A framework for describing nutritional diseases

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Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) that affects more than 2.5 million people worldwide, including 400,000 Americans. Though no cause has been identified in the 140 years since Charcot's identification of MS as a distinct demyelinating disease, epidemiological and heredity studies have strongly suggested an important role of environmental factors in the development of MS. Frequency of MS favors women over men by a factor of 2 to 1. Worldwide, MS develops with greater frequency in populations living at higher latitudes. Studies of medical histories suggest that individuals moving between geographies of high or low incidences before adulthood seem to inherit the ' risk' of the new locale. Results of familial studies indicate that while genetic background plays a role in MS risk, the incomplete concordance between identical twins implies that genetic factors are of limited importance. These studies suggest that environmental stimuli may act as a trigger of pathogenesis in MS.

Nutrition is an often overlooked but profoundly influential element of all areas of human health. The human body has specific dietary requirements and a deficiency or imbalance of a single metabolite can potentially cascade into physically or mentally disabling and even fatal disease. Considering that environmental factors are likely involved in MS and that nutritional requirements influence every bodily function, it is appropriate to consider nutrition as a possible causative factor in MS.

The purpose of this document is to develop a framework for finding possible nutritional triggers of MS by investigating known nutritional diseases and organizing their causes into distinct classes based on their features. Subsequent steps will include analyzing available multiple sclerosis research to determine whether it exhibits features of these classes, and identifying promising areas that warrant further research into nutritional factors and causes of the disease. These classes of interest for understanding nutritional disease pathogenesis are:

- Basis of nutritional diseases
- Nutrient vector
- Nutrient properties
- Pharmacokinetics and pharmacodynamics of nutrients
- Individual and group factors influencing nutritional disease

While non-self agents such as pathogens, toxic agents, or trauma act to alter normal body function, nutritional diseases are unique because they are caused by: (1) a lack or surplus of *necessary* external entities and/or (2) an altered *internal* mechanism for making use of these entities. Understanding nutritional diseases requires describing what these external entities are and why they are important, and understanding the mechanisms of how these entities interact with the body's systems, so that disruptions and imbalances can be translated into malfunctions that lead to disease.

Basis of nutritional disease

Dietitians and nutritionists strive to define quantal or discrete doses of nutrients that fall into the tolerances constrained by deficiency and toxicity. These doses are per nutrient recommendations to fulfill the requirements and maintain the health of the general populace. Imagining all the states of human health as a U-shaped curve with much of the population occupying a low-disease middle blending into exponentially more ailing fringes at each end, nutritional deficiency and toxicity would lay these opposing extremes.

Essentiality is a nutritional concept used to qualify substances that the body requires for proper function but cannot synthesize and thus must ingest. Conditional essentiality is defined in three parts: Decline in the plasma level of the nutrient into a 'sub-normal' range; Appearance of chemical, structural, or functional abnormalities; Correction of these abnormalities by supplementation of the deficient nutrient. All nutrients must, by definition, meet the conditions of essentiality.

A state of **deficiency** may be defined by an insufficient amount of an essential nutrient leading to symptomatic disease. In deficiency, the underlying system is only malfunctioning for want of its required nutrient. Deficiency and its symptoms are alleviated, and often cured, by supplementing the nutrient or altering the diet. Scurvy is a classic deficiency of vitamin C causing tissue hemorrhaging and depressed immune response. It is prevented and cured with consumption of ascorbic acid, popularly known as vitamin C, found naturally in fruits and leafy green vegetables.

- There is a defined nutritional component requiring a minimum intake
- Intake of this component is below minimum level
- Symptoms are corrected by increasing intake above minimum level

A state of **toxicity** may be defined by an excessive intake of an essential nutrient leading to symptomatic disease. It is critical to distinguish, for our purposes herein, nutritional toxicity from the larger and separate domain of general toxicity. *Nutritional toxicity* shall be defined as an excessive amount of a biologically essential nutrient whereas compounds that have no 'natural' place or function within the body shall fall under *general toxicity*. See “Phase 1: Toxic Agents Cure Map Document” for information on general toxicity. Toxic symptoms arise from the burden placed upon the body's systems as it attempts to metabolize or expel the nutrient. Classic toxicity and its symptoms are diminished by reducing the intake and allowing the body to use and excrete the offending nutrient. Hypervitaminosis A among over-supplementing food faddists or arising from consumption of high vitamin liver tissues causes gastrointestinal distress and birth defects. While birth defects from retinoid poisoning are irreversible, other symptoms of toxicity are diminished over time as the body utilizes and depletes existing stores.

- There is a nutritional component with a maximum tolerable dose
- Intake of this component exceeds the maximum dose
- Symptoms are corrected by decreasing nutritional component intake below maximum dose

A state of **imbalance** reflects the interrelated mechanisms of nutrient absorption and use. It combines features of both deficiency and toxicity. In imbalance, associated biochemical processes fundamentally work but may be dysregulated. For example, situations in which an excessive amount of one nutrient impairs, blocks, or antagonizes the natural function of a second nutrient may produce deficiency symptoms when the root cause is actually an excess. Identifying the antagonizing factor and reducing it or supplementing the victimized nutrient often restores healthy state. Vitamin E toxicity from over-supplementation depletes and masks the body's supply of vitamin K. Bleeding symptoms are corrected by administering vitamin K to re-establish depleted stores and maintain equilibrium. Similarly, folic acid supplementation can mask the symptoms of vitamin B_{12} deficiencies. Supplementing with excess vitamin in the case of a cometabolism problem is not always the answer. For example, vitamin D, calcium and magnesium all exist in a delicate balance. If one has deficient vitamin D, then there tends to be deficiency of all three. However, if one has an excess of calcium, magnesium will always remain deficient.

- There are two (or more) nutritional components that interact
- Each of these components have defined thresholds for deficiency and toxicity
- Intake exceeding the threshold of one nutrient adversely changes the level of its sibling nutrient though the intake of the second is normal
- Symptoms may be corrected by altering intake level of antagonizing nutrient towards normalcy or likewise matching the dose of the affected nutrient to the antagonist

A state of **misuse** is a broad category that encompasses multifactorial diseases where the fundamental mechanics of nutrient processing or use have gone awry. It is neither a deficiency-toxicity because the patient ingests the recommended allowance nor is it an imbalance because peripheral nutrients are not out of equilibrium. The specific biochemical or cellular mechanisms necessary to process, use, or excrete a nutrient have been altered causing a nutrient or its daughter compounds to improperly build up within the body. Limiting these aggravating nutrients in the diet prevents toxicity states within the body. Phenylketonuria arises from a genetic miscoding that prevents an enzyme (phenylalanine hydroxylase) from decomposing the amino acid phenylalanine. Levels build up and lead to impaired mental function and retardation. With early diagnosis, progression can be generally prevented and ameliorated by lowering the amount of phenylalanine in the diet.

- A nutritional component interacts with some body system(s)
- This body system is altered in a way to prevent normal interaction
- Intake of the nutrient is within reference threshold but symptoms show abnormal utilization
- Symptoms corrected depending on cause of misuse (see Transformation)

It is important to differentiate the symptoms of nutritional disease and its causes. A primary disease is one directly linked to inadequate or excessive intake. Deficiencies and toxicities are always primary diseases. A secondary disease is one that impairs a pharmacokinetic or pharmacodynamic process hampering the nutrient's use. Misuse diseases are always secondary. Imbalance diseases may be either.

Nutrient vectors

Analogous to the definition of infectious vectors as routes for pathogenesis, we can define vectors that carry nutrients. Nutritional vectors are the means by which a nutrient enters the body. A disruption in a vector causes a deficiency. Vectors may be food, water, artificial supplements, and miscellaneous essential substances.

- **Food** is clearly the predominant vector for nutrient delivery. It is defined in common Western law (US, UK, EU) as “any substance or product, whether processed, partially processed or unprocessed, intended to be, or reasonably expected to be ingested by humans...” Food includes, but is not limited to, plant matter like grasses, grains, fruits, herbs, legumes, nuts, seeds, spices, vegetables and animal matter like dairy products, eggs, fish, insects, meat, poultry, seafood. Exotic foods can be factors in disease as the body is ill prepared to deal with unusual proteins or nutrient levels. Consumption of 500g of polar bear liver can deliver 1,800 times the RDA of vitamin A (9,000,000 IU v. 5,000 IU), a generally lethal dose.

- **Drinking water** is another vector containing both water and trace dissolved compounds. Water (H_2O) is used by the body as a solvent, reaction medium, and transport medium. Minerals are often dissolved as ions in the water in trace amounts. These ionized minerals are often readily absorbed by the body. Excesses of minerals in the diet, including those present in drinking water, can oversaturate the renal system (excretory system including kidneys) causing painful and dangerous kidney stones to precipitate from urine.

- **Supplements** are artificially synthesized or purified nutrients concentrated into pills, powders, or other products. They differ from foods because though they may offer a collection of nutrients, they lack the chemical precursors, cofactors, and enzymes in 'natural' foods as well as any kind of sustenance as an energy source. Though they do not fulfill the conditions of essentiality themselves, supplements contain essential substances that are generally intended to correct for deficiencies or imbalances. Nearly every classic toxicity disease can be linked to food faddists believing that the benefits of a nutrient scales upwards with increasing intakes. Acute, sub-chronic, or chronic mineral toxicities and hypervitaminosis can develop in people who ingest several times the recommended daily intake of a nutrient attempting to draw on its anti-oxidative, immune-boosting, metabolizing, or other properties.

- **Air** is an important vector since it carries oxygen, a component of respiration and other metabolic processes. It also serves as a medium to dispose of metabolic waste gases like carbon dioxide. Excessive oxygen creates highly reactive oxidants that damage and interfere with many bodily functions. Deficiencies of oxygen lead to progressively impaired mental and cardiovascular states and eventually death. Air is also a possible suspension medium for light-weight solid particles which can be inhaled. While these particles may consist of nutritional substances, they are not absorbed in nutritionally significant amounts. Air, as a vector, is better characterized in studies of exposure to toxic and infectious agents than as a source of nutrients for oxygen delivery.

- **Sunlight** carries various types of energy: radio, microwave, infrared, visible, ultraviolet, and x-rays. The earth's magnetic field, ozone layer, or other atmospheric layers filter out most of these energies prior to arrival at the Earth's surface. However, specific ultraviolet wavelengths are able to penetrate to the Earth's surface and interact with energetically similar chemical bonds in many compounds. UV light is a cofactor in the bio-synthesis of vitamin D which is derived from cholesterols. Deficiencies of sunlight-formed vitamin D classically manifests as rickets, with its accompanying bone deformities.

Nutrient properties

Classification of essential nutrients can be divided by their chemical composition and role in the body into vitamins, minerals, energetic molecules, peripheral chemicals, and water. Vitamins and minerals are critical components in larger biochemical processes. Energetic molecules, particularly lipids and carbohydrates, are sought by the body for the amount of energy they release and the ease with which they release it. Proteins are considered energetic molecules since they release energy upon degradation; however, their components are fundamentally important for construction of other proteins in the body. Peripheral chemicals are not traditionally defined as essential, but promote health upon consumption. Water is also not a traditional nutrient but is critically essential to health, and dehydration can have significant physiological effects.

Vitamins are organic (having carbon atoms) molecules distinct from the organic energy molecules of carbohydrates, lipids, and amino acids. They act as cofactors that assist enzymes, or are precursors of important bio-compounds. Most are considered essential nutrients, although Vitamins D, B_5, and K are not completely essential because the body is able to produce limited amounts from intestinal flora and vitamin D precursors need only to be activated by UV light. Vitamins have roles in all body systems, including the neurological, sensory, endocrine, digestive, immune, circulatory, and reproductive systems. Retaining an archaic alphabetic naming convention, some vitamins are specific compounds (ascorbic acid is vitamin C) and others are groups of precursors the body activates (retinyl esters, carotene, and other provitamin A carotenoids become vitamin A).

Vitamins can be differentiated by their solubility in either fat or water. Water-soluble vitamins are broadly distributed as cofactors for enzymes or biochemical processes all over the body. On the other hand, fat-soluble vitamins have specific roles in body systems like vision, bone formation, myelin formation and maintenance and blood clotting, and are largely confined to these systems.

- **Fat-soluble vitamins** include vitamins A, D, E, and K. These vitamins are stored in the fat tissues which are more difficult to deplete than in water. A prolonged deficiency in these vitamins over weeks or months is required to empty body stores. A deficiency of Vitamin D (rickets) is caused by inadequate exposure to sun which causes bone deformities. Supplementation of active vitamin D or increased ultraviolet light UV exposure corrects this disease and its condition in time.
  - Vitamin A functions include vision, wound healing, immune system, gene expression, reproduction and embryonic development, cellular differentiation, myelin formation, and glycoprotein formation. Sources include liver, egg yolk, chicken meat, whole milk, butter, fortified cereals. Deficiencies cause blindness, immunological depression, and dermatological changes. Excessive intake of carotene and other vitamin A precursors causes carotenemia and a yellowing of the skin, but is otherwise harmless. Acute toxicity from a massive dose of active vitamin A causes abdominal pain, nausea, vomiting, and disorientation while chronic toxicity results in joint pain, hyperosis, hair less, and weight-loss.
  - Vitamin D maintains calcium, magnesium, and phosphorus levels in the blood, promotes strong bones and teeth, and is important in immune function. Sources include fatty fish like salmon and fish oils, eggs, butter, liver, and fortified milk. Chronic deficiencies of vitamin D are a factor in the pathogenesis of rickets and its characteristic bone deformities and demineralization. Natural toxicities are rare (save for synthesis defects) and cause hypercalcemia, nausea, and general weakness.
  - Vitamin E is an antioxidant. Antioxidants act to block free radicals which are highly reactive compounds that damage body tissues. Sources include soybeans, sunflower, corn, cottonseed oils, whole grain germs, fish liver oils, and nuts. Rare deficiencies are caused by lipid malabsorption and cause loss of peripheral nerve sensations and coordination, spinal cord degeneration, and other neurological manifestations. Chronic toxicities have not been documented to cause overt symptoms but can cause an imbalance of vitamin K.
  - Vitamin K is a coenzyme for proteins involved in blood clotting and bone metabolism and is a post-translational cofactor for many proteins. Sources include green vegetables and plant oils. Deficiencies cause hemorrhaging but often manifest themselves terminally as is common in babies. Megadoses of vitamin K can block the action of anticoagulants and cause jaundice in newborns.

- **Water-soluble vitamins** include vitamins B_1 (thiamine), B_2 (riboflavin), B_3 (niacin), B_5 (pantothenic acid), B_6 (pyridoxine), B_7 (biotin), B_9 (folic acid), B_{12} (cobalamine), and C (ascorbic acid). While members of the vitamin B complex are distinct chemicals, they retain the B nomenclature because their distinct discoveries in the early 20th century were confused since they are found in many of the same food sources. Because they are water-soluble, unused excesses are excreted in the urine rather than being stored. While this prevents accumulation and makes toxicities extremely rare, deficiencies of these vitamins are more common. Symptoms can appear after a sub-chronic deficiency over several days to a week. Conversely, diseases arising from acute deficiencies of these vitamins present symptoms quickly and are quickly cured, preventing chronic damage.
  - Thiamin (B_1) is a coenzyme in metabolism of carbohydrates, fats, glucose, and branched-chain amino acids and is important in nervous system function. Sources include whole grains, dried legumes, pork, liver, and enriched flour. Beriberi is a classic deficiency present only in the severely malnourished, alcoholics, or food

faddists that causes capillary failure and heart failure or neurological wasting and peripheral nerve damage. Its symptoms are diminished within an hour of administering a supplemental dose of thiamine.

- Riboflavin (B_2) is a coenzyme in redox reactions and other energy metabolism as well as healthy skin. Sources include milk products, eggs, whole and enriched grain products, liver, poultry, fish, and dark-green vegetables (spinach, asparagus). Deficiency generally only occurs with other deficiencies in malnutrition and has indistinct symptoms like sore throat, hyperemia, and edemas.
- Niacin (B_3) is a coenzyme in redox reactions, required for energy metabolism, and is important to the nervous system. Sources include meats, poultry, fish, yeast, whole and enriched grain products, legumes, and nuts. Pellagra is a deficiency disease associated with high intake of maize for protein that results in chronic wasting accompanied by dermatitis, dementia, and diarrhea. Large doses increase the release of histamines and affect hepatic function.
- Pantothenic acid (B_5) is a coenzyme in fatty acid and adrenal gland function. Sources include poultry, meat, whole grains, liver, eggs, kidney, and yeast. Deficiencies are indistinct and generally occur with other vitamin deficiencies, but symptoms can include sore feet, gastrointestinal pain, and fatigue.
- Pyridoxine (B_6) is a coenzyme in the metabolism of amino acids and glycogen, and important in red blood cell production and myelin formation. Sources include meats, poultry, fish, bananas, yeast, bran, and nuts. Deficiencies are rare because of high natural occurrence, but some drugs antagonize absorption or use. Pyridoxine treats a variety of diseases: a genetic disease that prevents the formation of the neuroinhibitor γ-aminobutyric acid, some types of chronic anemia, and homocystinuria. Severe peripheral neuropathies develop after chronically toxic levels including ataxia, clumsiness, and loss of sensation.
- Biotin (B_7) is a coenzyme in the synthesis of fat, glycogen, and amino acids and in CO_2 transport. Sources include liver, kidney, soy flour, egg yolk, cereal, and yeast. Deficiency occurs after prolonged consumption of egg whites, parenteral nutrition, or misuse diseases and tend to resemble fatty acid deficiencies with symptoms like dermatitis, ataxia, and developmental and neurological delays.
- Folic acid (B_9) is a coenzyme in metabolism of nucleic and amino acids, prevents megaloblastic anemia, and is important to growth. It is found in liver, dark-green vegetables, beans, peanuts, whole grains, and yeast. Deficiencies during pregnancy have been implicated in neural tube defects and profound mental handicapping in neonates.
- Cobalamine (B_{12}) is a coenzyme in nucleic acid metabolism; prevents megaloblastic anemia; promotes cell division & growth; oxidizes fatty acids; and maintains nerves by promoting synthesis of myelin sheaths. Sources include meat, poultry, fish, liver, eggs, and milk. Deficiencies of cobalamine imitate symptoms resembling multiple sclerosis such numbness, altered gait, and demyelination, and can chronically result in dementia, neuronal and axonal death.
- Ascorbic acid (C) is a cofactor for reactions requiring reduced copper or iron metalloenzymes, is a protective antioxidant, and assists in wound healing. Sources include citrus fruits and dark-green vegetables. Scurvy is a classic deficiency of sailors, soldiers, and urbanites who do not consume fresh fruits and vegetables; the disease results in hemorrhaging, poor wound healing, and fragmenting buried hairs. Chronic megadoses of vitamin C inhibit vitamin B_{12} absorption and cause rebound scurvy if dosing discontinues.

Minerals are inorganic nutrients. Because the body's transport mechanisms are aqueous, minerals are found in the form of ionic (positively and negatively charged) particles. Metals such as sodium and potassium donate one electron to form monatomic cations, or single positively-charged atoms. Magnesium, calcium and zinc form divalent, or doubly positively-charged atoms. Minerals such as iron (di- or trivalent) and copper (mono- or divalent) can exist in multiple oxidation states; in the example of iron, the trivalent form often deposits in tissue (commonly the CNS) and is thought to induce oxidative damage. Non-metals generally accept electrons and form polyatomic anions, or negatively-charged molecules like sulfate, phosphate, and nitrate. The distinct sizes and electrochemical properties of these ions makes them well suited for roles in highly-specific tasks such as protein structure maintenance, signal transduction, transportation, and enzyme and hormone regulation.

The relative abundance and availability of minerals in the Earth's crust is closely correlated with their use in the body. Chemical precursors to life (self replicating proteins and information-storing sugars) are thought to have precipitated from mineral deposits whose chemical properties protected fragile molecules from the environment as well as provided substrates for growth and increased reactivity. We may classify minerals into three classes based upon their availability in the body: macrominerals, trace minerals, and ultra-trace minerals.

The ubiquity of minerals in all forms of ingested matter makes the study of their diseases unique because of their pervasive and specific roles in body systems. Pervasiveness in nature is reflected in the level of integration in diverse bodily functions. It is difficult to pinpoint mineral deficiencies since many minerals may functionally imitate and thus compensate for deficient minerals. Since their functions are so closely related, the symptoms observed in a deficiency of one mineral may actually be a result of an imbalance. Regardless, there are recommended daily intakes based on deficiency studies and mineral availability in a standard diet.

- **Macrominerals** compose more than 10 g of total body weight and require daily intake. Macrominerals play critical roles in large body systems such as the skeletal and nervous systems. Many are prevalent in chemicals that are present in every cell, and play a critical role in maintaining electrolytic balance in and out of the cell. Found at the center or active sites of proteins or enzymes, they provide current to run reactions.
  - <u>Calcium</u> has a profound structural and mechanical role in the bones and teeth. It is also a co-factor in protein folding and an intracellular messenger, particularly in the scenario of neurotransmission. Sources include milk products and dark-green vegetables. Calcium deficiency has been implicated in the onset of osteoporosis.
  - <u>Phosphorus</u> is present in bones with calcium as hydroxyapatite, phospholipids and cellular membranes, energy molecules like adenosine triphosphate (ATP), and many enzymes and proteins, and is critical to the backbone of DNA and solution buffers important in the regulation of pH levels. Sources include meat, milk products, and grains.
  - <u>Magnesium</u> is an active co-factor in many metabolic reactions, is found at enzyme active sites, forms complexes with many organic compounds and proteins, is an electrolyte, and is involved in ATP energy cycles. Sources include green vegetables, nuts, seeds, whole grains, and meats.

- Sulfur (covalent) is found in cysteine and methionine and is active in hemoglobin, hormones, and antibodies.
- Potassium is a common electrolyte and involved in neurotransmission. Sources include milk, fruits, vegetables, fish, meats, and poultry.
- Sodium is a common electrolyte and neurotransmitting factor. Sources include salt, cured meats, cheeses, and other preserved and processed foods.
- Chloride is a common electrolyte, neurotransmitting factor, acid, and enzyme component. Found with sodium in salt, other sources are preserved and processed foods.

- **Trace minerals** are those minerals that compose between 1 mg and 10 mg of total body weight. While many have recommended daily intakes, deficiencies are rarely observed outside of gross malnutrition or food faddism. Trace minerals are nevertheless essential nutrients and have specific roles in the body. Iron, zinc, copper, manganese, selenium, cobalt, and molybdenum have been found as components of numerous enzymes. Chromium and iodine are crucial in regulating hormone function. Silicon, fluoride, boron, and aluminum are active in bone formation. Selenium is an active antioxidant.
    - Iron is a component of hemoglobin and many other enzyme active sites. Sources include liver, red meat, whole and enriched grain products, beans, nuts, and dark-green vegetables. Deficiencies cause anemia and toxicities lead to hepatic failure, diabetes, cardiomyopathy, and peripheral neuropathy. Iron is also important to immune function.
    - Zinc is a structural component of biomembranes, is necessary for myelin formation and stability, assists protein folding, is present in the active site of many proteases, regulates gene expression, and activates lymphocytes. Sources include shellfish, meat, poultry, cheese, whole grains, beans, and nuts. Deficiencies retard growth and cause dermatitis, immunologic dysfunction, and reproductive malformations.
    - Copper is involved in the formation of many enzymes, metabolic co-factor production, collagen and elastin formation, myelin formation and stabilization, and pigment development. Sources include crab meat, fresh vegetables and fruits, nuts, seeds, and legumes. Deficiencies cause anemia and retard growth while toxicities cause hepatitis and renal dysfunction.
    - Iodine is a component of thyroid hormones and strongly prevents goiter and cretinism. Sources include iodized salt, fortified foods, and marine foods.
    - Selenium integrates into amino acids, is an antioxidant, and stimulates immune responses. Sources include liver, kidney, seafood, cereal, and eggs.
    - Chromium is a component of a protein regulating glucose levels in the blood. Sources include cereals, meat, poultry, fish, and yeasts.
    - Manganese is a component of several metalloenzymes and a co-factor for activating others. Sources include legumes, tea, and whole grains. Deficiencies cause bleeding disorders and toxic levels can lead to symptoms similar to encephalitis, Parkinsonism, and psychoses.
    - Molybdenum is an enzyme cofactor and component of metalloenzymes. Sources include legumes and grains.
    - Nickel may be an enzyme component and involved in vitamin B_{12} and folic acid absorption. Sources include legumes, chocolate, cereals, and sweeteners.

- **Ultra-trace minerals** encompass the remainder of low-abundance elements in Earth's crust. These have no recommended intake because deficiency studies yield inconclusive results concerning their essentiality. Some ultra-trace minerals are found in higher concentrations in certain tissues than in surrounding mediums. Because it is not evenly distributed by diffusion this means the body has absorption or expulsion pathways specific to these elements. This further suggests that the mineral may have some, as yet undiscovered, function within the body.

- Arsenic may have a role in enzymatic reactions, regulation of gene expression, and metabolism of the amino acid methionine. Sources include milk products, fish, meat, and grains.
- Fluoride protects against demineralization of calcified tissues, but is not essential. Sources include fluoridated water, fortified foods, and marine foods.
- Vanadium appears to mimic the effects of insulin, affect cell proliferation and differentiation, protein and enzyme component, and transmembrane signaling. Sources include mushrooms, peppers, and seeds.
- Silicon is found in areas of active growth in bones and collagen.
- Boron may regulate metabolism and may affect cell membrane function.
- Lithium and germanium may affect neurotransmission.
- Mimicry. Some minerals like rubidium, strontium, and tungsten replace or displace more common electrochemically similar metals like potassium, sodium, calcium, and molybdenum. The larger-scale biological consequences of these processes are uncertain, and difficult to understand.

All the processes and mechanisms of the body require energy. So far, we have considered vitamins and minerals as central to nutrition, but energy further meets the conditions of essentiality. In the classic five kingdoms of zoology, animals are generally distinct because they cannot generate their own energy (through photosynthesis or otherwise) like most plants, fungi, protists, and bacteria. Instead, animals rely upon ingestion of plants or other animals for their supply of energy. Plants and animals provide three broad types of energy: carbohydrates, lipids, and amino acids. It is important to note that these biomolecules are not solely energy sources but have other functional roles as well. The body uses carbohydrates for the ease with which they release energy, lipids for their high energy storage capacity, and proteins depending upon the body's physiological stress level.

Carbohydrates are the body's favorite energy source to use. While carbohydrates have a lower energy density than lipids, they are readily converted into the body's energy currency, glucose. Glycolysis, citric acid cycle, and oxidative phosphorylation are three metabolic pathways for carbohydrate catabolization. Carbohydrates are defined by a near 1:2:1 ratio between carbon, hydrogen, and oxygen atoms in each molecule. Carbon-oxygen bonding groups are found internally as ketones or terminally as aldehydes. Carbohydrates can be differentiated by chemical differences (occurrence) and variations in size (types).

- **Types**
  - Monosaccharides are the smallest carbohydrates. Ribose, glucose, galactose, and fructose are monosaccharides. Glucose is the basic metabolized carbohydrate found in the blood. Fructose is a carbohydrate found in fruits and is one of the sweetest natural sugars.
  - Disaccharides form from glycosidic binding between two monosaccharides. Disaccharides are intermediate sized carbohydrates like sucrose, lactose, and maltose. Sucrose and maltose are sweeteners and lactose is present in dairy products.

- Oligosaccharides and polysaccharides are macromolecules of more than three monosaccharide units. These very large groups of monosaccharides may be linear or branched. Starch, cellulose, and glycogen are large polysaccharide molecules.
- **Occurrence**
  - Starches are abundant in potatoes, rice, wheat, and maize.
  - Glycogen is a highly branched polysaccharide of glucose stored by animals.
  - Sugars contrast with starches in both size and taste. Sucrose disaccharides have a very distinctive and desirable taste and are found in cane, beet, and many fruits and become fructose and glucose. Animals, including humans, are evolutionary hard-wired from birth to seek out sugars because their taste, imitated in milks, indicates a ready and safe source of sustenance.
- **Use**
  - We've described glucose as an energy currency because plants and animals use and store it for many energetic functions, the most important being metabolic oxidation. Glucose is stored as glycogen in animals and as cellulose in plants. The brain and muscles like the heart use glucose as their primary energy source. Excess glucose is stored in liver, muscles, and kidneys as glycogen. Humans are able to digest starches and glycogen into glucose but lack cellulase enzymes to digest cellulose, also known as fiber. Human diets have thus shifted away from high-cellulose foods to embrace diets rich in starches and glycogen. Unlike lipids, glucose is hydrophilic which makes it impermeable in phospholipid cell membranes. It requires proteins called facilitative glucose transporters and Na^+-glucose cotransporters to move across cell membranes.
- **Diseases**
  - Diabetes is an inability to process blood sugars because of deficiencies of or resistances to insulin. Chronically elevated glucose plasma levels lead to cataracts, renal failure, and heart disease.

Lipids are hydrophobic organic molecules consisting of long chains of carbon molecules. Their hydrophobic property arises from the fact that they have a polar head and non-polar chains of fourteen to twenty-four carbon atoms surrounded by hydrogen atoms. We will consider four subtypes when defining lipids: fatty acids, phospholipids, triglycerides, and steroids. Occurring in both animal and plants, these molecules have very diverse structures because the bonds between carbons allow a considerable degree of structural freedom. Bonds have the effect of contorting the shape of the chain, imbuing lipids with completely different chemical and biological properties. Their metabolic fate depends on their length, the number of double bonds, the location of double bonds, and their orientation (see Chirality under Proteins).

- **Types**
  - Fatty acids are the simplest constituent of lipids (monoglyceride) consisting of a nonpolar open hydrocarbon chain and a polar carboxyl group. Generally, natural fatty acids have even numbers of carbons.
    - There are two essential polyunsaturated fatty acid types. They have various naming mechanisms, but an important nutritional classification describes the location of a double bond from the end of the carbon chain (omega carbon): a double bond three carbons away from the end is omega-3 and six carbons away from the end is omega-6. These essential fatty acids are linolein and arachidonic acids (omega-6) and linolenic, eicosapentaenoic, and docosahexaenoic acids (omega-3).

    - Saturated fats have only single bonds between the carbon atoms on the chain. These are solid at room temperature and have high melting points.
    - Trans fatty acids are the results of industrial processes that reacts unsaturated fatty acids to become more saturated, improving taste, stability, and shelf life.
    - Monounsaturated fats have a single double bond between carbon atoms on the chain and are liquid at room temperature.
    - Polyunsaturated fats have more than one double bond between carbon atoms on the chain.
  - Phospholipids are structurally similar to fatty acids with only the carboxyl group replaced by a phosphate group. This monoglyceride is best known for its role in cell membranes in the form of phospholipid bilayers. Compounds like lecithin (phosphatidylcholine), phosphatidylglycerol, phosphatidylinositol, phosphatidylserine, and phosphatidylethanolamine are all phospholipids found in various body tissues. Phospholipids are commonly found as components of triglycerides with fatty acids.
  - Triglycerides are esters (combinations of organic acids and alcohols) of three monoglycerides (fatty acids or phospholipids) joined at the carboxyl end (organic acid) to a glycerol (alcohol) backbone. The final structure forms an 'E' shaped macromolecule with the vertical glycerol binding the three monoglycerides together. The fatty acids and phospholipids may consist of different types and different chain lengths.
  - Steroids differ from the previous lipid subtypes because it does not have a chain structure. Steroids have four fused carbon rings (cyclopentanophenanthrene ring) forming a chemical skeleton upon which different combinations of functional groups may attach. These combinations of functional groups give rise to cholesterols, hormones, corticosteroids, and many others which are stripped, and then converted into various forms through enzyme activity. Vitamin D is formed from cholesterol, and many other fat-soluble vitamins are daughter molecules to cholesterol.
- **Occurrence**
  - Saturated fats are found in meat, poultry, dairy foods, palm oil, and coconut oil
  - Trans fats are found in commercially processed foods: fried foods, baked foods, snacks, margarine, and shortenings.
  - Monounsaturated fats are found in olive oil, peanut oil, canola oil, nuts, avocados, olives
  - Polyunsaturated fats are found in corn oil, soybean oil, safflower oil, sunflower seed oil, and fish.
  - Triglycerides are the most consumed group of dietary lipids. Triglycerides are found in adipose (fatty) tissue, butterfat, animal lard, and oils.
  - Cholesterol is synthesized by the liver or ingested from animal products.
- **Use**
  - Energy storage medium. Lipids store as many as 8 kilocalories in each gram. The body greatly prefers this form of energy storage which demonstrates while reviled adipose tissue may be so excessively prevalent.
  - Transportation medium. Non-polar chemicals, especially hydrophobic vitamins, can only be transported and stored with lipids.
  - Cellular structure. Phospholipids form cellular membranes. Very-long chain fatty acids are found in the brain, retina, and spermatozoa.

    - Chemical template. Steroids undergo biotransformations into cholesterol, hormones, and vitamins (Vitamin D especially).
- **Disease**
    - Chronically high intake of saturated and trans-saturated fats increase LDL (bad cholesterols) and decrease HDL (good cholesterols) levels. Cholesterol levels and high fat intake have both been linked to increased risk of heart disease.

Amino acids form the final class of energetic molecules. Their name comes from the fact that they have a nitrogen-containing amine group which can bind to carboxyl (C = O) groups. Proteins' significance is primarily transformational because they are involved in nearly all body processes and their catabolism into amino acids just happens to be energetically favorable. Long chains of individual amino acids become proteins and have an incredible ability to fold into many functional shapes to become enzymes, cellular signals, and biochemical structures. They are the body's least favored energy source because they contain less energy per gram than fats, are more difficult to digest than carbohydrates, and their conversion to glucose and glycogen generates toxic ammonia requiring further conversion (urea cycle) for expulsion. For this reason, amino acids are neither an accessible energy source like carbohydrates nor a significant energy reservoir like fats, but functionally essential building blocks to all body processes. Humans combine an 'alphabet' of twenty amino acids to form all proteins.

- **Types**
    - Essential. Tryptophan, lysine, methionine, phenylalanine, threonine, valine, leucine, and isoleucine. The body is unable to synthesize these amino acids and requires their intake.
    - Non-essential. Glycine, glutamine, proline, serine, alanine, asparagine, aspartic acid, glutamic acid. These are synthesized by biotransformations from other amino acids or chemical compounds. Phenylalanine, an essential amino acid, is biotransformed into tyrosine, which is partially essential.
    - Partially essential. Tyrosine and cysteine are semi-essential as the body may not always produce sufficient quantities to meet demand. Arginine and histidine are also considered essential for children but this requirement drops in time as either the body's demand abates or new biochemical pathways allow for synthesis.
    - Chirality. Some compounds can have the exact same chemical formula but different structures based upon the orientation of chemical groups around a central carbon atom which can produce very different reactions. Just as one hand is not symmetric about any axis, if a chemical group switches sides in some molecules, they become mirror images of each other and develop different chemical properties (chirality). Amino acids are chiral molecules. The “left-handed” (L) or “right-handed” (D) molecules are each equally likely to be synthesized, but in nearly all living things, only left-handed amino acids are used. The mechanisms that ensure this selective production and metabolic fate of unusable D-amino acids are poorly understood processes.
- **Occurrence**
    - Complete protein sources containing all essential amino acids are primarily found in animal sources like meat, poultry, fish, eggs, and dairy products.
    - Incomplete proteins do not contain all the essential amino acids, but are nutritionally important because they tend to be low in fat. Sources include cereals, grains, legumes, and vegetables.

- **Use**
  - Energy. Proteins differ from lipids and carbohydrates because they introduce nitrogen into the diet. Peptide bonds between amino acids are metabolized to meet energy needs at higher metabolic states. Infection and injury are two disease states that yield increased metabolism, oxidation of amino acids, and promoted loss of nitrogen byproducts in urea. Increased nitrogen loss in urine thus indicates the presence of a disease state requiring hypermetabolization of proteins. An inability to process (by digestion, absorption, biotransformation, or transportation) proteins or amino acids can cause accumulation, and leads to toxicity.
  - Enzymes. Proteins that assist and increase the rate of production of other chemicals are enzymes. Interactions between amino acids within a protein cause it to collapse and fold on itself into a specific shape. Pockets and cavities called active sites have a defined shape and sequence of amino acids necessary to attract, attach, and react with specific parts of molecules. These reactions can greatly increase the availability of products and eliminate harmful reactants. However, active site conformations can be extremely sensitive to change, and the substitution of chemically analogous structures into the active site, or mutations of even one amino acid can render the entire protein useless. Substitutions outside the active site have also been found to affect function in certain enzymes.
  - Transportation and signaling. Similar to enzymes, proteins involved in transportation and signaling can bind to specific molecules, particularly receptors, because of their unique shape. Once bound, these proteins may undergo an electrical, chemical, or structural change; these changes can significantly affect the behavior of other proteins. Hemoglobin binds oxygen and carbon dioxide in the blood, seratonin is a neurotransmitter, and major histocompatibility complexes reveal the presence of pathogens to the immune system. Like enzymes, signaling and transportation proteins can be rendered useless by mimetic chemicals or misplaced amino acids.
  - Structures. The largest source and destination for proteins in animals is muscle where long sheets of amino acids act in concert to mechanically contract. These contractions enable environmental mobility, cardiovascular function, and digestive processes. Proteins linking cells together can increase strength. Proteins also form the bone matrices into which calcium and phosphorus are deposited for strength.
- **Disease**
  - Abetalipoproteinemia is a genetic disease affecting lipid transport proteins in the circulatory system. It prevents the body from absorbing and using fat and causes ataxia (uncontrollable muscle movements) and peripheral neuropathy (loss of senses in limbs). It is treated with vitamin E whose antioxidant properties may come to bear on biochemical processes that modify proteins.
  - Protein-energy malnutrition (also PEM, kwashiorkor, or marasmus) is a clinical name for a state of overt malnutrition. Depletion of body fat stores, decreased muscle mass, multiple vitamin deficiencies, lethargy, blunted immune response, and sub-normal blood hormone levels are all symptoms. The primary form, of course, results from insufficient nutrient intake while the secondary form is associated with chronic wasting diseases like malignancies, malabsoption syndromes, AIDS, and renal failure. It is treated with improved diet and supplementation.

Peripheral chemicals or phytochemicals are interesting because they have no associated deficiencies, but their consumption has been clinically shown to protect humans from disease. These chemicals appear to be evolutionary responses developed to protect a specific organism from environmental insult; it appears that this results in benefit to humans as well. Phytochemicals limit damage induced by oxidation, pathogens, toxic agents, and malignancies while promoting immune function, all functions that can increase both health status and longevity. Some phytochemicals inhibit certain aspects of health, but overall this class of chemicals could potentially be applied as treatments of some diseases. Because this is a new field of study, we include a subtopic on issues that must be addressed to determine their potential.

- **Types and occurrence**
  - Catechins. These natural polyphenol antioxidants found in green tea strongly protect against red blood cell hemolysis and block tumor-stimulating enzymes.
  - Phytoestrogens. Found in soybeans and other soy products, phytoestrogens have three known classes which are isoflavones, coumestans, and lignans. They all structurally resemble natural estrogen and antiestrogens.
  - Lactoferrin. This iron transport protein, derived from animal products, resembles transferrin. Lactoferrin binding sites have been found on a variety of cells, but their specificity is unknown. Lactoferrin may have antimicrobial properties, enhance immune response, and have natural killer cell function.
  - Carotenoids. Carotene and xanthophylls are lipoprotein-delivered phytochemicals that have a demonstrated antioxidant and possible anticarcinogenic effect.
  - Flavonoids*.* Composed of a number of related compounds with a basic three ring structure with varying functional groups, chemicals in this class have demonstrated antimutagenic and anticarcinogenic properties.
  - Isothiocyanates*.* The volatility of isothiocynates contributes to the distinctive odor and flavor of cruciferous vegetables like cabbages and turnips. Their anticarcinogenic properties stem from their ability to enhance detoxification and inhibit activation pathways around the time of exposure to carcinogenic substances.
  - Diallylsulfides. Allium vegetables like garlic, onions, scallions, and chives generate organic sulfur molecules when cooked. These plants have been incorporated in traditional remedies for centuries because of their antibiotic and antithrombotic activity. More recent research has demonstrated their anticarcinogenic properties as well.
  - Monoterpenes. Citrus oils like orange peel oil and limonene have been demonstrated to reduce incidences of many types of cancers in animal models.
- **Use**
  - The mechanisms of phytochemical metabolization are poorly understood in general. They have been shown to have properties that include: antioxidation, protein phosphorylation, antiinflammation, anticarcinogenic, cell cycle regulation, protein kinase regulation, angiogenesis regulation, and estrogenic/antiestrogenic activity among others.
- **Issues**
  - Identifying more phytochemical classes and their physiological associations
  - Defining effective dose response and range: anticarcinogenic response and toxicity
  - Characterizing absorption and bioavailability
  - Researching cellular-level binding proteins, uptake mechanisms, metabolic products
  - Investigating variability among population groups: age, sex, health status, race, culture

Water is a critically essential nutrient requiring an intake of approximately 2 liters every day. It provides structure to body cells, is a medium for body processes, is involved in chemical reactions, and lubricates joints among other processes. Water is highly regulated within the body and dehydration, heat exhaustion, and heat stroke can occur with the loss of as little as 5% of body stores. Sources include drinking water, beverages, fruits, vegetables, and milk products.

Pharmacokinetics and pharmacodynamics of nutrients

Pharmacokinetics refers to the characteristics of drug or nutrient absorption, distribution, biotransformation, and excretion. In the case of nutrition, we will consider pharmacokinetics as processing of the nutrient. The processes of digestion, absorption, distribution, and excretion all have complex synergistic and antagonistic interactions with each other, and with other body systems. A malfunction in any one of these processes can upset the highly regulated body nutrient levels to quickly induce a disease state.

We will address the organs involved, specific processes, and examples of diseases afflicting the organs or processing.

Digestion encompasses the processes that break down vectors into usable nutrients. Mechanical action and enzymes in every organ of the digestive system reduce food into its building blocks of vitamins, minerals, and energy molecules.

- **Organs**
  - The mouth is the entry point for food, water, and supplements. It initiates digestion by mechanically breaking down food. The secretion of saliva further dissolves food particles and contains enzymes that can begin the chemical breakdown of nutrients.
  - The stomach is the cornerstone of the digestive system. Food is routed directly to the stomach from the mouth and esophagus. The extremely acidic environment and mechanical agitation ensure that ingested foods are reduced to small particles that can be readily absorbed. Only after the stomach excretes its dietary contents does the full spectrum of bodily processes come into play to digest and absorb specific compounds.
  - The liver has multifaceted roles in digestion, absorption, storage, and transformation. It produces bile from red blood cell components and waste cholesterol to emulsify fats for digestion. Bile is secreted into the gallbladder and duodenum of the small intestine.
  - The pancreas is an exocrine and endocrine digestive chemical factory. It produces enzymes for digestion and absorption like gastrin and secretin as well as important regulatory hormones like insulin and glucagon. Diabetes mellitus is a disease of excess blood sugar levels linked to an inability of the pancreas to secrete sufficient insulin.
  - The gall bladder stores bile secreted by the liver and releases it into the small intestine. Bile and its lipid components can solidify creating gallstones that cause intense abdominal pain. Gallstones blocking the bile duct connecting the

gallbladder and small intestine can cause jaundice, liver damage, and lipid malabsorption.

- **Processes**
  - Regulation. Organs release hormones into the bloodstream that stimulate secretion of chemicals and signal the brain. Gastrin causes the stomach to secrete acid as well as encourages the growth of linings for the stomach, small intestine, and colon. Secretin induces secretion of bicarbonate digestive juices from the pancreas, fat-emulsifying bile from the liver and protein-cutting pepsin from the stomach.
  - Vitamins. Water-soluble vitamins are freed from dietary particulate by stomach acids. Fat-soluble vitamins can only be absorbed with the fat particles in which they are transported. Some vitamins, like vitamin C and parts of the B complex, are extremely sensitive to degradation by heat, sunlight, acidity, or other processes common in modern food processing and storage.
  - Minerals. Some minerals are readily freed by the highly acidic stomach environment into ions which are small enough to passively diffuse into absorptive endothelial cells in the small intestine. Minerals bound to proteins within organic molecules require specific pancreatic enzymes to transform into effectively digestible forms. Minerals can compete for these enzymes and antagonize further absorption. These interactions have been observed between calcium and magnesium and between iron, zinc, and copper.
  - Carbohydrates. Large, complex carbohydrates are broken down by amylases secreted in the saliva into simpler di- and trisaccharides. Stomach acids render salivary amylases inert and remaining starches and glycogens are further digested in the duodenum by pancreatic amylases.
  - Lipids. Nonpolar substances, lipids included, are unaffected by the highly acidic stomach. They cannot be digested until they are emulsified (made soluble in water) with bile salts made by the liver, stored in the gall bladder, and secreted into the small intestine.
  - Proteins. The large structure of proteins allows them to be denatured (deformed) in the acidic stomach, cleaved by the protein-splitting enzyme pepsin, then moved to the small intestine where pancreatic enzymes like trypsin, chymotrypsin, and carboxypeptidase break remaining proteins into their constituent amino acids.
- **Diseases**
  - Ulcers occur when excessive acid is excreted and effectively overloads the protective mucous lining of the stomach, damaging the underlying tissue causing sharp burning pains in the stomach.

Absorption is the process following digestion where digested material crosses cellular membranes into tissues. The digestive system acts to absorb, as well as digest and free, nutrients.

- **Organs**
  - The small intestine, consisting of the duodenum, jejunum, and ileum, with a surface area exceeding 200 square meters is designed for absorption.
    - The duodenum absorbs Vitamins A and B_1, iron, calcium, glycerol, fatty acids, amino acids, and simple carbohydrates (di- and trisaccharides) .
    - The jejunum absorbs monosaccharides, amino acids, fatty acids, glycerides, copper, zinc, potassium, calcium, magnesium, phosphorus, iodine, iron, and vitamins D, E, and K, most of the B complex, and vitamin C.

    - The ileum absorbs sodium, potassium, chloride, calcium, magnesium, phosphorus, iodine, vitamins C, D, E, K, B_1, B_2, B_6, $B_{12,}$ and water.
    - The colon absorbs sodium, potassium, water, acids, gases, and short-chain fatty acids, and contains bacteria (intestinal flora) secreting biotin and vitamin K.
- **Processes**

  There are four cell types in the small intestine: absorptive enterocytes, goblet cells, Paneth cells, and enteroendocrine cells. Absorptive enterocytes digest small polypeptides (amino acid chains), disaccharides, vitamins, and minerals with the digestive enzymes that lie upon the surfaces of these cells. Goblet cells secrete mucus that serves as a lubricant and protective barrier to marauding infectious agents. Paneth cells have an immunological function by secreting protective proteins and enzymes. Enteroendocrine cells are involved in gastrointestinal hormone mediation which can stimulate secretions and gastrointestinal muscles. Absorption occurs through four different mechanisms:
    - <u>Active transport</u> requires energy (ATP) and a carrier protein to move a nutrient against a gradient, from a low concentration into a high concentration. Carriers are specific to their nutrient: retinol binding proteins carry only vitamin A, whereas lipoproteins carry only lipids and the fat-soluble vitamins within them. Water-soluble vitamins require coenzyme complexes and involve active carriers to transport across cell membranes in small concentrations. Malfunctions of carrier proteins, transmembrane signals, or enzymes are factors in malnutrition or deficiencies of these vitamins. The sodium transporters actively transport glucose against the gradient. These are expressed most prominently in the absorptive enterocyte cells of the small intestine and proximal tubules of the kidney.
    - <u>Passive diffusion</u> describes the free movement of small nutrients, like minerals, along gradients to equalize concentrations across membranes. Supplementation floods the digestive tract with free vitamins that can passively diffuse into cells down the gradient into the cell.
    - <u>Facilitated diffusion</u> moves nutrients against a gradient and requires carriers like active transport but is a low energy process like passive diffusion. Fat-soluble vitamins require bile salts for solubility and absorption into cells. Disorders involving bile salts or packaging of lipids into transportable chylomicrons can lead to A, D, E, and K deficiencies.
    - <u>Phagocytosis</u> is the engulfment of large molecules, like fats, by expanding the cell membrane around the nutrient and engulfing it.
- **Diseases**
    - <u>Malabsorption</u>. The complexity of these processes leaves ample room for problems. Malabsorption diseases have multifactorial causes and inevitably lead to nutritional deficiencies. Physical blockages, trauma, infectious agents, existing nutritional deficits, over- or underproduction of digestive enzymes, carrier-binding protein malfunctions, and poor peristaltic muscle function are all capable and identified factors in malabsorption.
    - <u>Celiac disease</u> is a genetic disease causing an autoimmune response that leads to malabsorption. Gluten is a protein found in wheat, rye, and barley. A genetic defect causes the body to react to gluten in intestinal cells by attacking the cells as though they were a pathogen. Symptoms including fatigue, cramping and gastrointestinal pain and distress are treated by eliminating gluten-containing foods from the diet.

    - Wilson's disease causes patients to store excessive amounts of copper in their tissues. The diseases can be treated with large doses of zinc to interfere with copper absorption.

Distribution describes how the body transports nutrients to their target tissues, organs, and systems after they have been digested and absorbed. This is accomplished by the circulatory system which uses the blood stream's vast network to deliver nutrients and energy and remove waste. The lymphatic system is the immunological circulatory system and it also has a role in slow circulation of fats from the small intestine.

- **Organs and systems**
    - Blood. Blood is a unique fluid (mixture, suspension, and solution) containing hemoglobin-carrying erythrocytes, thrombocyte binding platelets, leukocyte immune cells, binding proteins like cholesterol-carrying lipoproteins, hormones, and free nutrients like glucose. Arteries carrying oxygen-rich blood from the lungs pass through the heart, spread out into capillary beds in tissues and organs where decreased flow and increased surface area allows transmembrane transportation of these substances into and away from the local tissues before converging into veins to carry away waste.
    - Lymph. The lymphatic system is the utilitarian alleyway to the body's cardiovascular expressway. Consisting of lymph from the blood plasma lost by capillary beds, lymphocytes, and fats, this passive circulatory system filters foreign matter from the body. The spleen, thymus, and bone marrow are key tissues or organs that produce the immune cells that fill the lymphatic vessels. Lymph nodes are honeycombed filters filled with lymphocytes that protect us from disease. Their uneven distribution throughout the body reflects their role in preventing disease by centering around passageways and tissues that interface outside of the body such as the upper respiratory tract, small intestine, urinary tract and major arteries in the neck, arms, and groin. Lymphatic vessels are attached directly to the small intestine through Peyers patches. These intestinal lymph nodes play an immunological role by preventing invading bacteria from entering the blood stream and in the movement of lipids by transporting chylomicrons.
- **Processes**
    - Vitamins. Fat-soluble vitamins are transported in the blood plasma within chylomicrons and lipoproteins. Water-soluble vitamins bind to plasma carrier proteins like albumin which circulate throughout the blood.
    - Minerals. Some minerals have specialized transport proteins like transferrin and lactoferrin (iron) or ceruloplasmin (copper). Other minerals, like zinc, circulate with albumin or macroglobulins, or are bound to amino acids.
    - Carbohydrates. Facilitative transporters called glucose transporters, or GLUT, bind glucose and transport it by diffusion along concentration gradients (high to low). These facilitated-diffusion proteins are found in many tissues, but specifically concentrated in certain organs: GLUT 1 in the red blood cells; GLUT 2 in the liver, kidney, and intestine; GLUT 3 in the brain; GLUT 4 in muscles and fat; and GLUT 5 in the small intestine. Dysfunction of these glucose transporters in mouse models have been implicated in the development of diabetes and obesity.
    - Lipids. The non-polar chemical properties of lipids means transportation can only occur through interactions with binding proteins called lipoproteins. Triglycerides and cholesterol esters are packaged with fat-soluble vitamins into the lipid core of lipoproteins. Lipoproteins come in many sizes and are covered with different types of apoproteins which determine their biological function: chylomicrons are the

largest lipoproteins followed by very low density lipoproteins (VLDL), low density lipoproteins (LDL), intermediate density lipoproteins (IDL), and high density lipoproteins (HDL). Chylomicrons are secreted into the blood stream subsequent to intestinal absorption, and deposited in adipose tissue as free fatty acids or converted to VLDL in the liver. From the liver, receptors in tissues around the body recognize apoproteins on the surface of the VLDL and strip lipids from the lipoproteins to increase the density (LDL, IDL) and to modify or attach new apoproteins. HDL is a cholesterol-starved lipoprotein which binds readily to free or excess cholesterol secreted by cells to create IDL and LDL, which can be returned to the liver or reused.

  - Proteins. From their absorption, amino acids are routed to the liver where biotransformations occur, then are distributed to the muscles, blood plasma, and organs. There they serve as preformed building blocks (in the form of conjoined amino acids) within a cell until they are required for translation of messenger RNA sequence into a string of amino acids.
- **Diseases**
  - Anemia is a disease of erythrocytes (red blood cells) often caused by nutritional deficiencies. A microcytic (decreased cell count), normocytic (normal), or megaloblastic (enlarged cell size) anemia prevents an adequate amount of oxygen from reaching the tissues. Deficiencies of iron can result in microcytic anemia; vitamin B_{12} or folic acid deficiencies lead to megaloblastic anemia. Symptoms like fatigue and shortness of breath are treated and the deficiencies cured with appropriate diagnosis and supplementation of the deficient nutrient.
  - Glucose-Galactose malabsoption is a rare inborn error of the Sodium-Glucose Transport (SGLT-1) protein producing severe diarrhea that is only treated by removing these monosaccharides from the diet.

Transformations of precursor chemicals into specific, necessary compounds are quintessential biochemistry. Intrinsic to every chemical compound is a minimum amount of energy necessary to activate or transform them into other metabolites. Enzymes are chemical compounds that can trigger chemical reactions by acting, in conjunction with reactants, to lower activation energy of a reaction; this results in an increased number of molecules having the necessary energy to transform, and thus can result in an increased rate of the reaction.

Because body compounds are derived from non-specific molecules like amino acids and cholesterols, but ultimately have highly specific roles, they must undergo multi-step reactions to convert them into their final form. Multi-step reactions would take an impossibly long time and synthesize insignificant amounts of products if it were not for the presence of highly evolved enzymes. Biological enzymes are proteins that have specific conformations to allow for orientation of reactants to enable more frequent reactions. Because they are proteins, they must be translated from a copied DNA sequence which is specifically intended for that protein. A genetic defect in any part of the coding may severely affect the final product (see “Phase 1: Genetics Cure Map Document”). Genetic defects are the primary source of nutritional misuse diseases such as diabetes and phenylketonuria.

- **Organs**
    - Biotransformations occur in every cell of the body for energy production, DNA replication, protein synthesis, and the range of specific functions. We highlight a few systems that are important centers of biotransformations.
        - Liver. The liver is fundamental to the intermediate metabolism of biotransformation. It is largely responsible for the production of enzymes necessary for digestion and absorption of dietary nutrients. It plays a critical role in the metabolism of carbohydrates, lipids, and proteins. The liver also processes reactive ammonia in the blood and converts it into the more benign urea for expulsions when filtered through the kidneys. The kidney is also responsible for the biosynthesis and degradation of proteins like albumin.
        - Pancreas. The biotransformations of chemicals for digestion and absorption are dependent upon the proteins, enzymes, and hormones made by the pancreas. These are synthesized from amino acid and cholesterol precursors. The pancreas prevents the chemicals it produces from digesting itself by packaging them in protease inhibitors.
        - Brain and nervous system. Every nerve firing is the result of neurotransmitters being released from an axon, diffusing across a gap and binding to receptors on a neighboring neuron. These neurotransmitters must be cleared from the dendrite receptors and replacements made in the axon for the next nerve firing.
- **Processes**
    - Ingested molecules and nutrients often undergo chemical reactions to strip them of functional groups. These functional groups or the 'skeleton' molecules they were attached to can be used to generate new compounds. Metabolic processes are the body's energy production mechanisms. Generally, we will consider metabolism to be the biotransformation of foodstuffs into usable chemicals such as ATP, glucose, and pyruvate through metabolic pathways such as the Krebs cycle, glycolysis, or amino acid oxidation.
        - Carbohydrates. The liver processes carbohydrates and can release (glycogenolysis) or store (glycogenesis) glucose and glycogen based on the hormone levels of epinephrine, glucagon, and insulin. Liver cells also possess enzymes that can synthesize glucose from amino acids, pyruvate, and lactate.
        - Lipids. The liver secretes bile salts to absorb lipids into the small intestine which are transported back to the liver for fatty acid breakdown and triglyceride synthesis. Fatty acids can be degraded in the mitochondria into acetyl-CoA fragments via beta-oxidation. Acetyl-CoA can then enter the citric acid cycle to generate ATP. The liver can also manufacture triglycerides when carbohydrate intake exceeds energy requirements. Cholesterol undergoes reactions where functional groups are stripped to create hormones like estrogen, nutrient-precursors like retinol, and other bioactive chemicals.
        - Proteins. The liver contains enzymes that are necessary for breakdown of amino acids to products like pyruvate or other intermediates of the citric acid cycle. Plasma proteins like albumin, coagulation factors, transferrin, and ceruloplasmin are all synthesized in the liver. Protein synthesis is regulated by hormones like insulin, glucagon, and glucocorticoids.

- **Diseases**
  - These diseases are all examples of misuse. Biochemical pathways can cause any combination of deficiency, toxicity, or imbalance since the body is engaged in a dangerous cycle of worsening a problem by utilizing the system that initially caused the problem. Imagine a simple multi-step transformation that begins with reactant A, creates an intermediate B, which in turn creates a final product C. Gene AB codes for enzyme AB which enables a quick conversion of A into B. Likewise, gene BC codes for enzyme BC allowing for a quick conversion of the intermediate B into the final product C. Loss of enzyme BC because of an error in gene BC could lead to several similar outcomes: deficiency of C, loss of feedback control on the transformation, accumulation of B, accumulation of A, or creation of an alternate D. Disorders of lipid, carbohydrate, and protein metabolism are characterized by the body's inability to either catabolize something that should be broken down so that an intermediate accumulates causing toxicity, or an inability to produce a more complex and essential compound from basic components. These diseases are classified by the basic component affected.
    - Porphyria is a collection of diseases that affect the production of oxygen-carrying heme. The body is unable to transform heme precursors, called porphyrins because a dysfunction in the conversion enzymes causes them to accumulate. This misuse leads to an excess of highly reactive precursors sensitive to biochemicals and sunlight causing skin problems and affecting the nervous system.
    - Glycogen storage diseases are carbohydrate disorders. They are caused by a hereditary absence of one of the enzymes that participates in the conversion of glucose into glycogen. Weakness, low blood sugar, and hepatitis (enlarged liver) are symptoms shared by several of these diseases and are treated by eating a low-carbohydrate diet.
    - Maple syrup urine disease is an amino acid metabolism disorder. It is caused by the body's inability to metabolize certain types of amino acids (branched like leucine, isoleucine, and valine) which accumulate and cause neurotoxicity.
    - Niemann-Pick disease is a lipid metabolism disorder. It is caused by an enzyme deficiency that results in the accumulation of sphingomyelin or cholesterol and causes neurological and other physiological changes.
    - Lactose, a sweet disaccharide in milk is not well tolerated by many adults and animals because the genes coding for its digestive enzyme are progressively suppressed in a kind of genetic weaning as the person/animal grows older.

Storage of nutrients in tissues provides a reservoir to draw upon in times of increased demand or lowered intake.

- **Organs**
  - Liver. Glucose from digestion and absorption is stored in the liver as glycogen. Glycogen is a highly polar molecule and binds strongly with water. Oxidation of glycogen releases 4 calories/g and the body stores enough with water to provide 600 calories. These stores can be replenished by glucose from the diet, biotransformation of amino acids, or recycling of lactic acid into glucose. The liver is also a nutrient storage site for Vitamins A, D, and B-complexes as well as iron and copper.

    - Adipose tissue. Lipids absorbed from the small intestine are transported to groups of adipocytes, where they are converted and stored as triacylglycerols. Triacylglycerols yield 9 calories/g and the body stores over 100,000 calories in this manner. This energy density can be attributed to their ability to be stored without water (anhydrous) unlike glycerol. Previously thought to be passive fat deposits, their role in regulating and releasing hormones increasingly indicates an endocrine role. The number of these cells is thought to be constant and that the vesicles containing lipid triacylglycerols expand and contract depending upon energy demands.
    - Muscles. Muscles store glucose to be used as a short-term energy source before switching to fatty acid oxidation. As glucose is oxidized into pyruvate for energy, it generates lactic acid (characteristic burning sensation during strenuous, anaerobic exercise) or water and carbon dioxide during aerobic exercise.
    - Bones. Over 99% of the calcium in the body is stored in the bones as hydroxyapatite even though it has many other roles in the body. Similarly, 85% of body phosphorus is in a hydroxyapatite matrix in bones. In times of deficiency, the body decomposes this matrix to release calcium for other uses.
- **Processes**
    - Vitamins. Fat-soluble vitamins are stored with their lipoprotein carriers in the cores of fat droplets in adipocytes. Water-soluble vitamins are generally not stored because they diffuse throughout the body.
    - Minerals are stored in the liver to be incorporated into enzymes or distributed in the blood. Other minerals like iron and zinc are extremely well-guarded by the body in times of infection.
    - Lipids. Adipocytes are fat-storing and energy-regulating cells. Lipogenesis is the storage of lipids from dietary fats, carbohydrates, and amino acids. Triglycerides in the form of chylomicrons and lipoproteins are broken down by enzymes (lipases) where they can then cross the cellular membrane and reassemble into triacylglycerols. Insulin enhances this absorption and storage system by blocking the processes that oxidize stored lipids.
- **Diseases**
    - Wilson's Disease causes the body to accumulate copper in the liver. A genetic defect prevents a protein designed to remove copper from the liver from binding properly.
    - Obesity is attributed to the build-up and enlargement of adipose tissues. Improved diet and regular physical activity are able to treat many cases. Because the body regulates its energy metabolism and storage so closely, this disease may be more complex than an imbalance in energy input and output. Abnormal hormone regulation systems, such as thyroid dysfunction, can likewise cause obesity that cannot be fully treated by diet and exercise.

Pharmacodynamics refers to the mechanisms of drug or nutrient action and its pharmacologic effects. While pharmacokinetics described what the body does to a nutrient, pharmacodynamics explores what the nutrient does to the body. In this section, we will explore the links between nutrition and body systems and their diseases.

Nutrients can be translationally or transformationally essential when studying their pharmacodynamic roles. Translationally essential molecules are large compounds broken down into their constituent molecules. The process of forming proteins from amino acids or triglycerides from fatty acids and phospholipids are examples of processes that build or break down large molecules from distinct chemical building blocks that are unchanged in the reaction. Their essentiality is derived from the body requiring the building blocks to build specific chemicals (like proteins) or breaking down large molecules to form simpler and easier-to-handle chemicals (polysaccharides and triglycerides to monoglycerides and fatty acids respectively.)

Transformationally essential molecules are compounds that are unique products from the chemical reaction of precursors that have been fundamentally changed. These biotransformations of molecules from one type into another are irreversible and require the actions of enzymes to lower the activation energy to facilitate reaction initiation. The roles of vitamins and minerals are central to these reactions where they have specific roles in certain compounds that are highly regulated. The biotransformation of cholesterol into vitamin D and many hormones is another example.

- **Organs**
  - All organs use nutrients.
- **Processes**
  - Genetic expression*.* The central dogma of molecular biology states that information can only flow from DNA through RNA and into proteins. DNA has no use but to store information while proteins do all the body's work. Hormones and micronutrients can bind to membrane receptors or be absorbed into cells to activate a signal transduction pathway. This pathway can activate a transcription promoter in the nucleus which signals for transcription to RNA and translation to functional protein. Vitamin D has known receptors on the nuclear membrane inside a cell that affect genetic expression.
  - Metabolization. Glucose, fats, and proteins are converted into ATP which is used in reactions requiring energy like active transport, enzyme activation, DNA transcription, protein formation and others. ATP provides an initial burst of energy in muscles before switching to glucose metabolism and fatty acid oxidation over longer periods of physical exertion.
  - Enzyme activity. Amino acids are building blocks of proteins and minerals, and are often located at electrochemically active sites to allow for interaction with other molecules. Deficiencies in these nutrients are inherited by the enzymes that require them causing disease.
  - Hormone activity. Hormones are inter-organ signals that control appetite, digestion, emotional, sexual and other body functions. Hormones bind to the cell membranes of target cells that have receptors specific to their shape. The presence of food in the stomach induces the bile ducts and small intestine to begin secreting bile salts and digestive enzymes to prepare for further digestion and absorption.
  - Cellular communication. It is not sufficient to merely bind to a cell to effect a change. Proteins form the receptors that span the cell membrane and connect the exterior world of signals to actions within. Activation of a receptor sets off signal transduction pathways that can alter the chemical properties of other proteins and compounds, which can subsequently alter other proteins downstream. The result can be amplified signal until it reaches a target, like the nucleus to begin replication for new proteins, a secretory vesicle to release chemicals, or mitochondria to generate energy.
  - Binding and transportation. Proteins prefer the company of other proteins when traveling. Because their folded shapes are so susceptible to alteration by acidity,

temperature, free radicals, mechanical forces, and other destructive parts in the human body, proteins are often packaged with or bind to other carrier proteins to protect them from external forces or prevent them from acting prematurely.

- Structure. Calcium, phosphorus, and proteins can combine and aggregate to form huge space-filling matrices of hydroxyapatite, collagen, and muscle. Also, water is the most significant structural component of human bodies. It constitutes more than two-thirds of body mass and exerts osmotic pressure inside cells to maintain their shape. Overexposure to water can result in cell lysis however. Underexposure can result in a similar phenomenon of cell death.
- Replacing loss. Metabolism and protein synthesis are continuous processes necessary for life. The body sacrifices functionality to ensure the operation of core, life-sustaining functions. Nutrients feed into these continuous processes so that deficits do not occur in other parts of the body.
- **Diseases**
  - This section is intentionally short because, by definition, if nutrients are used correctly, nutritional diseases do not develop. Only in a poorly-fed state (starvation or protein-energy malnourishment) does the body cannibalize stores of glycogen, triglycerides, and protein for metabolization and energy from other parts of the body.

Excretion is the process of removing used or excess nutrients from their tissues, organs, and systems. Discrete from the digestive and circulatory systems, the excretory system specializes in removing waste products from the blood stream and confining unusable nutrients in the digestive tract until they can be expelled.

- **Organs**
  - Liver. Proteins and polypeptides (shorter amino acid chains) excreted into the blood stream by tissues are deaminated (decomposed) in the liver and converted to urea.
  - Kidneys. Liquid waste, a solution of urea, salts, and excess water, is removed from the bloodstream by the liver and kidneys. The kidneys filter 200 quarts of blood per day removing only 2 quarts of urea, water, and salts to pass on to the bladder for later expulsion out of the body. It is true of all nutrients that they can only be used and removed after they pass into the blood. Because kidneys filter the blood, the ultimate destination for all nutrients is in urine.
  - Colon. Solid waste consists of feces, kidney stones, and gallstones. Feces are the normal disposal route through the large intestine for water, undigested fibers (cellulose), unused nutrients, digestive bacteria, mucous, fats and their bile salts.
  - Skin. The skin contains pores which secrete fluids containing urea and other nitrogen compounds from amino acid catabolism.
  - Lungs. Carbon dioxide, CO_2, is a byproduct of the oxidation reactions and the citric acid cycle. Hemoglobin in the blood binds to carbon dioxide, transports it between tissues and the lungs where alveoli cause CO_2 to diffuse out of the blood.
- **Processes**
  - Excretion may be thought of as reversed absorption. As cells excrete waste products into the bloodstream, these chemicals are carried to the liver where they are degraded by active enzymes. This waste is then excreted or exchanged from the blood stream in the kidneys by absorption processes acting in reverse like active transport and diffusion.

- **Diseases**
  - Stones. Unlike feces, kidney stones and gallstones are not healthy expulsion routes for nutrients. Kidney stones are crystals precipitating from urinary solution with an excessive concentration of minerals. Gallstones form when insufficient bile salts cause blood components like bilirubin or cholesterol to precipitate and crystallize in the large intestine.
  - Colorectal cancer. Cancers of the colon or rectum have been observed in populations eating diets with high levels of fats, animal meats, and calories and low levels of calcium and folate.

Individual and group factors influencing nutritional disease

Epidemiology is the study of diseases among populations. A chief concern among epidemiologists is how to define a population and its risk. The idea of nature versus nurture determining one's risk may be simplistic, but it may also be sufficiently broad for describing the causes of diseases. Internal factors like genetics or physiology described above cannot be consciously altered. External factors like culture or occupation can vary between people.

The study of disease among populations requires understanding the roles and impact of extraneous factors. One's socioeconomic standing can determine the availability of healthy foods or practices. An understanding of cultural traditions, socioeconomic conditions, health status, and geography are effective measures for defining trends among varying populations.

Degree of deficiency is a means of describing severity of the disease and its symptoms. A phenotype is an expressed or observed trait determined by genetic makeup and environmental factors. Considering the broad influence of nutrition, the deficiency, toxicity, imbalance, or misuse of a nutrient can have significant effects on healthy body function. Nutritional etiology (study of disease origins) often reveals surprising connections between nutrients and seemingly unrelated systems.

- Acute symptoms involve sudden onset, sharp rise of symptoms, and a short course of the disease. They are associated with a single or many doses in quick succession and the onset of symptoms within days or a week. Asphyxiation is a shortage of oxygen in the body causing acute symptoms like loss of consciousness within minutes and without intervention, death. Dehydration is similar; loss of water to perspiration leads to heat exhaustion or heat stroke and requires rehydration and electrolytic infusions to restore equilibrium.
- Subchronic symptoms are associated with short-term exposure to an environmental factor. The exposure to the aggravating factor requires several weeks or months before the development of subchronic symptoms. Deficiencies often follow this model since consistent deficient dietary intake forces the body to deplete stores until physical symptoms develop. It is possible to treat the symptoms and identify the root of the disease and treat by supplementation or alteration of diet.
- Chronic symptoms are caused by long-term exposure to the offending environmental agent. Persistent or frequent symptoms progress after years of exposure. These are often genetic or multi-factorial diseases because the environmental agent is not

directly pathogenic but instead acts over time to knock out a protective component of the body which then causes disease. The effects of chronic symptoms are not limited to one system. Deficiencies and toxicities are associated with chronic diseases in cases where they have no perceptible symptoms until the damage is irreversibly done.

Genetics is a topic covered in far greater detail in the "Phase 1: Genetics Cure Map Document." Nevertheless, the confluence of factors in nutrition such as age, sex, and inherited tolerances are all determined by genetics. Every stage of growth and differentiation from baby, adolescent, adult, to elder is hardwired into our genetic code.

- Age*.* One's nutritional requirements vary greatly through the years. Nutrients for growth differ between a baby's need to grow and harden bones and an adolescent's need to develop sexual features in puberty. Adults' requirements remain largely unchanged until biological stresses accumulated over decades make new demands on the diet. Many newborn babies (neonates) initially do not have functioning biological systems. Babies unable to process bilirubin from decomposed red-blood cells develop jaundice when the chemical circulates in the bloodstream in toxic levels. As people grow older, their ability to take care of themselves diminishes. Diminished sensations for hunger and thirst, lack of money to buy wholesome foods, decreased physical activity, social isolation, and accumulated physiological and psychological stresses can make malnutrition common. Hormonal changes in post-menopausal women are a factor in osteoporosis as their bones lose calcium and become brittle.
- Gender*.* Until puberty, boys and girls are undifferentiated in their nutritional requirements. Sexual differentiation places stresses on men to support larger frames and constantly produce sperm and demands women to ovulate and store fat and water in preparation for pregnancy every month. Pregnant women have highly altered nutritional requirements as their body must protect itself and nourish the developing embryo. Maternal deficiencies in nutrients like folic acid have been implicated in neonate mental dysfunction and retardation. Each life stage demands different nutritional requirements and deficiencies can hamper growth and health.
- Ethnicity. The variation in genomes between any two people is around 0.1% for all base pairs. Nevertheless, population studies have shown wide variations in incidences of chronic and even infectious diseases. While socioeconomic status may be a factor in results, one's genetic heritage can determine your susceptibility to heart disease, diabetes, cancer, MS, and other complex multi-factorial diseases. Social pressures to marry within an ethnic group can often reinforce and express recessive genes. African-Americans are at a significantly higher risk of heart disease than the general population even when studies have corrected for age and socioeconomic status.
- Tolerances*.* Allergies and intolerances are complex mechanisms that may arise from an excessive immune response to proteins in foods that the body mistakes for pathogens. The immune response inevitably causes more damage than the insult and causes malabsorption, as in Celiac disease.

Modernization reflects the shift from subsistence farming and rural living towards the demands of urban living. The large-scale organization of crop planting and harvesting to feed large, non-farming populations is only possible with powerful industrial technology. The coordination of crop production, transportation, and market exchange are recent managerial and commercial developments. Modernized food production has lowered prices and increased access to quality foods in modern Western countries. Because of this super-availability, these populations are increasingly suffering from over-nutrition and obesity rather than the malnutrition and deficiencies common in the third world.

- Socioeconomic status. There is a highly-correlated link between socioeconomic standing and nutritional status in cultures across the globe. Greater wealth increases access to the necessary quantity, quality, and diversity of foods for consumption. Living in a developed country does not protect you from nutritional diseases. Even in modern countries such as the United States and United Kingdom, millions of poor people have little diversity in the diet and rely on lower-quality foods. Low-income groups have higher incidences of obesity, heart disease, stroke, diabetes, and cancer than middle or upper-classes in these developed nations. Furthermore, for the billions of people in the third world who live everyday on the threshold of malnutrition and deficiency, nutritional and health care conditions all but ensure that they will not live long enough to develop heart disease, cancer, and other scourges of modern longer life expectancies.
- Food processing. The development of food processing over the past century has greatly increased the availability of foods. Food can be processed to preserve and extend shelf life, to increase digestibility, to increase bio-availability of nutrients, to improve palatability and texture, to prepare foods for serving, to eliminate microorganisms, to destroy toxins, to remove inedible parts, to destroy anti-nutritional factors, and to create new types of foods. Thermal processing (pasteurization, canning, baking, and more) is the most prevalent form of food processing that generally preserves food by destroying microorganisms and enzymes that normally decompose food. Other forms of food processing include freezing, dehydration, concentration, irradiation, and milling. While these processing methods have measurable benefits, described above, they often destroy nutrients at the same time. More dangerously, food processing is an industrial modification that may unintentionally introduce non-nutritional and potentially toxic or carcinogenic chemicals that can accumulate in the diet. This topic is covered in greater detail in the "Phase 1: Toxic Agents Cure Map Document."
- Fortification. The identification of essential biochemical compounds occurred at nearly the same time as the synthetic chemical industry grew. It became possible to add synthetic vitamins into food to compensate for losses caused by processing, supplement existing levels, or add the nutrient to foods that never had it before. The practice of fortifying foods with higher levels of nutrients was encouraged by public health policies attempting to correct for deficiency diseases present in even developed countries. Adding Vitamin D to milk, calcium and B vitamins to white bread and fluoride to water are examples of food fortification that decreased or eliminated deficiencies in populations. Developments in genetic engineering have shown promise in allowing food staples, such as rice, to produce nutrients like β-carotene (a precursor to vitamin A) to reduce the incidence of deficiencies in dependent populations.
- Public health recommendations. We have shown that specific nutrients are required for normal body function, but defining one requirement or recommendation to fulfill this requirement for the general population has plagued modern public medicine and nutrition. Such a value would be helpful in food planning and procurement, evaluation of dietary survey data, guidelines for food selection, education, labeling, fortification, and supplementation. Trying to define a requirement based upon distribution studies has produced an alphabet soup of recommendations from public health organizations around the world: SLI (safe level of intake from the UN and WHO), RDA (recommended dietary allowance from US), RNI (recommended or reference nutrient

intake from Canada or UK), EAR (estimated average requirements from UK), and DRI (dietary reference intake from US) among others. But attempts to define recommendations or requirements for an individual always fail to account for the variability among a heterogeneous population. These organizations generally attempt to accommodate this variability by suggesting an amount two standard deviations above an average requirement. The U.K. Committee on Medical Aspects of Food Policy argues that "This level of intake is, therefore, considerably higher than most people *need*. If individuals are consuming the RNI of a nutrient, they are most unlikely to be deficient in that nutrient."

Health status is an independent factor that can affect people of all ages, gender, culture, or social status.

- Infection. Pathogens are opportunistic agents that capitalize on an ill-prepared body to reproduce and infect more victims. Diminished health status by any of the categories below can provide a ready environment for infection, further aggravating one's health. The body's response requires more fluids to flush systems out, proteins to replace amino acid loss, and a fever to deaminate enzymes and proteins. A disease state may also lower appetite and desire to seek out food which can quickly lead to malnourishment and deficiency. Requirements can also increase for water and water-soluble vitamins as the body tries to flush out the virus by excretion. The body has an amazing ability to sequester minerals like iron and zinc away in the liver during an acute infection. Pathogens make compounds to steal these highly-guarded minerals for their own use like DNA synthesis and pro-oxidants that damage DNA and cell membranes. This topic is covered in greater depth in "Phase 1: Infectious Agents Cure Map Document."
- Trauma. Injury changes the body's energy expenditure as it mobilizes to begin the healing process. Long bone fractures and burn injuries can increase energy expenditures 25 to 40% as the body metabolizes glycogen first, then fats and amino acids. These provide substrates for protein growth and hormone release which results in increasing urinary nitrogen losses with more severe injury. Hypermetabolic states such as this require increased nutritional support by supplementing macronutrients like vitamins and energetic molecules, conditionally essential bioactive chemicals like the amino acid glutamine, and micronutrient minerals like potassium, magnesium, and phosphate that are all depleted at rates reflecting the magnitude of the injury. This topic will be covered in greater depth in "Phase 1: Trauma Cure Map Document."
- Chronic diseases. Heart disease, cancer, obesity, arthritis, osteoporosis, diabetes, and AIDS are all chronic diseases that affect quality of life for long periods of time. They require pharmaceutical treatments and dietary restrictions that can affect the quantity and quality of nutrient intake. Malabsoption, nutrient antagonism, altered metabolic state, and other side effects of pharmaceuticals and treatments can impair normal organ and system function.
- Addiction. Alcoholism afflicts many segments of the population with profound effects on health. Ethanol alters the absorption and use of other nutrients while also being directly toxic to body tissues. While ethanol provides calories for metabolism, its consumption increases metabolic rate and nutritional demands. While moderate drinking is reported to have many beneficial effects, heavy drinking causes water-electrolyte imbalances and deficiencies in water-soluble vitamins and calcium, iron, fiber. Depressed consciousness, hangover, and gastroduodenitis all contribute to decreased desire for substantive food. Nutritional therapy is indicated to treat and prevent deficiencies, but not the underlying addiction. The effects of narcotics and

illegal substances on nutrition are not well understood, but altered absorption and metabolism are almost certainly indicated.

- Behavioral disorders. Anorexia nervosa and bulimia nervosa are eating disorders characterized by highly regimented fasting, food restriction, or binging and purging. These disorders often lead to a state of semistarvation in which the body uses fat while sparing glucose and proteins. Hormone levels and protein synthesis are also negatively affected and contribute to the symptoms of extreme thinness, cold intolerance, dry skin and hair, cardiovascular irregularities, and constipation. Patients with attention deficit disorders, depression, obsessive-compulsive tendencies, and schizophrenia have altered mental states that may induce them to avoid certain foods or eating in general.
- Incapacitation. Patients require nutritional support when they are not able to independently consume food. Starvation, prolonged illness, extreme weight loss, surgery, spinal cord injury or coma can all necessitate enteral or parenteral feeding. Enteral feeding involves infusing formulas via a tube inserted into the upper gastrointestinal tract. Parenteral feeding involves bypassing the gastrointestinal system and infusing nutrients directly into the bloodstream. Parenteral feeding is used only in severe cases and enteral feeding is preferred when possible because it sustains the gastrointestinal functions of digestion and absorption, maintains an immunological barrier against pathogens, overdoses, and toxins, and is generally more cost effective and less unsafe. These patients are entirely dependent upon catheter feeding and the formula must meet all nutritional requirements for either the short or long term.
- Fitness. Regular physical activity forces the body to adapt to the physiological stress of exertion. In addition to building muscle mass, promoting fat metabolism, and increasing caloric expenditure, exercise is clearly indicated for lowering the risk of heart disease, diabetes, osteoporosis, infection, cancer, and other chronic diseases. Sedentary lifestyles decrease oxygen delivery, lower cardiovascular efficiency, and decrease the body's ability to store glycogen and burn fat. It is readily clear that regular exercise improves overall health status and lowers the risk of disease across the board.
- Occupation. One's occupation can greatly determine health status. Occupations requiring intense or repeated physical labor have higher average fitness levels than sedentary office workers. Professional athletes, members of the armed forces, police, and firefighters all have increased nutritional requirements reflecting the physiological stress of their jobs.

Geography. The people inhabiting all the geographies of the Earth subsist on nutrition available in the environment around them. These communities are subject to variations and the nutritional diseases that arise from them.

- Flora and fauna. The biodiversity of the Earth determines what kinds of and how much food is available depending where one lives. Rain forest dwellers can have a hugely varied diet of plants and animals while communities at Arctic latitudes can choose only between some fish, whale, seal, birds, or bear. Communities living in temperate climates in between have been successful because they balance, through domestication and agriculture, the big game diets of the north and diverse diets of the south in a zone where both can survive. Cultures may develop (and become dependent on) a dietary staple because it can fulfill many nutritional requirements.
- Geology. Different parts of the earth have different distributions of minerals. Plants absorb these minerals from the soil or the water and they remain in the food chain as

herbivores eat the plants and carnivores eat the herbivores. Foods grown in North Dakota and China are profoundly deficient in selenium, while water in Bangladesh is tainted with toxic amounts of naturally-occurring arsenic. People who rely on food grown in these environments nutritionally inherit the problem and develop deficiencies or toxicities.

- Climate. Temperature generally decreases towards higher latitudes, but elevation and proximity to large bodies of water can also influence climate. While equatorial climates can support year round cultivation, temperate climates do not suffer the extremes of temperature, and Arctic climates are generally unsuited to any kind of agriculture. Large bodies of water moderate extremes in temperature (London, Paris, and Berlin are all north of Maine) and enable longer growing seasons. High elevations can change a tropical zone into a temperate or even Arctic zone. The seasonal diets of populations are subject to the whims of these climates. Coastal and fishing communities have nearly year-round access to food, while inland and farming populations have much higher energy yields for the same amount of work. Equatorial communities rarely have rickets (Vitamin D deficiency prevented by regular exposure to sunlight) while people living at high latitudes and longer winters are much more susceptible.

Cultural practices around the world reflect adaptations to fit local geographies and ideologies but also meet universal requirements of nutrition. Practices that eliminate sources of nutrition can only be evolutionarily justified when a replacement exists. In other words, certain cultures have established a nutritional equilibrium that allowed them to reject eating insects and rodents because the availability of cows, chickens, and pigs made better sources of energy and protein.

- Abstinence. Some religions demand practitioners to abstain from consuming certain types of foods or fast for periods of time. Followers of many religious faiths cannot eat certain animals deemed 'unclean' and must also fast while observing religious holidays. Those who practice vegetarianism and veganism abstain from consuming foods derived from animals and must be vigilant to avoid deficiencies in nutrients available primarily in meats and animal products. Aversion to food types may deprive the body of essential nutrients and beneficial peripheral chemicals.
- Staples. Some cultures have centered their diet so completely around a certain crop or animal that it becomes a dietary staple. Far-east Asian cultures rely on rice as a universal, though nutritionally empty, source of nutrition. Deficiencies in the staple are inherited by the population and preventable diseases are perpetrated by long-term consumption.
- Disgust is an ingrained bias that make some viable sources of nutrition wholly repulsive. While abstinence may be considered a conscious or learned cultural choice, disgust encompasses a natural subconscious aversion that can be unlearned or overridden by the conscious. Disgust is probably an evolutionary response meant to discourage consumption of dangerous food sources. Most cultures balk while others embrace ideas of eating rodents, insects, or spoiled food. The practice of consuming disgusting foods can provide a vector for toxic and infectious agents during times of increased susceptibility such as starvation.

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