamin A, 5,000–25,000 IU/d
 - » Vitamin E, 100–1,600 IU/d
 - » Vitamin C, 1,000–5,000 mg/d

- ◆ Treatment:
 - » Identify and treat underlying cause of elevated ADMA
 - » Avoid or decrease alcohol
 - » Decrease saturated dietary fats and increase healthy carbohydrates
 - » Folate, 400–5000 μ g/d
 - » B₁₂, 100–1,000 μ g/d
 - » B₆, 10–200 mg/d
 - » Arginine, 3–6 g/d

IF ADMA LOW:

- ◆ Causes:
 - » Consuming a diet rich in complex-low glycemic carbohydrates
 - » Arginine deficiency
 - » Tetrahydrobiopterin deficiency

- ◆ Symptoms/Conditions:
 - » Aging due to oxidative stress (excess NO reacts with superoxide to produce highly reactive peroxynitrite)
 - » Increased LDL oxidation
 - » Increased neurotoxicity

- ◆ Treatment:
 - » Evaluate markers of inflammation:
 - hsCRP, fibrinogen, Lp(a); ferritin
 - » Vitamin A, 5,000–25,000 IU/d
 - » Vitamin E, 100–1,600 IU/d
 - » Vitamin C, 1,000–5,000 mg/d

Celiac Disease; Gluten; IgA

Celiac Disease and Gluten Intolerance

Celiac disease is an autoimmune disorder of the small intestine leading to damage of the mucosa, resulting in malabsorption and autoimmune reactions. Malabsorption eventually results in multiple, potentially severe nutritional deficiencies, such as vitamin B₁₂ or iron (consider laboratory evaluation of nutrient levels).

Celiac disease is diagnosed more often in Caucasian or Western populations. It is estimated that 1:250 to 1:67 people may be inflicted with the disease, and more than 2 million people in the United States are currently undiagnosed. Genes associated with celiac include HLA DQ2 and Q8.

Unfortunately the clinical presentation of patients with celiac disease ranges from asymptomatic to severe, making it difficult to diagnose, often taking many years. Celiac disease significantly increases the risk of developing autoimmune diseases, such as arthritis or lupus. Early diagnosis and treatment may decrease the incidence of related diseases.

Gluten is a prolamin-type of protein that refers to the offending protein in wheat, barley and rye. Prolamins are plant proteins with high proline content that are difficult to digest by human gastric and pancreatic enzymes. Most commonly consumed cereal grains contain prolamins, including wheat (gliadin), barley (hordein), rye (secalin), corn (zein—not harmful for celiac patients) and oats (a minor protein, avenin). The standard recommendation is to avoid wheat, barley, rye and oats if the oats have been contaminated with the other three grains.

GI Symptoms of Gluten Intolerance

- ◆ Gastrointestinal distress (gas, bloating, diarrhea, constipation, vomiting, reflux, IBS symptoms)
- ◆ Dermatitis herpetiformis
- ◆ Fatigue
- ◆ Nutrient deficiencies
- ◆ Headaches (including migraines)
- ◆ Infertility
- ◆ Mouth sores
- ◆ Weight loss/gain
- ◆ Inability to concentrate—moodiness/depression

- ◆ Bone/joint/muscle pain
- ◆ Short stature
- ◆ Tingling numbness in the legs
- ◆ Anemia
- ◆ Renal disease

Total Immunoglobulin A (IgA)

- ◆ IgA is the second most abundant immunoglobulin in human plasma, accounting for 10–15% of the total
- ◆ It is the primary immunoglobulin found in mucosal surfaces, where it has a half life is 6 days
- ◆ It is secreted in tears, mucus



and saliva as a protection against microbial invasion

IF IgA HIGH:

- ◆ Causes:
 - » Bacteria, pathogen or yeast infection (confirm by GI fx profile)
 - » Certain liver diseases
 - » Food intolerances
 - » Some types of leukemia
 - » Kidney disease
 - » Respiratory and gastrointestinal infections
 - » Ataxia telangiectasia (rare)
- ◆ Treatment:
 - » Support immune function
 - » Identify and treat intestinal pathogens, bacteria or yeast overgrowth
 - » Rule out food sensitivities

IF IgA LOW:

- ◆ Causes:
 - » Protracted GI inflammation may result in IgA insufficiency
 - » Chronic stress, such as adrenal fatigue
 - » Immune suppressing medication
 - » Protein insufficiency
 - » IgA deficiency, 1 in 333 people have genetic IgA deficiency—can lead to false negatives on Celiac test

IF IgA tTG HIGH:

- ◆ Causes:
 - » Intestinal mucosal degeneration as found in celiac and non-celiac gluten sensitivity

IgA; IgA tTG

- » Support replacement of gut mucosa
 - Glutamine
 - Probiotics (*S. boulardii*, *Bifidobacterium*)
 - Colostrum
 - Zinc
 - Immunoglobulins
 - Essential fatty acids
- » Reduce stress
- » Assess vitamin D status

IgA Transglutaminase Antibody (IgA tTG)

- ◆ The IgA tTG antibody ELISA test has a high sensitivity (95–98%) and specificity (94–95%) in identifying those with untreated gluten sensitivities or celiac disease. The IgA tTG antibody is produced as part of the immune response to the release of transglutaminase from damaged enterocytes
- ◆ Children under 2 years of age are generally not able to mount an appropriate IgA tTG response and thus the anti-gliadin IgA is recommended
- ◆ Deficiency of total IgA can result in a false low IgA tTG

IgA tTG; Anti-gliadin IgA

- ◆ Treatment:
 - » Avoid gluten (wheat, barley, rye, and cross-contaminated oats)
 - » Evaluate for nutritional deficiencies resulting from malabsorption caused by damaged intestinal mucosa

Anti-gliadin IgA

- ◆ Anti-gliadin IgA antibodies develop against gliadin and are ideal for monitoring compliance to a gluten free diet.
- ◆ Anti-gliadin IgA is not as sensitive or specific for diagnosing celiac disease, however, it may be useful for early stage identification of gluten enteropathy and extraintestinal manifestations of gluten sensitivity.
- ◆ In previous years anti-gliadin IgA was used for diagnosis of celiac disease, but its sensitivity and specificity are lower than IgAtTG. Patients should be on a gluten-containing diet for at least 2 months prior to the test.

NOTES

Bone LossDeoxypyridinoline (DPD)

The rate of bone loss is highly variable from one individual to another. Bone resorption involves breakdown of bone-specific collagen and release of specific peptide fragments such as DPD into urine. Measuring these peptides can provide an accurate way of assessing the rate of bone resorption.

DPD can be used to identify increased bone turnover, including monitoring efficacy of anti-resorptive therapies (such as bisphosphonates) in postmenopausal women and in those at risk of osteoporosis. Testing of DPD provides the most accurate bone loss assessment when multiple readings taken over several months are compared.

IF DPD HIGH:

- ◆ Causes:
 - » Gluten sensitivity (may be celiac or non-celiac gluten sensitivity) and currently eating gluten and have an adequate IgA level
 - » Non-adherence to gluten-free diet in those that have been identified as gluten sensitive
 - » Strengthens diagnosis of celiac disease
 - » May identify autoimmune disorders in the absence of gastrointestinal disease
- ◆ Treatment:
 - » Avoid gluten (wheat, barley, rye, and cross-contaminated oats)
 - » Support replacement of gut mucosa (see low total IgA above)

◆ Treatment:

- » Weight bearing exercise
- » Bone-sustaining/building nutrients:
 - Calcium, 1000 mg/day
 - Magnesium, 400 mg/d
 - Vitamin D, 2000 IU/d (or test blood level for more accurate dose)
 - Vitamin K, 250 µg/d (or test blood level for more accurate dose)
 - Boron, 3 mg/day

10 Analysis of Multiple Analyte Patterns

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Among the endless potential analyte patterns found on Metametrix profiles, several are frequently encountered and have high clinical relevance. The text on the following pages gives a thumbnail outline of some conditions indicated by specific abnormality patterns. Frequently-used treatments are shown and some other tests that can provide confirmatory evidence are listed.

For further explanation of the rationales and scientific evidence regarding the association of specific analytes with each abnormality, see *Laboratory Evaluations for Integrative and Functional Medicine* by Richard S. Lord and J. Alexander Bralley (2008).

Doses specified under "Treatments" are usually considered to be adequate for repletion of adults.

B-Complex; Niacin; Vitamin B₆

B-Complex Vitamin Insufficiency

- ◆ Metametrix Profiles and Patterns:
 - » Organic Acids
 - Concurrent elevations of all five keto acids
 - Pyruvate
 - α-Ketoglutarate
 - α-Ketoisocaproate
 - α-Ketoisovalerate
 - α-Keto-β-methylvalerate
- ◆ Other Tests to Consider (Significant Findings):
 - » Adrenal Stress Panel (Low cortisol/DHEA)
- ◆ Treatments:
 - » B-complex vitamin formula

Niacin Insufficiency

- ◆ Metametrix Profiles and Patterns:
 - » Organic Acids
 - Pyruvate—High
 - Lactate—Low
 - Picolinate—Low
 - » Fatty Acids
 - Fatty Acids—High
- ◆ Other Tests to Consider (Significant Findings):
 - » Cardio profile (Hypertriglyceridemia)
- ◆ Treatments:
 - » Niacin, 50–3000 mg

Vitamin B₆ Insufficiency

- ◆ Metametrix Profiles and Patterns:
 - » Organic Acids
 - Xanthurenone—High
 - Kynurenate—High
 - » Amino Acids
 - Multiple essential amino acids—High (esp. leucine, isoleucine, valine, phenylalanine, tryptophan or glutamine)
 - » Homocysteine—High
- ◆ Other Tests to Consider (Significant Findings):
 - » RBC Essential Elements (Low RBC magnesium)
- ◆ Treatments:
 - » Pyridoxine HCl, 50–200 mg/d

Vitamin B₁₂ / Folate; Lipoic Acid; BH₄

Vitamin B₁₂/Folate Insufficiency

- ◆ Metametrix Profiles and Patterns:
 - » Amino Acids
 - Homocysteine—High
 - Phosphoethanolamine—High
 - » Organic Acids (Confirmatory)
 - Methylmalonate—High
 - Formiminoglutamate—High
- ◆ Other Tests to Consider (Significant Findings):
 - » GIfx (dysbiosis and/or malabsorption; elevated anti gliadin antibodies)
- ◆ Treatments:
 - » Vitamin B₁₂, 1000–5000 µg/d
 - » Folic acid, 400–800 µg/d

Lipoic Acid Insufficiency

- ◆ Metametrix Profiles and Patterns:
 - » Organic Acids
 - Concurrent elevation of pyruvate and lactate
- ◆ Treatments:
 - » α-Lipoic acid, 100–1800 mg/d

Tetrahydrobiopterin (BH₄) Insufficiency

- ◆ Metametrix Profiles and Patterns:
 - » Amino Acids
 - Phenylalanine—High and Tyrosine—Low
 - » Organic Acids
 - VMA, HVA and 5-HIAA—Low
- ◆ Other Tests to Consider (Significant Findings):
 - » Neopterin & Biopterin (Various patterns—refer to chapter 2 in *Laboratory Evaluations for Integrative and Functional Medicine*)
- ◆ Treatments:
 - » Folate up to 10,000 µg/d
 - » BH₄ (Sapropterin), 10–20 mg/kg/d
 - » L-Tyrosine, 500–1500 mg/d

Carnitine; Copper; Essential Amino Acid Insufficiency

Carnitine Insufficiency

- ◆ Metametrix Profiles and Patterns:
 - » Organic Acids
 - Adipate, suberate and ethylmalonate—High
 - » Amino Acids
 - Lysine—Low
 - Methionine—Low
- ◆ Other Tests to Consider (Significant Findings):
 - » GIfx (dysbiosis and/or malabsorption)
- ◆ Treatments:
 - » L-Carnitine or Acetyl-L-Carnitine, 500–2000 mg TID

Copper Insufficiency

- ◆ Metametrix Profiles and Patterns:
 - » Organic Acids
 - VMA—High
 - HVA—Low
 - » RBC Essential Elements (Confirmatory)
 - Copper—Low
- ◆ Treatments:
 - » Copper gluconate, 2–10 mg/d

Chronic Essential Amino Acid Insufficiency

- ◆ Metametrix Profiles and Patterns:
 - » Amino Acids
 - Multiple essential amino acids—Low
- ◆ Other Tests to Consider (Significant Findings):
 - » Serum albumin protein (Low values confirm long-term protein insufficiency)
 - » Organic acids (Low neurotransmitter metabolites)
- ◆ Treatments:
 - » Balanced mixtures of free-form amino acids with vitamin B₆ and α-KG, 5–7 gm BID

Methylation Precursor; Essential Fatty Acid; PUFA-Induced Oxidative Challenge

Methylation Precursor Insufficiency

- ◆ Metametrix Profiles and Patterns:
 - » Amino Acids
 - Glycine, threonine, sarcosine—High
 - Phosphoethanolamine—High
 - Homocysteine—High
 - Methionine—Low
 - » Organic Acids
 - HVA—Low
 - VMA—Low
 - Pyroglutamate—High
- ◆ Other Tests to Consider (Significant Findings):
 - » GIfx (dysbiosis and/or malabsorption; elevated anti gliadin antibodies)
- ◆ Treatments:
 - » Betaine HCl, 500 mg at meal time
 - » Vitamin B₁₂, 1000–5000 µg/d
 - » Folic acid, 400–800 µg/d

Essential Fatty Acid Deficiency

- ◆ Metametrix Profiles and Patterns:
 - » Fatty Acids
 - ALA, EPA, LA, AA—Low
 - Mead, palmitoleic—High
- ◆ Treatments:
 - » Increase EFA-rich dietary oils
 - Fish oil

PUFA-Induced Oxidative Challenge

- ◆ Metametrix Profiles and Patterns:
 - » Fatty Acids
 - Polyunsaturated fatty acids—High
 - » Vitamins
 - Vitamin E, CoQ10—Low
 - » Lipid Peroxides
 - High
- ◆ Treatments:
 - Reduce fish oil supplements and/or add antioxidants

Fat Malabsorption; Glutathione Demand

Fat Malabsorption

- ◆ Metametrix Profiles and Patterns:
 - » Vitamins
 - Vitamins A, E, β-Carotene, D, CoQ10—Low
 - » Fatty Acids
 - Linoleic—Low
 - α-Linolenic—Low
 - Arachidonic—Low
 - EPA—Low even with supplement use
 - Mead—High
 - » GI Effects
 - Triglycerides and fatty acids—High
 - Elastase 1—Low or Normal

Glutathione Demand

- ◆ Metametrix Profiles and Patterns:
 - » RBC Essential Elements
 - Magnesium—Low
 - » Amino Acids
 - Methionine—Low
 - Taurine—Low
 - Homocysteine—Low or High
 - Glycine, serine and threonine—Low
 - » Organic Acids
 - α-Hydroxybutyrate—High
 - Pyroglutamate—High
 - Sulfate—Low

- ◆ Other Tests to Consider (Significant Findings):
 - » Organic Acids: (TCA intermediate elevation > CoQ10 insufficiency)
 - » Cardio Profile (Triglycerides—Low)
- ◆ Treatments:
 - » Fat-soluble vitamin mixtures
 - » Vegetable, nut and seed oils and fish oil supplements
 - » Pancreatic enzymes, ox bile

Treatments continue on following page...

Metabolic Syndrome; Wicosanoid Precursors & Inflammation

- » L-Methionine, 1000 mg/d (monitor homocysteine)
- » Taurine, 500 mg BID

- » α-Lipoic acid, 200 mg/d
- » Balanced amino acid blend

Metabolic Syndrome

- ◆ Metametrix Profiles and Patterns:
 - » Fatty Acids
 - Palmitic and stearic—High
 - Palmitoleic and oleic—High
 - May see general pattern of elevation of most fatty acids in hypertriglyceridemia, with the exception of omega-3s
 - » Organic Acids
 - α-Hydroxybutyrate—High
- ◆ Other Tests to Consider (Significant Findings):
 - » RBC Essential Elements (Low RBC chromium and magnesium)
 - » Cardio profile: (Hypertriglyceridemia, hyperlipidemia, elevated insulin)
- ◆ Treatments:
 - » Low carbohydrate diet
 - » Chromium 1000 µg/day
 - » Biotin 5–8 mg/day
 - » Omega-3 fatty acids 3–9 g/day

Eicosanoid Precursors & Inflammation

- ◆ Metametrix Profiles and Patterns:
 - » Fatty Acids
 - ALA, EPA and DHA—Low
 - AA—High
 - AA/EPA ratio—High
- ◆ Other Tests to Consider (Significant Findings):
 - » Organic Acids (Quinolinate—High, picolinate—High; 8-Hydroxy 2'-deoxyguanosine—High)
 - » IgG food sensitivities (Pattern of multiple elevations indicating intestinal hyperpermeability)
- ◆ Treatments:
 - » Reduce/normalize insulin levels
 - » Reduce red meats and corn products

Intestinal Dysbiosis

Intestinal Dysbiosis due to Carbohydrate Malabsorption

- ◆ Metametrix Profiles and Patterns:
 - » Organic Acids
 - Tricarballylate and d-Lactate—High
 - Methylmalonate—High
 - β-Hydroxyisovalerate—High
 - » RBC Essential Elements
 - Magnesium—Low
 - » GIfx
 - Various patterns of dysbiosis
 - pH—Low
 - IgA—Low or High
 - IgA AGA—High
 - Vegetable fibers—Many
 - Elastase 1—Low
- ◆ Other Tests to Consider (Significant Findings):
 - » IgG4 food sensitivities (pattern of multiple elevations indicating intestinal hyperpermeability)
 - » RBC elements (general pattern of low levels indicating maldigestion and malabsorption)
- ◆ Treatments:
 - » Low carbohydrate diet, avoid gluten
 - » Digestive enzymes
 - » Pre and probiotics
 - » 4-R protocol as indicated (see “Treatment Using Four “R” Program for Intestinal Health” on page 133)
 - » B₁₂, 1000–5000 µg/d
 - » Biotin, 500–5000 µg/d
 - » Magnesium, 300–750 mg/d

NOTES

Appendix

Interactions of Drugs, Nutritional Supplements and Dietary Components

Prescription Drugs

Drug Category	Affected Nutrients	Mechanism
Analgesic		<p>Drug most likely to produce vitamin C deficiency in normal individuals. Chronic use can cause iron depletion due to blood loss in GI tract. Aspirin depletes folic acid by displacing bound serum folate. Causes urinary loss of potassium.</p> <p>Depletion-related symptoms: weakness & low energy from anemia. Salicylates in high doses can reduce vitamin K epoxide reductase, resulting in vitamin K deficiency.</p> <p>Detoxification effects: Salicylates can decrease histidine levels. Aspirin overdose depletes plasma glycine.</p>
Aspirin, salicylates	Vitamin C, Folic Acid, Glycine, Histidine, Potassium, Zinc, Vitamin K	
Female Hormones		<p>Estrogen metabolism interferes with absorption of both folic acid and vitamin B₆. Since B₆ is involved with synthesis of serotonin, depletion can cause anxiety, depression, sleep disturbances, and irritability. Anemia from folate depletion causes weakness and low energy. Low levels of folic acid are associated with increased incidence of birth defects, cervical dysplasia, and elevated homocysteine, which is a major risk factor for cardiovascular disease.</p> <p>Studies show reduced serum levels of nutrients listed. Depletions of vitamins B₆, B₁₂, and C are not as frequently seen with the use of newer low dose estrogen OCs. Zinc deficiency can lead to depressed growth, poor immune function, and alopecia. OCs may increase serum retinol.</p>
Estrogens	Vitamin B ₆ , Folic Acid	
Oral Contraceptives	Vitamin A, B ₂ , B ₆ , B ₁₂ , C, Folic Acid, Zinc, Magnesium	

Table continues on following page...

Prescription Drugs

Drug Category	Affected Nutrients	Mechanism
Diuretics		
Hydralazine (Apresoline)	Vitamin B ₆ , Magnesium	These antihypertensives also are diuretics and block an enzyme, which can cause vitamin depletion. B ₆ deficiency can cause depression and/or nerve damage, causing numbness or tingling of hands or feet.
Loop Diuretics: Furosemide (Lasix), Bumetanide (Bumex), Torsemide (Demadex), Ethacrynic acid (Edecrin)	Magnesium, Vitamin B ₁ , Vitamin B ₆ , Potassium, Zinc	Diuretic-induced magnesium and potassium deficiencies can cause increased irregularities in heartbeat and blood pressure. Increased urination may also cause depletion of vitamins B ₁ and B ₆ . Chronic use of furosemide can cause B ₁ deficiency.
Thiazide Diuretics: Hydrochlorothiazide (Esidrix, HydroDIURIL), Indapamide (Lozol), and Metolazone (Zaroxolyn)	Magnesium, Potassium, Sodium, Zinc	Urinary depletion of magnesium and potassium can exacerbate irregular blood pressure and cardiac function. Zinc depletion can suppress wound healing and immune function. Hyponatremia could also develop
Potassium-Sparing Diuretics: Amiloride (Midamor, Moduretic), Triamterene (Dyazide, Dyrenium, Maxzide), Spironolactone (Aldactazide, Aldactone)	Magnesium, Potassium, Sodium, Zinc	Inhibits enzyme necessary for folic acid synthesis. Chronic use can lead to folic acid depletion. Diuresis can also cause calcium depletion. CAUTION: Taking potassium with potassium-sparring diuretics could cause hyperkalemia (symptoms = weakness, impairment of speech cognition).
Anti-Hyperlipidemia		
HMG-CoA Reductase Inhibitors: Lovastatin (Mevacor), Simvastatin (Zocor), Pravastatin (Pravachol), Fluvastatin (Lescol) Atorvastatin (Lipitor)	Coenzyme Q ₁₀	These drugs block the liver enzyme necessary for synthesis of cholesterol but also block the body's ability to manufacture CoQ ₁₀ . CoQ ₁₀ has many important functions, including cellular energy production and regulation of blood pressure and cardiac function.
Bile Acid Sequestrant: Cholestyramine (Questran) and Colestipol (Colestid)	Vitamins A, D, E, K, B ₂ , B ₃ , and B ₁₂ , β-Carotene, Folic Acid, Iron, Fat	Nutrient depletions caused by poor absorption. Long time intervals are required between nutritional supplements and pharmaceutical dosing. Fat absorption is also inhibited. May decrease enterohepatic resorption of vitamin B ₁₂ .

Prescription Drugs

Drug Category	Affected Nutrients	Mechanism
Anti-Seizure		
Barbiturates: Phenobarbital (Luminal Sodium), Pentobarbital (Nembutal Sodium), Thiopental, Secobarbital (Seconal), Methohexitol	Vitamin D, Calcium, Folic Acid	Long-term use interferes with vitamin D metabolism and may reduce the absorption of calcium. Phenobarbital may reduce plasma levels of vitamins D and E. Folic acid levels are lowered in both plasma and erythrocytes.
Phenytoin (Dilantin) Carbamazepine (Tegretol), Primidone (Mysoline)	Vitamin D, E, Calcium, Folic Acid, Vitamin B ₁₂ , Biotin	Decreases vitamin D availability, reducing absorption of calcium. Decreases serum folate and phenytoin may decrease vitamins D and E in plasma. Vitamin B ₁₂ and folic acid absorption are also decreased. Can increase biotin metabolism, decreasing biotin plasma levels. Carbamazepine inhibits folate absorption; long-term use could create anemia. Carbamazepine decreases plasma levels of vitamin E and pyridoxal 5'-phosphate. These depletions can result in bone disease, anemia, neurological problems, as well as gum and periodontal disease.

Table continues on following page...*

For mechanisms of action, drug-nutrient contraindications, antagonisms, and synergies, please see the sources from which the table has been adapted.^{1,2}

For information on the symptoms of vitamin and mineral deficiencies induced by a given medication, see the corresponding chapters.

Online Resources:

- ◆ clinicalcenter.nih.gov/ccc/patient_education/drug_nutrient/ (accessed 3/09)
- ◆ www.guideline.gov/resources/summaryarchive.aspx#3631 (accessed 3/09)

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1. Company ME. *PDR for nutritional supplements*. Montvale, NJ: Medical Economics, Thomson Healthcare; 2001
2. Katzung BG, ed. *Basic & Clinical Pharmacology*. Eighth ed. New York: Lange Medical Books/McGraw-Hill; 2001

Prescription Drugs

Drug Category	Affected Nutrients	Mechanism
Anti-Inflammatory		
Corticosteroids: Prednisone (Meticorten), Dexamethasone (Decadron), Methylprednisolone (Medrol)	Calcium, Vitamin D, Potassium, Selenium	These drugs reduce levels of vitamin D and decrease the absorption of calcium, resulting in bone loss and skeletal problems. Long-term use may also deplete potassium, selenium, and zinc.
Gout Medications: Colchicine (ColBENEMID), Probenecid (Benemid)	β-Carotene, Folate, Vitamin B ₂ and D, Potassium, Sodium	Colchicine inhibits the absorption of all these nutrients. Changes in pH cause GI symptoms and B ₁₂ malabsorption. Decreases folate blood levels. Probenecid may inhibit absorption of B ₂ and renal tubular secretion. Symptoms from these nutrient depletions include weakness and peripheral neuritis.
Nonselective NSAIDs: Indomethacin, Indocin	Vitamin C, Folic Acid, Amino Acids, Iron	Decreases absorption of both vitamin C and folic acid. Increases rate of gastric emptying which decreases absorption of amino acids. Indocin can cause iron deficiency due to blood loss.
Other Nonselective NSAIDs: Ibuprofen, Naproxen (Naprosyn), Sulindac (Clinoril)	Folic Acid	These anti-inflammatory drugs competitively inhibit the enzymatic synthesis of folic acid. Long-term use could lead to anemia. Low levels of folic acid are associated with increased incidence of birth defects, cervical dysplasia, and elevated homocysteine, a major risk factor for cardiovascular disease.
Anti-Rheumatic		
Sulfasalazine (Azulfidine)	Folic Acid	Intestinal absorption of folic acid is inhibited, which can lead to anemia-related weakness and low energy.
Metal-binding: Penicillamine	Copper, Vitamin B ₆ , Zinc	When taken together, both these nutrients and penicillamine are poorly absorbed. By binding P5P, can result in functional vitamin B ₆ deficiency.

NOTES

Drug Category	Affected Nutrients	Mechanism
Anti-Bacterial		
Broad-spectrum: Amoxicillin / Clavulanic Acid (Augmentin), Vancomycin	All B-Vitamins, Biotin, Vitamin C, Vitamin K	Antibiotics kill pathogenic and beneficial bacteria such as <i>acidophilus</i> and <i>bifidus</i> . The "friendly bacteria" produce vitamins B ₂ , B ₃ , B ₆ , B ₁₂ , K, biotin, folic acid, pantothenic acid, and a number of natural antibiotics in our intestines. Destroying <i>acidophilus</i> & <i>bifidus</i> bacteria can cause nutrient depletions and impair the immune system.
Combination anti-fungal & anti-bacterial: Amphotericin B, nonlipid (Fungizone)		
Tetracycline Antibiotics: Demeclocycline, Doxycycline, Methacycline, etc.	Calcium, Magnesium, Manganese, Zinc, Vitamin B ₆ , Vitamin B ₁₂	Tetracyclines chelate calcium, magnesium, and zinc. Long term use can cause mineral depletions. Take manganese separately from antibiotic. Tetracyclines also interfere with the absorption of vitamins B ₆ and B ₁₂ .
Cycloserine, Ethionamide, Isoniazid (INH)	Vitamin B ₆	Can cause functional vitamin B ₆ deficiency by binding P5P. Ethionamide increases vitamin B ₆ requirements.
Cephalosporins: Cefoperazone, Cefotetan, Cefamandole, Latamoxef, Cefazolin	Vitamin K	Inhibit a liver enzyme that can result in vitamin K deficiency and hypoprothrombinemia.
Ciprofloxacin, Gatifloxacin, Levofloxacin, Lomefloxacin, etc.	Zinc	When taken together, both Zn and these antibiotics have decreased absorption.
Bactrim (also Septra, Trimpex)	Folate	Mild folate antagonists with only minimal risk. However, long-term use and/or high dose usage may create a deficiency, especially in compromised patients.
Anti-Fungal		
Ketoconazole (Nizoral)	Vitamin D	This antifungal may inhibit biosynthesis and breakdown of 1,25-dihydroxy-Vitamin D.

Table continues on following page...

Prescription Drugs

Drug Category	Affected Nutrients	Mechanism
Anti-Diabetic Drugs		
Sulfonylureas: Diabeta (Glynase, Micronase), Tolinsase	Coenzyme Q ₁₀	Inhibition of the NADH-oxidase enzyme can lead to a coenzyme Q ₁₀ deficiency.
Biguanides: Metformin (Glucophage)	Vitamin B ₁₂	Competitive inhibition of vitamin B ₁₂ absorption could cause depletion in some individuals.
Diabetic gastroparesis and heartburn: Metaclopramide HCl (Reglan)	Vitamin B ₂	May inhibit absorption and renal tubular secretion of vitamin B ₂ .
Antacid		
Aluminum-containing: (Gaviscon, Maalox, Mylanta)	Calcium, Phosphorus, Copper, Iron, Magnesium, Manganese, Potassium, Zinc, Protein, Folic acid, Vanadium	An alkaline pH inhibits the absorption of these nutrients. Chronic use can lead to skeletal problems due to calcium & phosphate depletion. The digestion of protein is also diminished. Sodium bicarbonate-altered intestinal pH specifically inhibits the absorption of folic acid. Magnesium-containing antacids can decrease manganese absorption if taken concomitantly. Aluminum hydroxide may decrease vanadium absorption.
H-2-Receptor Antagonists: Cimetidine (Tagamet), Famotidine (Pepcid), Nizatidine (Axid), Ranitidine (Zantac)	Vitamin B ₁₂ , Calcium, Folic Acid, Vitamin D, Iron, Zinc, Protein	Malabsorption of dietary B ₁₂ , iron, and folic acid by H-2 antagonists may contribute to nutrient depletions. Altered pH may also reduce absorption of calcium, vitamin D, and zinc. Altering gastric pH also interferes with digestion of protein. Folic acid depletion is associated with increased incidence of birth defects, cervical dysplasia, and elevated homocysteine, a major risk factor for cardiovascular disease.
Proton Pump Inhibitors: Omeprazole (Prilosec), Lansoprazole (Prevacid), Rabeprazole (AcipHex)	Calcium, Vitamin B ₁₂ , Protein	By altering the gastric pH, these drugs may cause malabsorption of vitamin B ₁₂ . Probable interference with protein digestion. Concomitant use of these medications with calcium may reduce calcium absorption.

Prescription Drugs

Drug Category	Affected Nutrients	Mechanism
Anti-Arrhythmia		
Digoxin (Lanoxin)	Calcium, Magnesium	Increased urinary excretion of both calcium and magnesium can lead to deficiencies. Magnesium deficiencies increase likelihood of cardiac dysrhythmias and atrial fibrillation.
Beta Blockers: Propanolol (Inderal), Metoprolol (Lopressor), etc.		
Coenzyme Q ₁₀		These drugs antagonize the activity of the enzymes involved in the synthesis of coenzyme Q ₁₀ . Deficiency can cause heart, blood pressure, and immune system-related problems.
Psychiatric Medications		
Tricyclic Antidepressants: Amitriptyline (Elavil), Nortriptyline (Pamelor), Imipramine (Tofranil), Desipramine (Norpramin), Doxepin (Sinequan), etc.	Coenzyme Q ₁₀ , Vitamin B ₂	Tricyclics inhibit enzymes necessary for production of coenzyme Q ₁₀ . Deficiency can cause cardiovascular symptoms. Both Elavil & Tofranil deplete vitamin B ₂ by interfering with absorption. Deficiency can cause skin, neurological and energy problems.
Antipsychotic Agents: Chlorpromazine (Thorazine), Thiothixane (Navane), Thioridazine (Mellaril), Fluphenazine esters (Prolixin), etc.	Coenzyme Q ₁₀ , Vitamin B ₂	These drugs inhibit the absorption of vitamin B ₂ & coenzyme Q ₁₀ . May inhibit conversion of riboflavin (to FMN and FAD). Depletion of these vitamins can cause skin, neurological, and energy-related problems.
Mood Stabilizer: Valproic acid	Vitamin B ₆	Can reduce plasma PSP.
Weight Management		
Orlistat (Xenical)	Vitamins A, D, E, K	May decrease exocrine output and reduces fat absorption.
Sibutramine (Meridia)	Tyrosine, Tryptophan	Simultaneous inhibition of serotonin (by 53%), norepinephrine (by 54%), and dopamine (by 16%)

Table continues on following page...

Prescription Drugs

Drug Category	Affected Nutrients	Mechanism
Laxative		
Mineral Oil, Sennosides (Agoral, Haley's M-O)	Vitamins A, D, E, and K, β-Carotene	Inhibits absorption—fat soluble nutrients dissolve in the mineral oil and are lost when the oil is excreted.
Docusate/Phenolphthalein (Feen-a-Mint)	Potassium	Causes decreased nutrient absorption due to increased intestinal motility and mucosal permeability
Bisacodyl (Correctol, Dulcolax)	Potassium	Intense peristalsis and rapid bowel emptying can cause hypokalemia.
Anti-Proliferative (Chemotherapy)		
Chemotherapy drugs	Most Nutrients	Many chemotherapy drugs cause nausea, vomiting, and significant damage to gastric and intestinal mucosa. These factors cause decreased appetite and malabsorption leading to a wide variety of nutrient depletions.
Anti-Asthmatic		
Theophylline (Theo-Dur)	Vitamin B ₆	Inhibits enzyme pyridoxal kinase causing vitamin B ₆ depletion.
Anti-Clotting		
Warfarin sodium (Coumadin)	Vitamin K	Interferes with the enzyme responsible for the synthesis of vitamin K.
Anti-Viral		
Zidovudine, Retrovir (AZT)	Copper, Zinc	Drug causes specific depletion of both copper and zinc.
Anti-Bone Resorptive		
Bisphosphonates: Etidronate (Didronel), Pamidronate (Aredia), Alendronate (Fosamax), Risedronate (Actonel), Tiludronate (Skeldil)	Zinc	When taken together, both zinc and the bisphosphonate have reduced absorption.

Nutrient Supplements

Supplement Component	Affected Nutrients	Mechanism
Boron, boric acid	Vitamin B ₂	Displaces riboflavin binding and increases excretion.
Calcium	Iron, Magnesium, Manganese, Zinc	May depress zinc absorption in postmenopausal women. Calcium (over 2 g) can decrease absorption of magnesium. Calcium and manganese taken together result in decreased absorption of manganese.
Chromium	Vanadium	May decrease vanadium absorption.
Copper	Zinc	Taking these essential minerals together may decrease copper absorption.
Iron	Copper, Manganese, Vanadium, Zinc	When taken together, absorption of both iron and these essential minerals can be reduced. High-dose nonheme iron can decrease copper status. Ferrous ion can decrease absorption of vanadium.
Magnesium	Manganese	Concomitant intake of these nutrients can reduce absorption of manganese.
Molybdenum	Copper	High intake of molybdenum can decrease copper status.
Pantothenic acid (high-dose)	Biotin	Can decrease absorption of biotin by competing for the same uptake mechanism in colonocytes
Phosphate salts	Magnesium, Zinc	When taken together, mineral absorption can be inhibited.
Phytosterols and phytostanols	Vitamin E	May lower plasma vitamin E.
Potassium (Chloride): Kaon-CL, Klor-Con, K-Dur, K-Tab, Slow-K, etc.	Vitamin B ₁₂	Slow release of potassium chloride salts alters intestinal pH, which decreases absorption of vitamin B ₁₂ . Depletion can cause weakness and tiredness associated with anemia.
Psyllium	Vitamin B ₂	Decreases absorption of riboflavin when taken together
Sodium alginate	Calcium, Magnesium	Decreases absorption of these minerals
Squalene	Vitamin K	May decrease absorption of vitamin K if taken together
Vitamin A (high-dose)	Vitamin K	High doses of vitamin A may decrease vitamin K.
Vitamin C	Copper	1500 mg vitamin C has been shown to decrease copper transporting protein.
Vitamin E (high-dose)	Vitamin K	A vitamin E metabolite can inhibit vitamin K-dependent gamma-glutamyl carboxylase activity.

Dietary Components

Food Component	Affected Nutrients	Mechanism
Alcohol	Vitamin B ₆	High alcohol intake increases P5P catabolism.
Chloride	Vanadium	May decrease absorption of vanadium
EDTA	Vanadium	May decrease absorption of vanadium
Fructose	Copper	High-fructose diets can decrease copper.
Phytic Acid or Inositol hexaphosphate	Calcium, Chromium, Copper, Manganese, Magnesium, Zinc	Foods high in phytic acid can reduce absorption of these minerals. Inositol hexaphosphate may depress absorption of calcium, magnesium, and zinc.
Olestra	Vitamins A, D, E, K	Inhibits absorption of vitamins
Oxalic acid	Calcium, Magnesium, Manganese, Zinc	Foods high in oxalic acid can reduce absorption of these minerals.
Sulfites, tea, coffee, and decaf coffee	Vitamin B ₁ (Thiamin), Zinc	Taken together with vitamin B ₁ , these foods can inactivate the vitamin. Caffeine and tannins can decrease zinc absorption.

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HYPERO/PRO	hydroxyproline/proline ratio
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
IFN-g	interferon gamma
IgA	immunoglobulin A
IgE	immunoglobulin E
IgG	immunoglobulin G
IgG4	immunoglobulin G ₄
IL-6	interleukin 6
IM	intramuscular
K1	pyloquinone
K2	menaquinone
K3	menadione
LA	linoleic acid
LCFA	long chain fatty acid
LDL	low density lipoprotein
LEIFM	<i>Laboratory Evaluations for Integrative and Functional Medicine</i>
LFT	liver function tests
MTHFR	methylenetetrahydofolate reductase
MUFA	monounsaturated fatty acids
NAC	N-Acetylcysteine
NAD	nicotinamide adenine dinucleotide
NMDA	N-methyl-D-aspartic acid
NO	nitric oxide
NOS	nitric oxide synthase
NSAID	non-steroidal anti-inflammatory drug
P450	cytochrome P450
PA	picolinic acid
PAH	phenylalanine hydroxylase
PAPS	phosphoadenosyl-phosphosulfate
PCOS	polycystic ovary syndrome
PCR	polymerase chain reaction
PDC	pyruvate dehydrogenase complex
PHY/TYR	Phenylalanine/Tyrosine ratio
PKU	phenylketonuria
PO	by mouth
PPAR	peroxisome proliferator-activator receptor
PTH	parathyroid hormone
PUFA	polyunsaturated fatty acids
PVC	polyvinyl chloride
QD	every day
RBC	red blood cell
SAME	S-adenosylmethionine
SCFA	short chain fatty acid
SFA	saturated fatty acid
SHBG	sex hormone binding globulin
SIDS	sudden infant death syndrome
SI	saturation index
slgA	secretory immunoglobulin A
SLE	systemic lupus erythematosus
SN1/SN2	amino acid transporter system
SNP	single nucleotide polymorphism
sp.	any one of several species that may appear on the report
spp.	all species in a genus
SSRI	selective serotonin reuptake inhibitor
TBARS	thiobarbituric acid reactive substance
TCA	tricarboxylic acid (also referred to as citric acid cycle or Kreb's cycle)
TID	three times a day
TPN	total parenteral nutrition
ucOC	undercarboxylated osteocalcin
VMA	vanilmandelate
WBC	white blood cells



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