Testing Nutritional Status: The Ultimate Cheat Sheet

Version 1.1
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This is a “cheat sheet” in two ways:

- All of the lab testing required for comprehensive nutritional screening is reduced to a single page, with hyperlinks making ordering any of the tests just one click away.
- In just five pages, I provide full instructions for lab testing, blood pressure, and dietary analysis, as well as an algorithm for quick decisions on what to do next for each marker that may be off.

This “cheat sheet” is *ultimate* because of what comes next:

- Over 70 pages list the signs and symptoms associated with all the possible nutrient imbalances, the potential causes of nutrient imbalances, and an action plan for correcting each imbalance.

While you can read the more than 75 pages assembled here straight through if it tickles your fancy, this guide is not meant to be used that way. It retains its “cheat sheet” status by making only the parts that are relevant to you one click away as you move through the findings of your initial nutritional screening.

To make the best use of this guide, please read the disclaimer and the instructions for use before beginning.

Important Disclaimer

This cheat sheet is meant for educational purposes only, and is not a substitute for or a component of a comprehensive training in medicine or dietetics, nor does it constitute medical or nutritional advice or act as a substitute for seeking such advice from a qualified health professional. If you are a health care practitioner, always do your due diligence to research alternative explanations for the information herein and ensure that any actions you take are consistent with the legal and ethical frameworks governing your practice. If you are an individual seeking to improve your own health, always ask your doctor about taking any health-related measures and never ignore professional medical advice on the basis of anything contained herein. As the author of this educational product I am not responsible or liable for the results of taking any actions on the basis of this information.

In order to make the cheat sheet easier to read, I have used a conversational tone in many places with personal pronouns, such as “I” and “you.” This is meant *only* to make it more pleasant to read, and is not meant to imply that the guide constitutes any form of advice, whether personal or general.

How to Use This Cheat Sheet

If you are a health care practitioner, you can use this cheat sheet to more quickly find information related to nutritional testing that could help your patients and clients. It is important to always cross-reference information in this guide with your own knowledge from your training, current research and treatment guidelines, and information about tests provided by the laboratories that offer those tests.

If you are an individual reading this for your own private benefit, it will help you better understand the tests your doctor may order for you, and provide ideas for testing or nutritional strategies that you could discuss with your doctor. Depending on where you live, you may be able to legally order tests through a direct-to-consumer service such as directlabs.com. If you do so, it is important to discuss all results with your doctor, because these tests might provide evidence of medical conditions that are not discussed in this guide, and your doctor can provide important input on the safety of any nutritional strategies you choose to use.

There are three ways you can use this cheat sheet, depending on your resources and priorities:

- **Option 1: The Comprehensive Approach**. This is the right option if money is not an issue for you, or if your medical insurance will cover all of the testing. In option 1, you order all of the lab tests listed in the comprehensive screening. While waiting for the test results, you conduct your own dietary analysis and measure your blood pressure. You then search through the index of the signs and symptoms of nutritional imbalances for any that apply to you. When all of the data is in, you read the full sections of the guide that are flagged as relevant to determine which nutritional imbalances are most likely to be affecting you and what the right course of action is.

- **Option 2: The Time-Saving Approach.** This is the right option if your time is severely constrained, making the dietary analysis infeasible. In this case, complete all aspects of option 1, but skip the initial dietary analysis. Only resort to dietary analysis when troubleshooting a specific nutritional imbalance proves difficult.

- **Option 3: The Cost-Saving Approach.** This is the right option if you want to be conservative about lab testing for any reason, including financial costs. Skip the lab tests and begin with the dietary analysis and blood pressure measurement. Browse through the index of the signs and symptoms of nutritional imbalances. Read through the full sections of the guide that are flagged as relevant by any of your data. Use the suggestions for lab testing only when needed to help clarify the appropriate nutritional strategy to implement.

If at any point you need help, head to the ask me for help section.

Ready? Choose your approach, and dig right in!

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Comprehensive Nutritional Screening

Lab Tests

The lab tests listed below are sufficient for a comprehensive nutritional screening.
They do not need to be measured all at once, but blood should be drawn for the ION panel, parathyroid hormone, and 1,25$(OH)_2$D at the same time if possible. Fasting is required for many of these tests, but not all. Always consult the instructions for the test regarding fasting and follow them strictly.

Many tests will advise removing nutritional supplements. I do not agree with this. My recommendation is to get the tests when your supplement regime has been stable for at least four weeks, and to avoid supplements the day of the test and during any longer period of fasting that might be recommended. This way, the results reflect what you normally do.

- Genova ION Profile + 40 amino acids
- From the HDRI site, on their requisition form, the following tests: ETKA, EGR, NADH/NADPH, EGOT, sulphur panel, GSH ox+red
- Complete Blood Count (CBC) (LabCorp, Quest)
- Comprehensive metabolic panel (LabCorp, Quest)
- Parathyroid Hormone (LabCorp, Quest)
- 1,25$(OH)_2$D (LabCorp, Quest)
- Serum magnesium (LabCorp, Quest)
- Whole blood vitamin B1 (LabCorp)
- Whole blood vitamin B2 (LabCorp)
- Vitamin B5 (LabCorp, Quest)
- Plasma vitamin B6 (LabCorp, Quest)
- Vitamin B7 (LabCorp, Quest)
- Serum and RBC Folate (single test: LabCorp; Quest offers serum and RBC separately)
- Serum B12 (LabCorp, Quest)
- Uric Acid (LabCorp, Quest)
- Plasma ascorbate (LabCorp, Quest)
- Manganese in whole blood (LabCorp) or red blood cells (Quest)
- Plasma selenium (LabCorp)
- Iron panel (LabCorp, Quest)
- Serum transferrin (LabCorp, Quest)
- Total Glutathione (LabCorp)
- 24-hour urine iodine (LabCorp, Quest)
- ***Optional Add-On***: Hair Elements (Doctor's Data)
- ***Optional Add-On:*** obtain a 23andMe genetic analysis and run the raw data file through StrateGene.

Interpreting Lab Tests

The Genova ION Panel

- If alanine (page 3), lactate (page 9) or pyruvate (page 9), and alpha-ketoglutarate (page 9) are elevated, see the thiamin section.
- If methionine or glycine (page 1) are outside of the green range or near the edge, if sarcosine (page 3) is in the 3rd quintile or higher, If homocysteine (page 4) is below 5 or above 9, or or if urinary formiminoglutamate or methylmalonate (page 9) are elevated, see the methylation section.
- If vitamin A (page 5) is below 0.4 or above 0.74, see the vitamin A section.
- If 25-hydroxyvitamin D (page 5) is below 30 or above 40, see the vitamin D section.
- If either of the forms of vitamin E (alpha- or gamma-tocopherol, page 5) are outside of the green range or near the edge, see the vitamin E section.
- If vitamin A, 25-hydroxyvitamin D, or alpha- or gamma-tocopherol are affected (page 5), see also the section, "General Concerns for Fat-Soluble Vitamins."
- If citrate is high, isocitrate is low, or if alpha-ketoglutarate or succinate are high (page 9), see the antioxidant section.
- If lipid peroxides or 8-hydroxy-2-deoxyguanosine (page 6) are elevated, see the antioxidant section.
- If xanthurenate (page 9), kynurenate (page 10), or quinolinate (page 10) are high, see the vitamin B6 section.
- If β-hydroxyisovalerate (page 9) is high, see the biotin section.
- If plasma zinc (page 5) is outside the green range or near the edge, see the zinc section.
- If plasma copper (page 5) is outside the green range or near the edge, see the copper section.
- If pyroglutamate (page 10) is elevated above the 3rd quintile, see the glutathione section.
- If either zinc, copper, *or* pyroglutamate are altered as discussed above, see also the introduction to the antioxidant vitamins and minerals.
- If erythrocyte magnesium (page 5) is outside the green range or near the edge, see the magnesium section.
- If docosahexaenoic acid (22:6n3) (page 7), arachidonic acid (20:4n6) (page 7), or the AA/EPA ratio (page 8) are outside of the green range or near the edge, see the essential fatty acid section.

The HDRI Tests

- If ETKA is low, see the thiamin section.
- If EGR is low, see the riboflavin section.
- For the NADH/NADPH test, divide NADH by NADPH and multiply by 100. The resulting number should be between 10 and 1000 if the math was done correctly. If the number is below 175 or above 600, see the niacin section.
- If EGOT is low, see the vitamin B6 section.
- If the sulphur panel shows that sulfite is high or sulfate is low, see the molybdenum section.

- If the GSH ox+red test shows that reduced glutathione is low or oxidized glutathione is high, see the glutathione section. Additionally, you can plug the numbers into this calculator. If the output of the calculator is less negative than -140 mV (for example, -137 is less negative, while -143 is more negative), see the glutathione section.

LabCorp/Quest Tests

- On the **complete blood count (CBC)**, if the hemoglobin, MCH, MCV, or RDW are altered, see the sections on iron, methylation, and copper.
- On the **comprehensive metabolic panel**, if the sodium, potassium, or chloride are altered, see the section on electrolytes.
- If **parathyroid hormone (PTH)** is above 30 pg/mL, see the section on vitamin D, calcium, and phosphorus.
- If **serum magnesium** is out of range, see the magnesium section.
- If **whole blood vitamin B1** is out of range, see the thiamin section.
- If **whole blood vitamin B2** is out of range, see the riboflavin section.
- If **vitamin B5** is out of range, or in the lower half of the normal range, see the pantothenic acid section.
- If **plasma vitamin B6** is out of range, see the vitamin B6 section.
- If **vitamin B7** is out of range, see the biotin section.
- If **serum folate, RBC folate**, *or* **serum B12** are out of range, see the methylation section.
- If **uric acid** is low, see the molybdenum section.
- If **plasma ascorbate** is low, see the vitamin C section.
- If **manganese** is low, see the manganese section.
- If **plasma selenium** is below 90 or above 140, see the selenium section.
- On the **iron panel**, if **iron saturation** is below 30% or above 40%, or if ferritin is below 60 ng/mL or higher than 150 ng/mL, see the iron section. Divide the **serum iron** from this panel by the **serum transferrin** measured separately and multiply by 70.9%. If this number is below 30% or above 40%, see the iron section.
- If the **LabCorp total glutathione** is low, see the glutathione section.
- If there are any alterations found in plasma ascorbate, manganese, selenium, iron, or glutathione as described above, see also the introduction to the antioxidant vitamins and minerals.
- If 24-hour urine iodine is out of range, see the iodine section.

Hair Elements (Optional Add-On)

- If chromium, boron, lithium, or strontium are low, or if any of the heavy metals are high, see the Other Minerals section.
- Other minerals measured on the hair analysis should either be dismissed or confirmed with the other testing recommended in this guide.

StrateGene (Optional Add-On)

- If SLC19A1, MTHFD1, MTHFR, MTRR or PEMT are yellow or red, see the methylation section.
- If HFE is yellow or red, see the iron section.

Blood Pressure

Measure blood pressure at home, following the instructions of the blood pressure monitor carefully. Take at least three measurements per session and measure it on at least three different occasions. If blood pressure is consistently higher than 130/80, see the electrolyte section.

Dietary Analysis

There are many ways to conduct a dietary analysis. In its simplest form, you can record what you eat and look up the nutritional contents in the USDA Database or NutritionData.Com. There are many software applications available that will track and calculate the nutritional value of the foods you eat, dramatically reducing the amount of work required. I recommend using the Cronometer smartphone app.

In order to generate accurate data, several things must be kept in mind:

- **Tracking has to be comprehensive.** It is better to track every last thing for a short period of time such as three days or a week than to track 80% of what you eat and ignore the 20% when it is least convenient. If eating out, search the database for the closest approximation to your meal. At home, track everything down to the milligrams of salt you use.
- **Tracking has to be representative.** If your diet changes often, you'll have to take more data so that the different trends in your diet are all reflected in the analysis.
- **Most foods need to be weighed with a food scale.** The exceptions are processed foods and prepared meals that have their own entry in the Cronometer database and that you consume completely in one sitting, and foods like flour that pack well and can be accurately measured in volume. For most foods, precision requires weighing. For example, 256 grams of potato is much more precise than "one large potato" or "two cups of diced potatoes."
- If you cook food in batches, or in large recipes where only a portion is for yourself, you will have to **account for changes in water weight during cooking.** For example, let's say that you want to cook lentils, rice, and potatoes together. Create a recipe in Cronometer, and record the weight of the each individual ingredient before cooking. After cooking, measure the full weight of the entire dish. Take the weight in grams and divide it by 100. Take this number and enter it in Cronometer as the number of servings for the recipe. When you eat the food, weigh the portion you consume, and count each 100 grams as one serving.
- **Screen the entries for false zeros.** Many entries in Cronometer are missing data for individual nutrients. You need to look at the entry you use to make sure it is not missing data (usually a 0.0 value indicates missing data, especially if you know a food of that nature should have more than zero of that nutrient). If data is missing, use the closest approximation where the data is present. **The entries that are most likely to be complete are those that list USDA or NCCDB as their source.** For example, when I was tracking the potassium content of my food, I would eat Farmers Market pureed pumpkin. The entry for this specific product in Cronometer says it has zero potassium.

This is clearly false, because pumpkin is very high in potassium. So I instead used the "canned pumpkin" entry from NCCDB that had full data for potassium to ensure I had a reasonably accurate estimate.

Tracking nutrients has several limitations that must always be kept in mind:

- Databases occasionally contain errors.
- Nutrients vary in foods according to environmental conditions and methods of production and preparation. Tracking provides a best estimate, but it will never be completely accurate.
- Cronometer will report the percentage of the United States Dietary Reference Intake (DRI) that you meet for each nutrient. The DRI is either a recommended dietary allowance (RDA), which is an estimation of the intake that will meet or exceed the needs of 97.5% of the population, or an adequate intake (AI), which is established based on what appears consistent with health when there is insufficient evidence to determine an RDA. If you do not meet the DRI, this does not necessarily mean you are deficient, because your needs could be significantly lower than the DRI. Conversely, if you meet the DRI it does not necessarily mean you are sufficient, because your needs could be higher. The percentage of the DRI you attain is nevertheless a good starting place to assess the probability that you may need to optimize a certain nutrient.

Track your food for at least three days. If your diet changes a lot, take more data until you are confident you have a representative sample. For nutrients where you consistently attain less than 100% of the DRI, review their respective sections within this guide to determine whether your current health challenges line up with the signs and symptoms of deficiency and what follow-up testing may be needed.

If you take vitamin supplements at doses higher than 100% of the DRI, review the full section for each of those nutrients to check for indicators of toxicity. If you consume more than two 100 gram servings of liver per week, review the sections on vitamin A and copper for indicators of toxicity of those nutrients. Toxicity is *not* likely at these intakes, but it is good to be familiar with the toxicity information for any nutrients that you consume large amounts of.

The Fat-Soluble Vitamins and Related Minerals

This section covers vitamins A, D, E, and K, as well as calcium, phosphorus, and magnesium. The first section, "General Concerns for Fat-Soluble Vitamins and Saponifiable Minerals," also makes brief comments about sodium, potassium, iron, zinc, copper, and manganese.

General Concerns For Fat-Soluble Vitamins and Saponifiable Minerals

Vitamins A, D, E, and K are all fat-soluble. Dietary fat enhances their absorption, but we never absorb as little as zero or as much as 100% no matter how much fat we eat. For example, we will absorb about 10% of the vitamin E from a fat-free meal, and we will absorb 33% from a meal

containing 21% of calories as fat. There is not enough data to justify an algorithm such as “x% will be absorbed for every gram of dietary fat.” However, the effect can be large, so we should assume that deficiencies are more likely on low-fat diets than on moderate- or high-fat diets. Nevertheless, if we eat a low-fat diet, we can still obtain enough fat-soluble vitamins simply by eating foods with a larger amount of vitamins to compensate for a lower rate of absorption.

Because these vitamins are absorbed along with fats, disorders that cause fat malabsorption can cause deficiencies of all four vitamins.

Fat malabsorption can also cause deficiencies of saponifiable minerals. Saponification is the process of a mineral binding to a fatty acid. Fatty acids are negatively charged, and they can be saponified by minerals that form positively charged ions. This is only nutritionally relevant if those ions are formed in large quantities in the digestive tract. The most relevant minerals include sodium, potassium, calcium, and magnesium, and to some extent iron, zinc, copper, and manganese may also be affected.

Diagnosing and treating disorders of fat malabsorption is beyond the scope of this guide, but they include abetalipoproteinemia, hypobetalipoproteinemia, Crohn’s disease, celiac disease, cystic fibrosis, and a rather large collection of disorders of the liver, pancreas, gall bladder, bile ducts, and small intestine.

There are three hints of such disorders that might be uncovered during the course of nutritional testing:

- Low levels of all four fat-soluble vitamins, rather than low levels of only one. You can use Genova’s fat-soluble vitamin panel for this, and the Genova ION Profile + 40 amino acids, frequently recommended in this guide, has markers of A, D, and E, but not K.. Alternatively, you can look at each vitamin individually: **vitamin A**, LabCorp, Quest; **25(OH)D**, LabCorp, Quest; **vitamin E**, Labcorp, Quest; and **vitamin K**, LabCorp, Quest. Of these, vitamin D the most likely to be normal because it can be made in the skin during sun exposure without the need to absorb it from the diet.
- A **standard lipid panel** (LabCorp, Quest) showing cholesterol and other blood lipids below the reference range.
- High levels of **fecal fat** (LabCorp, Quest). Fecal fat is often a component of more stool panels as well.

While the nutritional deficiencies themselves deserve specific attention and management according to the general framework for each vitamin listed below, anyone with signs of a malabsorption disorder should be referred to the appropriate specialist for treatment of that disorder.

Vitamin A

Signs and Symptoms of Deficiency: Well established signs and symptoms of vitamin A deficiency include the following: poor night vision; dry eyes; hyperkeratosis around hair follicles, or appearing as bumps on the skin that can be mistaken for goosebumps or acne, or on the

surface of the conjunctiva (Bitot's spots); poor immunity to infectious diseases. Less well established but plausible signs and symptoms of deficiency include the following: kidney stones; disrupted circadian rhythm and an inability to use light therapy to entrain a healthy circadian rhythm; autoimmune disorders; asthma and allergies; food intolerances; low sex hormones; and delayed puberty.

Risk Factors for Deficiency: Diets that do not contain at least one of the following: a weekly serving of liver; regular use of cod liver oil, a multivitamin, or another supplement providing 100% of the US RDA for vitamin A as retinol. If the diet is also poor in dairy products and eggs, and does not contain several servings per day of red, orange, yellow, or green vegetables, vitamin A deficiency becomes very plausible. Diets where fats come from polyunsaturated vegetable oils are more likely to produce vitamin A deficiency than diets where the fat is mostly saturated or monounsaturated. A low-fat diet will not intrinsically produce vitamin A deficiency, but it will increase its likelihood by leading to lower absorption of vitamin A from food. Long-term use of glucocorticoids, high-protein diets, and high-dose vitamin D may contribute to vitamin A deficiency in combination with poor dietary intake.

Signs and Symptoms of Toxicity: Most commonly, nausea, vomiting, and headache. In extremes, anorexia, blurred vision, scaling skin, hair loss (alopecia), organ damage, death. Osteopenia and osteoporosis can be worsened by vitamin A at non-toxic levels when vitamin D and calcium are deficient. It is prudent to keep vitamin A below 10,000 IU per day during the first eight weeks of pregnancy due to a possible risk of birth defects unless blood measurements, signs, and symptoms justify higher intakes to prevent deficiency.

Risk Factors for Toxicity: Months or years of consistently taking at least 165 IU per kilogram body weight per day, and in the majority of cases greater than 2300 IU per kilogram body weight per day. For a person weighing 70 kilograms (154 pounds), this is a minimum of 11,550 IU and higher than 161,000 IU per day in the majority of cases. These figures apply to cases where vitamin D was not supplemented alongside it. When vitamin D is taken alongside vitamin A, the majority of vitamin A toxicity cases involve months or years of consistently taking more than 4620 IU vitamin A per kilogram body weight per day, which for a person weighing 70 kilograms is 323,400 IU per day. Almost all vitamin A is prepared in oil; however, vitamin A preparations that are water-soluble, emulsified, or solid may cause toxicity in weeks rather than months and at ten times lower doses.

Testing for Vitamin A Deficiency:

- **Serum vitamin A** (individually: LabCorp, Quest, in panels: Genova ION Profile + 40 amino acids, Genova's fat-soluble vitamin panel). This should be kept toward the middle of the reference range (third quintile) and low-normal results do not necessarily rule out a problem.
- **Retinol-binding protein** (LabCorp, Quest) can be measured alongside serum vitamin A, but may be affected by a greater number of variables unrelated to vitamin A status (it is increased in insulin resistance and type 2 diabetes, and decreased in type 1 diabetes, systemic inflammation, and a variety of liver and kidney diseases).

Testing for Vitamin A Toxicity:

- **Serum vitamin A** (LabCorp, Quest) will be high in most cases.
- In descending order of likelihood, the following tests may show elevations: **γ-glutamyltransferase** (LabCorp, Quest), **triglycerides** (LabCorp, Quest), **alkaline phosphatase** (LabCorp, Quest), **prothrombin time** (LabCorp, Quest), **cholesterol** (LabCorp, Quest), **aspartate aminotransferase** (LabCorp, Quest), **bilirubin** (LabCorp, Quest), and **calcium** (LabCorp, Quest).

Testing Caveats: Zinc is necessary for virtually every step in vitamin A metabolism, including its transport in the blood. Zinc deficiency should *always* be considered as an explanation for an apparent case of vitamin A deficiency that does not respond well to dietary and supplemental strategies, regardless of whether serum vitamin A is altered. Adiposity may cause cellular vitamin A deficiency without lowering serum levels. Fatty liver disease compromises the liver's ability to store vitamin A and may raise serum levels. Drugs that are vitamin A derivatives (known as retinoids; e.g., isotretinoin, marketed as Accutane) may cause vitamin A deficiency signs by hurting the body's utilization of natural vitamin A. Chronic alcohol abuse and protein deficiency also hurt vitamin A utilization.

Correcting Vitamin A Deficiency: The strategy to fix the deficiency should be determined by the cause. If the cause is a dietary deficiency, the first step is to reverse the dietary risk factors listed above. Supplements providing 25,000-50,000 IU per day appear to be well within the margin of safety for short-term use (several weeks) in an adult, and may help resolve a deficiency more quickly, but should not be used without close monitoring of serum vitamin A to ensure it stays within the normal range. Someone who develops vitamin A deficiency on an apparently adequate diet may need higher doses long-term (months, years, or indefinitely), but again, you should only use high doses if you consistently monitor serum levels. You may often need trial and error to find the right dose. You should rule out deficiencies of other nutrients, especially vitamin D, before initiating high-dose vitamin A. If malabsorption is the cause of deficiency, the solutions listed under "General Considerations for Fat-Soluble Vitamins" should be followed. If factors listed under "testing caveats" are responsible for deficiency signs, these should be resolved independently and vitamin A supplementation should not be used to compensate for them.

Correcting Vitamin A Toxicity: The only well established treatment for vitamin A toxicity is the removal of the toxic dose of vitamin A. Many of the secondary effects of vitamin A toxicity, such as organ damage and hypercalcemia, require medical care that is beyond the scope of this guide. I recommend testing for deficiencies of the other fat-soluble vitamins and correcting any that exist.

Vitamin D, Calcium, and Phosphorus

Vitamin D, calcium, and phosphorus are intimately related with one another and we must consider them together to make proper sense of them. As a result, I have organized this section differently than the others in this guide. Each subsection leads with a clinical sign or a laboratory test and then describes how it is impacted by each of the three nutrients.

Osteopenia and Osteoporosis: Of the disorders listed in this section, these are the most common. Osteopenia is a less severe form of osteoporosis and both involve decreased bone mineral density and increased risk of fracture. A DXA scan is required for early diagnosis and without one signs and symptoms may not be apparent. Elevated parathyroid hormone (PTH) is a major factor in these conditions, and it is raised by deficiencies of vitamin D or calcium, or by excess phosphorus. **Therefore, these disorders are caused by *deficiencies* of calcium or vitamin D, or an *excess* of phosphorus.**

Rickets and Osteomalacia: Rickets is the childhood version of osteomalacia. We therefore often use the term osteomalacia to refer only to the disease in adults. Key sign and symptoms include bone pain, muscle weakness, fragile bones, and skeletal deformities such as thickened wrists and ankles, compressed vertebrae and pelvis, and bowed legs. Skeletal deformities are more common and obvious in children. An X-ray would show poorly mineralized, overgrown bone matrix, and, in children, expanded growth plates. These are driven by hypocalcemia (low blood calcium) or hypophosphatemia (low blood phosphorus), so **deficiencies of all three nutrients -- vitamin D, calcium, or phosphorus -- can cause rickets.**

Tetany: Tetany is a neuromuscular condition resulting from hypocalcemia. It can involve muscle twitching, tremors, or spasms; confusion; and in extreme cases seizures, coma, and death. Most scientists and clinicians consider it the rarest of the diseases in this section, and to require a more extreme degree of deficiency than rickets and osteomalacia. However, some people may have genetics that favor giving priority to the skeletal system over the nervous system and may develop tetany without developing rickets or osteomalacia. Since tetany is driven by hypocalcemia, **deficiencies of vitamin D or calcium cause it. A large excess of phosphorus may also contribute to tetany by depleting blood levels of calcium.** It is low ionized calcium rather than low total calcium that drives the condition, and alkalosis or high albumin may decrease ionized calcium even when total calcium is normal.

Soft Tissue Calcification: Deposits of calcium in tissues other than the bones and teeth can take many forms, including kidney stones and cardiovascular disease. In children, early calcification of cartilage interferes with growth. Soft tissue calcification can be caused by hypercalcemia or hyperphosphatemia. In the urinary system, it may be caused by high levels of calcium or phosphorus in the urine, known as hypercalciuria and hyperphosphaturia. **Excesses of all three nutrients -- vitamin D, calcium, and phosphorus -- can cause it.** Nevertheless, **calcium at healthy intakes protects against kidney stones** because it prevents excess phosphorus absorption and favors net movement of phosphorus into bone rather than kidney.

Hypercalcemia: High levels of ionized calcium in the blood can be caused by excess calcium or vitamin D, but not phosphorus. They are usually driven by a high amount of total calcium, but acidosis or low albumin may increase ionized calcium even when total calcium is normal. Chronic excess of vitamin D will cause more persistent hypercalcemia than chronic excess of calcium when either are present on their own. However, excess calcium can cause persistent hypercalcemia in the presence of alkalosis and impaired kidney function. In addition to soft tissue calcification as described above, hypercalcemia can lead to frequent thirst and urination, confusion, lethargy, fatigue, depression, bradycardia (slow heart rate), arrhythmia, palpitations, or fainting. Hypercalcemia may be driven in part by calcium moving from bone to blood,

especially in response to vitamin D toxicity, in which case it will be accompanied by lower bone mineral density.

Hyperphosphatemia: Phosphate binds to calcium, causing the calcium phosphate to leave the blood as it deposits in other tissues, both in healthy ways (e.g., bone) and unhealthy ways (e.g. kidney stones). Thus, hyperphosphatemia can cause tetany (deficient calcium available to the nervous and muscular systems) and soft tissue calcification (excess calcium phosphate deposited in soft tissues) but not osteomalacia (deficient calcium phosphate available to bone). Symptoms will primarily be those associated with tetany.

Osteopetrosis: Osteopetrosis is an extremely rare condition of increased bone mineral density and brittle bones. Most scientists and clinicians consider it a genetic disorder, but researchers have induced it in animals by giving them excess calcium. It is very unlikely to find it as a nutritional disorder in humans. Nevertheless, I recommend that if you are supplementing with enough calcium to bring your total intake above 2 grams per day, you should cut back if your bone mineral density increases to levels above the maximum found in healthy, young adults.

Less Well Established But Plausible Signs of Vitamin D and Calcium Deficiency: These include the following: high blood pressure, poor immunity to infectious diseases, autoimmune conditions (especially psoriasis, multiple sclerosis, and type 1 diabetes), asthma and allergies, certain cancers (estrogen-responsive breast cancer, and cancers of the prostate, colon, rectum, ovary, and endometrium), low sex hormones, high androgens in women, insomnia, and cardiovascular disease. These possibilities are largely driven by research on vitamin D, but due to its intimate relationship with calcium, we should see them as possible indicators of calcium deficiency as well. Some of these conditions, particularly cardiovascular disease, asthma, allergies, and cancer, may be associated with excesses of vitamin D as well as deficiencies.

Less Well Established But Plausible Signs of Phosphorus Deficiency: These include fatigue, weakness, and carbohydrate intolerance.

Risk Factors for Vitamin D Deficiency, Excess, and Toxicity:

We synthesize vitamin D in response to sunshine and also obtain it from food and supplements. I have chosen to use its primary marker of nutritional status, 25(OH)D, when referring to vitamin D exposure rather than the amount of dietary vitamin D in IU because the 25(OH)D reflects the total exposure from all sources.

- *Deficiency:* An indoor lifestyle combined with a low or absent intake of fatty fish, pasture-raised egg yolks, cod liver oil, and vitamin D supplements is the primary risk factor. If you spend a lot of time outdoors, you may still develop deficiency if you use sunscreen and sunblock, clothing that covers most or all of your skin, or if environmental factors such as clouds, pollution, atmospheric ozone, and tall buildings block your exposure to UV-B rays. Inflammation (from infection or from recovery from injury or surgery), excess phosphorus or vitamin A, and calcium deficiency can all deplete vitamin D levels. Disorders of fat malabsorption hurt the ability to absorb vitamin D in the diet, but do not hurt the ability to obtain it from sunlight.

- *Excess:* Although controversial, I consider vitamin D supplementation that raises your 25(OH)D (see blood markers below) higher than 50, and especially 60, ng/mL present an increased risk of soft tissue calcification even if you have no evidence of hypercalcemia. I recommend you avoid these levels unless unless signs, symptoms, and blood markers justify achieving them to prevent deficiency.

- *Toxicity:* Hypercalcemia is the hallmark of frank vitamin D toxicity. Case reports have associated it with 25(OH)D levels as low as 56 ng/mL, but most cases are associated with levels higher than 200 ng/mL. I believe it is prudent to completely avoid levels that exceed the typical laboratory reference range of 100 ng/mL, and, as stated above, to keep levels under 50-60 ng/mL without a clear justification for doing otherwise.

Risk Factors for Calcium Deficiency and Excess:

- *Deficiency*: A diet low in dairy products, edible bones (e.g., those in canned fish), green vegetables, calcium-containing multivitamins, or calcium supplements is the primary risk factor. Excess phosphorus inhibits calcium absorption and may aggravate a dietary deficiency. This is primarily a risk from phosphorus additives in processed foods, which are often unlabeled.

- *Excess*: The tolerable upper intake limit (TUIL) set by the Institute of Medicine for calcium is 2.5 grams per day for adults under the age of 50 and 2 grams per day for adults over this age. This is based on the risk of calcium-alkali syndrome, where hypercalcemia occurs alongside alkalosis and impaired renal function. This requires causes of alkalosis and impaired renal function in addition to high calcium intakes. Populations at risk for this syndrome are pregnant women, elderly women, and bulimics. In these populations, calcium supplementation contributes to the syndrome when it takes the form of calcium oxide, hydroxide, or carbonate, or when it is accompanied by antacids, diuretics, ACE inhibitors, or NSAIDs. Since the TUIL was established, more recent reports have shown the syndrome to occur with calcium intakes as little as one gram per day, well within the needs of most people, emphasizing that factors other than calcium supplementation are required. If you fit the criteria for a high risk of calcium-alkali syndrome, you should discuss this information and any calcium supplementation with your doctor. Outside of these predisposing risk factors, I consider it prudent to keep the sum of diet and supplements under two grams per day, especially if there are any signs of soft tissue calcification or abnormally high bone mineral density, and to use calcium citrate as a supplement rather than calcium oxide, hydroxide, or carbonate.

Risk Factors for Phosphorus Deficiency and Excess:

- *Deficiency*: Phosphorus is ubiquitous in the food supply, so food selection is extremely unlikely to produce phosphorus deficiency. High levels of calcium in the diet may interfere with phosphorus absorption, but the reverse problem is far more likely to occur.

  Two syndromes lower blood phosphorus to dangerous levels by moving it into other tissues. Hungry bone syndrome involves the movement of phosphorus into bone when bone mineral content starts increasing suddenly after the correction of a bone resorption

disorder, for example by surgical removal of the parathyroid gland. Hypocalcemia and low levels of magnesium (hypomagnesemia) also develop during hungry bone syndrome. Refeeding syndrome occurs after aggressive correction of starvation or of chronic malnutrition, as might occur in alcoholism, eating disorders, or illnesses that impact food intake. During these conditions, dietary phosphorus drops to low levels or even zero, the loss of lean mass causes loss of phosphorus stores, and the drop in carbohydrate metabolism causes the loss of the phosphorus needed for that process. Serum phosphate tends to remain stable during malnutrition. During refeeding, however, insulin and the rise in carbohydrate metabolism bring phosphate into cells, causing hypophosphatemia to develop. This is aggravated by the large demand for cellular repair and rebuilding of phosphorus stores. Hypomagnesemia and low levels of potassium (hypokalemia) also occur during refeeeding syndrome.

- *Excess*: The principle cause of hyperphosphatemia is chronic kidney disease, the management of which is beyond the scope of this guide. Excess dietary phosphorus, however, contributes to low bone mineral density and the risk of kidney stones. The standard American diet contains almost a half gram per day of phosphorus additives in processed foods. Some of these are labeled, as in the phosphoric acid added to soft drinks, but there are dozens of additives and they are often not listed on the label. Phosphorus is more bioavailable from animal products than from plant products, and unlike bones and dairy products, animal flesh contains very little calcium. A diet rich in animal flesh may therefore may provide sufficient phosphorus to aggravate a deficient level of calcium. The main dietary risk factor, however, is a diet rich in processed foods.

Testing for Vitamin D, Calcium, and Phosphorus Status:

- **25(OH)D** (LabCorp, Quest), also known as 25-hydroxyvitamin D, calcidiol, or “vitamin D, 25-hydroxy.” While controversial, I recommend maintaining this marker between 30-40 ng/mL, with concern increasing under 25 ng/mL or over 50 ng/mL and becoming more serious under 20 ng/mL or over 60 ng/mL. To convert these units to nmol/L, multiply by 2.5. To convert nmol/mL back to ng/mL, divide by 2.5. Although 25(OH)D is very responsive to vitamin D status, it is also decreased by calcium deficiency, excess phosphorus, vitamin A, inflammation, and genetic factors that increase its conversion to calcitriol or its inactivation. I recommend *always* using the other markers in this section to properly interpret altered 25(OH)D status.

- **Parathyroid Hormone** (LabCorp, Quest), abbreviated as PTH and often referred to as intact PTH, or “PTH, intact.” Calcium and vitamin D suppress PTH, while phosphorus raises it. If PTH is maximally suppressed, the body perceives calcium and vitamin D as adequate and does not perceive any crisis of excess phosphorus. The point of maximal suppression appears to be approximately halfway through the normal range (around 30 pg/mL) and may be as low as 20 pg/mL. The ultimate test of whether your PTH is suppressed is whether the nutritional approaches I have outlined in this section lower it further. I consider a PTH higher than 35 pg/mL as a cause for nutritional action, and as PTH increases toward the top of the normal range, my confidence in the need for action increases. If PTH is maximally suppressed, there is likely no need for action even if 25(OH)D appears low (unless there is evidence of a frank magnesium deficiency). The other markers in this subsection and the risk factors below should be used to determine

what action is needed for a high-normal PTH.

- **1,25(OH)$_2$D** (LabCorp, Quest), also known as 1,25-dihydroxyvitamin D, calcitriol, "Vitamin D, 1,25-Dihydroxy" or "1,25 di-OH Vitamin D." In vitamin D deficiency, calcitriol remains normal until the deficiency is beyond the degree needed to cause serious rickets and osteomalacia, at which point it may become elevated briefly and finally become low. By contrast, in calcium deficiency calcitriol rises linearly with the degree of deficiency. Phosphorus tends to have no net effect on calcitriol levels. Unless there is evidence of *severe* vitamin D deficiency, the following rule can be applied: the lower calcitriol is within the normal range, vitamin D is a more likely deficiency than calcium; the higher calcitriol is within the normal range, calcium is a more likely deficiency than vitamin D. If PTH is high, excess phosphorus may be an issue regardless of the calcitriol level. If PTH is normal, variations of calcitriol within the normal range probably do not reflect a nutritional problem at all. In all cases, elevations in calcitriol are best interpreted when high-sensitivity C-reactive protein is measured.

- **High-Sensitivity C-Reactive Protein** (LabCorp, Quest), abbreviated hs-CRP. hs-CRP is a marker of systemic inflammation. It rises during acute inflammation and becomes modestly elevated during chronic inflammation. Inflammation causes the conversion of calcidiol to calcitriol. Values of 1-3 suggest chronic, low-grade chronic inflammation, and values above 3, especially those above 10, suggest an acute infection or serious inflammatory disorder. hs-CRP values associated with low-grade inflammation could be considered likely to make a modest contribution to low 25(OH)D, especially if calcitriol is on the higher end of normal. Higher values associated with acute inflammation could make a very large contribution. Infection is not the only source of inflammation. Recovery from surgery or injury elicits acute inflammation, for example. Adiposity, smoking, poor diet, and physical inactivity contribute to chronic, low-grade inflammation.

- **Calcitonin** (LabCorp, Quest) and **FGF23** (LabCorp, Quest) are, in my opinion, generally not necessary but could theoretically be helpful. Excess calcium will raise calcitonin, and excess phosphorus will raise FGF23.

- **Total calcium** (LabCorp, Quest)**, ionized calcium** (LabCorp, Quest)**, and phosphorus** (LabCorp, Quest)**.** Changes in these markers always require more severe nutritional imbalances than those that alter the markers above. Serum calcium declines in deficiencies of vitamin D or calcium that are severe enough to cause rickets. It rises in clinical hypercalcemia caused by excesses of these two nutrients.Only *ionized* calcium is biologically relevant. Total calcium usually faithfully reflects ionized calcium, and we usually use it because it is easier to collect the blood and cheaper. Nevertheless, total calcium will underestimate ionized calcium during acidosis or in the presence of low albumin, and it will overestimate it during alkalosis or in the presence of high albumin. Phosphorus levels decline in phosphorus deficiency and rise in phosphorus excess.

Testing Caveats:

- *Other Nutrient Deficiencies.* Although zinc is not as prominent in vitamin D metabolism as it is in vitamin A metabolism, the activity of the vitamin D receptor is dependent on zinc, so zinc deficiency may cause resistance to vitamin D and cause clinical signs of

deficiency to develop at normal 25(OH)D levels. Magnesium is critical to all aspects of vitamin D and calcium metabolism, and a frank deficiency of magnesium will cause hypocalcemia (thereby contributing to tetany and osteomalacia) and interfere with the interpretation of the blood markers covered in this section. For example, PTH may be low in magnesium deficiency even though the hypocalcemia that accompanies this deficiency should raise it. Nevertheless, few people are sufficiently deficient in magnesium to interfere with the interpretation of PTH or other markers in this section. A deficiency of vitamin K will contribute to osteopenia or osteoporosis without affecting any of these blood markers.

- *Pregnancy.* Pregnancy lowers 25(OH)D, calcium, and PTH, and raises calcitriol. These are probably adaptations to supply calcium to the fetus while minimizing the risk of bone loss to the mother. Total calcium may drop as low as 8.2 mg/dL, which is below the typical bottom of the reference range. Whether ionized calcium also drops is unclear, and pregnancy may induce a mild acidosis that keeps ionized calcium normal while total calcium drops. PTH is typically between 10 and 25 pg/mL. Alterations to 25(OH)D and calcitriol mainly occur in the second and third trimesters, where 25(OH)D is cut in half and calcitriol is doubled.

- *Kidney Disease.* In chronic kidney disease, the excretion of phosphate declines, which causes calcium levels to fall. The hyperphosphatemia and hypocalcemia elicit a rise in PTH. Although kidney disease requires nutritional management, this is a component of medical treatment that is beyond the scope of this guide.

- *Sarcoidosis.* Sarcoidosis is a poorly understood overactivation of the immune system. Calcitriol is high, 25(OH)D is often low, and hypercalcemia may occur. It requires medical attention and its treatment is beyond the scope of this guide.

- *Tumors and Genetic Disorders.* There are a significant number of tumors and rare genetic disorders that alter the metabolism of the nutrients in this section. This is more likely the case when there is a constellation of blood markers that otherwise do not seem to make sense. For example, a deficiency of vitamin D or calcium will cause a rise in PTH that brings calcium levels up to normal. High PTH should therefore be associated with normal or low calcium. If high PTH is associated with *high* calcium, PTH is being overproduced, raising calcium higher than normal, and this is likely the result of a medical condition outside the scope of nutrition. As another example, excess phosphorus will raise FGF-23 and this will bring phosphorus levels down to normal. High FGF-23 should be associated with normal or high phosphorus. If high FGF-23 is associated with *low* phosphorus, FGF-23 is being overproduced, causing hypophosphatemia, and this is another likely case of a medical condition outside the scope of nutrition. Additionally, some cases may appear nutritional in nature at first, but if they do not respond to nutritional strategies appropriately, this could be a sign of an underlying medical condition. These possibilities reinforce the importance of having all of your blood work reviewed by a physician even if you are able to obtain it from a direct-to-consumer testing company.

Correcting Nutritional Imbalances in Vitamin D, Calcium, and Phosphorus

Most scientists and clinicians use 25(OH)D as the principle marker of vitamin D status, and do not routinely monitor the nutritional status of calcium are phosphorus in an analogous way. I use these markers differently. I see the principal sign that this system is in balance as a PTH suppressed to near or below 30 pg/mL. If PTH is significantly higher than this, I use the other markers as well as diet and lifestyle to determine the most likely cause. For example, here are some common clusters that may be encountered:

- Low 25(OH)D, indoor lifestyle, low dietary vitamin D, normal calcium intake, low hs-CRP, and middle-of-the-range calcitriol. Vitamin D deficiency is most likely.
- Low 25(OH)D, outdoor lifestyle, adequate dietary vitamin D, low calcium intake, low hs-CRP, and calcitriol on the high end of the range. Calcium deficiency is most likely.
- Low 25(OH)D, outdoor lifestyle, adequate dietary vitamin D, adequate calcium, high hs-CRP, and calcitriol on the high end of the range. Inflammation is most likely.
- Low or normal 25(OH)D, outdoor lifestyle, adequate dietary vitamin D, adequate calcium, high intake of processed foods, calcitriol normal or low, calcium normal or low, phosphorus normal or high, and high FGF-23. Excessive intake of phosphorus is most likely.

Alternatively, PTH may be normal or low in a case of excess vitamin D, and the earliest sign may be an elevated 25(OH)D. Very elevated 25(OH)D and hypercalcemia would be the principle markers of frank vitamin D toxicity.

After identifying the principal imbalance, I would correct it by reversing the most likely causes and would use the blood markers to monitor the efficacy of the approach. Reasonable daily targets are as follows: a half hour a day of outdoor sun exposure with at least the hands and face, if not more, exposed; vitamin D intake in the range of 600-2000 IU; 800 to 1200 milligrams of calcium; minimal processed foods. Due to the large variation in endogenous vitamin D synthesis with lifestyle and environment, the vitamin D intake target may have to be modified substantially according to blood work.

If inflammation is the cause of low vitamin D in a person with frequent or chronic infections, I would still try to improve the 25(OH)D level with vitamin D supplementation because more vitamin D may be needed to support the immune system. In other cases, however, transient and self-limiting inflammation may resolve on its own.

A variety of medical conditions discussed above can act as both causes and consequences of imbalances in these nutrients, and it is imperative that they be managed by the appropriate medical professional.

Magnesium

Signs and Symptoms of Deficiency: The following are signs and symptoms of frank clinical deficiency: cardiac arrhythmia, palpitations, weakness and fatigue, ataxia (loss of full control over body movements), muscle twitches and spasms, low blood levels of calcium

(hypocalcemia) and related disorders such as tetany and osteomalacia, low blood levels of potassium (hypokalemia), apparent vitamin D deficiency and resistance to standard treatment. More moderate magnesium deficits may contribute to the following disorders: osteopenia and osteoporosis, soft tissue calcification (such as kidney stones), high blood pressure (hypertension), preeclampsia and eclampsia, migraines, and many aspects of cardiovascular disease. Hypothetically magnesium protects against muscle cramps, though evidence for this is limited mainly to cramps at rest during pregnancy. Magnesium is needed for all uses of ATP and for the production of all proteins, so its deficiency could plausibly play a role in many other health problems.

Risk Factors for Deficiency: A diet low in plant foods or high in refined foods is the principal dietary pattern that would cause a nutritional magnesium deficiency. The following cause malabsorption of magnesium: proton pump inhibitors and other antacids, vomiting and diarrhea, ulcerative colitis, pancreatitis, and any disorders that cause fat malabsorption. Urinary magnesium excretion is proportional to urinary volume and is increased by anything that causes increased urination, such as diabetes or diuretics. A number of other pharmaceutical drugs including epidermal growth factor blockers and some antibiotics and antifungal medications increase urinary magnesium loss. Chronic alcohol abuse causes both malabsorption and urinary wasting of magnesium. Sweating and burn injury cause loss of magnesium through the skin. The importance of sweating means that athletes and sauna users have higher magnesium needs.

Two syndromes lower blood magnesium to dangerous levels by moving it into other tissues. Hungry bone syndrome involves the movement of magnesium into bone when bone mineral content starts increasing suddenly after the correction of a bone resorption disorder, for example by surgical removal of the parathyroid gland. Low levels of calcium (hypocalcemia) and phosphorus (hypophosphatemia) also develop during hungry bone syndrome. Refeeding syndrome results from the aggressive correction of starvation or chronic malnutrition, as might occur in alcoholism, eating disorders, or illnesses that impact food intake. During these conditions, dietary magnesium drops to low levels and possibly zero, and loss of lean mass causes loss of magnesium stores. During refeeding, insulin brings magnesium into cells, causing hypomagnesemia to develop. This is aggravated by the large demand for cellular repair and rebuilding of magnesium stores. Low levels of hypophosphatemia and low levels of potassium (hypokalemia) also occur during refeeeding syndrome.

Signs and Symptoms of Toxicity

Hypermagnesemia (especially when blood levels are near or above twice the top of the reference range) can lower blood pressure to dangerous levels. Both bradycardia (slow heart rate) and tachycardia (fast heart rate) may occur. Paradoxically, hypermagnesemia can cause hypocalcemia, one of the major features of clinical magnesium deficiency. Thus, many of the signs and symptoms of magnesium deficiency are also signs of magnesium toxicity.

Excessive supplementation with magnesium can cause diarrhea, and clinicians take advantage of this to use it as a laxative. The Institute of Medicine set the tolerable upper intake limit for supplemental magnesium at 350 mg/d to avoid loosening stools, but the form of magnesium and an individual’s bowel tolerance can cause large variation in the amount needed for this effect. Supplements are unlikely to cause worse problems than this if you have healthy kidneys.

In those with poor kidney function, however, the use of high doses of magnesium for medical purposes can cause hypermagnesemia. One example of this is administration of magnesium to prevent convulsions in preeclampsia and eclampsia. Another example is excessive use of over-the-counter magnesium-containing medications, such as the 2 grams per day you could obtain by using milk of magnesia as an antacid at the maximal dose prescribed on the label. For magnesium as a nutritional supplement, the upper limit of 350 mg/d should be used as a rough indicator of potential risk in the context of poor kidney function. If you choose to consistently use higher doses than this, I recommend discussing this with your doctor so you can review your kidney function and magnesium levels to ensure your use of the supplement is safe.

Testing for Magnesium Status:

- **Serum magnesium** (LabCorp, Quest)
- **Red blood cell magnesium** (LabCorp, Quest)
- **24-Hour urine magnesium** (LabCorp, Quest)

Serum magnesium declines in deficiency and rises in toxicity, but it is less sensitive than red blood cell and urine to changes in magnesium status. Red blood cell magnesium may be low when serum is not, and while this could indicate an early deficiency, it could also indicate a deficiency in factors needed for bringing magnesium into cells, such insulin signaling, energy production, and sodium. Urine magnesium will be low in nutritional deficiency, but high in deficiencies caused by urinary loss.

The interpretation of magnesium markers is best facilitated by taking all three measurements. A nutritional magnesium deficiency is likely to produce low values across all three measurements. Low blood values coupled to high urine values reveal urinary magnesium wasting. A large discrepancy between serum and red blood cell magnesium could suggest a problem with magnesium transport.

Testing Caveats: Since red blood cells are higher in magnesium than serum, hemolysis will falsely elevate serum magnesium. Hemolysis can occur inside your body if you have certain medical disorders, but it can also occur during blood collection due to poor positioning of the needle or other technical difficulties. If serum is implausibly high, especially when urine and red blood cell are normal, the serum measurement may have been falsely elevated from hemolysis and should be repeated from a new blood draw. There is a collection of rare genetic disorders that cause poor magnesium absorption, urinary magnesium loss, or both. Many of the signs and symptoms of magnesium deficiency are results of hypocalcemia or disordered calcium handling, and many result from hypokalemia. Therefore, I recommend consulting the section on vitamin D, calcium, and phosphorus as well as the section on electrolytes when interpreting altered magnesium status.

Correcting Magnesium Deficiency: How you approach a magnesium deficiency should depend on its cause. If your diet is low in unrefined plant foods, your first approach should be to eat more magnesium-rich foods. If this is not possible, practical, or sufficient to reverse signs, symptoms, and blood work, you can use a supplement, such as magnesium glycinate or malate. Keep the dose low enough to avoid loosening stools. Review your use of the supplement with the doctor if it is higher than 350 mg/d or if you have any signs of poor kidney function. If you have identified any of the non-dietary causes of magnesium deficiency, they must be addressed

directly, with appropriate medical treatment where warranted. Supplementation to compensate for urinary loss makes sense, but it should not replace correcting the cause of urinary loss.

Correcting Magnesium Toxicity: If hypermagnesemia is found, poor kidney function is a likely cause and must be addressed with appropriate medical treatment. Nutritionally, supplemental magnesium should be removed.

Vitamin K

Signs and Symptoms of Deficiency: Severe vitamin K deficiency involves defective blood clotting. Easy bruising or blood accumulating at the surface of the skin may be most apparent, but widespread internal bleeding and hemorrhage are possible. It is far more likely to encounter moderate deficiencies of vitamin K. These deficiencies are less well established and are an active area of research. They may contribute to osteopenia, osteoporosis, short stature in children, soft tissue calcification (e.g., calcified atherosclerotic plaque; calcification of the vascular media that occurs in diabetes, kidney disease, and with age; kidney stones). Even less well established but plausible signs and symptoms include insulin resistance, inadequate insulin and hyperglycemia, low testosterone and fertility in men, high androgens in women, poor exercise performance or tolerance, and cancers of the liver, lung, and prostate.

Risk Factors for Deficiency: Vitamin K refers to a collection of compounds that have different distributions in foods and have different tissue distributions within the body. Vitamin K_1 occurs mainly in greens. Vitamin K_2 refers to a collection of compounds known as menaquinones that are individually designated menaquinone-n, abbreviated MK-n, where n is a number between 4 and 13. MK-4 is found primarily in animal products, and MK-7 through MK-13 are found primarily in fermented foods. A severe vitamin K deficiency of dietary origin is rare, and would require a diet devoid of green plants, animal foods, and fermented foods. However, far less vitamin K_2 is present in the diet than K_1, and K_2 is more effective at supporting most functions of vitamin K besides clotting. Most diets contain inadequate K_2 to support these functions and in this sense moderate vitamin K deficiency may be the norm.

Humans are able to convert other forms of vitamin K into MK-4, but cholesterol-lowering statins decrease this conversion and presumably make it more important to obtain MK-4 in the diet. High-dose vitamin E supplementation increases the breakdown of vitamin K and may contribute to deficiency. Vitamin D, chronic kidney disease, and anything else that causes soft tissue calcification raises the need for vitamin K. Any disorders leading to fat malabsorption may induce deficiency. The vitamin K status of newborns is often deficient because of inadequate intake by the mother during pregnancy.

Drugs known as 4-hydroxycoumarins, such as warfarin (Coumadin), inhibit vitamin K recycling. Clinicians use them as anticoagulants and many individuals or organizations use them in homes, businesses, or public buildings as a rodenticide. Severe deficiencies of vitamin K can be produced by an overdose of anticoagulant medication, or accidental poisoning with rodenticides in the case of children and pets.

Special Note on Anticoagulant Medication: 4-hydroxycoumarins require dietary and supplemental vitamin K to be maintained very stably over time because the dose of the medication must be adjusted to handle the vitamin K load of the diet. These drugs introduce a state of partial vitamin K deficiency to manage the risk of a fatal blood clot from forming. It is not possible to eliminate this aspect of the treatment. However, since vitamin K_2 better supports the non-clotting functions of vitamin K than K_1 does, and since it is present in the diet in much lower quantities than K_1, low-dose K_2 supplementation (e.g. 45 micrograms per day of MK-7) may be a safe way of supporting these other functions. If you choose to use this approach, you must do so with the knowledge and strict supervision of the prescribing physician. Doing so without the knowledge of the physician is dangerous because it could alter the dose of the medication needed.

Excess and Toxicity: Vitamin K has no clearly established syndrome of toxicity. In fact, 45 milligrams per day of MK-4, which is 375 times the RDA, has been used as a pharmaceutical drug to treat osteoporosis and to reduce the risk of liver cancer associated with viral cirrhosis, with no clearly established adverse effects. Nevertheless, high-dose vitamin K stimulates the breakdown of vitamin E and has the potential to deplete glutathione, both of which are critical components of the antioxidant system (see the antioxidant system). High doses also inhibit bone resorption, which may help preserve bone mass but may also interfere with blood sugar control, sex hormone balance, and energy utilization during exercise. I recommend keeping vitamin K supplements under one milligram per day unless there is strong justification to do otherwise, such as in kidney disease, or in the use of pharmacological doses of MK-4 for osteoporosis or cancer prevention, all of which should be done under medical supervision.

Testing for Vitamin K Status:

- **Serum vitamin K** (LabCorp, Quest, Genova fat-soluble vitamin panel) is not a good marker of vitamin K nutritional status because it only reflects recent intake. However, it will be low even after normal intake or supplementation if a deficiency is caused by malabsorption.
- **Prothrombin time** (LabCorp, Quest) is a functional marker of blood clotting. It is used to calculate the international normalized ratio (INR), a value used to adjust the dose of anticoagulant medication. In the absence of 4-hydroxycoumarin treatment, it could reflect vitamin K deficiency, but could also reflect many other factors that interfere with blood clotting.
- **Des-γ-carboxy Prothrombin** (LabCorp, Quest), also known as DCP or protein induced by vitamin K absence or antagonism-II (PIVKA-II) rises when the vitamin K status of the liver is inadequate to support blood clotting. In the absence of 4-hydroxycoumarin treatment, high PIVKA-II strengthens the interpretation that prothrombin time is elevated because of vitamin K deficiency. PIVKA-II will rise during treatment with 4-hydroxycoumarins and this is expected. In the absence of 4-hydroxycoumarin treatment, elevated PIVKA-II suggests a relatively severe deficiency of vitamin K.
- **The vitamin K status of extrahepatic tissues** (tissues other than the liver) will be the ideal tests of vitamin K status for routine screening and disease prevention. Adequate tests of this nature are not yet available. LabCorp and Quest both offer osteocalcin, and Genova offers undercarboxylated osteocalcin (ucOCN). The ratio of undercarboxylated to total osteocalcin would be ideal to assess the vitamin K status of bone, but dividing the Genova value by the LabCorp or Quest values would produce potentially spurious

results since the values come from different blood draws and the labs have not calibrated the assays to be used together. Immunodiagnostic systems has produced an assay for uncarboxylated MGP, which is a very good marker of the vitamin K status of blood vessels, but it is not yet available clinically. I will update this guide when it is.

At the present time, there are no available markers of marginal vitamin K status, and I did not include any markers of vitamin K status in the comprehensive screening. I included recommendations for preventative supplementation in the "Correcting Vitamin K Deficiency" section below.

Correcting Vitamin K Deficiency: Severe vitamin K deficiencies resulting from overdose or poisoning with vitamin K antagonists will involve removing the antagonist exposure and administration of vitamin K, but this must be done as part of medical treatment that also manages the bleeding and any secondary complications, which can be serious and even fatal. If the diet is devoid of leafy greens, they should be added to the diet at one or two servings per day. If this is not possible or practical, supplemental vitamin K_1 (phylloquinone) can be added at a dose of 100-500 micrograms per day. Most people who do not consume natto or goose liver, and do not consume a lot of egg yolks and cheese, would benefit from supplementing with 200-1000 micrograms per day of K_2, preferably as a mix of MK-4 and MK-7. Individuals with chronic kidney disease, and perhaps other diseases involving soft tissue calcification, need at least 500 micrograms per day of supplemental K_2 and probably more than one milligram per day.

Caveats: Thiamin is required for the recycling of vitamin K and should be considered if strategies to correct vitamin K status listed in this section do not work, or if there are other reasons to suspect thiamin deficiency. Glucose 6-phosphate dehydrogenase (G6PD) deficiency (LabCorp and Quest) can also impair vitamin K recycling.

B Vitamins Involved in Energy Metabolism

The B vitamins involved in energy metabolism are thiamin (vitamin B1), riboflavin (vitamin B2), niacin (vitamin B3), pantothenic acid (vitamin B5), pyridoxine (vitamin B6), and biotin (vitamin B7). The B vitamins listed in the next section on methylation do have roles that intersect with energy metabolism, but since they are more central to methylation than they are to energy metabolism I discuss them separately. The system of energy metabolism directly supports the antioxidant system, so consider vitamins in this section alongside the nutrients more directly involved in the antioxidant system when dealing with conditions of oxidative stress.

All B vitamins are water-soluble. As a result, excessive fluid loss, as in the frequent urination that accompanies diabetes, can be a source of deficiency. Additionally, cooking foods in water that is then discarded will cause some loss of most B vitamins.

Because these vitamins play so many roles in the metabolism of fat, protein, and carbohydrate for energy, the signs and symptoms of their deficiencies overlap and present many similarities. This is augmented by the fact that some B vitamins are often needed for the endogenous synthesis or metabolic activation of other B vitamins, so deficiencies of one often cause deficiencies of another.

The signs and symptoms in this category frequently impact the nervous system, the skin, the hair and nails, and the gastrointestinal tract.

The best markers of nutritional status are often intermediates in the metabolic pathways that stop working when they are deficient and that can be found on plasma amino acid profiles and urinary organic acid profiles. **Plasma amino acid profiles** can be obtained from LabCorp, Quest, Great Plains, the Genova ION Profile + 40 amino acids, and the NutrEval. **Urinary organic acid profiles** can be obtained from LabCorp, Quest, Great Plains, the Genova ION Profile + 40 amino acids, and the NutrEval. Of these, only LabCorp's urinary organic acids profile does not have its analytes listed on the web site. For this reason, although it may include many or all of the markers that the others do, I do not list it below as a way to obtain any markers. My preference is to use the Genova ION Profile + 40 amino acids for plasma amino acid and urinary organic acids because it contains the largest number of important nutritional markers, and I included the ION in the comprehensive screening.

With the exception of vitamin B6, these vitamins have no known toxicity syndromes. Sections on B6 toxicity and concerns about niacin excess are included, but toxicity and excess sections are otherwise excluded for these vitamins.

Thiamin (Vitamin B1)

Signs and Symptoms of Deficiency

There are three classical syndromes of thiamin deficiency, each with distinct but overlapping clusters of signs and symptoms:

- *Beriberi*. Peripheral neuropathy (weakness, numbness, pain, or tingling in the hands and feet), impairment of reflexes, with or without cardiovascular signs that include enlarged heart, elevated heart rate (tachycardia) and cardiac output, and congestive heart failure.
- *Wernicke's Encephalopathy*. Weakness, paralysis, or disordered movement in the muscles around the muscles of the eye (ocular palsies, ophthalmoplegia, nystagmus) ataxia (loss of full control over body movements), confusion, often with peripheral neuropathy.
- *Korsakoff's Psychosis*. Amnesia, confabulation (fabricated, distorted, or misinterpreted memories), decreased spontaneity and initiative. This is often but not always a progression of Wernicke's encephalopathy. Prompt treatment of Wernicke's encephalopathy with with high-dose intravenous thiamin as part of emergency medical care prevents its progression to Korskoff's psychosis.

Very severe thiamin deficiency may cause seizures, paralysis, and death. Tragically, severe thiamin deficiency is underdiagnosed in emergency medicine and often diagnosed at autopsy. Poor glucose tolerance may occur in less severe thiamin deficits. Less well established but plausible signs and symptoms include improvements in energy or neurological health on a low-carbohydrate diet, low levels of neurotransmitters, and apparent deficiencies of folate and vitamin K that do not respond well to dietary or supplemental corrections.

Risk Factors for Deficiency: Dietary thiamin deficiency occurs when the diet does not contain several 100 gram servings per day of meat, legumes, whole grains, or enriched grains (e.g., a diet based mostly on fat, or on refined foods that are not fortified with thiamin) and does not contain thiamin supplements or thiamin-containing multivitamins. Other well established causes of thiamin deficiency include persistent vomiting, alcoholism, gastrointestinal diseases that cause malabsorption, liver diseases that impair hepatic thiamin storage, and HIV/AIDS. Diabetes increases the need for thiamin. Less common but well established causes of thiamin deficiency include thiamin antagonists that occur in raw fish and shellfish, seasonally in ferns, and in the edible larvae of the African silkworm *Anaphe venata*. Less well established but plausible causes include sulfite accumulation, which may be driven by molybdenum deficiency and high intake of animal protein or sulfite used as a food additive; thiamin-destroying bacteria and fungi in the human gut; thiamin-destroying amoebas that may pollute water; and perhaps thiamin antagonists produced during infections or from exposure to toxic indoor molds.

Testing for Thiamin Status

From among those listed below, I recommend using whole blood thiamin pyrophosphate (LabCorp) and Genova ION Profile + 40 amino acids to assess thiamin status, which are included in the comprehensive screening.

The following changes are found in thiamin deficiency:

- **Whole blood thiamin pyrophosphate** (LabCorp) is low.
- **Erythrocyte transketolase activity** (available from HDRI as "ETKA" on their requisition form) is low.
- **Alanine** measured on a plasma amino acid profile (***preferred:*** Genova ION Profile + 40 amino acids; ***also****:* LabCorp, Quest, Great Plains, and the NutrEval) is high.
- **Lactate** (LabCorp) and possibly **pyruvate** (LabCorp) are elevated in the blood. Quest offers them together.
- **Alpha-ketoglutarate**, also known as 2-oxoglutarate, **lactate**, and possibly **pyruvate** are elevated on a urinary organic acid analysis (***preferred:*** Genova ION Profile + 40 amino acids; ***also****:* Quest, Great Plains, and the NutrEval).

Testing Caveats: Transketolase activity is subject to genetic polymorphisms that may impact its activity, and alcoholism may cause epigenetic decreases in its activity; these caveats do not rule out the sensibility of supplementing thiamin when transketolase activity is low, since it may be responsive to extra thiamin, but they complicate a straightforward interpretation of thiamin deficiency. The pattern of metabolites that rises in thiamin deficiency is best interpreted as a complete pattern. If only one or two metabolites are high, the interpretation is less clear. Most thiamin-dependent enzymes also depend on lipoic acid and are subject to inhibition by oxidative stress and heavy metals, which may mimic the metabolite pattern of thiamin deficiency.

Correcting Thiamin Deficiency: Thiamin deficiency that is severe enough to cause the signs and symptoms of the classical syndromes described above requires emergency medical attention, which may involve high-dose intravenous thiamin according to protocols that are beyond the scope of this guide. In the cases of more moderate thiamin deficiencies, they should be addressed according to the root cause. If the diet is poor in thiamin, thiamin-rich foods should be introduced. Many disease states cause thiamin deficiency that must be addressed

independently with appropriate medical care. Thiamin supplementation is safe even at high doses and may help resolve a dietary deficiency more quickly or compensate for poor absorption or a high rate of urinary loss. If deficiencies of other B vitamins have not been adequately screened for, it would be prudent to include a B complex alongside thiamin. Thiamin hydrochloride is likely adequate in most cases. Benfotiamine may be beneficial for the neuropathy of diabetes and alcoholism but its superiority over thiamin hydrochloride has not been clearly demonstrated. Thiamin pyrophosphate (thiamin diphosphate) is the active form of thiamin, and supplements of this form could plausibly overcome impairments in thiamin activation, which are known to occur in alcoholism.

Riboflavin (Vitamin B2)

Signs and Symptoms of Deficiency: Lesions on the outside of the lips (cheilosis) or corners of the mouth (angular stomatitis); inflammation of the tongue (glossitis); redness, bleeding, and swelling inside the mouth (hyperemia and edema of the oral cavity); dermatitis or other inflammatory conditions of the skin; weakness, numbness, pain, or tingling in the hands and feet (peripheral neuropathy); hair loss (alopecia). Although riboflavin is ubiquitous in energy metabolism, fatty acid oxidation is impaired first in deficiency, so improvements in energy and well being on a low-fat diet may be an indication of deficiency.

Risk Factors for Deficiency: Riboflavin is most abundant in yeast and organ meats but is otherwise widely spread across the food supply, present in the water-soluble fractions of food. Diets that contain mostly fat or refined foods that are not fortified with riboflavin, and do not include riboflavin supplements or riboflavin-containing multivitamins, may induce a riboflavin deficiency. Diabetes, trauma, stress, and oral contraceptives increase the excretion of riboflavin and can contribute to deficiency. Riboflavin is very sensitive to light, so consumption of foods that have not been properly protected from light at home or during transport and distribution could theoretically contribute to deficiency.

Testing for Riboflavin Status

- **Whole blood total riboflavin** (LabCorp), which is mainly intracellular riboflavin in its active form, is low in deficiency.
- **Erythrocyte glutathione reductase activity** (available from HDRI as “EGR” on their requisition form) is low in deficiency.

Testing Caveats: Glucose 6-phosphate dehydrogenase (G6PD) deficiency is the most common enzymatic defect in the world. LabCorp and Quest both offer tests for it. G6PD deficiency increases the binding of riboflavin to glutathione reductase, which can mask riboflavin deficiency by elevating glutathione reductase activity. Low thyroid or adrenal activity compromises the activation of riboflavin to flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN). This may result in signs and symptoms of riboflavin deficiency when the underlying problem is hormonal rather than nutritional. Rare genetic disorders in fatty acid oxidation or riboflavin metabolism may induce signs of riboflavin deficiency but require highly specialized diagnosis and medical treatment outside the scope of this guide. Some of the signs and symptoms of riboflavin deficiency, especially the skin lesions, are due to deficient metabolic activation of the form of vitamin B6 found in plant foods, and are seen in vitamin B6 deficiency as well.

Correcting Riboflavin Deficiency: In a dietary deficiency, riboflavin-rich foods should be introduced into the diet. Nutritional yeast and organ meats will be particularly useful. To correct a deficiency more quickly or compensate for increased excretion, riboflavin supplements may be used according to the label, but if other deficiencies have not been properly screened it is prudent to include a B complex in place of or alongside riboflavin. Although standard riboflavin supplements should be sufficient in most cases, Source Naturals flavin mononucleotide may be more effective in hypothyroidism and adrenal insufficiency, where activation of riboflavin is impaired. The rare genetic defects in fatty acid oxidation may respond well to extremely high doses of riboflavin, such as 10-50 milligrams per kilogram body weight per day. Although riboflavin has no established syndrome of toxicity, doses this high should not be used outside of medical supervision. They are unnecessary except in these disorders, and the disorders themselves require close medical attention.

Niacin (Vitamin B3)

Signs and Symptoms of Niacin Deficiency: The classic signs of niacin deficiency are the "3 Ds" of pellagra: dermatitis, diarrhea, dementia. Untreated, niacin deficiency causes the 4th D, death. The dermatitis of niacin deficiency results from impaired DNA repair of sun-damaged tissue, and it is unique among the skin problems caused by B vitamin deficiencies in that it is provoked by normal sun exposure. The diarrhea results from inadequate energy to maintain the absorptive villi of the small intestine and involves generalized malabsorption that might cause deficiencies of many other nutrients. The "dementia" may become so extreme that it leads to incarceration in a mental institution, but it often begins as depression, insomnia, headaches, and dizziness. The possibility that many of the negative effects of aging are due to mild deficits of the niacin needed for DNA repair is currently an area of active research.

Risk Factors for Niacin Deficiency: Niacin is obtained in the diet and also synthesized endogenously from the amino acid tryptophan in a process requiring vitamin B6 and iron. Frank niacin deficiency requires deficiencies of niacin *and* one of the following: protein, vitamin B6, or iron. Historically, pellagra epidemics occurred in the United States when the standard diet of many regions was low in protein and high in corn that had not been treated with nixtamalization, the traditional process whereby lye was used to render the niacin within the corn bioavailable. In the modern era, niacin deficiency could be caused by diets based mainly on fat or on unrefined foods that are not fortified with niacin, in the absence of niacin supplements or niacin-containing multivitamins. DNA repair consumes niacin, so any conditions causing damage to DNA may contribute to niacin deficiency. Serotonin production taxes the supply of tryptophan, so serotonin-producing tumors can cause niacin deficiency. Hartnup disease is a rare genetic disorder in the absorption of tryptophan that can cause deficiency. Alcoholism, HIV/AIDS, malabsorption disorders affecting the small intestine, kidney disease, and cancer all increase the risk of niacin deficiency.

Niacin Excess: Niacin is well known to cause flushing, itching, and blistering of skin at doses used medically to lower blood lipids, and this may be accompanied by elevated glucose, liver enzymes, and uric acid. This occurs with the nicotinic acid form of niacin but not niacinamide or nicotinamide. This is a well characterized acute reaction, and there is no established syndrome of chronic niacin toxicity. However, excess niacin is excreted in the urine largely as methylated

metabolites, regardless of the form of niacin used. This drains methyl groups and may cause deficiency signs or symptoms of the B vitamins involved in methylation. Methylation status should be monitored carefully if using high-dose niacin in any form.

Testing for Niacin Deficiency: Niacin is a component of two major substrates for energy metabolism, NAD(H) and NADP(H). In deficiency, NADP(H) stays constant while NAD(H) falls. The **"niacin number"** can be calculated by dividing the concentration of NAD(H) by NADP(H) and multiplying by 100. Healthy adults not taking niacin supplements have a niacin number close to 175. Niacin supplementation can raise this over 600, while 5 weeks of moderate, experimental niacin deficiency drops it to 60. This can be obtained from HDRI as "NADH/NADPH" on their requisition form. As the niacin number declines under 175, deficiency should be considered progressively more likely, and this can be used as a target for correcting deficiency.

Correcting Niacin Deficiency: The introduction of niacin-rich foods or the correction of deficiencies of protein, vitamin B6, or iron should form the approach to correction, depending on which cause is identified. Nicotinamide riboside supplements can be used to increase NAD without risk of flushing, but high doses will still tax the methylation system so care to optimize methylation status should be used in this approach.

Pantothenic Acid (Vitamin B5)

Signs and Symptoms of Pantothenate Deficiency: Clinical pantothenate deficiency results in numbness, especially in the toes, burning in the feet, irritability, restlessness, disturbed sleep, and gastrointestinal distress. Pantothenic acid deficiency is not well researched because it is considered extremely unlikely. Additional signs that should be considered plausible in more moderate deficits could include a vulnerability to hyperammonemia (which would make someone feel sick and fatigued on a high-protein diet), general fatigue and weakness, improved health and well-being on a low-fat diet, and the pain associated with rheumatoid arthritis.

Risk Factors for Deficiency: Pantothenate is named after the Greek word *pantos* for "everywhere" or "everything," reflecting its ubiquity in the diet and the low likelihood of deficiency. Pantothenate is also produced by gut microbes, which may protect against frank deficiency on low-pantothenate diets. Clinical deficiency has only been observed in experimental studies and in prisoners of war during World War II. Nevertheless, yeast, liver, eggs, and mushrooms stand out as excellent sources. Refining of grains removes most of the pantothenate, and it is not added to enriched grains. Therefore, diets high in refined grains and devoid of pantothenate-rich foods will be low in pantothenate and this may contribute to moderate deficits when pantothenate supplements or pantothenate-containing multiviamins are not used. The contribution of gut pantothenate production to nutritional status is not well characterized, but gut dysbiosis might be seen as a plausible contributor to deficiency.

Testing for Pantothenate Status: Plasma levels of pantothenate (LabCorp, Quest) decline in nutritional status. References range are extremely wide, and since deficiency is poorly characterized, I believe it makes sense to target the middle or upper half of the range, especially if this can be achieved through pantothenate-rich foods alone.

Correcting Pantothenate Deficiency: If your blood levels are low or in the bottom half of the range and any potential signs or symptoms exist, I recommend placing more emphasis on pantothenate-rich foods and considering the use of a supplement. If other B vitamin deficiencies have not been ruled out, supplementation is best as a component of a B complex. Nevertheless, there is no known toxicity and supplements of one gram per day of calcium pantothenate have shown promise in rheumatoid arthritis. Calcium pantothenate is about half pantothenate and one gram of it provides approximately 50 times the RDA.

Vitamin B6

Signs and Symptoms of B6 Deficiency: In its most severe form, vitamin B6 deficiency causes convulsive seizures; cognitive symptoms such as irritability, depression, and confusion; vulnerability to infection, lesions similar to those of riboflavin deficiency (cheilosis, angular stomatitis, glossitis, oral hyperemia and edema), and sideroblastic anemia (normal hemoglobin concentrations that accumulate around the edges of red blood cells, seen under a microscope). More moderate deficits of B6 elevate homocysteine, contribute to cardiovascular disease, and contribute to chronic low-level inflammation. Less well established but plausible signs and symptoms of moderate B6 deficits include cognitive decline, depression, anxiety, insomnia, hypoglycemia, oxalate kidney stones, and the morning sickness of pregnancy.

Vitamin B6 is needed for the endogenous synthesis of niacin, and may contribute to niacin deficiency in the presence of other predisposing factors. It is also needed for the metabolic activation of essential fatty acids, and may contribute to essential fatty acid deficiency in the presence of other predisposing factors.

Risk Factors for B6 Deficiency: Deficiency severe enough to produce seizures has only been observed historically because of errors in the manufacture of infant formula. However, there are rare genetic defects that cause dramatic increases in the need for vitamin B6 to prevent either seizures or sideroblastic anemia. Moderate deficits of B6 may have many common causes. Diets low in animal foods, low in riboflavin, low in raw foods, or dominated by overcooked foods may contribute to deficiency. Gut flora and the enzyme pyridoxine 5'-phosphate oxidase (*PNPO*) are important for deriving B6 from plant foods, and variations in these factors may contribute to deficiency. Inflammation raises the need for B6 and also increases its degradation. Oral contraceptives, high estrogen levels, non-steroidal anti-inflammatory drugs (NSAIDs), and drugs used to treat tuberculosis and Parkinson's increase the need for B6. Sulfite accumulation, which may be driven by molybdenum deficiency and a high intake of animal protein or sulfite used as a food additive, contributes to B6 deficiency. Pyroluria, a disorder proposed decades ago but never adequately followed up, was thought to contribute to B6 deficiency, and Great Plains currently offers a test for it.

Vitamin B6 Toxicity: Long-term use of doses above 500 miligrams per day of pyridoxine may cause ataxia (loss of full control over body movements), and sensory neuropathy, with symptoms such as numbness to touch or temperature change, tingling, burning, or pain in the extremities. To provide a window of safety, the Institute of Medicine set the tolerable upper intake level (TUIL) at 100 milligrams per day, which is over 50 times the RDA. I consider it important to stay below the TUIL unless there is strong justification to do otherwise. If you are not trying to correct a deficiency, I consider it wise to stay under 10 milligrams per day.

Testing for B6 Status:

- **Plasma B6** (LabCorp, Quest) is low in deficiency.
- **Erythrocyte transaminase activity** (available from HDRI as "EGOT" on their requisition form) is low in B6 deficiency.
- The combination of elevated **xanthurenate, kynurenate, and quinolinate** on a **urinary organic acids** profile is robust evidence of B6 deficiency. In early deficits, xanthurenate is most likely to be elevated and quinolinate is least likely. All three are found only in the Genova ION Panel. The NutrEval has kynurenate and Great Plains has kynurenate and quinolinate. The ideal way to test for these is in a 24-hour urine collection after a 2-gram tryptophan load, but this is not practical with the available tests and if basic screening shows these markers elevated it is clear evidence of a B6 deficiency.

Testing Caveats: Oral contraceptives, and presumably high estrogen, may cause the signs of B6 deficiency to appear on an organic acid profile, but it is not clear whether higher doses of B6 will correct them. It is therefore unclear whether this should be regarded as B6 deficiency. Nevertheless, anecdotally, 100 mg/d of pyridoxal 5'-phosphate seems to mitigate the insomnia that sometimes accompanies high estrogen levels.

Correcting B6 Deficiency: Increasing the proportion of animal foods in the diet, using more gentle cooking techniques, and including more raw foods may all help improve B6 status. Among plant foods, bananas are an excellent source of B6 because it is easy to eat them raw and because their B6 is absorbed more effectively than the B6 in most other plant foods. Pyridoxal 5'-phosphate is the ideal supplement because it does not require riboflavin-dependent metabolic activation in the liver. 5 milligrams per day should be adequate to correct a deficiency that results from poor dietary intake. Nevertheless, there are many factors that disrupt B6 metabolism, and doses between 30-100 milligrams per day may be needed to reverse signs of deficiency in some individuals. Because of the risk of toxicity, doses this high should be used with care and only when there is clear justification. Higher doses are only needed in the context of professional medical care for rare genetic disorders.

Correcting B6 Toxicity: Neurological problems induced by toxic doses of B6 generally resolve when B6 is withdrawn. Nevertheless, signs and symptoms of toxicity should always be reported to a physician as they could require medical care or be mistaken for other conditions that require medical care.

Biotin (Vitamin B7)

Signs and Symptoms of Deficiency: Scaly, red dermatitis around the nose, mouth, and perineum (between the anus and genitals), hair loss (alopecia), conjunctivitis, ataxia (loss of full control over body movements), depression, lethargy, paresthesia (tingling, numbness, or a feeling of something crawling on the skin). Biotin deficiency during pregnancy may contribute to birth defects.

Risk Factors for Biotin Deficiency: The principal determinants of biotin status are egg yolks and liver, which are far more abundant in biotin than any other foods; egg whites, which contain

a heat-sensitive compound known as avidin that impairs biotin absorption; and pregnancy, which raises the need for biotin. The overwhelming risk factor for biotin deficiency is the consumption of egg white, especially raw and when consumed without equal numbers of egg yolks and without biotin supplements or biotin-containing multivitamins. Although cooking degrades avidin, substantial proportions remain in cooked egg white. Whole eggs do not not pose a risk of deficiency, and this is probably true even if raw. On the other hand, egg whites should not be consumed without the yolks unless biotin supplements are also used. The same is true for egg white protein powders. Pregnancy raises the need for biotin, and about one-third of mothers become temporarily biotin deficient during pregnancy.

Testing Biotin Status:

- **Urinary 3-hydroxyisovalerate,** also known as **beta-hydroxyisovalerate** is the most sensitive and robust marker of marginal biotin deficiency. Quest and Genova ION include it. The ideal way to measure this when looking specifically for biotin deficiency is in a 5-hour urine collection after a challenge with 70 milligrams of leucine per kilogram of bodyweight. However, this is not practical with the available tests, and if basic screening shows it elevated, it should be regarded as a sign of biotin deficiency.
- **Blood levels of biotin** (LabCorp, Quest) decline in deficiency, but they are less sensitive than urinary 3-hydroxyisovalerate.

Correcting Biotin Deficiency: If the deficiency can be plausibly attributed to egg whites, the potential source of avidin should be removed by more thoroughly cooking egg whites or consuming fewer of them. Liver and egg yolks are the best food sources of biotin. Liver can be consumed up to two 3.5-ounce servings per week, and 3-4 egg yolks per day can be used for most people, but may need to be moderated for individuals with elevated blood cholesterol. Biotin supplements can be safely used according to the label with no known concerns of toxicity.

B Vitamins Involved in Methylation

The system of methylation involves nutrients with tightly interdependent and overlapping roles. Because of this, the nutrients are better discussed together than apart.

A methyl group, CH_3, is the simplest way to add a carbon atom to an organic (carbon-containing) molecule. All of the molecules within the human body are organic, and methylation is often used to synthesize them or to alter them for the purposes of regulation.

The B vitamins most centrally involved in methylation include **folate (vitamin B9), vitamin B12**, **choline,** and **betaine**. Then amino acids **methionine, serine**, and **glycine** are also central to the system. Finally, the system of energy metabolism directly supports the methylation system, with especially prominent roles for thiamin, riboflavin, niacin, and vitamin B6.

Most of the nutrients in this pathway act as **methyl donors:** folate, B12, choline, betaine, methionine, and serine. However, **glycine** acts as a **methyl buffer**, removing excess methyl groups from the system to prevent overmethylation. Methylation remains adequate and in balance when all parts of the system are optimized.

When reviewing the list of signs and symptoms of methylation imbalances below, it is important to realize that there are many genetic polymorphisms and other factors that will alter the prioritization of methyl groups. It is possible to have some indications of overmethylation coinciding with some of undermethylation. It is also possible to have the buffering system poorly supported so that one swings between indications of undermethylation and indications of overmethylation. With that said, *generally* undermethylation can be seen as a sign of deficient methyl donors and overmethylation as a sign of deficient glycine. Notably, while the relationship between methylation and cancer is controversial, it may be the case that both deficiencies of methyl donors *and* glycine contribute to cancer.

Signs and Symptoms of Imbalances

Signs and Symptoms of Deficient Methylation: Fatty liver disease, neural tube birth defects, elevated homocysteine and associated cardiovascular risk, fatigue, poor exercise capacity, histamine intolerance, difficulty ignoring negative thoughts and thought patterns, depression, anxiety, obsessive compulsive disorder, histamine intolerance, inability to adequately eliminate arsenic, inability to properly utilize selenium or excrete excess selenium. Severe deficiencies in methylation could contribute to deficiencies of zinc, copper, and perhaps other positively charged minerals. As with excessive methylation, possibly cancer.

Signs and Symptoms of Excessive Methylation: Generally understudied with lower confidence compared to undermethylation. Among the best supported: distractibility, difficulty focusing, impulsivity, and substance abuse. More speculative: difficulty breaking free from psychological conditioning, difficulty falling asleep or poor quality sleep, and faster aging skin. As with deficient methylation, possibly cancer.

Signs and Symptoms Specific to B12 and Folate Deficiencies: Both B12 and folate deficiencies lead to macrocytic, megaloblastic anemia. This is independent of their role in methylation. This may be asymptomatic, or may make you feel tired, weak, short of breath on exertion, and cause heart palpitations and paleness.

Signs and Symptoms Specific to B12 Deficiency: Vitamin B12 deficiency causes neurological degeneration that is largely independent of its role in methylation and does not involve folate. Mental changes include memory loss, changes of personality or mood, and in the most severe cases delirium and psychosis. Outside the brain, changes generally begin in the feet and work their way upwards with lost sense of position and vibration and paresthesia (tingling, numbness, or a feeling of something crawling on the skin), possibly progressing to ataxia (loss of full control over the muscles), spacticity (constant contraction) and gait abnormalities (difficulty walking correctly). Other signs and symptoms include optic neuritis, visual disturbances, and autonomic dysfunction, which may manifest as dizziness or faintness upon standing in the case of orthostatic hypotension, or exercise intolerance if the heart rate does not appropriately adjust to exercise.

Risk Factors for Imbalances

In addition to the factors listed in this section, the need for these nutrients is impacted by common genetic polymorphisms, discussed separately in the next section.

Folate Deficiency: The principal cause of inadequate folate status is poor food selection combined with lack of supplementation and exclusion of enriched grains. Meeting the folate requirement requires two to three 100-gram servings of liver, legumes, or greens per day. Liver should not be used more than twice a week in most cases and legumes and greens can be used to meet the remainder of the requirement. Folate is stable in liver when frozen and in legumes when dried, but not in frozen vegetables. To prevent neural tube defects, most refined grains are fortified with folic acid, a synthetic form of folate. Folic acid is also present in multivitamins and in many breakfast cereals. Prior to the fortification of refined grains with folic acid, the average American consumed hardly more than half the RDA of folate. Removing refined grains from the diet could be well intentioned and is highly desirable in many respects, but could nevertheless make a major contribution to folate deficiency if the foods that replace them are not selected properly. Mistaken reliance on frozen vegetables as a source of folate without realizing that most of the natural folate in these foods has degraded before consumption may also be a major contributor. Folate is stable in liver during cooking. In plant foods, however, cooking causes loss of up to half the folate, with about half recoverable in the cooking water. Thus, preventing deficiency may take 3-5 servings of these foods rather than 2-3 if they are cooked and the cooking water is discarded. There are a number of genetic polymorphisms that impact folate requirements and these are discussed in a separate section below. There is also a rare genetic defect in the primary intestinal folate transporter known as hereditary folate malabsorption.

Folate Excess: Although there is no well characterized syndrome of folate toxicity, excess folate can have several undesirable effects. First, it can mask B12 deficiency by preventing the associated anemia without doing anything to prevent the degeneration of the nervous system. Second, although the mechanism is poorly understood, folate supplementation has been associated with the onset of nervous system degeneration in B12-deficient patients and could be the factor that provoked the degeneration. Third, although rare, supplementation with as low as 1 milligram per day of folate has provoked hypersensitivity reactions in some individuals. The Institute of Medicine set the tolerable upper intake level for supplemental folate at 1 milligram per day to provide a window of safety for provoking neurodegeneration in B12-deficient patients. I do not see any justification for using doses higher than 1 milligram in any circumstances, so I find it prudent to keep supplemental folate under this level.

Vitamin B12 Deficiency

In the general population, the major cause of vitamin B12 deficiency is poor absorption. Pernicious anemia occurs in 0.1% of the general population and close to 2% of the elderly. It consists of an autoimmune attack on components of the digestive system specific to B12 absorption. Chronic gastritis, on the other hand, is usually caused by *H. pylori*, may affect half or more of the population, begins in childhood, and advances with age. In the elderly, gastritis may be severe enough to cause vitamin B12 deficiency in 10-15% of the population.

Signs of B12 deficiency are found in over 70% of vegetarians and 90% of vegans, due to low intake without supplementation. B12 is found almost exclusively in animal products, and the bioavailability in eggs is low, making milk the only food source for most lacto-ovo-vegetarians. Some research indicates that there is B12 in a small selection of vegan foods: shiitake, chanterelle, and black trumpet mushroom; and chlorella and green or purple nori (laver).

Nevertheless most mushrooms and edible bacteria or algae do not contain B12 and the levels found in chlorella have been shown to be extremely inconsistent. Therefore, it is prudent for vegetarians and vegans to supplement with B12 and proactively monitor B12 status.

It is important to realize that even animal products rarely have more than a third of the daily requirement of B12, meaning most require consistent consumption of three servings per day to meet the RDA. Some animal products, such as liver and clams, have far more than the RDA for B12, but you can only absorb one day's worth of B12 in each meal. If you eat one large serving of clams, your data may indicate that you've eaten enough for at least the week and maybe even the month, but you've only absorbed enough for the day. Thus, a diet that does not contain, on average, at least seven B12-rich meals per week *and* meet the RDA for an average intake, is at risk of suboptimal B12 status.

Choline and Betaine Deficiency

Within the methylation system, choline is converted to betaine, and betaine acts as the direct methyl donor. Therefore, we must be consider them as a single requirement. The principal cause of inadequacy is poor food selection without supplementation. Choline is much more abundant in liver and egg yolks than in any other foods. Meeting the requirement for choline requires 2-3 egg yolks per day if obtained exclusively from egg yolks. One 100-gram serving of liver provides the equivalent of two egg yolks, and one 100-gram serving of most cruciferous vegetables or nuts provides the equivalent of half an egg yolk.

I would not use betaine alone to meet this requirement because choline fulfills other functions outside of methylation that betaine cannot fulfill. However, I consider it reasonable to obtain up to half of this requirement from betaine, which can only be done with three foods. One egg yolk's worth of choline can be obtained in betaine using any of the following: 100 grams of spinach (measured raw), 100 grams of raw beets or 50 grams of cooked or canned beets, or 25 grams of wheat germ.

Diets that do not emphasize the foods described above do not provide enough choline. Indeed, the average choline intake in the United States provides about half the DRI, and 90% of Americans consume less than the DRI. Many multivitamins do not provide any choline at all, so an individual eating a standard diet without intentionally supplementing choline will most likely not be consuming enough. There are a number of genetic polymorphisms that impact choline requirements and these are discussed in a separate section below.

Choline Excess: Although controversial, excess choline may be converted in the colon to trimethylamine oxide (TMAO), which may contribute to cardiovascular disease. This can be minimized by 1) spreading choline out across meals rather than taking it all at once, and 2) getting choline mainly from food, and if using supplemental choline to use phosphatidylcholine (see the correcting imbalances section for important dosing information). The Institute of Medicine set the upper limit for choline at 3.5 grams per day to avoid a risk of low blood pressure (hypotension) and fishy body odor. I do not see a reason for anyone to use more than 1200 milligrams per day, which is well under this level.

Amino Acid Deficiencies

Serine and glycine can be synthesized by the body, while methionine cannot. Nevertheless, endogenous synthesis of any amino acids only occurs adequately when total protein requirements are met. These requirements are at least 0.8-1.2 grams protein per kilogram bodyweight for most people and arguably higher for athletic populations. As long as the protein comes from animal products or from plant products that are well diversified (for example, does not come exclusively from legumes), methionine and serine needs will be met. Falling below this intake or failing to diversify protein sources on a vegan diet could cause amino acid deficiencies.

Although glycine is not an essential amino acid and there is no "deficiency" syndrome, typical needs for optimal health may include up to 5-10 grams of glycine over and above what would be obtained from meeting total protein requirements. Methionine, present in all proteins and especially rich in animal protein, increases the need for glycine. Therefore, this extra glycine requirement is best fulfilled by the inclusion of collagen in the diet, which is much higher in glycine than other proteins and quite low in methionine. 5 grams of glycine could be obtained from ⅔ of an ounce of bone meal, or with one to two servings of hydrolyzed collagen.

Amino Acid Excesses

Excess protein generates ammonia, which is toxic if it accumulates but is usually safely converted to urea. Rare genetic disorders or urea-degrading microbes in the gut may impair the disposal of ammonia but for most people the ability to dispose of ammonia is not overwhelmed until protein intakes reach 8 grams per kilogram body weight, which cannot be obtained from food and would be extremely difficult to achieve even with protein supplements.

Nevertheless, some hypothetical concerns apply to lower intakes of the amino acids described here. Methionine increases the need for glycine, and high intakes of animal protein or supplementation with *S*-adenosylmethionine (SAMe) may deplete glycine to suboptimal levels. Unfortunately, there is inadequate data to define the optimal ratio or range of acceptable ratios, but care should be taken to include extra sources of glycine on high-protein diets and glycine status should be monitored carefully if signs, symptoms, or blood work described herein suggest they may be out of balance. Collagen supplementation has the potential to increase oxalate accumulation and could pose a risk of kidney stones. Individuals at risk of kidney stones should be careful with collagen and preferably monitor oxalate levels. Oxalate excretion in response to collagen is more likely to occur if you are deficient in B6 (see the vitamin B6 section). The oxalate is produced mainly from the hydroxyproline in collagen, not the glycine, so if you cannot resolve increased oxalate excretion in response to collagen supplementation, you should try supplemental glycine as an alternative. To test this, I would collect 24-hour urine oxalate (LabCorp) while consuming the amount of collagen you usually consume or random urine oxalate (Quest) after a collagen-rich meal.

Effects of Common Genetic Polymorphisms

I recommend assessing methylation genetics by obtaining a 23andMe analysis and running the raw data file through StrateGene. 23andMe offers two options: "ancestry" and "health and ancestry." "Ancestry" is less expensive and adequate for this purpose, although I recommend getting "health and ancestry" if you can afford it simply to obtain 23andMe's own health reports.

From among these genes, only MTHFR has been well studied for its impact on nutritional requirements. Nevertheless, I will cover those I believe likely to be most relevant.

MTHFR

MTHFR enables the production of methylfolate, which allows folate to support the methylation process. Methylfolate is also the off switch for the glycine buffer system, so low methylfolate levels cause increased wasting of glycine as methylated metabolites. This depletes glycine and methyl groups, even if there is an inadequate supply of methyl groups. There are two common polymorphisms: A1298C and C677T. One A1298C allele decreases MTHFR activity by 17%. One C677T decreases it 33%. Two A1298C decrease it by 39%. One of each decreases it 53%. Two C677T decrease it by 75%. The homozygous C677T genotype is best studied, and it is used as the reference point for the nutritional recommendations below. Less severe genotypes are still affected in proportion to the decrease in MTHFR activity.

A 75% decrease in MTHFR activity has several important impacts on nutritional requirements:

- The choline requirement is doubled to about 900-1200 mg/d, which is the equivalent of 4-5 egg yolks.
- Methylfolate production is lower. This can *not* be compensated for proportionally with methylfolate supplements. A typical folate molecule is recycled 18,000 times per day, and it is not safe to take 18,000 times the RDA for folate. Nevertheless, it is important to maintain enough methylfolate to switch off the glycine buffer system and using between 400 and 1000 micrograms of supplemental methylfolate may be helpful.
- Since almost half of methylation is used to synthesize creatine, 3-5 grams per day of supplemental creatine may cut the methylation demand in half and help to better conserve methylfolate to more effectively stop glycine wasting. The best form to use is anything made from Creapure. Ideally the dose is taken with meals spread throughout the day but usually it is more practical to take it with a single meal per day. The full effects take 4-6 weeks to set in.
- Glycine requirements are presumably higher. Putting more emphasis on obtaining dietary sources of collagen makes sense, and you may try supplements providing 3-10 grams of glycine (such as one to three servings of hydrolyzed collagen).
- Excess methionine from high animal protein intake or from *S*-adenosylmethionine (SAMe) supplementation will exacerbate glycine wasting. Unless there are specific athletic goals requiring higher protein intakes, you should keep your protein intake below 2 grams per kilogram body weight and diversify it among animal and plant proteins. Only use SAMe if you have good justification based on blood work or signs and symptoms. If you do have a high protein intake or use SAMe, monitor your glycine status carefully.

SLC19A1 and **MTHFD1**

SLC19A1 is needed to transport folate into cells and MTHFD1 is an enzyme that produces methylenefolate, a precursor to methylfolate and the form of folate that is required to prevent anemia. Unlike MTHFR, which plays no role in preventing macrocytic anemia, both of these could increase the risk of anemia because they can both impair the intracellular supply of methylenefolate. Homozygosity for the G80A allele of SLC19A1 decreases its activity 50%, and

homozygosity for the of the G1958A allele of MTHFD1 decreases its activity by 34%. Presumably heterozygosity causes half the effect although this has not been clearly studied.

Although no research has documented the exact effect of combinations of these polymorphisms on methylfolate production, one can *presumably guestimate* the effect by multiplying the residual activities. For example, let's consider homozygosity for SLC19A1, MTHFD1, and the A1298C mutation in MTHFR. If 50% of folate enters the cell and 66% is converted to methylenefolate, from which 61% is converted to methylfolate, presumably this lowers methylfolate production to 0.5*0.66*0.61= 20% of normal. I would use these estimates only as as best guesses. Nevertheless, I would use these best guesses to gauge the strictness with which you observe the above recommendations for MTHFR.

Since these polymorphisms also impact the supply of methylenefolate, folate supplements, if they are used, should be a mix of folinic acid (formylfolate) and methylfolate, since folinic acid will be more easily converted into methylenefolate.

MTRR: MTRR is an enzyme that repairs vitamin B12 when it has been damaged by oxidative stress. Homozygosity for A66G *or* C524T lowers the activity of the enzyme 3-4-fold. This may cause no problems at all if oxidative stress is minimal. Under conditions of oxidative stress, however, individuals with these polymorphisms may become more vulnerable to vitamin B12 deficiency. These mutations do not directly impact nutritional requirements, but reinforce the need to be proactive about measuring B12 status.

PEMT: PEMT is an enzyme that uses the methylation system to produce phosphatidylcholine. If you follow my nutrition recommendations in this section, I do not believe this will impact your choline requirement. Rather, if you have decreased PEMT activity, you will have a higher risk specifically of fatty liver and liver damage when you do *not* follow the choline recommendations. I believe the choline recommendations I've made should be followed regardless of the PEMT genetics inadequate dietary choline will still compromise methylation and potentially acetylcholine levels in someone with high PEMT activity.

Testing for Methylation-Related Nutrients

- **Homocysteine** (in amino acid profiles: ***preferred***: Genova ION Profile + 40 amino acids ***also:*** Great Plains; individually: LabCorp, Quest;) The homocysteine levels associated with optimal health are 5-9 micromoles per liter. If your homocysteine is elevated, it could be due to a deficiency of one or more methyl donors (B12, folate, choline/betaine), a deficiency of vitamin B6, which is needed for its catabolism, or a deficiency of any of the B vitamins that enable the production of methylfolate (thiamin, riboflavin, niacin, B6).
- **Methionine** on an **amino acid profile** (***preferred***: the Genova ION Profile + 40 amino acids, ***also:*** LabCorp, Quest, Great Plains, and the NutrEval). If methionine is low when homocysteine is high, it makes it more likely that homocysteine is high as a result of deficient methyl donors. If methionine is mid-range when homocysteine is high, homocysteine is more likely high as a result of deficient B6. If methionine is high and homocysteine is low, it suggests that there is a backup in the conversion of methionine to its activated form, *S*-adenosylmethionine (SAMe). This may be caused by rare genetic mutations that are not included in the common genetic polymorphism section above, or

to deficiencies of magnesium or ATP, and it would be a good reason to try SAMe supplementation at doses ranging from one tablet or up to 1600 milligrams per day.

- **Glycine** and **sarcosine** on an **amino acid profile** (***preferred***: the Genova ION Profile + 40 amino acids, ***also:*** LabCorp, Quest, Great Plains, and the NutrEval) Ideally glycine should be toward the middle or higher end of the normal range, and sarcosine should be close to zero. If glycine is low, it suggests that more glycine is needed. However, if sarcosine is elevated, even toward the middle or higher end of the normal range, it suggests that low methylfolate levels are causing glycine wasting, which calls for strict implementation of the MTHFR-specific recommendations above (these should be tried even in the absence of MTHFR polymorphisms if sarcosine is elevated).
- **Mean Corpuscular Volume (MCV)** on a **complete blood count (CBC)** (LabCorp, Quest) High MCV is a sign of macrocytic anemia and suggests a deficiency of folate or vitamin B12. Deficiencies of other nutrients may elevate MCV, such as copper, thiamin, riboflavin, niacin, and vitamin B6, but folate and B12 are much more common, especially if there are no independent indications that these other nutrients may be deficient. Choline/betaine should not impact MCV. It is, therefore, more specific to folate and B12 than the alterations of homocysteine and methionine listed above. Rare mutations in dihydroflate reductase (DHFR), and possibly common polymorphisms may increase MCV. Unfortunately, common DHFR polymorphisms are not characterized well enough to be included in the section above on common polymorphisms.
- **Serum and RBC Folate** (single test: LabCorp, Quest only offers serum and RBC separately) Folate in red blood cells reflects total folate status, while folate in plasma or serum reflects almost exclusively methylfolate. If total folate status is low, it suggests a general folate deficiency. If only serum (or plasma) folate is low, it suggests a specific deficiency of methylfolate due to impaired MTHFR activity, or a deficiency of any of the B vitamins that enable the production of methylfolate (thiamin, riboflavin, niacin, B6). Excess intake of methionine or supplementation with *S*-adenosylmethionine will inhibit MTHFR activity and may also contribute to low methylfolate levels.
- **Urinary FIGlu** on a **urinary organic acid profile** (***preferred:*** Genova ION Profile + 40 amino acids; ***also:*** the NutrEval) Formiminoglutamate (FIGlu) is a functional marker specific to folate that is independent of the methylation process and other methylation-related nutrients and rises in folate deficiency.
- **Serum B12** (LabCorp, Quest) If serum B12 is low, it shows B12 is deficient. Serum B12 should not be used as the only marker of B12 status, however, because adequate serum levels do not show that B12 is getting into cells and fulfilling its function, and a suitable functional marker, methylmalonic acid, is described below.
- **Methylmalonic acid** in urine (in organic acid panels: ***preferred:*** Genova ION Profile + 40 amino acids; ***also:*** Quest, Great Plains, the NutrEval; as a single test: LabCorp, Quest;) or in blood (LabCorp, Quest). Methylmalonic acid (MMA) is a functional marker specific to B12 that is independent of the methylation process and other methylation-related nutrients and rises in B12 deficiency. If the increase is moderate and the kidneys are healthy, it is more likely to be found in the urine, but an impairment in kidney function could make it more apparent in the blood, so it is better to measure both. Although generally a very specific indicator of B12 deficiency, a biotin deficiency could blunt the production of MMA and thereby make this marker appear falsely normal. Further, there are two rare genetic disorders that could affect its levels independent of B12 status: methylmalonic acidemia will increase it and propionic acidemia will decrease it.

Testing Caveats

Numerous reactions in the methylation pathway require magnesium and ATP. Magnesium deficiency or metabolic disruptions that affect ATP production such as hypothyroidism, diabetes, insulin resistance could contribute to methylation imbalances, and this becomes more likely if no nutrient deficiencies can be supported. Extra niacin is excreted in methylated form, and high-dose niacin supplements (in any form: niacin, niacinamide, or nicotinamide) may be the cause of an apparent deficiency in methylation.

Correcting Imbalances in Methylation-Related Nutrients

Due to the complexity and interdependence of the methylation system, it is ideal to collect maximal data when there are signs of imbalances. The common genetic polymorphisms should be assessed because they may call for the MTHFR-specific recommendations listed above. There are no satisfactory tests of choline status, but most people do not consume enough choline and the choline recommendations listed above should be implemented in most cases. Lack of evidence for deficiencies of other nutrients should also point attention to choline when the data suggest a deficiency of methyl donors. A step-by-step analysis of each marker should point to the most probable deficiencies. When identified, the possible causes should be considered. If the cause is a medical issue, such as a malabsorption disorder, it will need appropriate medical treatment. If the cause is poor diet, the dietary targets, or supplements within the ranges listed in “Causes of Deficiencies and Imbalances” should be used, with doses adjusted over time to bring blood markers in range and successfully improve health and well being. If creatine is used to reduce the methylation demand, it should be noted that, anecdotally, some people develop overmethylation symptoms such as insomnia. This appears to be a temporary effect, and it may take up to 6 weeks for the full effects of creatine to settle in.

Molybdenum and Sulfur Catabolism

The transsulfuration pathway is closely connected to the methylation pathway and represents the intersection between the methylation pathway and the antioxidant system by providing the amino acid cysteine for the synthesis of glutathione, the master antioxidant of the cell. The pathway is activated by high methionine inputs, serving to get rid of the excess (as would occur after a high-protein meal), and by oxidative stress, serving to increase the synthesis of glutathione when it is most needed. If the sole need is to get rid of excess methionine, the cysteine is catabolized to taurine and sulfate. If the sole need is to increase glutathione synthesis, it is directed into that pathway. Most of the time, cysteine meets a mix of these fates.

Regardless of the fate of cysteine, the amino acid serine and vitamin B6 are needed for its production from homocysteine. The conversion always generates alpha-ketobutyrate as a byproduct, which is the major source of methylmalonic acid, discussed above as a marker of vitamin B12 status. The methylmalonic acid requires biotin to be produced, and vitamin B12 to be eliminated. The synthesis of glutathione from cysteine requires glycine, magnesium, and ATP. On its way to sulf**a**te, cysteine first generates sulf**i**te. Sulfite is toxic and its accumulation can cause deficiencies of thiamin and vitamin B6. The conversion of sulfite to sulfate requires **molybdenum**, an essential mineral.

Of the many nutrients that make an appearance in sulfur catabolism, only molybdenum is unique to the pathway. Therefore, this section is devoted specifically to molybdenum.

Signs and Symptoms of Molybdenum Deficiency: Molybdenum deficiency is not well characterized and is conventionally thought to be uncommon except as a rare genetic disorder in its utilization, sulfite oxidase deficiency. This causes severe defects such as seizures, mental retardation, and dislocated lenses within the eye, all occuring in the newborn, and is unlikely to be informative for what moderate deficits in molybdenum might look like. More moderate sulfite accumulation may impair thiamin and B6 status and cause the signs and symptoms discussed in those sections. Presumably, molybdenum deficits could contribute to sulfite sensitivity as well, which results in in allergy-like reactions (dermatitis, hives, flushing, low blood pressure, abdominal pain, diarrhea, anaphylaxis, asthma) to the sulfites used as food additives.

Risk Factors for Molybdenum Deficiency: Molybdenum is very rich in legumes. The need for molybdenum increases with high intakes protein, especially of animal proteins, as a result of their high methionine content. Thus, a diet rich in animal proteins and low in legumes is likely to lead to significantly lower molybdenum status than the opposite pattern. The need for molybdenum appears to also increase during pregnancy, where the production of hydrogen sulfide, essential to the growth of the placenta and embryo, provides an additional source of sulfite. The morning sickness of pregnancy may result from sulfite-induced B6 deficiency that occurs on the background of low molybdenum intakes.

Molybdenum Excess: There is no evidence for molybdenum toxicity in humans. Excess molybdenum induces copper deficiency in ruminants, but this has no relevance to humans because it results from byproducts produced in the rumen. The Institute of Medicine set the tolerable upper intake level (TUIL) for molybdenum on the basis of reproductive defects induced in female rats by taking the lowest level that caused no harm, dividing it by 30, and adjusting it for bodyweight. The upper limit is set at 30 micrograms per day per kilogram bodyweight, which in a 70 kilogram individual is 2100 micrograms per day. There is no reason to use doses higher than this, and supplements often contain as little as 150 micrograms and rarely contain more than one milligram. Thus, molybdenum supplements according to the labeled use should be overwhelmingly safe.

Testing for Molybdenum Status

- **Serum or Whole Blood Molybdenum** (HDRI) Many blood tests of molybdenum levels are designed to only look for excess and only report whether molybdenum is below the range of excess. HDRI, by contrast, reports an exact value within a normal range. Either test will work, but ideally it should be tested along with one or more of the functional markers listed below.
- **Uric Acid** (LabCorp, Quest) In addition to converting sulfite to sulfate, molybdenum is also necessary to make uric acid. Uric acid is low in molybdenum deficiency.
- **Urinary Sulfite and Sulfate** (available from HDRI as part of the “sulphur panel” on their requisition form) High urinary sulfite and low urinary sulfate indicates a molybdenum deficiency.

- **Serum Sulfate and the Cysteine-to-Sulfate Ratio** (Genova Oxidative Stress 2.0 Blood Panel) Although not a direct measure of sulfite accumulation, low serum sulfate and a high cysteine-to-sulfate ratio may indicate molybdenum deficiency.

Correcting a Molybdenum Deficiency: Increasing legumes and decreasing animal protein may help correct a molybdenum deficit, but animal protein is nutritionally important and some individuals do not tolerate legumes well. If dietary measures are unfeasible or insufficient, 500-1000 micrograms per day of molybdenum supplementation should be more than adequate, and this can likely be dropped to 100-200 micrograms per day as a maintenance dose once markers and signs and symptoms resolve.

Antioxidant Vitamins and Minerals

The antioxidant system helps support metabolic health and prevent the natural wear and tear on our tissues that occurs with age and that becomes aggravated by toxin exposure, metabolic dysfunction, and various illnesses. It is especially important to thyroid function, immunity, and insulin sensitivity. It can be seen as critical to protecting general health and well being and protecting against most degenerative diseases, including fatty liver disease, heart disease, and cancer. This section will focus on specific indicators for each nutrient, but it should be kept in mind that, because of the centrality of the antioxidant system in general health, their deficiencies could contribute to a broad range of health problems.

While **vitamins E and C** are best known as antioxidants, the antioxidant system also depends on the following minerals: **zinc, copper, manganese, iron, and selenium. Glutathione** is not a nutrient, but it is the master antioxidant and serves as the interface between the antioxidant system and the system of energy metabolism, allowing glucose to act as the ultimate antioxidant. Glutathione synthesis also interacts with the methylation system through the transsulfuration pathway.

General Testing for Oxidative Stress

If general markers of oxidative stress are found, anything within this section may be responsible. The ultimate test of whether a given nutrient deficiency is causing the oxidative stress is to see whether correcting the deficiency corrects the oxidative stress markers. If addressing this section is inadequate to resolve them, you should consider the energy metabolism nutrients next, since the system of energy metabolism directly supports the antioxidant system.

Useful markers include **lipid peroxides**, a measure of oxidative damage to lipids, and **8-hydroxy-2-deoxyguanosine**, a marker of oxidative damage to DNA. Additionally, in panels that include **citric acid cycle metabolites**, the following can be seen as indicating oxidative stress:

- A high citrate-to-isocitrate ratio is the earliest sign of oxidative stress.
- High alpha-ketoglutarate suggests more severe oxidative stress, but if isocitrate is extremely low this sign may not be observed.
- High succinate, when found alongside a high citrate-to-isocitrate ratio, suggests the most severe oxidative stress.

I recommend using the Genova ION Panel With 40 Amino Acids for this because it contains all of these markers and many others covered within this guide, and is included in the comprehensive screening.

Vitamin E

Signs and Symptoms of Deficiency: Vitamin E deficiency is best understood from malabsorption disorders impacting all fat-soluble vitamins and from a rare genetic disorder known as alpha-tocopherol transfer protein deficiency that causes a specific disruption of vitamin E supply to all tissues except the liver. These result in ataxia (loss of full control over body movements), peripheral neuropathy (weakness, numbness, pain, or tingling in the hands and feet), retinopathy (damage to the eye's retina). The ataxia of vitamin E is often mistaken for Friedrich's ataxia, a genetic disorder in iron metabolism. Vitamin E derives its name from the Greek words for bringing a pregnancy to term and bearing a child because early animal experiments showed it was necessary for fertility. Currently, the only well established role of vitamin E is as an antioxidant, so moderate deficits are likely to increase the risk of a broad range of degenerative diseases without causing more specific signs.

Risk Factors for Deficiency: Vitamin E's only well established role is to protect polyunsaturated fatty acids (PUFAs) from a process known as lipid peroxidation, which is a form of oxidative damage. Moderate vitamin E deficiency has been produced experimentally in humans by feeding rancid corn oil. This oil is high in PUFAs, stripped of vitamin E, and high in lipid peroxidation byproducts, which raise the need for vitamin E. Moderate deficits of vitamin E are most likely to occur on diets that cause tissue concentrations of PUFA to increase without a proportionate increase in vitamin E. Most high-PUFA oils are rich in vitamin E. However, years of consuming them can cause tissue concentrations of PUFA to remain elevated for up to four years after one stops consuming them. By contrast, vitamin E levels drop very soon after discontinuing these oils. This may cause an extended period where dietary vitamin E is inadequate to protect tissue concentrations. As an example, someone who eats sunflower oil (high in PUFA and vitamin E) for years and then switches to coconut oil (low in PUFA and low in vitamin E) may spend up to four years in a moderate vitamin E deficit because coconut oil does not provide enough vitamin E to protect the fatty acids that came from the sunflower oil.

Excess Vitamin E: Excess vitamin E is broken down and excreted in the urine, so there is no toxicity syndrome associated with it. However, vitamins E and K share the same catabolic pathway, and excess vitamin E may cause a vitamin K deficiency and thin the blood. Additionally, while alpha-tocopherol is the most important form of vitamin E and is the most effective antioxidant, there are seven other forms of vitamin E that may also have importance. High doses of alpha-tocopherol lower the levels of the other seven forms. To protect against these effects, I recommend limiting supplemental alpha-tocopherol to 20 IU per day and providing it in the context of a blend of vitamin E forms. I recommend Jarrow Tocosorb to meet these criteria. Higher doses should only be used with strong justification.

Testing for Vitamin E: Plasma vitamin E is the best marker of vitamin E status (***preferred:*** Genova ION Panel With 40 Amino Acids; ***also:*** LabCorp, Quest, Genova Fat-Soluble Vitamin Panel). It is low in deficiency.

Testing Caveats: Since vitamin E is carried in lipoproteins, hypolipoproteinemias may cause vitamin E status to appear lower than it is and hyperlipoproteinemias may have the opposite effect.

Correcting Vitamin E Deficiency: Frank vitamin E deficiency only occurs with malabsorption disorders or defects in alpha-tocopherol transfer protein, and these must be managed with appropriate medical treatment. I recommend one Jarrow Tocosorb per day with the largest or highest-fat meal to correct more moderate deficits. If you are transitioning from years of high-PUFA oils, I recommend using this proactively for four years.

Vitamin C

Signs and Symptoms of Deficiency: Scurvy is the classical vitamin C deficiency disease. The most widespread visible signs are defects in collagen synthesis that cause bleeding at or underneath the surface of the skin and oral cavity. The skin may appear to bruise without requiring any physical trauma. Hairs may become more kinky and appear in a “corkscrew” shape. Fatigue and shortness of breath on exertion also occur. Plausible signs of more moderate deficits include decreased immunity (especially more frequent colds), faster aging skin, low bone mineral density and an increased risk of osteopenia and osteoporosis. Vitamin C recycles vitamin E, and its deficiency lowers vitamin E status. It is also possible that moderate deficits might cause low noradrenaline production resulting in lethargy and trouble focusing, and low oxytocin, compromising the sense of affection and bonding in response to physical intimacy.

Risk Factors for Deficiency: A diet low in fresh foods, especially fruits and vegetables, that does not contain vitamin C supplements or vitamin C-containing multivitamins is most likely to produce scurvy. Diets poor enough to cause scurvy can sometimes be found among chronic alcoholics. There are opposed claims that carbohydrates increase and decrease the vitamin C requirement but at the present time neither high nor low carbohydrate intake should be considered a direct cause of vitamin C deficiency. High levels of physical activity, illness, and exposure to toxins including ethanol and especially cigarette smoke, increase the need for vitamin C.

Vitamin C Excess: Vitamin C is not toxic, but when consumed above the rate of intestinal absorption it may cause diarrhea. Bowel tolerance occasionally occurs as low as 4 grams per day but often takes more than 10 grams per day. The Institute of Medicine used a large window of safety to set the upper limit at 2 grams per day. Diarrhea is only an acute effect, and will cease upon withdrawal of the high dose, so vitamin C above the upper limit does not seem dangerous in most cases. Excess vitamin C may cause some problems in vulnerable individuals: it increases iron absorption and possibly iron-induced oxidative damage in individuals with hemochromatosis; it increases the risk of oxalate stones in individuals with kidney disease; it increases the risk of hemolysis in newborns with glucose 6-phosphate dehydrogenase deficiency, a genetic disorder. Care should be exercised with vitamin C supplementation in these vulnerable populations but otherwise high doses appear safe.

Testing for Vitamin C: Fasting plasma ascorbate (LabCorp, Quest) is the best marker of vitamin C status. It is very important that it be fasting and that vitamin C supplementation be

avoided the evening prior because vitamin C will transiently rise to high levels after acute intake even in deficiency.

Correcting Vitamin C Deficiency: If a dietary pattern can be identified that would cause vitamin C deficiency, the diet alone should be corrected. If this is infeasible or insufficient, supplementation with 200 milligrams per day of ascorbic acid is adequate in most cases. Athletes, smokers who cannot quit, and individuals with frequent illness or who otherwise appear to have a high need may raise this dose to two grams. Many people believe that food-source vitamin C is superior. It is always ideal to use foods to supply nutrients because they have a complex array of beneficial characteristics, but there is no evidence that other components in food are needed for vitamin C to fulfill its function or to prevent vitamin C deficiency specifically. As such, it is perfectly acceptable and perhaps beneficial to use food-source vitamin C supplements for *the other components*, but this should not be regarded as necessary to obtain the benefits of the *vitamin C.*

Manganese

Signs and Symptoms of Manganese Deficiency: Manganese deficiency can cause miliaria crystallina, a form of dermatitis resulting from blocked sweat glands that appear as tiny clear bubbles on the skin. This can also result from excessive sweating, sunburn, or fever. It may also cause bone irregularities, low bone mineral density, low cholesterol, slow hair and nail growth, and reddening of beard hair. Moderate deficits of manganese may accelerate atherosclerosis.

Risk Factors for Deficiency: Manganese is particularly rich in whole grains, legumes, nuts, seeds, coffee, tea, spices, and mussels. Diets low in plant products are likely to be considerably lower in manganese than diets rich in plant products. Clinical manganese deficiency is not documented in humans outside of errors in infant formula or research diets, and in one study of experimental manganese deficiency. Nevertheless, the higher concentrations in the foregoing foods may help protect against oxidative stress and offer independent protection against heart disease.

Manganese Toxicity: Industrial exposure to manganese through coal mining or the inhalation of gasoline vapors when manganese additives are used can cause manganese to deposit in the brain and cause a variety of neurological problems including headaches, dopamine depletion, and Parkinson-like symptoms. Drinking water is sometimes contaminated with toxic levels of manganese. Manganese toxicity from food is very unlikely. Manganese intakes may reach up to 11 milligrams per day in vegetarian diets, with no known adverse effects, and the upper five percent of intakes in the general population at large is about 6 milligrams per day. It is prudent to avoid supplements of manganese with more than 5 milligrams per day and for vegetarians to avoid manganese supplements so that the total manganese intake remains within 11 milligrams, which is the upper end of the intakes that have a track record of safety. Chelation therapy is used for clinical manganese toxicity, but this requires close medical supervision and is beyond the scope of this guide. Chelation poses a risk of other mineral deficiencies, so anyone using chelation therapy should monitor the status of other minerals.

Testing Manganese Status: Manganese should be measured in whole blood (LabCorp) or red blood cells (Quest) and not in plasma or serum.

Testing Caveats: It is very easy for a technical error to occur in laboratory measurements of manganese levels. The syringe used to draw the blood can contaminate the blood with manganese and the first draw should be discarded so the second draw can be used for the measurement. If heparin is used as an anticoagulant in the blood tube rather than EDTA, the heparin can provide manganese contamination. The water used for dilutions in the laboratory analysis must be properly purified because it also can be contaminated. Red blood cell or whole blood measurements are ideal bause red blood cells contain 25 times as much manganese as plasma or serum. This brings the concentration far away from the limit of detection and makes the possibility of contamination less threatening to the interpretation. It also eliminates the possibility that hemolysis could release manganese to contaminate the serum or plasma. Little can be done to ensure proper laboratory techniques by anyone ordering a test, but the possibility of contamination should be kept in mind if levels appear implausibly high.

Correcting Manganese Deficiency: Dietary manganese deficiency is very unlikely, but increasing the amount and diversity of plant foods is the most likely thing to improve manganese status. Supplements often contain 8 milligrams or higher. I recommend cutting these in half or taking them every other day, or taking a daily supplement with 3-5 milligrams.

Zinc

Signs and Symptoms of Zinc Deficiency: The earliest sign of zinc deficiency is usually patches of dry skin. These often progress to acne, blisters, or pustules. Infection risk increases, resulting in sore throat or diarrhea. Poor glucose tolerance, impaired wound healing, low or dysregulated sex hormones, and hair loss (alopecia) also may occur. Lower appetite and increased caloric needs often result in weight loss, especially of lean mass. In children, zinc deficiency delays puberty. Zinc deficiency may cause resistance to vitamin A, vitamin D, thyroid hormone, sex hormones, cortisol, and pharmaceutical glucocorticoids. Zinc is involved in virtually every aspect of vitamin A metabolism, and an apparent vitamin A deficiency that cannot be corrected with vitamin A should be seen as a major indicator of zinc deficiency. Zinc deficiency may also impair acid-base balance and increase the vulnerability to heavy metal toxicity.

Risk Factors for Zinc Deficiency: Zinc is most abundant in oysters, red meat, and cheese, and the its principal inhibitor of absorption is phytate. Phytate is found in whole grains, nuts, seeds, and legumes, and is especially high if these foods have not been prepared through soaking, sprouting, or fermentation. The overwhelming risk factor for zinc deficiency is a diet low in animal products and high in phytate. Chronic diarrhea, persistent vomiting of bile (giving the vomit a green color), malabsorption disorders, impaired methylation (see methylation section), and rare genetics in zinc transporters can all cause zinc deficiency as well. A collection of disorders in the production of heme, known as porphyrias, can cause zinc deficiency. If this is the cause of zinc deficiency, zinc protoporphyrin (LabCorp) should be elevated. A related disorder, pyroluria, was proposed decades ago to cause zinc deficiency but has never been adequately followed up. Great Plains currently offers a test for it.

Zinc Excess and Toxicity: Acutely, zinc toxicity can cause gastric distress, such as nausea and vomiting, and dizziness. A high-dose zinc supplement of 50 mg or more on an empty

stomach can cause mild nausea (lower doses can also impact some individuals), but dangerous levels of toxicity are generally found only in rare cases of people eating pennies. One death has been attributed to an accidental intravenous infusion of seven grams of zinc over a 60-hour period. Chronically, excess zinc can impair immune function and lead to copper deficiency, and perhaps deficiencies of other poorly studied minerals like molybdenum and chromium. To prevent this, zinc should supplements should not be used at doses higher than 45 milligrams per day unless there is strong justification to do so, and the ratio to copper should be kept between 2:1 and 15:1, preferably toward the middle of that range. If you use doses higher than 45 milligrams per day, I would include a broad-spectrum trace mineral supplement or use this guide to closely monitor status for the other minerals.

Testing Zinc Status: Plasma zinc (***preferred:*** Genova ION Profile + 40 amino acids; ***also:*** LabCorp, Quest) is the best marker of zinc status. It is very important to measure it in plasma rather than serum, and if the order says “serum or plasma” explicit instructions should be put in the order to use plasma and not serum, and the phlebotomist should be verbally reminded of this at the time of the blood draw. Most ranges are too broad, with the lower end at 50-60 micrograms per deciliter. Measured in micrograms per liter, as on the LabCorp and Quest tests, plasma zinc should be at least 70 in females and 74 in males, and the sweet spot is likely between 100-120. Measured in parts per billion, as on the ION panel, zinc should be above 700 in females and 740 in females, with the sweet spot likely to be between 1000 and 1200.

Testing Caveats: Inflammation lowers plasma zinc, but this might simply reflect increased needs during inflammation. Plasma zinc modestly declines during pregnancy, but this also might indicate increased needs during pregnancy. Hemolysis can release zinc from red blood cells and cause falsely high zinc levels. Hemolysis can occur inside your body if you have certain medical disorders, but it can also occur during blood collection due to poor positioning of the needle or other technical difficulties. Plasma zinc in significant excess of 130 micrograms per liter or 1300 parts per billion is implausible in the absence of outright zinc poisoning and the measurement should be repeated.

Correcting Zinc Deficiency: If the cause is a dietary pattern with a low zinc-to-phytate ratio, the ideal strategy is to alter the dietary pattern to one with a higher zinc-to-phytate ratio. If the cause is malabsorption, the malabsorption should be addressed as the root cause. Nevertheless, you may choose to supplement in either case. Supplements are very helpful in overcoming poor absorption, especially if the causes of the malabsorption are difficult to identify or fix. Zinc acetate, gluconate, sulfate, citrate, or methionine should be used, and not zinc oxide or zinc picolinate. Ideally the zinc should be taken on an empty stomach, but if this causes nausea it should be taken with some food and should at least be taken far away from phytate-rich meals. The zinc should be spread out as much as possible to ensure better absorption. For example, 15 milligrams three times per day five hours apart is much better than taking 45 milligrams once per day.

The goal should be correction of the plasma zinc and any signs and symptoms of deficiency. It is important to realize, however, that normalizing the plasma zinc means the deficiency is *being* fixed, not that it *has been* fixed. A zinc deficiency that has been sustained over months may take months to correct. Resolution of signs and symptoms is an important benchmark, and being able to cut down the dose of the supplement without plasma zinc falling back into the deficient range is the other key benchmark to reach before considering the deficiency fixed.

Correcting Zinc Excess: In acute zinc poisoning, medical treatment beyond the scope of this guide is required. Cases of zinc-induced copper deficiency should be corrected by removing the supplemental zinc and following the instructions for correcting a copper deficiency in that section. Screening for other mineral deficiencies is highly advised in this context because the ability of zinc to induce deficiencies in other positively charged minerals is very plausible and has not been well studied.

Copper

Signs and Symptoms of Copper Deficiency: Anemia that may mimic iron deficiency or B12/folate deficiency, malabsorption of iron causing actual iron deficiency, leukopenia, neutropenia, high cholesterol, osteoporosis, histamine intolerance, hypopigmentation of skin and hair, neurotransmitter imbalances such as low adrenaline or high serotonin.

Risk Factors for Copper Deficiency: The best food sources of copper are liver, oysters, shiitake mushrooms, pure chocolate, and spirulina. Other good sources are most shellfish, whole grains, legumes, and potatoes. Diets low in these foods will predispose an individual toward copper deficiency. Soil variation is large, and low soil copper is another major factor predisposing toward deficiency. Improperly formulated infant formula and total parenteral nutrition have resulted in copper deficiency. Zinc supplementation can cause copper deficiency, especially if the dose is over 45 milligrams or if the ratio of zinc to copper is greater than 15. Impaired methylation (see methylation section), antacids, proton pump inhibitors, gastric bypass surgery, and any digestive problems affecting the stomach or upper intestine can cause copper malabsorption. High doses of vitamin C may impair copper metabolism but evidence for this is limited. Menkes disease is a very rare defect in copper metabolism that causes copper accumulation in some tissues but overall presents as systemic copper deficiency.

Copper Toxicity: In theory excess copper may cause oxidative stress and contribute to Alzheimer's disease and other neurodegenerative diseases. However, the only well established syndrome of copper toxicity is Wilson's disease, which is a genetic defect in the ability to excrete copper into the bile. This results in unregulated copper absorption, impaired transport into some tissues causing local deficiency, but net copper overload and deposition of excess copper in the liver, brain, and cornea, where it causes oxidative damage. Wilson's disease affects one in 30,000 people and is treated with chelation therapy, which requires close medical supervision and is beyond the scope of this guide. There is a single case of someone developing liver failure and requiring a transplant after taking 30 milligrams of copper per day for two years and 60 milligrams per day for a poorly defined period of up to a year. The Institute of Medicine set the tolerable upper intake level for copper in adults at 10 milligrams per day. Copper-rich diets are unlikely to meet the upper limit, and they are also rich in zinc, which protects against copper toxicity. Supplemental copper should be kept under 10 milligrams per day, and ideally should be kept under 3 milligrams per day unless higher doses are needed to correct a deficiency or to prevent the zinc-to-copper ratio from exceeding 15. Copper may contaminate water at doses that exceed the upper limit, but this will make you nauseated and turn your laundry, sinks, toilets, and bathtubs light blue or green, giving a clear warning signal. Filtering the water or running it for a minute before consumption will eliminate a large amount of contaminating

copper. Infants cannot regulate their copper absorption and should not be given copper supplements.

Testing Copper Status:

- **Serum Copper** (LabCorp, Quest) Serum copper declines in deficiency and is more sensitive and perhaps more specific than ceruloplasmin. Serum is preferable, but plasma is also acceptable. The Genova ION Profile + 40 amino acids, frequently recommended throughout this guide and used in the comprehensive screening, contains a plasma copper measurement. Despite the overall picture of copper toxicity, serum copper is normal or low in Wilson's disease. Based on anecdotal experience, I believe the bottom of the reference range is too low and that one should aim to be mid-range.
- **Ceruloplasmin** (LabCorp, Quest) Ceruloplasmin declines in deficiency but is less sensitive and perhaps less specific than serum copper. Despite the overall picture of copper toxicity, ceruloplasmin is usually low in Wilson's disease.
- **Urinary Copper** (LabCorp, Quest) This is increased in Wilson's disease.

Testing Caveats: Ceruloplasmin is increased by inflammation and estrogen. Since most copper within serum is bound to ceruloplasmin, this tends to elevate serum copper as well, but to a lesser degree. Pregnancy nearly doubles the levels of these markers. Lactation has a significant but weaker effect. Supplemental estrogen increases copper by 30 to 90%. Whether these markers remain suitable for assessing copper deficiency during these conditions and how the ranges should be altered has not been studied. These should be kept in mind as confounding factors, and the total picture including signs and symptoms and the response to dietary or supplemental copper should be used to assess the likelihood of deficiency or excess.

Correcting Copper Deficiency: 7 milligrams of supplemental copper per day for two months has been shown to fully correct anemia and neutropenia associated with celiac-induced copper deficiency. Ideally copper-rich foods should be emphasized, but this can serve as a general strategy for supplementation. The aim should be to normalize blood markers and resolve any related signs and symptoms. If the cause is zinc supplementation, the zinc should be removed until the deficiency is fixed, and the dose should be lowered or its ratio to copper should be improved if the supplement is reintroduced. If the cause is antacids or proton pump inhibitors, alternative strategies for improving these symptoms should be sought if possible. Malabsorption disorders require medical treatment beyond the scope of this guide.

Correcting Copper Toxicity: Wilson's disease requires chelation therapy that is beyond the scope of this guide. However, chelation therapy may cause deficiencies of other minerals, so screening for other deficiencies is advised. The rare cases of outright copper poisoning require close medical attention. Other potential harms of excess copper are speculative and if suspicions are raised, improving zinc status is likely the best protection.

Selenium

General Note on Selenium: Due to the extremely wide variation of soil selenium and the fact that hardly anyone knows *exactly* where *all* of their food comes from, I assume everyone is at approximately equal risk of having too much or too little selenium, and believe everyone should

measure their plasma selenium to confirm their actual selenium status. Deficiency and toxicity look very similar to one another, underscoring the need to measure selenium status even further.

Signs and Symptoms of Selenium Deficiency: Keshan disease is the classical deficiency disorder. It includes hepatic cirrhosis, white nail beds and fingernails falling out, and cardiac insufficiency with fibrosis and necrosis. Generally, selenium deficiency increases the vulnerability to infections, toxins, and other nutrient imbalances, especially to those that cause oxidative stress, such as vitamin E deficiency and iron overload. Less well established but plausible signs of selenium deficiency include the following: poor production of T3, the active thyroid hormone, from its precursor, T4; Hashimoto's thyroiditis; and cancer, especially prostate, colorectal, and lung cancers. While not clearly documented, white spots and streaks in the fingernails might occur in deficiency; however, these are more clearly documented in toxicity.

Risk Factors for Selenium Deficiency: Selenium content is richest in organ meats and seafoods. Brazil nuts are rich in selenium but more variable than animal foods. Diets lower in these foods are more likely to produce selenium deficiency than diets high in them. However, the overwhelming risk factor for selenium deficiency is deficient levels of selenium within the soils where most of the foods are grown. Deficient methylation should not lower blood levels of selenium but might impair the utilization of selenium for biological functions (see the methylation section).

Signs and Symptoms of Selenium Toxicity: In cases due to extremely high soil levels, the following have been observed: hepatic cirrhosis, hair loss (alopecia), and nails that are brittle with white spots and streaks and may fall out. In cases of acute poisoning due to errors in formulating supplements, the following have been observed: muscle cramps, nausea, diarrhea, irritability, fatigue, loss of the hair and nails, and peripheral neuropathy (weakness, numbness, pain, or tingling in the hands and feet). More moderate excesses of selenium may increase the risk of diabetes.

Risk Factors for Selenium Toxicity: High soil levels are the main cause of toxicity, but in the past, poisoning has occurred from mistakes in the formulation of supplements. Deficient methylation may impair the ability to excrete excess selenium (see methylation section).

Testing for Selenium Status: Plasma selenium (LabCorp) is the ideal marker of selenium status. Serum and whole blood are likely to be equivalent, but plasma selenium is better studied and preferred. Plasma selenium should be kept between 90 and 140 µg/L, with the possible sweet spot being 120. For units, µg/L and ng/mL are interchangeable. The Genova ION panel measures selenium in whole blood and reports the results in parts per million, which must be multiplied by 1000 to yield the values discussed herein. Converted to µg/L, the ION lists a range of 130 to 320, which is inconsistent with studies showing deficiency is completely avoided above 90 and the risk of diabetes increases above 140. I recommend not using the whole blood measurement from the ION panel and instead measuring plasma selenium separately.

Correcting a Selenium Deficiency: Organ meats, seafood, and Brazil nuts can be used in the diet to increase selenium intakes, but it must be kept in mind that Brazil nuts are extremely variable in their selenium content. Some sources may advocate using mushrooms, but selenium is poorly bioavailable from mushrooms. For supplements, selenomethionine should be used.

Selenite and selenate are acceptable but not preferable. Methylselenocysteine should be avoided. 100 micrograms per day is fully adequate to correct a deficiency, but 200 micrograms per day could be used for 3-4 weeks if faster progress is desired. Regardless, five months should be given to see the full effect. If plasma levels cannot be sustained in the optimal range with diet alone, the long-term maintenance dose of a supplement should be 100 micrograms per day for adults, or 1-1.5 micrograms per kilogram body weight per day for children. It is important to follow up plasma selenium to ensure the target range has been reached and not exceeded. If the deficiency is severe enough to result in organ damage, medical care is needed.

Correcting Selenium Toxicity: In the case of frank toxicity, liver damage and other complications will require close medical care. For less severe excesses of selenium, the source of excess selenium, whether supplements or foods, should be removed. Since excess selenium causes oxidative stress, the other nutrients in the antioxidant section should be examined and optimized.

Iron

Signs and Symptoms of Iron Deficiency: Iron deficiency leads to anemia, which may be asymptomatic early on, but which can cause declining work performance, fatigue, weakness, pale skin, arrhythmia, palpitations, dizziness or lightheadedness, and muscle cramps. During anemia, blood is rerouted to supply the brain and heart at the expense of most other tissues, which causes a decline in many other bodily functions, such as digestion and skin health. Iron deficiency also causes hypothyroidism, leading to signs such as cold hands and feet, increased sensitivity to cold in general, hair loss, and swelling (edema) in the face. In children, iron deficiency causes short stature and permanent decrements in brain function manifesting as low IQ, and it is especially critical to catch it and correct it early. Iron deficiency also delays puberty.

Risk Factors for Iron Deficiency: Loss of blood during menstruation and increased needs during childhood and pregnancy are the major risk factors for iron deficiency. Additionally, the absorption of iron is more reliable from animal foods than from plant foods, and the phytate found in whole grains, nuts, seeds, and legumes (especially abundant when these foods are not processed by fermentation, soaking, or sprouting) is a major inhibitor of iron absorption. Polyphenols, found generally in plants, and especially rich in fruits and vegetables, are also inhibitors of iron absorption. Thus, a dietary pattern low in animal foods and rich in plant foods is an additional risk factor for iron deficiency, especially when iron-containing supplements and iron-fortified foods such as enriched flour are not used.

Signs and Symptoms of Iron Overload: Clinical iron overload is known as hemochromatosis. Classically, it is understood as causing four manifestations, known as a tetrad: hepatic cirrhosis, diabetes, hyperpigmentation of the skin, and cardiac failure. The hyperpigmentation increases in response to sun exposure and generally consists of brown, bronze, or gray coloring. It can be driven by iron deposits or increased melanin; however, iron overload is a major risk factor for a collection of disorders known as porphyrias, where intermediates in heme synthesis known as porphyrins may also accumulate in skin and generate brown or red coloration in response to sun exposure. The hyperpigmentation may also affect the teeth and be accompanied by enamel loss. In addition to the classic tetrad, patients also report fatigue, joint pain, depression and mood swings, hair loss (sometimes manifesting as alopecia), chest pain, dizziness, impaired

sexual function, menstrual problems, and abdominal pain. Iron overload appears to raise blood cholesterol and to contribute to Alzheimer's, and possibly to Parkinson's. Iron overload causes oxidative stress, so general wear and tear on the tissues, problems associated with the *deficiencies* of other antioxidant nutrients, and aggravation of most chronic disease risk, should be expected.

Risk Factors for Iron Overload: The overwhelming risk factors for iron overload are genetic impairments in iron homeostasis. In the *HFE* gene, there are two notable variants, C282Y and H63D. Globally, for C282Y, 7.5% are heterozygous and 0.5% are homozygous; for H63D, 17% are heterozygous and 2% are homozygous. Conventionally, homozygosity for C282Y is considered the major risk factor for hemochromatosis. However, clinical hemochromatosis does occur in patients homozygous for H63D. Moreover, if one considers the oxidative stress of more moderate iron overload, then having any of these genotypes is a very significant risk factor. Although most hemochromatosis results from these mutations in the HFE gene, there are at least other six rarer genes in which mutations can be the cause, and tests for these genes are not accessible. It is therefore imperative to use blood tests as the major means of assessing iron status and to only use genetic tests as a means of explaining the results and determining what to do about them. Blood transfusions, hemodialysis, and liver diseases may also contribute to iron overload. Iron-rich diets, iron-containing supplements, and foods fortified with iron such as enriched flour, may make a contribution to iron overload but are unlikely to cause even moderate iron overload if there are not additional risk factors present.

Testing for Iron Status:

- On a **complete blood count (CBC)** (LabCorp, Quest) low **hemoglobin**, low **mean corpuscular hemoglobin (MCH)**, and high **red blood cell distribution width (RDW)** are indicators of iron deficiency anemia. **Mean corpuscular volume (MCV)** is likely to be low (making the anemia microcytic), unless a deficiency of vitamin B12 or folate also exists. Iron deficiency anemia should be confirmed with the other markers of iron status below and subject to the testing caveats in the next section.
- Spectra Labs offers a reticulocyte hemoglobin test. Reticulocyte hemoglobin (CHr) may decrease earlier than the other markers and may be particularly useful in children, where catching anemia early is critical to preserving the brain from irreversible decrements in function. (Download the test menu and search for "reticulocyte.")
- **Iron saturation** can be found on an **iron panel** (LabCorp, Quest) and is an estimate of transferrin saturation. **Transferrin saturation** can be calculated directly by getting the iron panel and **serum transferrin** (LabCorp, Quest) at the same time. To calculate it, divide the **serum iron** from the iron panel by the serum transferrin and multiply by 70.9%. It is always preferable to use transferrin saturation over iron saturation because iron saturation often underestimates transferrin saturation and sometimes the gap is large. At a minimum, test both one or two times to determine whether iron saturation is a good proxy for transferrin saturation in your specific case and only substitute the former if it appears reliable for you. Ideally your transferrin saturation is between 30 and 40%. Consistent deviations from these percentages, even in the normal range, should be considered potential early signs of deficiency (under 30%) or overload (over 40%). Deviations out of the normal range should be considered very clear indicators of a current problem.

- **Ferritin** is found on the iron panels linked to above. Ferritin is a good indicator of long-term iron stores when oxidative stress and inflammation are not present. However, oxidative stress and inflammation both increase ferritin levels independently of iron status and can create the false impression of iron overload. Oxidative stress and inflammation may also keep ferritin normal when it would otherwise drop, masking cases of iron deficiency. When ferritin is normal or high and all other signs suggest iron deficiency anemia, this indicates **anemia of chronic disease.** It is harmful and potentially fatal to treat this as a case of iron deficiency and requires medical care beyond the scope of this guide. When there are no signs of oxidative stress or inflammation, low ferritin should be taken as a sign of iron deficiency and high ferritin as a sign of iron overload, especially when corroborated by transferrin saturation.
- **High-Sensitivity C-Reactive Protein** (LabCorp, Quest), abbreviated hs-CRP. hs-CRP is a marker of systemic inflammation. Inflammation may drive up ferritin but make all other markers look like iron deficiency. When ferritin is critical to the interpretation, hs-CRP should be measured to rule out a contribution of inflammation to the ferritin measurement. If hs-CRP is high, ferritin is normal or high, and all other markers look like iron deficiency, anemia of chronic disease should be considered and any nutritional treatment should pend proper medical diagnosis and care.
- The markers of oxidative stress discussed in the beginning of this section should be evaluated whenever ferritin is critical to the interpretation. While iron overload will itself cause oxidative stress, if the transferrin saturation does not confirm iron overload, markers of oxidative stress combined with elevated ferritin suggest that oxidative stress is driving the high ferritin and that there is no iron overload.
- When iron overload is suspected, I recommend assessing *HFE* genetics by obtaining a 23andMe analysis and running the raw data file through StrateGene. This is not a complete picture of iron genetics, but no complete picture is available, and this report is also used in the methylation section of this guide.

Testing Caveats: The anemia of other nutrient deficiencies, especially copper but possibly vitamin B6, may cause similar alterations to hemoglobin levels. Macrocytic anemia caused by vitamin B12 or folate deficiencies could coexist with iron deficiency and make the red blood cell measurements more difficult to interpret, especially the MCV. Anemia can have other causes such as kidney disease, bone marrow disease, thalassemia minor, sickle cell anemia, autoimmune disorders and exposure to certain toxic chemicals. As noted above, the anemia of chronic disease may masquerade as iron deficiency but is usually accompanied by normal or high ferritin. Due to the many different causes of anemia, and the possibility that serious medical treatment may be needed, it is critical to discuss any signs of anemia with your doctor.

Friedrich's ataxia is a genetic disorder of iron distribution that causes some manifestations of deficiency and others of iron overload, but with normal iron markers. The ataxia (loss of full control over body movements) resembles that seen in vitamin E deficiency and the latter is often mistaken for the former.

Correcting an Iron Deficiency: Correcting an iron deficiency with food is best achieved by temporarily reducing plant foods across the board and using iron-rich foods such as clams, liver, and red meat multiple times a day. For vegetarians, sprouted legumes, greens, seaweed, and potatoes are the best food sources, and the iron will be best absorbed if accompanied by 500-1000 mg of vitamin C per meal. Individuals who are not vegetarian for ethical reasons

should take the first approach over the second because it will be much more effective. Supplements that promote detoxification, such as sulforaphane or milk thistle, should be avoided until the deficiency is corrected.

Iron supplements may often be needed. Ferrous sulfate is the most common, but it contributes to oxidative stress and bacterial dysbiosis in the intestines and causes constipation and other undesirable side effects. The supplements I recommend to avoid the risk of these side effects are Iron Smart liposomal iron and Proferrin ES heme iron. A meal of clams can provide 10-20 milligrams of iron per meal. This alone meets the RDA for everyone except pregnant women, who require 27 milligrams per day. I recommend using the above iron supplements at one dose three times per day with a meal. They provide 10-15 milligrams per dose, which is 30-45 milligrams per day. This is similar to what you can get from eating clams twice a day and is within the tolerable upper intake level set by the Institute of Medicine on the basis of the gastrointestinal side effects of ferrous sulfate. I would maintain this high dose and retest monthly until the markers are in range. These can be dropped to once per day as a maintenance dose thereafter, except for pregnant women the appropriate maintenance dose is twice a day. Iron supplements should not be given to infants under the age of six months.

The goals for correcting the deficiency, whether with foods or supplements, are to bring all anemia markers into the normal range, bring transferrin saturation between 30 and 40%, and bring ferritin up to at least 60 ng/mL and preferably 100-150 ng/mL.

Correcting Iron Overload: Clinical hemochromatosis can cause organ failure and it is imperative to achieve a proper diagnosis and medical treatment, which may involve chelation or phlebotomy. When correcting more moderate iron overload, I recommend using blood donation as the primary approach. This removes iron with little risk of causing deficiencies in other nutrients, and it is far more simple than trying to manage the iron overload with diet. Organizations that collect blood donations such as Red Cross generally allow you to donate once every two months or 56 days. They will check your iron levels prior to donation and will not let you donate if you are at risk of deficiency. I believe the best approach is to donate once every two months two or three times, and then recheck the iron markers four weeks after the last blood donation. The primary goal is to bring transferrin saturation under 40%, but not lower than the bottom of the reference range and not consistently under 30%. The secondary goal is to bring ferritin below 60 ng/mL, and as low as 20 mg/mL if it improves signs, symptoms, oxidative stress markers, or the individual's subjective sense of well being. If you do not qualify for blood donation, I recommend you discuss the possibility of phlebotomy treatments with your doctor.

Consuming 300 miligrams of calcium per meal and including sources of phytate such as whole grains, legumes, nuts, and seeds can help reduce iron absorption from food. If taking this approach -- or if using chelation treatment -- it is important to assess the status of zinc and the other minerals in this guide, since their absorption could be hurt as well.

Excess iron causes oxidative stress, and it makes sense to accompany the correction of iron overload with other strategies to protect against that oxidative stress. The most important thing to do for this is to evaluate the status of all other nutrients in the antioxidant section and follow the steps to optimize them. Additionally, detoxification-promoting supplements such as milk

thistle or sulforaphane will help shuttle iron into ferritin, which is protective (see the section on iodine when using sulforaphane).

Glutathione

Signs and Symptoms of Poor Glutathione Status: Glutathione is the central cellular antioxidant, and should always be considered when markers of oxidative stress are elevated, especially when they cannot be explained by the other nutrient imbalances covered in the antioxidant section or when they disproportionately affect the thyroid gland or the lungs. Other signs of inadequate glutathione include poor immune function, asthma, respiratory congestion, and in severe cases liver failure.

Risk Factors for Poor Glutathione Status: Acetaminophen (Tylenol) depletes glutathione, which is the mechanism by which it causes liver failure when overdosed. Glutathione levels decrease during fasting, and diets that are low in protein or carbohydrate decrease its synthesis. Glutathione is is made from three amino acids: glutamate, cysteine, and glycine. Glutamate is rarely limiting except in disease states that consume it, such as cancer. Cysteine is often limiting, especially in the fasting state. Glycine is often limiting, especially after a meal rich in animal protein. Magnesium deficiency or metabolic disruptions that affect ATP production or insulin sensitivity such as hypothyroidism, diabetes, and insulin resistance decrease the synthesis of glutathione. Diets low in plant polyphenols also decrease the synthesis of glutathione. Deficiencies of glucose 6-phosphate dehydrogenase, thiamin, niacin, and riboflavin compromise the recycling of glutathione. Diets low in meat and in low-calorie fruits and vegetables provide less exogenous glutathione than diets high in these foods. Rare genetic defects can impair glutathione synthesis.

Testing for Glutathione Status:

- **Total Glutathione** (LabCorp) If low, this test suggests low glutathione synthesis or loss of glutathione from the body due to detoxification processes. This test may miss having an oxidized glutathione pool due to oxidative stress or a poor rate of recycling.
- **Oxidized and Reduced Glutathione** (available from HDRI as “GSH ox+red” on their requisition form). If the reduced glutathione is low, the oxidized glutathione is high, or both, this indicates that the glutathione pool is being oxidized faster than it can be recycled. The causes could be excess oxidative stress, poor recycling, or both. A low rate of synthesis also makes the glutathione pool become oxidized more easily, so this should also be considered. At present, my confidence that HDRI conducts this test properly is decreasing. Pending further investigation of the blood collection procedures, I may remove my recommendation to use this test. At present, I include it because it is the only test I know of that measures glutathione in its reduced and oxidized forms.
- **Pyroglutamate** (***preferred:*** Genova ION Profile + 40 amino acids; ***also:*** NutrEval) Also known as oxoproline, when elevated, pyroglutamate indicates that glycine is limiting for glutathione synthesis. When normal or low, and the other tests suggest a low rate of glutathione synthesis, cysteine is more likely to be limiting.

Further Testing:

If the testing in the previous section suggests that glutathione synthesis is compromised and pyroglutamate is *not* elevated, then the following possibilities should be given the most weight:

- **Low total protein intake.** Conduct a dietary analysis and ensure that daily protein meets at least one gram per kilogram body weight.
- **Low conversion of methionine to cysteine**. Consult the methylation, sulfur catabolism, and vitamin B6 sections. The combination of high methionine and low homocysteine supports this, as does the combination of high homocysteine and signs of vitamin B6 deficiency.
- **Low insulin signaling**. Fasting insulin (LabCorp, Quest) is optimally 2-6 uIU/mL. If elevated above this range, insulin resistance could be compromising glutathione synthesis. Optimizing body composition, increasing physical activity, and fixing any nutrient deficiencies determined through other testing are the strategies most likely to help improve insulin sensitivity. A dietary analysis can be conducted to examine carbohydrate intake. There are a wide range of carbohydrate intakes compatible with health, but anything under 200 grams per day should be considered as a possible cause of low glutathione synthesis from inadequate insulin.
- **Magnesium deficiency.** Consult the magnesium section.
- **Low ATP**. Insulin resistance, hypothyroidism, or diabetes could compromise the supply of ATP. For insulin resistance, see the bullet point above on low insulin signaling. For hypothyroidism, consult the iron, iodine, and selenium sections and discuss diagnosis and treatment with your doctor. For diabetes, discuss diagnosis and treatment with your doctor.
- **Low intake of fruits and vegetables**. A dietary analysis can be conducted to examine fruit and vegetable intake. If lower than five to nine servings per day, there may be inadequate polyphenol stimulation of glutathione synthesis.

If the testing in the previous section suggests that glutathione synthesis is compromised and pyroglutamate *is* elevated, then the following possibility should be given the most weight:

- **Glycine.** Consult the methylation section.

If the testing in the previous section shows that the glutathione pool is oxidized (low reduced glutathione, elevated oxidized glutathione, or both), then the following possibilities should be given the most weight:

- **Glucose 6-phosphate dehydrogenase (G6PD) deficiency** (LabCorp and Quest). This is the most common genetic defect in the world and compromises glutathione recycling.
- **Thiamin**. Consult the thiamin section.
- **Riboflavin**. Consult the riboflavin section.
- **Niacin**. Consult the niacin section.

Testing Caveats: Many infections and serious illnesses requiring medical care may deplete glutathione and their diagnosis and treatment are beyond the scope of this guide.

Correcting Poor Glutathione Status: Ideally, the most likely causes are identified with the testing above and specifically corrected. Exhaustive testing of all the possibilities may be cost-prohibitive and time-consuming, however, and some of the strategies are low-cost and

low-risk and can be implemented all at once. For example, consuming at least one gram per kilogram body weight of protein, consuming >200 grams of carbohydrate per day (for someone without digestive or blood sugar issues prohibiting this), supplementing with one or two servings of hydrolyzed collagen, eating a diet rich in fruits and vegetables, implementing a good physical activity routine, and optimizing body composition are all good strategies to improve glutathione status that are safe to implement without exhaustive testing.

Apart from correcting specific issues revealed through testing as described above, several strategies to boost glutathione status deserve special comment:

- N-acetyl-cysteine at up to 1600 milligrams per day in divided doses has been used to increase glutathione status. This is most likely to be effective when glycine is not limiting, as in the fasting state or after a collagen-supplemented meal, and in individuals who do not show elevated pyroglutamate.
- Unpasteurized milk, raw egg white, and whey protein supplements all contain glutamylcysteine bonds that overcome the first step of glutathione synthesis. Consuming these foods to provide 30 grams or more of protein per day may be particularly advantageous if low insulin signaling, low polyphenol stimulation of glutathione synthesis, or genetic impairments in the first step of glutathione synthesis are at issue. Unpasteurized milk is considered a foodborne illness risk by the CDC and FDA, though all available data indicates that it is much safer than other foods commonly consumed, such as deli meats and hot dogs. Raw egg whites will cause a biotin deficiency (see the biotin section) if not accompanied by supplemental biotin and their protein is less bioavailable than from cooked egg white.
- Supplements designed to upregulate detoxification, such as milk thistle or sulforaphane, increase glutathione synthesis. These may be especially helpful if a diet rich in fruits and vegetables in infeasible, or to compensate for low insulin signaling. See the iodine section when using sulforaphane.
- Glutathione supplements at 500-1000 milligrams per day overcome all possible problems in glutathione synthesis and may compensate to some degree for poor glutathione recycling. Non-liposomal glutathione is less expensive than liposomal. If cost is an issue, I recommend trying non-liposomal first, and only using liposomal glutathione if markers of glutathione status, or certain signs and symptoms that you suspect are related to glutathione status, fail to improve. If speed of results is more important, I recommend starting with liposomal glutathione since there is a chance it will be more effective than regular glutathione.

Iodine

Iodine is given its own section because its principle and only well-established role is to become part of thyroid hormone, and it is the only mineral that becomes part of thyroid hormone. The thyroid gland has the highest need for antioxidant protection in the body, however. Thyroid hormone also regulates the rate of ATP production, and ATP is needed to support the antioxidant system through the synthesis of glutathione. For these reasons, the iodine section could be seen as a natural extension of the antioxidant section.

Signs and Symptoms of Iodine Deficiency: The only well established sign of iodine deficiency is hypothyroidism. When iodine deficiency occurs during pregnancy and the first year of life, it results in cretinism. This causes a general stunting of physical and neurological development with a lifelong decrease in IQ. Hypothyroidism at any age during development will slow growth, and will prevent the development or maintenance of fertility. More generally, hypothyroidism causes signs such as fatigue, brain fog, cold hands and feet, increased sensitivity to cold in general, hair loss, and swelling (edema), especially in the face. Iodine deficiency hypothyroidism may be accompanied by goiter, which manifests as a swelling in the neck due to an enlargement of the thyroid gland, and may feel like a lump in the throat. Hypothyroidism compromises immune function, and iodine itself is antimicrobial; either of these may account for increased vulnerability to infections. Poor digestive function, including constipation, small intestinal bacterial overgrowth (SIBO), and fat malabsorption may could be considered plausible results of hypothyroidism due to a slowing of gastric motility. Fibrocystic breast disease may also be a manifestation of iodine deficiency.

Risk Factors for Iodine Deficiency

Risk factors for iodine deficiency include consuming foods grown in low-iodine soil, not consuming many seafoods, not using iodized salt, and not using iodine supplements or iodine-containing multivitamins. Women who are pregnant or lactating, and probably women with large breasts, have increased iodine needs.

Low iodine intakes are aggravated by high exposure to thiocyanate, a compound that inhibits the transport of iodine into the thyroid and mammary glands. Thiocyanate is produced during the detoxification of cyanide from cigarette smoke or from the cyanogenic glycosides in many plant foods, and is produced from glucosinolates found in cruciferous vegetables. The most important sources of cyanogenic glycosides are cassava (from which tapioca is derived, also known as manioc and yucca), lima beans, sorghum sprouts, flax, the seeds of apples and pears, and the leaves, fruit and seeds of black cherries, cherries, almonds, plums, peaches and apricots. The most widely used cruciferous vegetables belong to the genus *Brassica* and include broccoli, Brussels sprouts, cabbage, cauliflower, collard greens, kale, kohlrabi, mustard, rutabaga, turnip, and bok choy. Other crucifers include arugula, horseradish, radish, wasabi, watercress, and maca. Sulforaphane, used as a supplement to promote detoxification, generates isothiocyanate.

Isoflavones derived from soy also bind to iodine and prevent its utilization for the production of thyroid hormone. Fluoride and bromine compete with iodine for transport and utilization. Fluoride is found mainly in toothpaste and fluoridated water. Bromine is put to a multitude of uses, such as flame retardants, dyes, insecticides, furniture foam, gasoline, and the casings of electronics, and is thus ubiquitous in the modern environment.

The exact quantitative effect of any of these iodine antagonists on iodine status is not well characterized, but it is clear that iodine deficiency is more harmful when exacerbated by iodine antagonists.

Signs and Symptoms of Iodine Excess: While goiter is considered primarily a manifestation of iodine deficiency, its risk also increases with chronic iodine intakes above 18 milligrams per day. Some authors argue that the risk of autoimmune thyroid conditions such as Hashimoto's

thyroiditis and Graves' disease increase above intakes of 200 micrograms per day, but the evidence for this is weak. Acute administration of iodine to individuals with underlying thyroid diseases, especially those resulting from iodine deficiency, may cause transient hyperthyroidism. Iodine supplementation above 1 milligram per day increases TSH over the course of two weeks, with no established clinical consequences. While a theoretical risk, prolonged elevation of TSH could contribute to goiter or thyroid cancer. Exposure to grams of iodine at once causes acute poisoning. This is extremely rare, but results in abdominal pain, fever, nausea, vomiting, and possibly coma. Allergies to iodine are possible, but very rare. Iodermia is a rare reaction to iodine that causes skin eruptions that appear as acne, itching (pruritis), and hives (urticaria).

Risk Factors for Iodine Excess: While the clinical risk of increased TSH from more than one milligram per day is theoretical, I consider it prudent to keep iodine intakes lasting longer than two weeks below an average of 1 milligram per day unless done under medical supervision to ensure the long-term health of the thyroid gland. Consumption of very iodine-rich seaweeds in their raw state (mainly kelp, which is also known as kombu, haidai, or by various scientific names beginning with *Laminariales*) could lead to iodine excess. Boiling for 15-30 minutes removes the iodine risk. Consuming one gram per day of raw kelp provides more than 1 milligram per day of iodine, and consuming 8 grams per day provides more than 20 milligrams. Use of iodine supplements or topical use of iodine could also provide excess. Iodine is often used in medicine as a sterilization agent or as a contrast dye for imaging procedures. Many people supplement with doses of iodine ranging from 6 to 50 milligrams per day, which should be done under medical supervision.

Testing for Iodine Status: The best marker of iodine status is urinary iodine excretion. Iodine is excreted in the urine when the body perceives that dietary iodine exceeds the body's needs. This makes it more reliable than blood levels of iodine. Nevertheless, urinary iodine will fluctuate widely according to recent dietary intake. I recommend using **24-hour urine iodine** (LabCorp, Quest) and taking it as reflective of the iodine status produced by the diet consumed on the day of and the day before the test, providing that the individual has not recently made a dramatic change to their iodine intake. The reason this is useful is that land foods can be rich in iodine but are extremely variable based on the soil the food is grown in. If urinary iodine appears adequate on a given diet, it suggests that maintenance of that diet over time will ensure iodine adequacy in that individual.

Testing Caveats: Urinary iodine assesses iodine intake, but it cannot assess whether iodine intake is sufficient to overcome iodine antagonists. If these antagonists stop iodine from getting into the thyroid gland, this does not necessarily stop it from being excreted in the urine (nor would it decrease iodine concentrations in the blood). Therefore, signs and symptoms are important to take into account when assessing the likelihood that you should reduce the iodine antagonists in your diet.

Correcting Iodine Deficiency: The simplest way to correct an iodine deficiency is to take a kelp supplement providing 2-300 micrograms per day. Maine Coast Sea Seasonings also sells shakers of kelp granules or of salt and spices with added seaweed that can be used in foods to ensure adequate iodine. While you are correcting an iodine deficiency, it is best to strictly moderate or eliminate the foods listed under "Risk Factors for Iodine Deficiency" as containing iodine antagonists. Over the long term, it is wise for anyone predisposed to poor thyroid health

to keep these foods to a maximum of 2-3 servings per day in total, and 1-2 servings per day from each category (where the “categories” are cyanogenic glycosides, crucifers, and soy).

Correcting Iodine Excess: If adverse effects on thyroid health accompany the use of high-dose iodine, the main nutritional strategy is to remove the source of iodine. Since the thyroid gland has the highest antioxidant needs in the body, optimizing the nutrients in the antioxidant section can be used to augment this strategy. Nevertheless, attention to all other nutrients is important because these systems are interconnected, with the most notable example that the antioxidant system is fully dependent on the system of energy metabolism for its function. It is important that thyroid health be fully evaluated by a physician.

Electrolytes: Sodium, Potassium, and Chloride

An electrolyte is a substance that dissolves into ions (fully charged particles) in a solvent, enabling the conduction of electricity in the presence of an electrode. In human physiology, the major electrolytes are sodium, potassium, calcium, magnesium, chloride, phosphate, and bicarbonate. Calcium, magnesium, and phosphate play their primary roles in other systems and are therefore not addressed in this section. Bicarbonate is produced endogenously and is not an essential nutrient. Sodium, potassium, and chloride are the three essential minerals whose primary purpose is to serve as electrolytes, and this section focuses on them. Chloride almost universally accompanies sodium both in the diet and in physiological regulation of electrolytes, so it is discussed together with sodium. For simplicity, I often refer to sodium and chloride together as “salt,” and to the ratio of sodium and chloride to potassium as “the salt-to-potassium ratio.”

Signs, Symptoms, and Risk Factors for Electrolyte Imbalances

Signs and Symptoms of Sodium and Chloride Deficiency

Well established effects of low-sodium diets include insulin resistance and elevated total cholesterol, LDL cholesterol, and triglycerides. Less well established but plausible effects include overactivation of the sympathetic nervous system and increased vulnerability to developing anxiety, dehydration and weakness, and poor intestinal absorption of many nutrients. The nutrients most likely to be affected are glucose, vitamin C, biotin, pantothenic acid, phosphorus, magnesium, and iodine. Calcium, niacin, and thiamin could also be affected. Chloride is required for the secretion of stomach acid (which is hydrochloric acid, made from hydrogen and chloride) and low chloride intakes presumably compromise digestion by causing hypochloridia (low stomach acid).

Hyponatremia refers to low blood levels of sodium and should be seen as distinct from inadequate dietary sodium. Signs and symptoms include nausea, vomiting, headache, confusion, weakness and fatigue, cramping, muscle spasms, ataxia (loss of full control over body movements) restlessness, irritability, and in extreme cases seizures or coma.

Hypochloremia refers to low blood levels of chloride. It is far rarer than hyponatremia and very rarely occurs to a clinically important extent on its own. It causes metabolic alkalosis, especially if produced from loss of stomach acid during extended vomiting. This can mimic the symptoms of hypocalcemia by decreasing the concentration of ionized calcium in the blood and can cause hypokalemia (see below) by driving potassium from the serum into cells. Possible signs and symptoms of hypocalcemia and hypokalemia include muscle spasms, twitching, tremors, cardiac arrhythmia, palpitations, bradycardia (slow heart rate), and confusion. In severe cases seizures, coma, and death could result but this has never been documented from isolated hypochloremia. Isolated chloride deficiency has only been produced from errors in the production of infant formula, where it produced growth failure, irritability, anorexia, gastrointestinal distress, and weakness, and in some cases metabolic alkalosis and hypokalemia. None of the infants died and the only sign that persisted after correction of the diet was delayed speech development and language skills.

Risk Factors for Sodium and Chloride Deficiency

Sodium and chloride are primarily consumed in table salt, where they occur together, or in the salt added to processed foods (not only industrially processed foods but also traditionally processed foods, such as cheese, fermented vegetables and meats, and brines). Sodium and chloride are also found in fresh foods in roughly equal proportions, although meat, fish, and eggs are somewhat richer in sodium, while nuts, vegetables, fruits, and grains are somewhat richer in chloride. A mix of natural foods that is diversified among plant and animal foods and among land and sea foods may provide sufficient sodium and chloride for many individuals, but it is also possible that chronic stress increases the need for salt beyond what natural, unprocessed foods can provide. The amount of salt recommended as sufficient for adults by the Institute of Medicine translates to two thirds of a teaspoon of regular table salt per day. This includes the sodium and chloride found in foods and is met by the DASH diet, a low-salt diet designed to reduce blood pressure. My personal opinion is that anyone who does not suffer from high blood pressure or a high risk of kidney stones or osteoporosis should be liberal with salt and salt their food to taste, while also trying to eat a potassium-rich diet for balance.

All electrolytes, especially sodium, chloride, and potassium, are lost in vomit, diarrhea, sweat, and urine. Common causes of fluid loss are foodborne illnesses, gastrointestinal infections, diuretics, diabetes, sauna use, and intense physical activity. Persistent vomiting will disproportionately cause alkalosis and loss of chloride because of the expulsion of stomach acid. Untrained individuals will lose large amounts of sodium when engaging in exercise that causes intense sweating. As individuals train, especially in hyperthermic conditions, they adapt by excreting less sodium into sweat. Mixing some electrolytes into water as a workout fuel, such as 1/16th teaspoon of salt and the juice of one quarter lemon per bottle of water, and consuming a diet that is salted to taste, should protect against this.

Hyponatremia is not usually caused by low sodium intake, though low sodium intake may aggravate the risk in the presence of more direct causes. Hyponatremia always requires medical attention and is usually caused by factors that are not nutritional in nature. The one nutritional cause of hyponatremia is consuming water at a faster rate than the kidneys can excrete it. This usually occurs either because an altered mental state interferes with an individual's sense of thirst, or because intense exercise drives an excessive thirst response. An athlete who performs in hyperthermic conditions for the first time without training under those

conditions, who loses excessive sodium in the sweat, and who is driven by thirst to drink water beyond the capacity for urine formation, is a prime candidate for hyponatremia.

Isolated hypochloremia is rare and most likely would occur from persistent vomiting. As with hyponatremia medical attention should be sought.

Signs and Symptoms of Excess Sodium and Chloride

The effects of excess sodium and chloride are best seen as resulting from too much sodium and chloride relative to potassium. A high salt-to-potassium ratio increases blood pressure and may also increase extracellular fluid in general, contributing to edema (swelling). It also contributes to a chronic acid burden, which lowers bone mineral density and increases the risk of osteopenia, osteoporosis, and kidney stones.

Hypernatremia is a rise in the serum concentration of sodium. It always requires medical treatment, is never caused by excess salt intake, and usually has non-nutritional causes related to medical disorders or errors in medical treatment. In an individual with intact thirst, the primary symptom is thirst. However, hypernatremia is sometimes caused by a defect in the sense of thirst. Weakness, nausea, and loss of appetite are other early symptoms. In severe cases, it may lead to cerebral edema and shrinkage of brain cell volume, muscle twitching or spasming, confusion, seizures, coma, and death.

Risk Factors for Excess Sodium and Chloride: In theory, the salt content of processed foods and the practice of salting foods during cooking and while eating contributes to risk of excess sodium and chloride. In the United States, the National Heart, Lung and Blood Institute and the National Blood Pressure Education Program recommend limiting salt intake to 2300 mg/d of sodium (one teaspoon of salt) for the general public and 1500 mg/d (⅔ teaspoon of salt) for those with hypertension (high blood pressure). The Institute of Medicine set the tolerable upper intake limit at one teaspoon of salt as well, though acknowledging that increased sweating may increase needs. The value of salt restriction is hotly contested in the scientific literature, however, and both known physiology and clinical evidence suggest that consuming adequate potassium is far more important than restricting salt for blood pressure. My personal opinion is that anyone who does not suffer from high blood pressure or a high risk of osteoporosis or kidney stones should be liberal with salt and salt their food to taste, while also trying to eat a potassium-rich diet for balance.

Hypernatremia never occurs from excess salt intake by mouth alone. Errors or complications in the use of hypertonic saline infusions during medical procedures are the most common cause. It also occurs in individuals with a severe deficit in water intake. Possible causes of the water deficit include coma or other incapacitation, having no access to water (especially if losing water at an unusually fast rate, as with vomiting), having a mechanical obstruction impairing water intake such as an esophageal tumor, or having an impaired sense of thirst, usually due to an altered mental state. Water loss in diabetes or in the use of diuretics could contribute to hypernatremia when combined with excess salt intake.

Signs and Symptoms of Potassium Deficiency: Inadequate potassium elevates the salt-to-potassium ratio (see excess sodium and chloride above). A high ratio contributes to high blood pressure, edema (swelling), and chronic acid burden (leading to increased risk of

osteopenia, osteoporosis, and kidney stones). Potassium stimulates insulin, and it is plausible to suggest a high-carbohydrate meal would destabilize blood sugar more when it is also low in potassium.

Hypokalemia refers to low blood levels of potassium. Low-potassium diets can contribute to hypokalemia, but are rarely the cause all on their own. Hypokalemia leads to a slower heart rate (bradycardia); cardiac arrhythmia or palpitations; reduced intestinal motility (which could lead to constipation and theoretically to small intestinal bacterial overgrowth, SIBO); muscle spasms and twitches; lower levels of insulin secretion, leading to hyperglycemia; low blood pressure (hypotension) and in severe cases, hypokalemia can result in skeletal muscle necrosis (cell death), rhabdomyolysis (damaged muscles spilling their contents into the blood), and life-threatening changes in heart function. Hypokalemia always warrants medical attention.

Risk Factors for Potassium Deficiency: The Institute of Medicine recommended in 2005 that Americans consume 4.7 grams of potassium per day to lower the risk of kidney stones and high blood pressure, and this will be revised in 2018. Some authors have estimated that preagricultural diets contained over 12 grams of potassium per day. I consider 4.7 grams a reasonable target for a minimum. However, less than two percent of Americans meet this goal. I therefore consider it reasonable to say that inadequate potassium resulting from poor food selection is almost universal.

The primary dietary risk factors are a low intake of fruits and vegetables, high intake of added fats and oils and of refined carbohydrates, and discarding the juices of meat and the cooking water used for plant foods. Additionally, foods prepared in brines reduce the potassium content of the diet because brines exchange sodium for potassium. See the section below on correcting electrolyte imbalances for specific dietary recommendations.

Refeeding syndrome is a major cause of hypokalemia. During starvation or chronic malnutrition (as might occur in alcoholism, eating disorders, or illnesses that impact food intake), catabolism releases intracellular potassium stores and causes loss of potassium from the body. During refeeding, insulin brings potassium into cells, lowering its concentration in the serum, causing hypokalemia. The high rate of cellular repair and need to rebuild intracellular potassium stores aggravates the hypokalemia. Low levels of magnesium (hypomagnesemia) and phosphorus (hypophosphatemia) are also found in refeeding syndrome.

Diarrhea and vomiting both cause direct loss of potassium. Vomiting also causes alkalosis from the loss of stomach acid, and alkalosis drives potassium into cells and increases its excretion in the urine, both of which lower its concentration in the serum. During illnesses that cause vomiting and diarrhea, dietary potassium is usually low, making it difficult to replenish serum levels. Thus, illnesses that cause vomiting and diarrhea are a major cause of hypokalemia, with the vomiting making the most important contribution.

Signs and Symptoms of Excess Potassium: In the context of a low-salt diet, high intakes of potassium could theoretically aggravate the signs and symptoms of sodium deficiency. Supplemental potassium on an empty stomach could stimulate insulin secretion and lower blood sugar, contributing to hypoglycemia. Symptoms of hypoglycemia include hunger, fatigue, shakiness, irritability, anxiety, sweating, and in extreme cases confusion, visual disturbances,

seizures, and loss of consciousness. Extreme hypoglycemia causing seizures has not been documented from potassium supplementation, however.

Hyperkalemia refers to high blood levels of potassium and should be seen as distinct from excess dietary potassium because it will not occur in response to potassium-rich foods alone. It always warrants medical attention. Hyperkalemia can cause fast heart rate (tachycardia) and cardiac arrhythmia, and palpitations. Confusion, paresthesia (tingling, numbness, or a feeling of something crawling on the skin) may also occur. In severe cases, hyperkalemia causes weakness, paralysis, and cardiac arrest, and can be fatal.

Risk Factors for Excess Potassium

Few individuals meet the recommended intakes for potassium, let alone the levels found in preagricultural diets. In theory, someone could aggravate a sodium deficiency by intentionally eating an extremely low-salt, high-potassium diet. If this occurs it should be seen as a sodium deficiency because it can easily be corrected by salting food to taste.

Potassium supplements are generally safe for healthy adults. Potassium chloride supplements have caused gastrointestinal distress when provided in a wax matrix or microencapsulated gelatin capsule, but not as a powder mixed with water. Supplemental potassium has been used in amounts as high as 15.6 grams per day in healthy adults without causing any instances of hyperkalemia.

Dietary potassium may contribute to hyperkalemia in diabetes or insulin resistance, where the insulin response to potassium is inadequate. It may also contribute to hyperkalemia in cases of drugs or medical conditions that impair the excretion of potassium into the urine, which include Addison's disease, a selective deficiency in adrenal production of aldosterone, and therapy with heparin, ACE inhibitors, beta-blockers, and nonsteroidal anti-inflammatory drugs (NSAIDs). In these cases, supplemental potassium is more dangerous than food potassium because it raises blood levels of potassium faster. Acidosis, cellular damage, low ATP production from hypothyroidism or diabetes, and digitalis overdose can all shift potassium from the cells into the blood, causing hyperkalemia.

The FDA limits the content of potassium supplements to less than 100 milligrams per serving to avoid the small risk of hyperkalemia when used by individuals vulnerable to this disorder. However, potassium supplements can be taken in multiple servings, and bulk powders can make it easy to do so. 15 grams per day have been used safely in trials, potassium-rich foods may provide 5 to 15 grams per day, and a healthy adult has the capacity to excrete up to 33 grams of potassium per day. On an empty stomach, high-dose potassium supplements may cause hypoglycemia. Taken with a meal and spread evenly through the day, however, they are safe for healthy individuals. Nevertheless, the conditions that impair potassium excretion are numerous, and some of them -- insulin resistance and NSAID usage -- are common. If you are using potassium supplements that provide more than a gram per day spread evenly across meals, I recommend you consult with your physician to ensure healthy insulin secretion and sensitivity, healthy kidney function, and that you are not taking drugs that contraindicate the use of potassium supplements.

Testing for Electrolytes

Sodium, chloride, and potassium are routinely measured on a **metabolic panel** (either basic: LabCorp, Quest; or comprehensive: LabCorp, Quest).

These are not measures of nutritional status. Deviations from the normal range are usually caused by non-nutritional factors. Medical attention should always be sought so that the many non-nutritional causes may be considered. Nevertheless, nutrition may make a partial contribution and should not be ignored. Consideration of the nutritional factors should be given as follows. For alterations in sodium concentration, too much or too little water should be considered first, and extremes in sodium intake should be considered second. For low potassium, loss of body fluids should be considered first and low dietary intake second. For high potassium, use of supplements should be considered first and high dietary intake second.

Electrolytes being in the normal range does not rule out nutritional imbalances. Rather, dietary analysis, blood pressure, and edema should be considered the primary nutritional markers:

- **Dietary Analysis**. (Instructions) Intake of potassium should be higher than 4.7 grams per day and may safely reach double or triple this. Intake of sodium should be at least 1.5 grams per day. Intake of sodium above 2.3 grams per day may pose a risk when potassium is deficient, but is unlikely to pose a risk when potassium is adequate. Chloride follows sodium closely enough that it can be ignored.
- **Blood Pressure.** Taking blood pressure at home can remove the anxiety of white coat syndrome and provide you with a large amount of objective data. You should follow the instructions that come with the monitor closely, take the measurements when you are calm, repeat the measurement three times per session, and measure it on at least three different occasions. Repeated measurements showing blood pressure higher than 130/80 suggest the need for dietary strategies to reduce the salt-to-potassium ratio.

The perception that one is retaining water, especially in the eyes and face, may indicate edema and is another possible indicator of an excessive salt-to-potassium ratio.

Testing Caveats

Maintaining healthy blood pressure also requires maintaining healthy body composition, a good physical activity routine, avoiding excess alcohol, proper stress management, and adequate intake of other minerals, such as calcium and magnesium. Blood pressure elevations are not specific indications of the salt-to-potassium ratio and are not necessarily related to diet or lifestyle. For these reasons, you should always discuss your blood pressure with your doctor. Nevertheless, decreasing the salt-to-potassium ratio is very likely to improve blood pressure, and if it does, this alone confirms that the salt-to-potassium ratio was a contributor to the high blood pressure. Edema may have many other causes, most notably hypothyroidism (especially when affecting the face) or diabetes (especially when affecting the lower legs). You should always discuss signs of edema with your doctor. Toxic levels of barium and thallium may mimic

potassium deficiency (see the other minerals section for detoxification suggestions if this applies).

Correcting Electrolyte Imbalances

Suggestions for Increasing Salt

I recommend that healthy individuals who do not have high blood pressure or a high risk of kidney stones or osteoporosis salt their food to taste. It is unlikely that anyone would self-select a diet and salt to taste yet still consume under 1.5 grams of sodium. In such a case, I recommend increasing the sodium content to at least 1.5 grams, especially if any signs of sodium or chloride deficiency are present.

For individuals with high blood pressure, a high risk of kidney stones (having had a kidney stone in the past, or signs of high risk discovered on a urinalysis, such as a high presence of calcium oxalate crystals), or a high risk of osteoporosis (postmenopausal women, anyone with low bone mineral density), I recommend first following the recommendations below to construct a potassium-rich diet. After that, I recommend working with a qualified health care practitioner to monitor blood pressure, kidney stone risk, and bone mineral density to provide a safe context for increasing salt intake to the point where salt cravings are lowest, there are no signs of sodium or chloride deficiency, and subjective sense of wellbeing and resilience to stress is greatest.

Suggestions for Increasing Potassium and Decreasing Salt

In the case of high blood pressure or edema, the first nutritional effort should be to raise the dietary potassium. This interpretation is especially strong if dietary potassium is under 4.7 grams, but could be plausible at almost any level. Salt should be restricted gradually if raising dietary potassium does not work.

Three options for constructing a potassium-rich diet are provided below: 1) a diet very rich in fruits and vegetables, 2) a low-fat diet that is low in grains and free of refined carbohydrates, and 3) a low-carbohydrate, high-fat diet that emphasizes vegetables with high ratios of potassium to net carbs.

For all the foods below, it is important to consume them raw or to consume the cooking water and juices. Otherwise, significant amounts of potassium will be lost.

Diets Rich in Fruits and Vegetables

Fruits generally provide 100-500 mg of potassium per 100 gram serving, and vegetables generally provide 200-1000 mg per 100 gram serving. When adjusted per calorie, vegetables are extremely rich in potassium. For example, 300 Calories of spinach provides over 7 grams of potassium. Following the official recommendations to consume five to nine servings of fruits and vegetables per day and selecting them for their potassium content can easily provide the recommended amount of potassium, regardless of the rest of the diet.

Diets Low in Fat, Moderate in Grains, and Free of Refined Carbohydrates

Alternatively, reducing the fat content of the diet, moderating grains, and eliminating refined carbohydrates can allow the broad selection of alternative foods to fulfill the potassium requirement. 300 Calories of butter contains only 10 milligrams of potassium. 300 Calories of enriched white flour contains 91 milligrams of potassium. While much better than butter, this is only a quarter as potassium-rich as whole wheat flour, which at the same caloric load provides 358 milligrams of potassium. Nevertheless, 300 Calories worth of beans or potatoes provides close to 1.5 grams of potassium each, which is about quadruple that provided by whole wheat. 300 Calories of fat-free milk provides 1.4 grams of potassium, whereas the same caloric load of whole milk provides only 715 milligrams, about half as much. 300 Calories of sirloin steak with all the fat trimmed off provides 700 mg of potassium. By contrast, beef tallow does not contain any potassium. In a single large egg, there are 67 mg of potassium, 80% of which is in the white. For each 300 Calories, egg whites provide over 1 gram of potassium, while whole eggs provide only 281 milligrams and egg yolks provide a dismal 103 milligrams.

Low-Carbohydrate, High-Fat Diets

It is possible to eat a low-carbohydrate, high-fat diet with adequate potassium, but it requires much more attention to food selection. 75 grams of protein obtained from meat will provide about 750-1000 milligrams of potassium. 150 grams of protein from meat will provide about 1.5-2 grams of potassium. The following is a list of mg potassium per gram net carb (total carbohydrate minus fiber) in some of the best choices for vegetables: watercress, 431; spinach, 399; purslane, 329; mustard greens, 221; bamboo shoots, 178; arugula, 176; red leaf lettuce, 170; celery, 144; white mushrooms, 138; green leaf lettuce, 129; zucchini, 119; Chinese cabbage, 119; asparagus, 106; common cabbage, 79; iceberg lettuce, 71; tomatoes, 66. If one were to eat 100 grams of each of these vegetables per day, this would yield 4.9 grams of potassium and less than 32 grams of net carbs. The lean portion of the protein would bring the total to anywhere from 5.6 to 6.9 grams of potassium and the remainder of the diet could be fat.

Summary of the Dietary Options

I do not recommend high-fat ketogenic diets unless there is a demonstrated medical purpose for this diet or trial and error has proven it useful to increase well being or resolve health problems that have not been resolvable through other means. I do not recommend using egg whites without the yolks unless one also supplements with biotin, monitors biotin status, and ensures an adequate intake of choline through other foods. I do not recommend foods that have their natural fats removed, including yolk-free egg whites, unless one is using them temporarily to meet a body composition goal or one has demonstrated difficulties digesting or metabolizing fats. Nevertheless, many people practice these dietary restrictions and the information in this section can be used to meet the potassium requirement in any of those contexts.

In summary:

- Consuming foods raw or consuming the cooking water and juices always helps improve potassium intake.
- Avoiding refined carbohydrates always helps improve potassium intake.

- The lean portions of meat, eggs, and dairy always make a significant contribution to potassium intake.
- If you are focusing on cutting calories, a high volume of fruits and especially vegetables is the best way to improve potassium intake.
- If you have difficulty eating high volumes of low-calorie foods due to time constraints, digestive difficulties, or difficulty meeting caloric requirements, then a diet with moderate amounts of whole grains and larger amounts of potatoes and legumes is the best way to improve potassium intake.
- If you have trouble digesting or metabolizing fats, or need to temporarily reduce fat to extreme levels for body composition goals, then consuming fat-free dairy products, lean cuts of meat, and egg whites supplemented with biotin and alternative sources of choline is the best way to improve potassium intake.
- If you are eating a low-carbohydrate, high-fat diet, selecting the foods with the highest potassium-to-net carb ratios and eating them in large volumes is the best way to improve potassium intake.
- Depending on your goals, any of the above strategies can be mixed and matched.

Potassium Supplements

I recommend exhausting the above possibilities before resorting to potassium supplements. If all of the above strategies prove infeasible or unsustainable, you can obtain a portion of the potassium requirement from supplements. In such cases, I recommend mixing potassium citrate powder in water for the least risk of gastrointestinal distress. Potassium should always be taken with a full meal and the dose should be spread out across the day. Potassium supplements should not be used by anyone with diabetes, insulin resistance, impaired kidney function, or who is using ACE inhibitors, beta-blockers, and nonsteroidal anti-inflammatory drugs (NSAIDs), unless prescribed by a physician. Anyone using more than one gram per day should discuss it with their physician to ensure that there are no contraindications with current health status or medications.

Vomiting and Diarrhea

Vomiting and diarrhea may indicate a serious illness. Severe pain, loss of blood in the vomit or stool, confusion or other cognitive symptoms, fever, and the inability to keep down even clear fluids are grounds for seeking emergency medical attention. Calling your doctor is wise if you are unsure whether the condition could be serious. In cases of moderate, self-limiting illness, it makes sense to replete electrolytes once fluids can be kept down. ¼ teaspoon each of table salt, baking soda, and potassium bicarbonate, along with some juice containing natural sugars to balance the potassium, will replace the major electrolytes lost. If the fluid loss was overwhelmingly from vomiting rather than diarrhea, doubling the table salt and taking out the baking soda will help replete the lost chloride better, and apple cider vinegar can help replete the lost acid.

Extended fluid loss may cause the loss of other electrolytes, such as calcium, magnesium, and phosphorus. Loss of bile in vomit or diarrhea can deplete zinc and copper, and thiamin deficiency is also found in persistent vomiting. Illness causing vomiting and diarrhea for an extended period of time warrant medical attention as well as an evaluation or repletion strategy for these other nutrients.

Altered Electrolyte Concentrations

Signs and symptoms of altered electrolyte concentrations or deviations from the normal range on serum tests always warrant medical attention. Nutritional strategies to alter water, salt, and potassium intake may be sensible adjuncts to medical treatment but should be discussed with a physician, because altered electrolyte concentrations almost always indicate deeper problems that are not nutritional in nature.

Other Minerals

There are several minerals that appear to have essential roles that are not listed in other sections.

Boron appears to support executive brain function, to improve testosterone in men, and to protect against prostate cancer in men and lung cancer and cervical dysplasia in women. **Chromium** appears to support glucose tolerance, insulin sensitivity, and to raise HDL-cholesterol.

Evidence for beneficial effects of other trace elements is scant:

- **Strontium** has shown benefits to bone mineral density in osteoporotic women when supplemented as 2 grams per day of strontium ranelate, which provides about 340 milligrams of elemental strontium. There is no evidence on which to consider this a nutritional effect rather than a pharmacological effect, however, and it is not clear that strontium has an essential role in human biology.
- There are observational studies associating low-dose **lithium** in drinking water with benefits such as lower risks of dementia, homicide, and suicide, but also studies associating it with harms, such as impaired calcium metabolism. There is no basis on which to make recommendations around lithium intakes or supplements.
- **Silicon** might support bone health and **nickel** might support reproductive function and liver health, but the evidence for this is limited to animal experiments and there is no evidence supporting these roles in humans. Harms of silicon to humans are only well demonstrated in the case of inhalation of silica particles in industrial settings. Harms of nickel are shown only in animals, like its benefits.
- **Vanadium** supplementation has improved insulin sensitivity in people with diabetes, but it is not clear that it has any role as an essential nutrient and animal experiments suggest that it has a very narrow therapeutic window, causing harms at doses that are not much higher than the doses that cause benefits.
- While there is some evidence that **arsenic** deprivation in animals can produce deficiency signs, there is no evidence of this in humans, no known essential roles of arsenic in animal biology, and clear evidence of its toxicity.

Out of all of these, only boron and chromium have strong support as nutrients. Nevertheless, much less is known about them compared to the other nutrients discussed in this guide, and there are no good markers of nutritional status.

Boron is widely distributed among plants, and the major food sources in a diet depend mainly on which plant foods dominate the diet. Food selection is an unlikely cause of inadequate boron, but low plant food intake could contribute. Low accumulation in the food chain can be caused by low soil boron, low soil organic matter, or soil pH below 5.0 or above 6.5. Taking boron supplements does not eliminate the harms of eating low-boron foods, because low boron uptake into plant tissues also compromises their content of chlorophyll and fat-soluble vitamins. Nevertheless, supplemental boron at 3 milligrams per day has shown some promise for increasing testosterone levels in men.

Chromium is found in the highest concentrations in whole grains, unrefined sugars, and brewer's yeast (but not other edible yeasts), and in lesser amounts in fruits and vegetables. Needs for chromium are probably proportional to carbohydrate intake. The refining of grains and sugars removes chromium and this may contribute to poor glucose tolerance on diets high in refined carbohydrates. It may be that choosing unrefined grains and unrefined sugars over their refined counterparts is adequate. Nevertheless, soil chromium varies and this influences the chromium stores of plants. Supplementation of 200 micrograms per day of chromium has shown some promise for improving glucose metabolism.

My recommendations are as follows:

- For those who wish to err on the side of supplementing with what shows the most promise, or who wish to improve functions described above for these minerals, take one to two capsules per day of Pure Encapsulations Boron Glycinate and one capsule per day of Jarrow Chromium GTF with a meal.
- For those who wish to monitor nutritional status and use targeted supplementation, the only sensible option available is to get a hair mineral analysis (for example, Drs. Data) and supplement with the minerals that are low. If this approach is taken, I recommend following up all minerals outside this section with the recommended tests. Boron and chromium should be taken using the doses and forms recommended above if they are low. Strontium and lithium are probably safe to take in the lowest doses available if they are low, but the benefits are less clear. I do not recommend making any attempts to increase exposure to silicon, nickel, vanadium, or arsenic even if they appear low.
- While this guide is not meant to for dealing with heavy metal toxicity, three nutritional factors are notable. Zinc promotes the production of the endogenous metal chelator, metallothionein, even when provided over and above the levels needed to support all other aspects of zinc nutritional status. If hair mineral analysis shows elevated levels of heavy metals, zinc supplementation, along with careful evaluation of the status of zinc, copper, and the other positively charged minerals, may help promote detoxification (see the zinc section). Arsenic is specifically detoxified using methylation, and if arsenic is elevated, nutritional support for the methylation process may promote its clearance (see the methylation section). Barium is most effectively detoxified with sulfate, so support for sulfur amino acids, vitamin B6, and molybdenum may help promote its clearance (see the sections on methylation and sulfur catabolism). Comprehensive handling of heavy metal toxicity is beyond the scope of this guide, and a knowledgeable health care practitioner should be consulted for any concerns on this topic and before commencing any nutritional strategies described here.

Essential Fatty Acids

There are two fatty acids for which the evidence of essential roles in animals and humans is strong: **arachidonic acid (AA)** and **docosahexaenoic acid (DHA)**. A third fatty acid, **eicosapentaenoic acid (EPA)**, has demonstrated benefits at high doses for lowering extremely high triglyceride levels, but this is a pharmacological action, not a nutritional one. There is some evidence suggesting it improves mental health outcomes more effectively than DHA. Nevertheless, EPA can interfere with the function of AA and there is no clear evidence that it has essential roles in human nutrition.

Other fatty acids, such as **linoleic acid (LA)** and **alpha-linolenic acid (ALA)** are defined conventionally as “essential fatty acids” because we cannot synthesize them. By contrast, we synthesize AA from LA, and we synthesize EPA and DHA from ALA, so AA, EPA, and DHA are not considered essential. Nevertheless, there is no clear evidence that we require LA or ALA to be present in our bodies to support our health, and there is clear evidence that we require AA and DHA.

Signs and Symptoms of Arachidonic Acid Deficiency: The only well established deficiency sign for arachidonic acid in humans is eczema. In laboratory animals, the eczema presents as irritated, sore, scaly skin and is accompanied by dandruff and hair loss. Lab animals subject to severe deficiency also develop bleeding at the surface of the skin, internal bleeding and infertility. Females develop anovulation and if the deficiency develops during pregnancy they have extended labor and increased risk of death during labor. Males lose interest in sex, stop producing sperm, and their testicles degenerate. Mechanistic evidence suggests that arachidonic acid deficiency also increases the risk of food intolerances, infectious diseases, autoimmune disorders, and chronic, low-grade inflammation. Drugs that interfere with AA metabolism cause gastrointestinal distress. The blood thinning effect of fish oil results from EPA interfering with AA metabolism.

Risk Factors for AA Deficiency: AA is abundant in egg yolks and liver. It can be made from LA, which is found in small amounts in animal products and olive oil, and in larger amounts in vegetable oils, but the conversion depends on genetics, insulin sensitivity, protein, calories, calcium, zinc, biotin, and vitamin B6. Thus, a diet that lacks egg yolks and liver does not necessarily lead to AA deficiency but increases its risk due to the many difficulties synthesizing AA from LA. Oxidative stress (see the antioxidant section) and chronic inflammation deplete AA. Nonsteroidal anti-inflammatory drugs (NSAIDs) interfere AA metabolism and may contribute to deficiency signs regardless of AA levels. High-dose EPA, as would be found in high-dose fish oil or used pharmacologically to lower triglycerides, causes a similar effect as NSAIDs. AA needs are highest during childhood growth, bodybuilding, pregnancy, lactation, and recovery from injury.

Signs and Symptoms of DHA Deficiency: DHA deficiency predisposes to low-grade, chronic inflammation, poor visual acuity, slower mental processing, learning deficits, and possibly Alzheimer’s disease and psychiatric conditions such as depression, anxiety, and attention deficit and hyperactivity disorder (ADHD).

Risk Factors for DHA Deficiency: DHA is found in large amounts in seafoods (mainly fish, also some crustaceans and certain algae used in supplements) and in smaller amounts in egg yolks when chickens are raised on pasture. A diet low in seafood and based on grain-fed animal products is the major risk factor for low DHA levels. DHA can be made from EPA in fish oil and from ALA in plant oils but the conversion depends on genetics, insulin sensitivity, protein, calories, calcium, zinc, biotin, and vitamin B6. Oxidative stress (see the antioxidant section) and chronic inflammation deplete DHA. High intakes of LA from vegetable oils aggravate the effect of low DHA intakes by replacing DHA in tissues with an different fatty acid, docosapentaenoic acid (DPA).

Testing for Essential Fatty Acids:

The Genova ION Profile + 40 amino acids and NutrEval offer comprehensive fatty acid analyses, and Quest offers one more narrowly focused on EPA, DHA, and AA.

If ordering the test specifically for this purpose, I consider the Quest test sufficient. However, the Genova ION + 40 is used in the comprehensive screening because it contains so many other analytes discussed in this guide.

Testing Caveats: Low essential fatty acids across the board may indicate oxidative stress (see the antioxidant section). If this is the case, optimizing the antioxidant nutrients should take precedence over repleting the fatty acids. If AA, and perhaps DHA, are specifically low, and high-sensitivity C-reactive protein (hsCRP, LabCorp, Quest) is high, inflammation may be driving the utilization of these fatty acids. In this case the source of inflammation deserves independent attention, but dietary strategies to replete the fatty acids still deserve central importance because deficiencies of AA and DHA can be the cause of chronic inflammation.

Correcting Essential Fatty Acid Imbalances:

If AA is low, I recommend increasing AA intakes by consuming one 100 gram serving of liver per week and up to 3-4 whole eggs or egg yolks per day. If this is not feasible, an arachidonic acid supplement can be used at 250 milligrams per day with a meal.

If the AA/EPA ratio is low as a result of high or high-normal EPA, I would first try reducing or removing EPA supplements. If the EPA is needed for pharmacological management of high triglycerides, or if it is proving useful for management of a psychiatric condition, then I recommend working with a health care practitioner to find the minimum effective dose, and utilizing the strategies described above for boosting AA intake to see if the ratio can be normalized.

I do not consider a high AA/EPA ratio worth acting on.

If DHA is low, I would increase the intake from natural foods by using 3-4 whole eggs or egg yolks per day from chickens raised on pasture, consuming 2-3 100 gram servings of fatty fish per week, or using ½ teaspoon of cod liver oil per day. There is some evidence supporting the use of krill oil to improve the brain content of DHA more rapidly, which may be helpful for psychiatric conditions.

Further Reading

If you would like to take a deep dive into managing each individual nutrient in the style found here, but in much more detail, my podcast series on managing nutritional status begins with this episode: What Makes a Good Marker of Nutritional Status? The episode list contains a running list of all the episodes in the series. Each episode contains a transcript and a list of scientific references. The full series will be rolled out over the course of 2018.

To learn more about nutrition more generally, I would start with one of the following textbooks:

> **Beginner:** Gropper, Advanced Nutrition and Human Metabolism. 7th edition. 2017.
> **Advanced:** Ross, Modern Nutrition in Health and Disease. 11th edition. 2012.

If you are a clinician, I recommend keeping chapter 57 of Modern Nutrition in Health and Disease, "Clinical Manifestations of Nutrient Deficiencies and Toxicities" handy because it contains a condensed summary of all such manifestations with technical language and pictures.

The Linus Pauling Micronutrient Information Center has an excellent list of articles on each nutrient that is regularly updated and fairly comprehensive.

Index of Signs and Symptoms

The purpose of this index is to allow you to quickly find the sections of the main text that are most useful or interesting to you. The index is not meant for making conclusions. It includes associations that are speculative or have weak evidence behind them, as well as associations that are well established. The main text makes these distinctions and provides additional context needed to form conclusions and develop an action plan. You should always discuss any of these signs or symptoms with your doctor before taking action, because they could require medical treatment and they may indicate medical conditions that are not discussed in this guide.

Abdominal pain	iron overload, iodine deficiency, acute iodine poisoning
Acid-base imbalance	zinc deficiency, electrolyte imbalances
Acne	zinc deficiency, vitamin A deficiency, rare reactions to iodine
Adrenal hormones, resistance to	zinc deficiency
Adrenaline, low	copper deficiency, vitamin C deficiency
Allergies	risk is increased by vitamin A deficiency and deficiencies or excesses of vitamin D and calcium; may occur in response to iodine; allergy-like reactions to sulfites that result from molybdenum deficiency
Alopecia	deficiencies of riboflavin, biotin, zinc, iron, or iodine; iron overload, selenium toxicity or vitamin A toxicity
Alzheimer's disease	DHA deficiency, copper toxicity, or iron overload
Androgens in women, high	deficiencies of vitamin D and calcium or vitamin K
Anemia, megaloblastic, macrocytic	deficiencies of folate, B12, or copper
Anemia, sideroblastic	vitamin B6 deficiency

Anemia, microcytic	deficiencies of iron or copper
Angular stomatitis	deficiencies of riboflavin or vitamin B6
Anxiety	deficiency of methylation, vitamin B6, molybdenum, DHA, or salt; acute hypoglycemia in response to potassium on an empty stomach
Arsenic, slow rate of detoxification	deficient methylation
Asthma	deficiencies of glutathione or vitamin A; deficiencies or excesses of calcium and vitamin D; allergy-like reactions to sulfites that result from molybdenum deficiency
Ataxia (loss of full control over body movements)	deficiencies of magnesium, thiamin, biotin, vitamin B12, or vitamin E; hyponatremia; vitamin B6 toxicity; Friedrich's ataxia, a genetic disorder in iron distribution
Atherosclerosis	See cardiovascular disease.
Attention deficit	See distractibility.
Autoimmune disorders	deficiencies of vitamin A, vitamin D and calcium, or arachidonic acid, excess EPA from fish oil
Beard hair, reddened	manganese deficiency
Bitot's spots	vitamin A deficiency
Bleeding disorders	Deficiencies of vitamin C, vitamin K, or arachidonic acid, excess vitamin E or EPA from fish oil
Blisters	zinc deficiency, flushing reaction to niacin
Blood pressure, high (hypertension)	a high salt-to-potassium ratio, deficiencies of vitamin D and calcium or magnesium
Blood pressure, low (hypotension)	Excess choline or magnesium; orthostatic hypotension from vitamin B12 deficiency; allergy-like reactions to sulfites that result from molybdenum deficiency; hyponatremia; hypokalemia
Blood sugar problems	deficiency or excess of vitamin K; oxidative stress and imbalances of antioxidant nutrients, especially zinc; chronic potassium deficiency or high-carbohydrate, low-potassium meals; acute hypoglycemia in response to potassium on an empty stomach; phosphorus deficiency; see also diabetes.
Bone mineral content, low	deficiencies of manganese, vitamin C, glycine, calcium and vitamin D, and vitamin K; excess phosphorus and vitamin A; a high salt-to-potassium ratio
Bone mineral content, high	Excess calcium
Bone pain	In rickets and osteomalacia, deficient vitamin D, calcium, phosphorus, or magnesium
Bradycardia (slow heart rate)	hypercalcemia, hypermagnesemia, hypokalemia, hypochloremia,
Brain fog	hypothyroidism due to iodine or iron deficiency (see also selenium); anemia due to deficiencies of iron, copper, B6, B12, or folate; methylation imbalances
Breast, fibrocystic disease	Iodine deficiency
Bruising	deficiencies of vitamin C or vitamin K
Burning in the feet	pantothenic acid deficiency
Cancer	Oxidative stress, deficient or excess calcium and vitamin D, deficient or excess methylation, selenium deficiency, vitamin K deficiency

Cardiac arrhythmia or palpitations	hypercalcemia, hypochloremia, hypokalemia and hyperkalemia, magnesium deficiency, anemia due to deficiencies of iron, copper, B6, B12, or folate; methylation imbalances
Cardiovascular disease	atherosclerosis and heart disease risk: oxidative stress, deficient or excess calcium and vitamin D, excess phosphorus, and deficiencies of methylation, magnesium, molybdenum, vitamin B6, or manganese; enlarged heart and elevated cardiac output in thiamin deficiency; cardiac insufficiency in selenium deficiency; cardiac failure in iron overload
Cheilosis	deficiencies of riboflavin or vitamin B6
Chest pain	iron overload
Cholesterol, high	deficiency of copper or salt, iron overload
Cholesterol, low	manganese deficiency
Circadian rhythm, disrupted	vitamin A deficiency
Confusion	deficiencies of thiamin or vitamin B6; the delirium of B12 deficiency; hypocalcemia or hypercalcemia, hyponatremia or hypernatremia, acute hypoglycemia in response to potassium on an empty stomach
Conjunctivitis	biotin deficiency; increased risk of eye infections more generally in vitamin A deficiency
Constipation	iodine deficiency, hypokalemia
Cramping	Hyponatremia, selenium poisoning, magnesium deficiency
Dehydration	sodium and chloride deficiency
Depression	deficiencies of niacin, vitamin B6, biotin, methylation, DHA; iron overload, hypercalcemia
Dermatitis	deficiencies of riboflavin, niacin, biotin, manganese, arachidonic acid, or molybdenum
Diabetes	oxidative stress, iron overload, selenium toxicity; as an autoimmune disease, type 1 diabetes risk may be increased by deficiencies of vitamin A, vitamin D, or arachidonic acid
Diarrhea	deficiency of zinc or niacin, excess magnesium or vitamin C, allergy-like reactions to sulfites that result from molybdenum deficiency
Distractibility	excess methylation
Dizziness or lightheadedness	Niacin deficiency; anemia due to deficiencies of iron, copper, B6, B12, or folate; upon standing, due to autonomic dysfunction in B12 deficiency; iron overload, zinc toxicity
Eclampsia	magnesium deficiency
Eczema	See dermatitis.
Edema	hypothyroidism from deficiencies of iodine, selenium, or iron; high salt-to-potassium ratio; edema of the oral cavity, deficiencies of riboflavin or vitamin B6; cerebral edema, hypernatremia
Enamel loss	iron overload
Excessive sweating	manganese deficiency, acute hypoglycemia in response to potassium on an empty stomach
Exercise, poor performance or intolerance	deficient methylation; deficient or excess vitamin K; autonomic dysfunction from vitamin B12 deficiency; shortness of breath on exertion due to vitamin C deficiency, or to anemia resulting from deficiencies of iron, copper, B6, B12, or folate

Eyes, dry	vitamin A deficiency
Fatigue and weakness	deficient methylation, folate and B12 deficiency, hypochloremia, hyperkalemia, hypernatremia, iodine deficiency, iron deficiency and overload, magnesium deficiency, pantothenic acid deficiency, biotin deficiency, phosphorus deficiency, selenium toxicity, sodium and chloride deficiency
Fatty liver disease	deficient methylation, oxidative stress
Fertility and Sex Hormones	deficiencies of vitamin A, vitamin D and calcium, vitamin K, zinc, vitamin E, iodine, or arachidonic acid; iron deficiency and overload
Fibrocystic breast disease	See breast, fibrocystic disease.
Fingernails, white spots, streaks, brittle, falling out	selenium deficiency or toxicity
Food intolerances	deficiencies of vitamin A or arachidonic acid
Gait abnormalities (difficulty walking correctly)	See ataxia.
Glossitis	Deficiencies of riboflavin or vitamin B6.
Goiter	deficient or excess iodine
Graves' disease	excess iodine
Hair and nail growth, slow	manganese deficiency
Hair loss	See alopecia.
Hair, corkscrew-shaped	vitamin C deficiency
Hands and feet, cold	hypothyroidism due to deficiencies of iron or iodine (see also selenium)
Hashimoto's thyroiditis	selenium deficiency or excess iodine
Headache	deficiencies of magnesium or niacin, toxicities of vitamin A or manganese, hyponatremia, histamine intolerance from deficient methylation or copper
Heart palpitations	See cardiac arrhythmia or palpitations.
Heavy metal toxicity, vulnerability to	zinc deficiency
Heart rate, slow	See bradycardia.
Heart rate, fast.	See tachycardia.
Hepatic cirrhosis	iron overload, selenium deficiency and toxicity
Histamine intolerance	copper deficiency, deficient methylation
Hives (urticaria)	See itching (pruritis) and hives (urticaria).
Homocysteine, elevated	deficiencies of methylation, vitamin B6, thiamin, riboflavin, or niacin; see methylation testing for a full explanation
Hypochloridia (low stomach acid)	deficient salt
Hypoglycemia	See blood sugar problems.
Hypothyroidism	deficiencies of iron or iodine (see also selenium),
Immunity to infection, poor	Deficiencies of vitamin A, vitamin D and calcium, vitamin B6, zinc, selenium, iodine, or vitamin C; oxidative stress
Impulsivity	Excess methylation
Inflammation, chronic systemic	Deficiencies of arachidonic acid, DHA, vitamin A, vitamin D and calcium, and vitamin B6
Insomnia and related sleep problems	Methylation imbalances; deficiencies of vitamin A, vitamin D and

	calcium, niacin, vitamin B5, vitamin B6.
Insulin	See blood sugar problems and diabetes.
Itching (pruritis) and hives (urticaria)	flushing reactions to niacin, rare reactions to iodine, allergy-like reactions to sulfites that result from molybdenum deficiency; histamine intolerance from deficient copper or methylation
IQ, low	deficiencies of iron or iodine during childhood
Irritability and restlessness	Deficiencies of vitamin B5 or vitamin B6, selenium poisoning, hypochloremia, hyponatremia, acute hypoglycemia in response to potassium on an empty stomach
Joint pain	iron overload
Kidney stones	a high salt-to-potassium ratio; deficiencies of vitamin A, vitamin B6, or magnesium; both deficiencies and excesses of calcium; excess vitamin D and phosphorus; excess collagen supplementation and vitamin C
Lethargy	See fatigue and weakness.
Leukopenia	copper deficiency
Lightheadedness	See dizziness and lightheadedness
Light therapy, inability to benefit from	vitamin A deficiency
Lips, lesions on the outside of (cheilosis)	deficiencies of riboflavin or vitamin B6
Liver failure	glutathione depletion
Low-Fat and Low-Carb	Improved health on low-fat diets, deficiencies of riboflavin or pantothenic acid; improved health on low-carbohydrate diets, thiamin deficiency
Malabsorption	from an autoimmune condition, deficient vitamin A or arachidonic acid; generalized, from pellagra, niacin deficiency; of many water-soluble nutrients with no intestinal damage, deficient salt
Menstrual problems	See fertility and sex hormones.
Mental and cognitive health	imbalances of methylation and deficiencies of related nutrients, electrolyte imbalances, hypocalcemia and hypercalcemia, deficiencies of thiamin, niacin, and vitamin B6
Miliaria crystallina *(a form of dermatitis resulting from blocked sweat glands that appear as tiny clear bubbles on the skin)*	manganese deficiency
Mouth, lesions in and around	deficiencies of riboflavin or vitamin B6 in cases of cheilosis (lips), angular stomatitis (corners of mouth), glossitis (inflamed tongue), hyperemia and edema of the oral cavity (red, swollen, and bloody inside the mouth); biotin for dermatitis around the mouth; vitamin C deficiency for bleeding gums and other bleeding inside the mouth
Muscle spasms and twitching	Magnesium deficiency, hypocalcemia, hypokalemia, hyponatremia and hypernatremia
Nails	See fingernails, white spots, streaks, brittle, falling out.
Nausea	vitamin A toxicity, too much zinc on an empty stomach, excess copper in drinking water, hyponatremia and hypernatremia, poisoning with iodine or selenium
Neural tube birth defects	deficient methylation
Neutropenia	copper deficiency

Night vision, poor	vitamin A deficiency
Numbness	pantothenic acid deficiency
Nutrient imbalances, vulnerability to	selenium deficiency
Obsessive compulsive disorder	deficient methylation
Optic neuritis	deficiency of thiamin or vitamin B12
Osteomalacia	deficiencies of calcium, phosphorus, vitamin D, or magnesium
Osteopenia	See bone mineral content, low.
Osteopetrosis	See bone mineral content, high.
Osteoporosis	See bone mineral content, low.
Oxytocin, low	vitamin C deficiency
Paleness	anemia due to deficiencies of iron, copper, B6, B12, or folate
Palpitations	See cardiac arrhythmia or palpitations.
Paralysis	thiamin deficiency or hyperkalemia
Paresthesia *(tingling, numbness, or a feeling of something crawling on the skin)*	biotin deficiency, vitamin B12 deficiency, hyperkalemia
Parkinson-like symptoms	manganese toxicity
Parkinson's disease	iron overload
Peripheral neuropathy	deficiencies of thiamin, riboflavin, and vitamin E; toxicity of selenium and vitamin B6
Preeclampsia	magnesium deficiency
Pregnancy, morning sickness	molybdenum deficiency, vitamin B6 deficiency
Pruritis	See itching (pruritis) and hives (urticaria).
Psychological conditioning, difficulty breaking free from	Excess methylation
Puberty, delayed	deficiencies of vitamin A, iron, and zinc
Psychosis	deficiencies of thiamin, niacin, and B12, hypocalcemia and hypercalcemia, hyponatremia
Pustules	zinc deficiency
Respiratory congestion	deficient glutathione
Restlessness	See irritability and restlessness.
Retinopathy *(damage to the eye's retina)*	vitamin E deficiency
Rhabdomyolysis *(damaged muscles spilling their contents into the blood)*	hypokalemia
Rheumatoid arthritis pain	pantothenic acid deficiency
Rickets	deficiencies of calcium, phosphorus, vitamin D, or magnesium
Scurvy	vitamin C deficiency
Seizures	deficiencies of vitamin B1 or B6, hypocalcemia, hyponatremia and hypernatremia, hypochloremia, thiamin deficiency, hypoglycemia
Sense of position and vibration, lost	vitamin B12 deficiency
Sensitivity to cold in general, increased	Hypothyroidism from deficiencies of iron or iodine (see also selenium)

Serotonin, high	copper deficiency
Shortness of breath on exertion	vitamin C deficiency, or anemia due to deficiencies of iron, copper, B6, B12, or folate
Skin aging, faster	Deficient vitamin C or glycine, oxidative stress
Skin and hair, hypopigmentation	copper deficiency
Skin, dermatitis	See dermatitis.
Skin, itching or hives	See itching (pruritis) and hives (urticaria).
Skin, dry patches	zinc deficiency
Skin, hyperpigmentation	iron overload
Skin, scaling	vitamin A toxicity, arachidonic acid deficiency
Sleeping problems	See insomnia and circadian rhythm.
Small intestinal bacterial overgrowth *(SIBO)*	Hypothyroidism from deficiencies of iodine or iron (see also selenium), hypokalemia
Soft tissue calcification	Deficiencies of magnesium, vitamin A, and vitamin K, deficient or excess calcium, excess phosphorus or vitamin D
Sore throat	zinc deficiency
Spasticity *(constant muscle contraction)*	vitamin B12 deficiency
Spasms	See muscle spasms and twitching.
Substance abuse	Excess methylation
Swelling in the face	Hypothyroidism from iron or iodine deficiency (see also selenium)
Tachycardia *(fast heart rate)*	thiamin deficiency, hypermagnesemia, hyperkalemia
Tetany	Deficiency of calcium and vitamin D, or magnesium; excess phosphorus
Thirst	high salt-to-potassium ratio, hypernatremia
Thyroid hormone, resistance to	zinc deficiency
Toxins, vulnerability to	Vulnerability to tissue damage from a wide variety of toxins, selenium deficiency; vulnerability to toxic metal accumulation, zinc deficiency
Tongue, inflammation	See glossitis.
Tremors	hypocalcemia
Triglycerides, elevated	deficient salt
Twitching	See muscle spasms and twitching.
Urticaria	See itching (pruritis) and hives (urticaria).
Visual disturbances	vitamin B12 deficiency, vitamin A toxicity
Wound healing, impaired.	zinc deficiency

How to Ask for My Help With This Cheat Sheet

If you would like to ask me specific questions by email and receive a private response, please use this link. The questions should be precise, specific, and should not contain links, attachments, or details of individual cases that I would have to consider. I charge a small fee for this service.

If you would like to discuss your own case with me or the cases of others you are helping, you may sign up for a single consultation or a consulting package using this link.