Orthomolecular Medicine: A History of the Treatment of Disease Using Individualized Nutrition

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Abstract

This paper provides an overview of the principles and applications of orthomolecular medicine, the use of optimal amounts of substances naturally found in the human body to prevent, treat, and cure disease. Cellular nutrition is the fundamental determining factor in health, and the technology of modern society contributes to malnutrition and illness. This paper proposes orthomolecular nutrition as a safe and effective solution to mitigate the suffering caused by rampant chronic disease. It traces the history of the field of orthomolecular medicine over the past century, from its roots in the discovery of vitamins and their deficiency disorders, through the development of the genetotrophic theory of disease, the theory of biochemical individuality, the use of high doses of vitamins to treat psychiatric disorders, its expansion into physical illness, and its integration with environmental and energy medicine. Research scientists spanning the fields of chemistry, biochemistry, biophysics, physiology, immunology, and endocrinology have contributed to the knowledge of how the body works at the cellular level. Orthomolecular physicians, which comprise less than one percent of all health care professionals, have used this knowledge to refine their clinical practices and help patients restore health through balancing their biochemistry. Despite opposition from the mainstream medical establishment, orthomolecular physicians continue to treat a wide range of chronic diseases, including cancer, autoimmune disorders, cardiovascular diseases, and diabetes, through proper nutrition. The field continues to evolve, as new technological and conceptual innovations increase our ability to meet the body's individual biochemical needs.

Introduction

We live in a world of chronic illness and degenerative disease. While modern medicine has made great strides in reducing and eradicating some sources of life-threatening disease, including deadly viral and bacterial contagions, and has dramatically improved surgical precision, it has failed to sustain a healthy general population. Modern doctors are more helpful at prescribing an antibiotic and performing corrective surgery than preventing the devastating effects of increasingly prevalent chronic illnesses. Documented chronic diseases, defined as physical or mental health conditions that last more than one year and cause functional restrictions or require ongoing monitoring or treatment, affect nearly half (approximately 45%, or 133 million) of Americans (W. Raghupathi and V. Raghupathi, 2018). Five chronic diseases: heart disease, cancer, stroke, chronic obstructive pulmonary disease, and diabetes account for over two thirds of all deaths in the U.S., not to mention years of untold misery (W. Raghupathi and V. Raghupathi, 2018).

As those suffering from undiagnosed "mystery" afflictions know, true health is not merely the absence of disease. A state of health at the cellular level requires appropriate energy production, structure formation, tissue growth and repair, cell differentiation, detoxification, and production of all the necessary chemicals (e.g. hormones, neurotransmitters, cytokines, and growth factors) in the correct, dynamic proportions (Gonzalez *et al.*, 2018). Chronic illness involves persistent, complex, systemic disruption of the body's ability to maintain this state. This disorder of biochemical processes causes long-term bodily dysfunction, often making life's activities difficult and painful for the patient. The stress placed on the body by some chronic conditions may become severe enough to cause cell, tissue, organ, and ultimately organism

death. The etiology of a particular chronic illness cannot be reduced to a single cause, but emerges from environmental conditions, genetic predisposition, and perhaps one or more triggering factors.

Strangely, medical doctors seem preoccupied with identifying and recording specific diagnostic labels for this mélange of maladies. Patients with a variety of concurrent chronic symptoms, such as arthritis, irritable bowel syndrome, chronic fatigue syndrome, and depression, may not realize the biochemical links among their ailments when doctors label them as separate diagnoses, treat each individually with its own prescription, and neglect to investigate their root causes. The medical paradigm of "one pill for one ill" serves no lasting utility to the chronically ill patient. The goal of maintaining or restoring a functional body rather than chemically or surgically altering a diseased one promises greater and more sustainable health.

A different medical paradigm purports that illness arises from a poor cellular nutrition. Biochemist and orthomolecular research pioneer Dr. Roger Williams states that "the nutritional microenvironment of our body cells is crucially important to our health and that deficiencies in this environment constitute a major cause of disease" (Williams, 1971, p. 4). A subset of "alternative" medical practitioners adopts such a root-centered approach to medical care, using nutrition to cultivate a working cellular environment to promote a functional body system. This is orthomolecular medicine, the practice of supplying the individual with the correct amounts of the nutrients he needs to cultivate balance in the biochemical pathways of the body (Pauling, 1968). Orthomolecular medicine places no distinctions between disease prevention and cure, food and medicine, body and mind. With origins in the discovery of vitamin deficiency states, this approach emerged from the molecular theory of disease. It evolved from the use of high

doses of vitamins in psychiatry to the expansion of nutrient therapy to all medical conditions and the incorporation of environmental and energy medicine. Today, orthomolecular physicians, which make up less than one percent of all medical professionals, continue to advance the practice of individualized clinical nutrition (Hoffer and Saul, 2008, p. 328). While the medical establishment still resists the spread of orthomolecular theory and implementation, the public's call for greater awareness of its healing power is gradually strengthening (Hoffer and Saul, 2008, p. 2).

Our government and mainstream scientific community superficially acknowledge the importance of good nutrition on overall health but do not understand how to apply this nebulous concept effectively. Whether through ignorance or explicit rejection, the modern physician often considers proper nutrition irrelevant to the treatment of acute or chronic diseases, or as a subsidiary approach to the primary pharmaceutical model (Kalita, 1977). Orthomolecular theory describes a different primary approach to preventing and treating the chronic conditions that plague our modern society. It proposes the replacement of the search and *destroy* mentality toward *disease* with a search and *restore* attitude toward *health*. This idea arises from the understanding that the body has the ability to heal itself when provided with the right substances in the right amounts to reestablish the appropriate balance in the biochemical pathways affected by disease (Kalita, 1977). Because this form of treatment uses the cells' natural processes to foster healing, the substances provided are those native to the cells' chemical milieu. Thus *nutrition*, a shunted term in mainstream medicine, becomes the central doctrine.

The principle of using nutrients to treat illness did not originate from any single practitioner, geographic location, or time. Hippocrates espoused this philosophy in the 5th

century BCE with his axioms “Let good food be thy medicine” and “one man’s meat is another man’s poison” (American Academy of Environmental Medicine, 2010). Practitioners of traditional Chinese medicine prescribed certain foods and systems of eating for particular disease states, as described in 2000-year-old medical texts (Kaptchuk, 2000, p. 162). Over the centuries, we have gained a greater knowledge of the components in our food essential to survival and health and, particularly in the last century, the biochemical pathways in which these substances participate. Now, we categorize dietary molecules into macronutrients, micronutrients, toxins, and waste products and study the roles these individual pieces play in health and disease. Nutritional science and its application in medicine require an understanding of biochemistry, physiology, and pathology, involving the interactions among nutrients and cells in the body (Williams *et al.*, 1977). The modern study of nutritional therapy by different scientists and medical practitioners with diverse academic and professional backgrounds testifies to the universality of this concept. Viewing the body from the lens of the physicist, the biochemist, the evolutionary biologist, or the clinician does not change the essential realities of cellular life, and each lens deepens our collective understanding of the natures of health and disease.

Orthomolecular medicine describes the underlying causes of disease in terms of biochemical imbalances in the cells and asserts that this is the most accurate way to characterize disease. It logically follows that the orthomolecular physician rectifies these imbalances by supplying the substances that restore the functionality of the biochemical pathways involved. Orthomolecular scientists view health at the cellular and subcellular levels, where the machinery of life’s processes reside. Dwight Kalita, Ph.D. describes this perspective by saying, “orthomolecular medicine seeks such an understanding [of the fundamental mechanisms of

cellular activity] by postulating that if the biochemical individual integrity of each cell is nourished with the optimum nutrients necessary for its proper functioning, then our internal environment can be brought into line with individual human needs, and all forms of disease will eventually be controlled" (Kalita, 1977, p. 2). Practitioners of orthomolecular medicine acknowledge that there are normal cellular functions that, when carried out properly, manifest in a person healthy in mind and body. Any breakdowns in these metabolic, signaling, immunity, and detoxification pathways lead to the systemic responses we call illness.

According to the orthomolecular paradigm, non-biological medications, also known as xenobiotics, or drugs, are ineffective or only partially effective at combatting long-term illnesses. These artificial compounds often interact with symptoms, rather than the underlying disease process. They contaminate the cellular environment with foreign material the cell's machinery is not adapted to process, deplete cellular nutrients, and mask important signs physicians may use to identify the source of the problem (Williams, 1971, p. 11). Synthesized biological treatments, such as antibiotics, hormones, enzymes, and antibodies derive from, or closely mimic, natural molecules that are normally present in living organisms. Whether by inhibiting a bacterium or compensating for a hereditary enzyme defect, these substances may deal with the causes of disease (Williams, 1971, p. 13). However, orthomolecular substances are nearly always the safest and most effective tools for treating chronic ill health, as they respond to the body's most fundamental needs, and the body may safely dispose of excess amounts (Williams, 1971, p. 13). One the most important aspects of orthomolecular medicine is that it embodies the Hippocratic principle "first do no harm." Nutritional therapy administered by a physician knowledgeable about cellular life will not wreak lasting damage, and will more likely provide enduring benefit.

History and Discovery of the Vitamins

In addition to the macronutrients—carbohydrates, proteins, and fats—which provide the body with metabolic energy and building blocks for cell materials, the human body requires smaller amounts of numerous other molecules, called micronutrients. By the early twentieth century, biochemists such as Nikolai Lunin studied the nutritional components of food, demonstrating that whole foods contain substances besides proteins, fats, and carbohydrates that are essential to mouse and human life (Pauling, 2006, p. 54). The term "vitamin," used to describe substances the body requires for health and obtains in the diet, was developed in the first half of the twentieth century (Pauling, 2006, p. 55). The vitamins, minerals, essential amino acids, essential fatty acids, and other vital substances serve a diverse array of functions in the cells. Micronutrients act as coenzymes and cofactors in metabolic reactions, antioxidants, and gene control factors (Shenkin, 2006). While a vitamin was originally defined as a substance the body needs in small amounts (e.g. tens to hundreds of milligrams), some research in the past fifty years has indicated that people often need significantly more than these amounts of many vitamins in order to fight disease and achieve optimal health. However, scientists in the past century have focused much more on assessing the proper amounts of macronutrients a person should consume than on optimum doses of vitamins and other micronutrients.

Individual vitamins were discovered by means of the diseases that result from their absence in the diet. In 1911, Polish biochemist Casimir Funk created the term "vitamines" and published his theory that four "vitamine" substances from food protect against four diseases: scurvy, beriberi, pellagra, and rickets (Williams, 1971, p. 6). The term comes from the Latin word *vita* (life) and the chemical term *amine* (a class of nitrogen-containing compounds)

(Pauling, 2006, p. 55). The word changed to "vitamin" when such substances lacking nitrogen were uncovered (Pauling, 2006, p. 55). The current vitamin nomenclature emerged from Elmer McCollum's research team's discovery of two essential food factors, which they called "fat-soluble A" and "water-soluble B" (Pauling, 2006, p. 55). This "B" factor contained not only the anti-beriberi compound, but others as well, labeled with number subscripts (Pauling, 2006, p. 55). The anti-scurvy, or ascorbic, molecule was named water-soluble C and the substance active against rickets was termed fat-soluble D (Pauling, 2006, p. 55). Subsequently discovered vitamins reflect this alphabet and subscript formula.

Scurvy, or extreme vitamin C deficiency, had plagued sailors on long sea voyages for centuries before anyone linked the disease to diet. Reports of deadly scurvy decimating crews date back to the fifteenth century, and people gradually began to associate the condition with the absence of fresh fruits and vegetables, primary sources of the vitamin, onboard (Pauling, 2006, p. 50). In 1747, James Lind, a Scottish physician in the British navy, conducted the first known experiment explicitly linking scurvy to diet (Pauling, 2006, p. 50). In an attempt to determine what alimentary components alleviated the condition, he divided a group of twelve severely ill scurvy patients into six groups and provided each pair with a different addition to their general diet (Pauling, 2006, p. 50). The groups received treatments of oranges and lemons, cider, dilute sulfuric acid, vinegar, seawater, or a drug mixture (Pauling, 2006, p. 51). After six days, only the pair receiving the citrus fruits had recovered (Pauling, 2006, p. 51). Lind included this and other studies in his *Treatise on Scurvy* (1753) (Pauling, 2006, p. 51). Famous English explorer captain James Cook ensured his sailors obtained fresh fruits and vegetables whenever they landed ashore and supplied his ships with large amounts of vitamin C-containing sauerkraut

(Pauling, 2006, p. 51). Consequently, few members of his crew became ill with scurvy and none died of it on his voyages (Pauling, 2006, p. 51). The British Admiralty codified the daily ration of fresh lime juice to all sailors in 1795, though merchant crews still commonly suffered from the disease until the Board of Trade passed a lime juice regulation in 1865 (Pauling, 2006, p. 52). Today, scurvy primarily affects communities in extreme poverty experiencing starvation, with a few instances in first world countries in individuals with diets devoid of all fruits and vegetables (Pauling, 2006, p. 53).

Beriberi, a deadly paralytic condition, was recognized as another diet-related disease in the late nineteenth century (Pauling, 2006, p. 53). Dutch physician Christiaan Eijkman studied the disease in chickens (Williams, 1971, p. 6). The ill chickens began to survive when their caretaker changed their diet from polished (milled to remove husks and bran) rice to unpolished, whole rice (Williams, 1971, p. 6). Eijkman and collaborator Dr. Gerrit Grijns discovered that the rice bran contained the anti-beriberi substance, later called thiamine, or vitamin B_1, and Eijkman won the Nobel Prize in medicine for this finding in 1929 (Pauling, 2006, p. 54). As institutions such as prisons and military hospitals replaced the milled, or white, rice served to residents with whole rice, instances of the disease dropped significantly (Pauling, 2006, p. 53).

Epidemiologist Joseph Goldberger studied the poor physical and mental health of many people living in poverty in the southern United States in the early 1900s (Pfeiffer, 1975, p. 117). He connected the deadly disease pellagra, manifesting in dementia, diarrhea, and dermatitis, with malnutrition (Pfeiffer, 1975, p. 117). In 1937, Dr. Conrad Elvehjem isolated an anti-pellagra substance from the liver extract used to treat dogs with the disease and called it nicotinic acid (Pfeiffer, 1975, p. 117). Administration of this niacin, or vitamin B_3, cured pellagra patients of

their physical and psychological symptoms (Pfeiffer, 1975, p. 117). Later research expanded the understanding of pellagra as a combined deficiency of vitamins B_3, B_6, and tryptophan (a precursor to B_3) (Pfeiffer, 1975, p. 118). As with this example, nutrient deficiencies are complex and interrelated. Illness rarely manifests from the lack of a single vitamin or mineral, but from widespread biochemical imbalances in the cells.

Following the discovery of the existence of vitamin substances, biochemists undertook the task of isolating and characterizing them. Research physician Herbert Evans and his associate Katherine Bishop discovered vitamin E, also called tocopherol, in 1922 (Hoffer and Saul, 2008, p. 107). They first identified the vitamin as the substance in lettuce that prevented toxin absorption into fetal tissue in animals fed a rancid diet (Hoffer and Saul, 2008, p. 107). Initially called the fertility food factor, tocopherol was later found to be the body's primary fat-soluble antioxidant, protecting fats, phospholipids, and other lipophilic substances from oxidation (Hoffer and Saul, 2008, p. 108). Tocopherol comprises a mixture of several chemical forms, including d-alpha- (the most active), beta-, gamma-, and delta-tocopherol (Hoffer and Saul, 2008, p. 108). The vitamin performs critical functions in the endocrine, muscle, and vascular systems and is particularly important during gestation (Hoffer and Saul, 2008, p. 108). Rich food sources of vitamin E include whole grains, wheat germ, and various seeds and nuts (Hoffer and Saul, 2008, p. 109).

While studying the biological oxidation process, biochemist and physiologist Albert Szent-Györgyi purified vitamin C, at that time recognized as the reducing agent that prevents brown pigmentation in certain plants (Pauling, 2006, p. 55). Szent-Györgyi and his collaborators identified the substance's structure and in 1932 demonstrated that this molecule, isolated from

plant tissues and animal adrenal glands, was the anti-scurvy factor, calling it ascorbic acid (Pauling, 2006, p. 55). The vitamin is known as the human body's primary water-soluble antioxidant, donating electrons to oxidized molecules (Pfeiffer, 1975, p. 129). It may alternatively act as a pro-oxidant in the presence of catalytic metals, performing hydroxylation reactions (Levy, 2002, p. 394). It is ubiquitous in nearly all cell types and is necessary for synthesizing many essential molecules within and around cells, regulating the body's defense system, and converting lipophilic toxins into hydrophilic molecules for excretion (Pfeiffer, 1975, p. 132). Compositional studies have revealed some foods, including green and red peppers, parsley, turnip greens, citrus fruits, and some berries as rich sources of the vitamin, with many other fresh vegetables and fruits containing moderate levels (Cameron and Pauling, 2018, p. 101).

Vitamin D, a prohormone sterol produced in the body, was first isolated in 1936 from fish oil (Hoffer and Saul, 2008, p. 133). In Sir Edward Mellanby's 1918 research, he used cod liver oil to cure rickets in dogs fed a diet of oatmeal, initiating the path to the vitamin's discovery as the anti-rickets nutrient (Hoffer and Saul, 2008, p. 133). The UV-B band of light converts 7-dehydrocholesterol in human skin into its active form, vitamin D_3 (cholecalciferol) (Hoffer and Saul, 2008, p. 133). Severe vitamin D deficiency, associated with lack of sunlight exposure in addition to inadequate dietary intake, leads to weakened bones and osteoporosis (Hoffer and Saul, 2008, p. 135). The vitamin facilitates calcium and phosphate absorption into the body and the maintenance of appropriate bone density (Hoffer and Saul, 2008, p. 133). While traditionally associated with skeletal health, this vitamin's metabolites appear to play roles in the skin,

intestines, pancreas, gonads, heart, brain, and white blood cells, and are involved in gene regulation (Hoffer and Saul, 2008, p. 133).

In 1926, Drs. George Minot and William Murphy discovered that liver consumption caused remission of pernicious anemia, and they won the Nobel Prize in 1934 for successfully implementing oral liver therapy (Pfeiffer, 1975, p. 156). Scientists later identified the "extrinsic factor" in liver as vitamin B_{12} and described its structure in 1955 (Pfeiffer, 1975, p. 156). Vitamin B_{12} is a complex molecule with many forms called cobalamins, all with a central cobalt atom (Pfeiffer, 1975, p. 156). The vitamin requires the presence of folic acid for absorption and utilization (Pfeiffer, 1975, p. 157). Though highly concentrated in the liver, vitamin B_{12} performs functions in all cells and is essential for protein, fat and carbohydrate metabolism, the regeneration of bone marrow, and the production of red blood cells (Pfeiffer, 1975, p. 157). It acts as a methyl group transporter, helping synthesize lipotropic molecules, and it increases absorption of other vital substances, such as vitamin A (Pfeiffer, 1975, p. 156). Physical difficulties such as fatigue, weakness, and heart and digestion disturbances, and neurological symptoms including neuritis, numbness, tingling, impaired memory and concentration, confusion, depression, and psychoses may result from vitamin B_{12} deficiency (Pfeiffer, 1975, p. 159). Mainstream medical doctors tend to implement megadoses (e.g. 1000 times the reported daily requirement) of B_{12} more readily than the other vitamins, often in intramuscular injections (Hoffer and Saul, 2008, p. 129). Physicians must take care to administer a metabolically active form and provide adequate folic acid (Hoffer and Saul, 2008, p. 129).

Canadian biochemist, physician, and psychiatrist Abram Hoffer first described the link between schizophrenia and decreased intake of the B vitamins (Hoffer, 2005, p. 316). The first

schizoaffective disorders were recorded at the turn of the nineteenth century, the same time flourmills succeeded in producing "white" refined flours that completely extracted the B vitamin-rich bran and germ (Hoffer, 2005, p. 316). With the dramatic decrease in whole grain consumption came a corresponding increase in manifestations of vitamin B_3 deficiency, from arthritis, to abnormal blood lipid levels, to alcohol addiction, to various forms of mental illness (Hoffer, 2005, p. 316). Vitamin B_3, as well as the essential fatty acids, are cofactors in the production of prostaglandins, the lack of which causes pellagra and other mental deficits (Hoffer and Saul, 2008, p. 148). Chemist Robert Williams successfully synthesized thiamine, or vitamin B_1, the primary anti-beriberi substance, in 1936, and his brother Roger Williams later isolated pantothenic acid (vitamin B_5), and pyridoxine (vitamin B_6) (Hoffer and Saul, 2008, p. 123). Carbohydrate metabolism requires all of these B vitamins, and their dietary reduction through grain refinement and other food processing procedures causes debilitating physical and neurological symptoms (Hoffer and Saul, 2008, p. 124). As nutritional biochemists have realized, each of the vitamins performs a variety of functions in diverse metabolic pathways. In the latter half of the twentieth century, researchers continued to discover uses and structures of vitamins, though many micronutrients have yet to be identified, isolated, and characterized.

The concept of vitamin deficiency as a cause of disease received slow acceptance into prevailing scientific opinion. In the wake of the reception of the germ theory of disease in the late nineteenth century, microbial explanations of disease etiology were generally favored. Perhaps this was because microbial pathogenicity is more universally identifiable, with one pathogen matching one disease, characterized by specific, predictable symptoms in any person (Williams, 1971, p. 6). Nutrient deficiencies, on the other hand, can produce seemingly

unrelated symptoms that vary greatly in different individuals. Mainstream medicine combats infectious disease through vaccination and antibiotic medications, but no comparably straightforward and universal treatment exists for malnutrition. Indeed, nutrition complicates the seemingly simple etiologies of microbial disease. Inadequate diets induce susceptibility to infection, and good food has long been associated with strengthened defense against pathogens (Williams, 1971, p. 7). In the twentieth century, epidemiologists have paid increasing attention to the role of nutrition in infectious disease in search of an answer to the question of what makes some people more resistant to infection than others (Williams, 1971, p. 7).

Sir Robert McCarrison, a British army doctor in India initially studying nutritional causes of goiter in the early twentieth century, promoted nutrition as a crucial field of medical research (McCarrison, 1936). His ideas helped shift medicine from the age of confining nutrition research to the established deficiency diseases (scurvy, beriberi, rickets, pellagra, etc.) to a new recognition of nutrition as essential to the epidemiology of all disease (McCarrison, 1936). He summarized the sequence simply: "faulty food, faulty nutrition, faulty function, faulty structure, faulty health, disease," and stated, "It is in most cases the patient who must be treated rather than the disease from which he suffers, and in this treatment nothing is so important as maintaining nutrition" (McCarrison, 1936). McCarrison argued for the rationality of focusing medicine as a whole on nutrition, asserting that inadequate nutrition was more widespread and destructive than commonly believed.

General Malnutrition

Most organisms experience suboptimal nutrition throughout their lifetime under normal environmental conditions (Williams et al. 1973 p 4). Dr. Roger Williams states, "Natural

selection favors short term (emergency) survival at the expense of long-term health," and the body prioritizes nutrient allocation to the most essential processes, like ATP production, at the expense of complex metabolite synthesis (e.g. immune system components) (Gonzalez *et al.*, 2018). Prolonged moderate nutritional deficits result in disorders in any organ or system, from weakened immune function to decreased brain efficiency, and a spiral of perpetuating chronic diseases. Malnutrition is defined by the American Medical Association Council on Foods and Nutrition as "A state of impaired functional ability or deficient structural integrity or development brought about by a discrepancy between the supply to the body tissues of essential nutrients and calories, and the biologic demand for them" (Pfeiffer, 1975, p. 4). There are two categories of malnutrition: primary and secondary (Pfeiffer, 1975, p. 4). Primary malnutrition is caused by food source factors including inadequate food availability, poor food choice, contaminated foods, and insufficient soil nutrients (Pfeiffer, 1975, p. 4). Secondary malnutrition results from the body's inability to use necessary amounts of nutrients because of interference with digestion, essential nutrient absorption or utilization, or increased requirement, destruction, or excretion (Pfeiffer, 1975, p. 4). Even in first-world countries, where calories are abundantly available, inadequate nutrition and the long-term degenerative diseases it causes are prevalent. Research surveys in the 1970s suggested that up to 80% of Americans were malnourished, having low levels of one or more essential nutrients (Pfeiffer, 1975, p. 3). Most cases of malnutrition in America are not identified by patient or doctor, even after complications of deficiencies lead to disease diagnoses.

Poor eating habits, unavailability of nutritionally rich foods, and nutrient depleting agricultural and food processing practices account for much of this rampant malnutrition

(Pfeiffer, 1975, p. 21). Soil erosion and adulteration with chemical fertilizers and pesticides diminish the nutritional quality of our crops (Pfeiffer, 1975, p. 24). In the 1950s, physician and researcher Dr. Maynard Murray investigated the soil demineralization caused by large-scale agriculture (American Academy of Environmental Medicine, 2010). He found that replenishing soil with a trace mineral extract from seawater improved crop nutrient content and the health of lab animals who consumed these re-mineralized plants (American Academy of Environmental Medicine, 2010). Modern livestock feeding practices reduce the nutrients obtained from our meat, and refinement and use of additives severely limits the nutritional quality of our packaged foods (Pfeiffer, 1975, p. 25). Most of these industrialized techniques result in faster, cheaper and longer lasting food products and provide more people with basic macronutrients without the correct corresponding ratios of micronutrients they need to process them (Pfeiffer, 1975, p. 26). Restoring, enriching, or fortifying processed foods, such as refined flours, with vitamins and minerals based on government recommended values or "population needs" cannot reestablish the complex nutrient composition of the original food (Pfeiffer, 1975, p. 31).

Preventive nutrition is important in reducing infant and maternal mortality, infectious disease mortality, and overall life expectancy, productivity, and quality (Pfeiffer, 1975, p. 7). The medical community has recognized the correlation between poor diet and incidence of overweight and obesity, and it has linked overweight with numerous other chronic conditions, including diabetes, heart disease, and rheumatic disease (Pfeiffer, 1975, p. 7). There has been less explicit research on the direct relationship between nutrient deficiencies and chronic illnesses, though many sources indicate that poor nutrition constitutes a primary factor in the development of these diseases (Robinson, 1977). Dr. Miles Robinson, former medical advisor to

two U.S. Senators, articulated the public health hazard of a modern medical dogma that ignores Americans' poor diet (Robinson, 1977). He wrote, "The ever present risk in medical research and practice is that we may accept as basically normal a common practice of today (for example, the eating of sugar and other refined food) and then build a massive structure on top of this premise which never gets to the bottom of the problem" (1977). Indeed, the medical establishment has adopted this avoidance approach. The pharmaceutical model of medicine is the "massive structure" and its intrinsic inefficacy is evidenced by the dramatically increased costs of chronic debilitating disease (W. Raghupathi and V. Raghupathi, 2018).

In their book on naturopathic nutrition, or "the therapeutic use of nutrient-rich foods and nutritional supplements to improve health and prevent disease," Abram Hoffer, PhD, MD and Jonathan Prousky, ND describe the phenomenon of general malnutrition sprouting diseased states:

> Poor eating and nutritional ignorance have…led to an increase in chronic disease. The dilemma is caused by the combination of the pervasive power of the high tech food processing industry and the poor quality of the nutritional education given to our children. It follows that there will be no solution to the problem of chronic illness until we become aware that only by eating foods that can nourish us properly will there ever be a decrease in the growth of chronic disease. (Hoffer and Prousky, 2006, p. 9)

Though essential to good health, obtaining a state of optimal nutrition is not often simple, especially if one is already ill. The body requires vastly different quantities of nutrients depending on its state of health or disease. For example, in biochemical stress situations, many animals' vitamin C synthesis increases about ten-fold in response to greater demand (Levy,

2002, p. 40). In non-vitamin C producing animals such as humans, stress situations, from acute infection to schizophrenia to cancer, cause the use of vitamin C to far outpace its intake (Levy, 2002, p. 40). While the Recommended Daily Allowances (RDAs), established by the Food and Nutrition Board of the National Academy of Sciences, specify nutrient requirements for avoiding the severe deficiency diseases, they do not address the needs for optimal health (Pfeiffer, 1975, p. 22). The National Institutes of Health Office of Dietary Supplements defines RDA as the "average daily level of intake sufficient to meet the nutrient requirements of nearly all (97%-98%) healthy people" ("Nutrient Recommendations"). Percent daily values on food packaging labels are based on RDA amounts ("Nutrient Recommendations"). The maintenance of good health for most individuals requires amounts of micronutrients independent of RDA values. Orthomolecular physicians agree that eating a "balanced diet" seldom provides ill patients with the nutrients they require to combat disease. The vast differences in individuals' innate nutritional needs further complicates the determination of an adequately nutritious diet.

Genetic Variability and Biochemical Individuality

Orthomolecular nutrition diverges from the standard nutritional emphasis on eating certain amounts of each "food group" as the way to obtain all necessary nutrients. Orthomolecular philosophy is predicated on the individuality of people's metabolic biochemistry. The formal theory of biochemical individuality was proposed by Dr. Roger Williams, who published a book on the subject in 1956 (Hoffer and Saul, 2008, p. 9). He explains this principle in relation to any nutrition-related disease: "Those individuals who are susceptible to the disease have, because of their biochemical individuality, distinctive patterns of nutritional needs that are not adequately met when they eat in their accustomed manner"

(Williams, 1971, p. 8). Rather than define inadequate nutrition by set requirements for the average person, Williams defines it as an individualized state that produces a cellular environment in which cells cannot maintain their proper functions and in which pathogens can flourish. The likelihood of experiencing this state is wholly dependent on the person's genetic material and his cells' chemical environment.

In the 1970s, more diseases became recognized as genetotrophic, which Williams defines as "predisposed by heredity and precipitated by nutritional factors" (Williams, 1971, p. 21). As Dr. Abram Hoffer quips, "The problem is not in our genes, it is in the way we feed our genes" (Hoffer, 2005, p. 314). Modern clinicians studying epigenetics echo this assertion that gene expression determines the fate of the patient more than genetic predisposition (Gonzalez 2018). One example of an easily identifiable genetotrophic disorder is phenylketonuria. In this disease, an inherited heightened sensitivity to the amino acid phenylalanine produces brain cell toxicity and mental retardation (Pauling, 1968). Doctors understand that abnormal metabolic machinery precipitates this disease, and avoiding phenylalanine in the diet resolves the symptoms (Williams, 1971, p. 21; Pauling, 1968). Other micronutrients may inhibit genetic tendencies towards disease. Vitamin D, for example, regulates thousands of genes involved in cell growth, differentiation and cytokine production by directly interacting with DNA, actively preventing cellular malfunctions such as cancer (K. Emonds, personal communication, September 5, 2018). Most biochemical "abnormalities" do not manifest in such specific, compartmentalized diseases as phenylketonuria. It is often impossible to classify and differentiate "normal" and "abnormal" cell metabolic activity, as individuals experience a wide range of functionality that changes with life circumstances. The body may function

sub-optimally without a person approaching their doctor for treatment, and doctors themselves have few clear answers for those complaining of nebulous symptoms, termed low energy, forgetfulness, brain fog, or the vaguest, aging. The establishment of good health requires linking these symptoms with cellular needs.

A body needs the right combination of chemicals (macronutrients, vitamins, amino acids, minerals, etc.) in the right proportions for that body at that moment in time (Williams, 1971, p. 46). The production, assimilation, and active functions of nutrients depend on a plethora of variable factors. Many vitamins are not stored in the tissues and become permanently inactive after performing their biochemical function once, so regular oral intake is essential. Specific vitamin requirements depend on the intake of the substances that participate in its biosynthetic and functional pathways in addition to the body's innate capacity to form and use the vitamin (Williams, 1971, p. 72). Even a standard source, *The Heinz Handbook of Nutrition*, has stated, "There is little justification in nutritional thinking for the concept that a representative prototype of *Homo sapiens* is one who has average requirements with respect to all essential nutrients and thus exhibits no unusually high or low needs" (Williams, 1971, p. 71). While not every individual has "unusually high or low needs" for every nutrient, he or she likely has significantly above or below average need for some. When only considering the nutritional requirements of the statistically determined average person, scientists narrow their treatment efficacy to an impractically small pool of individuals (Williams, 1971, p. 72).

Molecular Basis of Disease

Dr. Linus Pauling, Nobel laureate for both Chemistry and Peace, developed the concept of molecular disease in the 1950s. He pioneered the idea that disease arises from physical

influences, primarily changes in metabolism or cellular nutrition, rather than inherently faulty organs or psychosocial causes (Hoffer and Saul, 2008, p. 14). He emphasized the role of molecules' structural chemistry in the disease process and proposed the use of biochemical manipulation in the body to treat disease (Pauling, 2001, p. 1237). As his interest in nutritional therapy increased, he specialized in the study of vitamin C, first as a cure for acute viral illnesses like the common cold, and then as a broader health-promoting substance, with potent effects against other diseases, such as cancer (Pauling, 2001, p. 1238). Pauling founded the Institute of Orthomolecular Medicine in 1973 to carry out scientific research related to the principles of nutritional medicine (Pauling, 2001, p. 1238). The center was later renamed the Linus Pauling Institute of Science and Medicine, now located at Oregon State University, Corvallis, Pauling's alma mater (Pauling, 2001, p. 1238).

In a monumental 1968 article published in the journal *Science*, entitled "Orthomolecular Psychiatry," Pauling provides a detailed chemical and evolutionary explanation of the molecular, genetotrophic theory of disease, addressing why some individuals (often those exhibiting illness) require vastly greater amounts of essential nutrients than other people (Pauling, 1968). Vitamins and minerals primarily function in enzymatic reactions, serving as coenzymes for important enzyme complexes (Pauling, 1968). A random genetic mutation may generate a structurally altered apoenzyme with a greatly reduced affinity for its coenzyme (Pauling, 1968). It has been shown that decreased affinity of an enzyme for its vitamin cofactor accounts for about a third of all genetic variations (via several single-nucleotide polymorphisms) (Ames *et al.*, 2002). For example, the enzyme methylmalonyl-CoA mutase requires vitamin B_{12} to convert methylmalonic acid to succinic acid, and in the disease methylmalonic aciduria, this reaction is significantly

slowed by the inability of the enzyme to effectively bind B_{12} (Ames *et al.*, 2002). Increasing the concentration of the coenzyme, B_{12}, can counteract the effect of the lowered combining constant value and allow the formation of enough of the active enzyme to catalyze the reaction effectively (Pauling, 1968). Allelic diversity in the genes that control the production of each enzyme causes different individuals to vary in the efficiency of their apoenzymes (Pauling, 1968). It follows that different people require different coenzyme concentrations to allow optimal enzymatic function, and that deficiency states are individualized and varied (Pauling, 1968).

Scientists have found specific genetic mutations that lead to dramatic changes in protein structure, rendering the protein dysfunctional. Pauling discovered that a substitution of one specific amino acid residue in the molecule hemoglobin's beta chain dramatically changes the molecule's properties and produces the serious disease sickle cell anemia (Pauling, 1968). Especially deleterious mutations are often selected against over evolutionary time. However, many variations in protein structure can cause sub-optimal functionality that persists as long as there are no resulting significant decreases in organism fitness (Pauling, 1968). It is difficult to detect less dramatic variances in enzymatic efficiency and pinpoint their exact effects through experimentation, but smaller changes in protein structure can nonetheless lead to long-term illness (Pauling, 1968). Many people produce malformed hemoglobin (over 100 abnormal forms are known), though they do not experience clinical anemia (Pauling, 1968). However, individuals with subtle deleterious changes in protein structure and function may suffer from different kinds of elusive "mystery" illnesses.

Pauling particularly focused his investigations on vitamin C, tracing its functions, the evolution of its biosynthetic pathway, and the manifestations of its deficiency. His research built

on previous work by biochemist Irwin Stone, who first theorized on the genetotrophic basis of hypoascorbemia, or insufficient ascorbate, and reported vitamin C's ability to treat the innumerable disorders generated by sub-clinical deficiency (Pauling, 1968). Humans lost the capacity to express the gene for the enzyme that produces ascorbic acid roughly 25-60 million years ago (Pauling, 1968). This liver enzyme, L-gulonolactone oxidase (GLO), converts glucose into the precursor of vitamin C (Levy, 2002, p. 41). The gene is present, though untranslated, in many non-human primates, some bats, and guinea pigs, as well (Levy, 2002, p. 39). Pauling makes the evolutionary argument that even a small fitness advantage would cause a GLO non-expressing mutant to eventually replace an earlier species (Pauling, 1968). Microbiological research has shown that in many cases, bacterial auxotrophs mutated to lose the genetic capacity to create an essential nutrient have a significant competitive advantage over prototrophs when both are grown on media supplemented with that nutrient (Pauling, 1968). Furthermore, a gene deletion mutant has a selective advantage over a point mutant—with both mutations inactivating the same biosynthetic machinery—when the needed substance is provided (Pauling, 1968). Eliminating the expression of an entire gene conserves more energy for the organism to devote to other growth and development processes (Pauling, 1968). This altered allocation of energetic resources may have been favorable for certain primates because they obtained an adequate supply of vitamin C in their diet (Pauling, 1968). Over time, our ancestors' environment may have changed to reduce the amount of dietary ascorbic acid available (Hoffer and Saul, 2008, p. 84). This may have involved early humans moving from tropical areas with abundant fruits and green vegetables to colder regions with fewer sources of the vitamin. Dr. Hoffer and scientist Harry Foster have proposed that a similar evolutionary change is occurring in which humans are

losing the ability to transform tryptophan into the coenzyme nicotinamide adenine dinucleotide (NAD), thereby increasing some people's need for supplemental niacin, another known precursor of NAD (Hoffer, 2005, p. 315).

Optimal Nutrition

Optimum cellular and organismal growth rates or functionality may require many times the amount of a vital substance than generally considered sufficient to avoid deficiency symptoms. Pauling based this theory on studies of the wild type fungus *Neurospora sitophila* and pyridoxine-requiring mutant strains reported by Drs. George Beadle and Edward Tatum in 1941 (Pauling, 1968). For this and most other unicellular organisms, a logarithmic-shaped growth rate curve occurs with increasing concentrations of a given life-sustaining substance (Pauling, 1968). When the substance is a substrate or a cofactor in an enzymatic reaction, the plot displays the characteristics of Michaelis-Menten kinetics (Pauling, 1968). The amount of the vital substance synthesized by an organism nearly always falls below the amount that produces optimal growth (Pauling, 1968). Beadle and Tatum demonstrated that wild type *N. sitophila* reached its peak growth rate with 7 percent more pyridoxine than it could produce endogenously (Pauling, 1968). Increased growth rate is balanced against the greater amount of energy required to synthesize more substrate (if not provided in excess in the growth medium) and more of the molecules that metabolize it (Pauling, 1968). This energetic tradeoff results in organisms that function adequately, though not optimally, on the nutrients available in the environment to which they have adapted. Using the principles of Michaelis-Menten reaction kinetics, Pauling observed that the lowered rates of reaction resulting from a mutated enzyme may be overcome by increasing substrate concentrations (e.g. 10- to 200-fold) compared to the

concentration needed to produce a normal rate in a non-mutated enzyme (Pauling, 1968). The term substrate includes coenzymes such as the vitamins and trace minerals, as they are consumed (i.e. not regenerated) at the end of the reaction. An individual may have many mutated enzymes with reduced efficiency and still function tolerably in the world. However, when damaging lifestyle factors, from poor diet to cigarette smoking, weaken already inefficient metabolic pathways, illness ensues. The amount of a vitamin required to avoid its associated deficiency disease has little relevance to the value required by an individual for optimal, or even fair, health (Pauling, 1968).

Pauling found that various mammals' production of vitamin C is proportional to their body weight. The corresponding optimal amounts for humans based on this proportion is 2-19 grams per day, about 10-100 times the RDA (Pauling, "Congress," 1977). Pauling asserts that we may compare human nutritional requirements to those of mammals because scientists have devoted much more effort to researching the dietary compositions that optimize growth, reproduction, and resistance to disease in laboratory mammals than humans, and human requirements are often analogous to those of other mammals (Pauling, "Congress," 1977). He paid particularly close attention to the recommended vitamin C in diets of guinea pigs and monkeys, as, like humans, these two mammals cannot produce the vitamin. Both animals have a standard intake in the gram range, over 10 times the RDA for humans (Pauling, "Congress," 1977). Ultimately, Pauling concluded that a human's optimal amount of vitamin C falls somewhere within the broad range of 250 mg to 10 g per day (5 to 200 times the RDA) (Pauling, "Congress," 1977). In his book on Vitamin C, physician Thomas Levy cuts out the low end of this spectrum, recommending 6 to 12 g for a healthy adult (Levy, 2002, p. 440). Based on lab

mammal data on some other vitamins, Pauling suggests that human optimal intakes for vitamins A, B_1, B_2, and B_6, are at least two to five times their respective RDAs (Pauling, "Congress," 1977).

While many orthomolecular researchers cite the general nontoxicity of most vitamins at higher than RDA doses, they provide the most detailed evidence regarding vitamin C. Extrapolations from mammal studies indicate that a human may ingest a daily dose of 350 g of ascorbic acid without experiencing toxic effects (Cameron and Pauling, 2018, p. 118). In observations and research on groups of people taking above RDA doses, one time ingestion of 125 g of the vitamin led to no harm, and at least hundreds of people maintain daily doses in the tens of grams for months and years without reporting any ill effects (Pauling, "Congress," 1977). When taken in large amounts, some ascorbic acid in some individuals may be converted into oxalic acid, a precursor to kidney stones, though the incidence of ascorbate-induced oxalate kidney stones has not been confirmed (Cameron and Pauling, 2018, p. 119). The estimated 50% effective lethal dose (LD_{50}) of vitamin B_3 is 200 g, 10,000 times the RDA (Pauling, "Orthomolecular Theory," 1977). Other water-soluble vitamins have no known lethal dose (Pauling "Congress," 1977). Fat-soluble vitamins, such as A and D, exhibit toxicity in some people at many times RDA values (Pauling "Congress," 1977). Most people who take a vitamin in extreme excess experience nausea and/or diarrhea, which alerts them to reduce their intake before the onset of more severe effects (Hoffer and Saul, 2008).

Mental Illness and Nutrition: Orthomolecular Psychiatry

Organisms interact with both their chemical environment and their psychosocial environment, and these contexts intertwine inextricably (Hoffer, "Supernutrition," 1977).

Psychological disorders emerge from a variety of causal factors, including infection; allergies, autoimmune, and other chronic inflammatory conditions; drugs; and severe emotional distress (Pauling, 2006, p. 210). Micronutrient deficiencies are involved in all of these etiologies and may comprise an independent cause, as well. It is dangerous for a psychiatrist to slap a psychogenic diagnosis on a patient, as this often stifles the search for the root cause and the patient's biochemical needs (Hoffer, 2005, p. vii). Abram Hoffer, M.D., Ph.D. opened the medical world's eyes to the value of using vitamins at doses many times higher than RDA values to treat mental disorders. Shortly after obtaining a degree in psychiatric medicine in 1949, Hoffer entertained doubts about psychosomatic theory and the ability of psychoanalysis to treat disease (Hoffer, 2005, p. 45). He worked with English psychiatrist Dr. Humphry Osmond on research initiated by Osmond and neuroscientist Dr. John Smythies that demonstrated similarities between the experience of mescaline intake and the schizophrenic state (Hoffer, 2005, p. 47). The first practitioner of orthomolecular psychiatry may have been Dr. Arthur Sackler, who observed positive results with some schizophrenic patients by subcutaneously injecting them with high doses of histamines (Hoffer, 2005, p. 53). Sackler's research inspired Hoffer's inquiry into niacin and niacinamide as a treatment to block the transmethylation of excess adrenaline in the brain into a mescaline-like, hallucinogenic substance (Hoffer, 2005, p. 54). Hoffer drew upon previous research on niacin as a successful treatment for the schizophrenia-like mental disorders associated with pellagra, the classic vitamin B_3 deficiency disease (Hoffer, 2005, p. 70). Niacin, a methyl group acceptor, was later confirmed to act as an antagonist to adrenaline, blocking its formation through the methylation of noradrenaline and preventing the formation of the toxic byproduct (Hoffer, 2005, p. 55).

The 1950s saw a biochemical revolution in psychiatry, in which scientists recognized that mental illness is predicted most strongly by family history or inherited genes and biochemical imbalances (Walsh, 2014). A growing understanding of the molecular biology of the brain undermined the *tabula rasa* theory, that every newborn's psyche is a blank slate for sensory inputs and experiences to influence (Walsh, 2014). This revolution instigated a turn to pharmaceuticals to alter brain biochemistry, producing marked but partial improvements, and serious side effects (Walsh, 2014). Orthomolecular physicians and nutritionists observed that long-term pharmaceutical prescriptions caused extensive cellular damage. Some tranquilizers and anti-psychotic drugs chelate trace metals, such as manganese, leading to deficiency states (Hoffer, 2005, p. 262). Manganese deficiency can produce involuntary muscle spasms, and supplementation with the element eliminates this side effect (Hoffer, 2005, p. 262). Anti-epileptic drugs interfere with vitamin E absorption, and several kinds of drugs reduce vitamin D activity (Hoffer and Saul, 2008, p. 116, 134). Cholesterol-lowering statin drugs destroy ubiquinones, such as coenzyme Q10, and metformin used for diabetics depletes magnesium (K. Emonds, personal communication, September 5, 2018). Oral hormone contraceptives lower blood levels of the B vitamins, folic acid and vitamin C, and elevate copper (Hoffer and Saul, 2008, p. 40). These are only a few representative examples of the nutrient depletion and metabolic interference caused by prolonged prescription drug intake, and this does not take into account many of their immediate toxic and allergenic effects. Medications prescribed by a qualified practitioner and taken as directed kill about 100,000 Americans each year, the fourth leading cause of death in the country (Gonzalez *et al.*, 2018). Orthomolecular physicians now administer nutrients to replenish the deficiencies caused by patients' prescription

drug use and to lower the drug doses necessary to produce the intended effects (Hoffer and Saul, 2008, p. 256). Some forward-thinking physicians in the 1950s believed that the future of psychiatric treatment would use natural body and brain chemicals to restore normal brain function.

With the help of their research team, Hoffer and Osmond proposed the adrenochrome hypothesis, that some individuals produce high levels of adrenochrome, a hallucinogen, as a byproduct of adrenaline, which causes schizoaffective disorders (Hoffer, 2005, p. vi). With this discovery in the mid-1950s, they developed the first major biochemical theory of the origin of schizophrenia (Hoffer, 2005, p. vi). In the absence of adequate NAD, oxidized adrenaline loses another electron to become adrenochrome, a highly reactive compound that forms other oxidized indoles (Hoffer, 2005, p. 63). Adrenochrome has been shown to slow the Krebs cycle (Hoffer, 2005, p. 64). The respiratory coenzymes involved in this process include cocarboxylase with thiamine (B_1), Flavin adenine dinucleotide (FAD) containing riboflavin (B_2), and nicotinamide adenine dinucleotide (NAD) containing niacinamide (B_3) (Hoffer, 2005, p. 66). The team proposed that supplementation with these vitamin coenzymes would decrease the toxic impact of adrenochrome in mentally ill patients (Hoffer, 2005, p. 66). Additionally, niacin dilates capillaries, improving blood flow and oxygen delivery to important areas such as the brain's frontal lobes, which often receive a poor supply of blood in schizophrenics (Hoffer, 2005, p. 73). Administering IV nicotinic acid has normalized irregular brain wave patterns and has been found clinically useful in treating epilepsy, lessening the needed dose of anticonvulsants (Hoffer, 2005, p. 106). After discovering that niacin therapy reduces or eliminates alcohol addiction, Hoffer communicated this effect to Bill W., cofounder of Alcoholics Anonymous, who became a strong

proponent of this treatment and supporter of Hoffer's research (Hoffer, 2005, p. 117). Further study indicates that vitamin B_3 therapy helps break other drug addictions, such as nicotine dependence, as the vitamin outcompetes the drug as the primary nicotinic acid receptor agonist in the brain (Hoffer, 2005, p. 118). Hoffer's study of a single nutrient and a single medical diagnosis expanded our understanding of the incalculable potential for vitamin therapy to heal mental illness.

Hoffer began to investigate the value of ascorbic acid as a powerful antioxidant in the brain that prevents the oxidation of adrenaline and other catecholamines into toxic byproducts (Hoffer, 2005, p. 73). Though vitamin C permeates nearly all tissues, the brain contains the second highest concentrations of this vitamin, after the adrenal glands (Hoffer, 2005, p. 65). Starting with low doses, Hoffer increased the amounts of niacin and vitamin C to reach therapeutic levels, typically 3-18 g niacinamide or nicotinic acid and at least 3 g ascorbic acid per day, with no apparent adverse effects (Pauling, "Orthomolecular Theory," 1977). Many patients experience a harmless flush on their faces and other parts of their bodies due to vasodilation immediately after the first dose of niacin, though severely ill patients rarely flush until years into treatment (Hoffer, 2005, p. 77). Hoffer first administered this treatment of gram doses of niacin and vitamin C to severely ill patients who did not respond to traditional psychoanalysis, electro-convulsive therapy, or even insulin coma therapy. When he realized the immense efficacy of the megavitamin treatment, he used it as a primary approach, often in conjunction with conventional pharmaceutical treatments such as antipsychotic, antidepressant, and tranquilizer drugs, as necessary (Hoffer, 2005, p. 84). Hoffer and his colleagues set in motion the use of megavitamin psychiatric therapy, which began with a combination of high

doses of vitamins B_3 and C and doubled the recovery rate of recent-onset schizophrenics (Hoffer, 2005, p. 84).

In the early 1950s, the placebo effect became a subject of scientific interest, and researchers first developed and used double blind, randomized, controlled studies to remove both the patient placebo effect and researcher bias from biomedical research (Hoffer, 2005, p. 90). Many physicians still relied heavily on clinical trials to assess the efficacy of treatments, comparing their results to those of existing methods, or to no treatment (Hoffer, 2005, p. 90). Hoffer's research team conducted the first double blind studies in psychiatry, paving the way for the modern treatment trial sequence (Hoffer, 2005, p. vi). Phase one testing evaluates the toxicity of the therapeutic substance, and phase two involves pilot trials of the substance to identify the optimally effective treatment dose, mode of administration, and duration, as well as side effects (Hoffer, 2005, p. 237). In phase three trials, multiple clinics perform double blind controlled studies to assess efficacy methodically and present results to the broader medical community (Hoffer, 2005, p. 237). Eight double blind, controlled, randomized trials from 1953 to 1960 on schizophrenic patients demonstrated that niacin or niacinamide treatment improved the two-year recovery rate from 35 to 75 percent (Hoffer, 2005, p. 93).

Despite devoting time and resources to these bias-reducing research methods, Osmond and Hoffer developed reservations about the use of this technique in clinical medicine. The sound statistical assessment of these experiments requires relatively homogenous study populations in controlled environments, which far from described the enrolled psychiatric patients. Moreover, Hoffer and Osmond believed it was unethical to mislead patients even under research circumstances, and to withhold potentially beneficial therapy (Hoffer, 2005, p. 93).

When kept ignorant about their treatment, patients often lost trust in their doctor, and some would not comply with their treatment conditions (Hoffer, 2005, p. 94). Hoffer also questioned scientists' headstrong faith in the efficacy of double blind studies in eliminating bias (Hoffer, 2005, p. 94).

Fifteen years into his work at the University of Saskatchewan, increased pressure from the Saskatchewan government and the University Hospital research director to cease publishing his team's findings on megavitamin therapy drove Hoffer to resign from his post in 1967 (Hoffer, 2005, p. 170). Hoffer then established a private practice in which he integrated traditional pharmaceutical and megavitamin therapies. During this time, he cofounded the American Schizophrenia Association (ASA) with Osmond and other collaborators in order to educate the public about the causes, symptoms, and treatment of the disorder and support physicians and patients implementing orthomolecular treatments (Hoffer, 2005, p. 200, 258). The ASA later merged with the Huxley Institute for Biosocial Research, a primary contributor to the development of orthomolecular practice in North America (Hoffer, 2005, p. 254). Hoffer also cofounded the Canadian Schizophrenic Foundation in 1969, which ultimately grew into the International Schizophrenia Foundation (Hoffer, 2005, p. 259). In 1967, he coedited the *Journal of Schizophrenia* with Osmond and Dr. David Hawkins, which became the *Journal of Orthomolecular Psychiatry* in 1972, and then the *Journal of Orthomolecular Medicine* in 1986 (Hoffer, 2005, p. 205). By 1970, David Hawkins, M.D., Ph.D., renowned psychiatrist, physician, researcher, and spiritual teacher, doubled the recovery rate among his seriously mentally ill patients using megavitamin therapy similar to Hoffer's (Hoffer, 2005, p. 212). He co-founded the Academy of Orthomolecular Psychiatry in 1971, which later replaced

"Psychiatry" with "Medicine" to accommodate the treatment modality's expanding applications (Hoffer, 2005).

Hoffer himself recognized the continuity between mental and physical health, observing that many of his psychiatric patient's physical complaints resolved during vitamin treatment (Hoffer, 2005). Though not a general practitioner, he saw patients with conditions from viral infections to cancer (Hoffer, 2005). Hoffer discovered kryptopyrrole, or mauve factor, a result of poor hemoglobin metabolism and a biomarker of oxidative stress in the body and a disrupted dopamine pathway in the brain (Hoffer, 2005, p. 313). He also first determined that vitamin B_3 intake helps maintain appropriate cholesterol levels in patients with hypertension (Hoffer, 2005, p. vii). Following his early work in a flour enrichment lab, he linked the widespread shift from whole grain flour to refined flour consumption with subclinical vitamin deficiencies and resulting mental disorders and physical illnesses (Hoffer, 2005, p. 14). He and Dr. Osmond developed a simple and effective questionnaire for diagnosing schizoaffective disorders, the Hoffer-Osmond Diagnostic (HOD) test, still used by psychiatrists today (Hoffer, 2005, p. vi). In the forward of Hoffer and Osmond's 1966 book, *How to Live with Schizophrenia*, Dr. Nolan Lewis articulates the philosophy of the original orthomolecular psychiatrists: "In order to get at the pathology of behavior we must not only study the individual in action, but also the brain and the other organs of the body, particularly those that support the brain directly, and finally the whole individual" (Hoffer, 2005, p. 145). This book greatly inspired Dr. Pauling to begin his investigations of megavitamin therapy (Hoffer, 2005, p. 147).

Linus Pauling began studying the molecular basis of mental disease in the 1950s (Pauling, 2001, p. 1237). He read work by Hoffer and Osmond on megavitamin therapy for

schizophrenia and studies of vitamins in connection to mental disease by Drs. Cleckley and Sydenstricker, and others (Pauling, "Orthomolecular Theory," 1977). Pauling explored the functions of vitamins in the brain and proposed mechanisms for how different concentrations may affect brain function. Pauling found that schizophrenic patients excreted significantly lower levels of ascorbic acid, niacin, and pyridoxine than controls, indicating lower levels in body tissues and perhaps increased use and subsequent elevated need of these substances (Pauling, "Orthomolecular Theory," 1977). He joined the scientific advisory board of the American Schizophrenia Association (ASA), actively contributing his research and insights (Hoffer, 2005, p. 206).

In his groundbreaking 1968 paper, Pauling first describes the concept of orthomolecular medicine in the context of mental illness. He states that in addition to the three primary treatment methods for psychiatric disorders—psychotherapy, chemotherapy, and convulsive shock therapy—there exists a different and better approach: orthomolecular therapy (Pauling, 1968). He defines orthomolecular psychiatric therapy as "the treatment of mental disease by the provision of the optimum molecular environment for the mind, especially the optimum concentrations of substances normally present in the human body" (Pauling, 1968). He rejects the division between mental and physical disease, asserting that both psychological and physiological conditions may result from low brain concentrations of the vitamins thiamine (B_1), nicotinic acid or nicotinamide (B_3), pyridoxine (B_6), cyanocobalamin (B_{12}), biotin (H), ascorbic acid (C), and folic acid (Pauling, 1968). He proclaims, "I believe that mental disease is for the most part caused by abnormal reaction rates, as determined by genetic constitution and diet, and by abnormal molecular concentrations of essential substances" (Pauling, 1968). His article

provoked immense criticism from the American medical establishment, which was especially hostile towards someone outside the medical profession making claims about their field (Hoffer, 2005, p. 209). None of his critics attempted to replicate his studies, a trend that continued with other orthomolecular scientists (Hoffer, 2005, p. 209).

Nutrient imbalances generated by genetic and environmental factors can influence brain biochemistry in multiple ways. Most of the neurotransmitters in the human brain are synthesized from nutrients (amino acids, vitamins, minerals, etc.) obtained from food (Walsh, 2014). For example, serotonin is produced from tryptophan, an essential amino acid, requiring vitamin B_6 as a cofactor, and dietary choline is a precursor for acetylcholine (Walsh, 2014). Vitamin C is a coenzyme in catecholamine synthesis, including the conversion of dopamine into norepinephrine and serotonin (Walsh, 2014). This vitamin also regulates levels of adrenal hormones and participates in myelin sheath synthesis (Hoffer and Saul, 2008, p. 85, 98). Diminishing the raw materials for neurotransmitter production disrupts healthy brain communication. Nutrients present in particular ratios also help control gene expression that affects the production of proteins that determine neurotransmitter activity, such as neuron transporter proteins that govern neurotransmitter reuptake (Walsh, 2014). DNA methylation may silence transporter gene expression, and DNA acetylation enhances expression (Walsh, 2014). In general, under-methylation is associated with depression and over-methylation with anxiety and schizophrenia (Walsh, 2014). Many nutrients perform methyl donor or acceptor functions, some binding directly to DNA, to regulate gene expression in the brain (Walsh, 2014). Additionally, antioxidant nutrient deficiencies weaken the brain's protection from toxins that wreak neurological havoc (Walsh, 2014).

People may not associate mental illness with inadequate nutrition because they only recognize the classic symptoms of the extreme deficiency diseases and because they believe eating a standard diet with each of the "food groups" precludes malnutrition (Hoffer and Saul, 2008, p. 7). Gradually, many scientists have acknowledged that sub-clinical deficiencies from poor nutrition cause behavioral disorders, from slightly lowered cognitive function to neurotic or psychotic behaviors (Pfeiffer, 1975, p. 10). Pauling asserted that symptoms of deficiency-related diseases may be localized to the brain because of its greater sensitivity to its molecular environment (Pauling, "Orthomolecular Theory," 1977). Also, a genetic mutation may lead to decreased production of an enzyme in one particular organ, such as the brain, and not another (Pauling, "Orthomolecular Theory," 1977). Decreased blood-brain permeability, inability to synthesize a vital substance in brain, or increased rate of substance breakdown in the brain may contribute to a brain-specific deficiency (Pauling, "Orthomolecular Theory," 1977). Blood tests for nutrient levels may not indicate a brain deficiency, as serum levels of a substance do not always correspond to cerebrospinal fluid and brain tissue levels (Pauling, "Orthomolecular Theory," 1977). This complication applies to other organs and tissues, as well. Estimates suggest that schizophrenic disorders come from roughly 25% genetic inheritance, likely including a mutated gene that controls the metabolism of one or more vital substances (Pauling, "Orthomolecular Theory," 1977). The other causes must include non-inherited genetic and environmental factors, such as toxin exposure and nutrition (Pauling, "Orthomolecular Theory," 1977). High dose vitamin therapy can reduce the penetrance of the schizophrenia-inducing genes, enhance related biochemical pathways to compensate for this inherited aspect, and remediate damage from malnutrition and toxicity (Pauling, "Orthomolecular Theory," 1977).

When conscientiously administered, orthomolecular therapy provides the most comprehensive treatment for diseases of the brain, and any other organ.

Carl Pfeiffer, M.D., PhD., a co-founder of orthomolecular medicine, collaborated with Dr. Hoffer and researched the relation of many vitamins and trace minerals to mental illnesses. He emphasized the importance of a nutritious diet for patients in psychiatric hospitals, condemning the decrease in food quality as mental hospitals have grown in size (Pfeiffer, 1975, p. 8). He improved diagnostics by defining diseases by their causal biochemical abnormalities, drawing attention to the absurdity of applying modern diagnostic labels to symptoms. "Even when used in the plural, the term "schizophrenia" is an inadequate and misleading diagnosis," he wrote. "'Disperceptions of unknown cause' is a better term" (Pfeiffer, 1987, p. 10). Ever questing to replace arbitrary labels with identifiable causes, he discovered several different etiologies of schizophrenic symptoms using blood histamine levels, urine kryptopyrrole levels, measures of trace elements and vitamins, and allergy testing. His five main biotypes of schizophrenia are histapenia, with low blood histamine and excess copper; histadelia, with high blood histamine and low copper; pyroluria, a zinc and vitamin B_6 double deficiency caused by excess kryptopyrrole; cerebral allergy (especially to wheat gluten); and nutritional hypoglycemia (Pfeiffer, 1987, p. 10). Other related contributors include thyroid disorders, folic acid and B_{12} deficiencies, heavy metal or drug toxicity, chronic *Candida* infection or other microbiota pathology, and metabolic imbalances of dopamine, serotonin, endorphins, or prostaglandins (Pfeiffer, 1987, p. 17).

Building upon previous knowledge of niacin and ascorbic acid deficiencies and mental illness, Pfeiffer investigated other nutrient imbalances in the mentally ill to form more

comprehensive treatment regimens. Recognizing the essentiality of biochemical individuality, he devised specialized treatments based on chemical tests, psychiatric evaluations, and consultations, in addition to previous experience and research (Pfeiffer, 1987). Pfeiffer's treatments implemented the synergistic effects of many orthomolecular substances. The powerful duo of vitamin C and niacin increased mental focus and clarity, and produced a lasting feeling of wellbeing in many of his patients, regardless of their exact diagnosis (Pfeiffer, 1987). Pfeiffer believed these results may relate to both these vitamins' capacity to decrease toxic copper levels (Pfeiffer, 1987, p. 24). Combining vitamin B_6, manganese, and zinc relieved symptoms of low blood sugar (Pfeiffer, 1987). Inositol (vitamin B_8) activated by the element lithium helped anxious or schizophrenic patients with high copper and low zinc levels (Hoffer and Saul, 2008, p. 144). Pfeiffer found these nutrient treatments preventive and curative for both chronic disorders and acute problems such as pain, insomnia, and headaches, with a remarkable lack of adverse side effects (Pfeiffer, 1987). Pfeiffer derided the notion of a sudden onset to any disease, and he worked tirelessly to uncover the deeply rooted and fomenting dietary and environmental catalysts of ill health (Pfeiffer, 1987).

In 1973, Pfeiffer founded the Brain Bio Center, later named the Princeton Bio Center, an outpatient clinic and leading institution of orthomolecular research (Hoffer, 2005, p. 262). In the same year, Hoffer, Osmond, Hawkins, Pauling, R. R. Williams, Pfeiffer and others published their findings on orthomolecular treatment of mental illness in a collection of papers entitled *Orthomolecular Psychiatry: Treatment of Schizophrenia* (1973) (Hoffer, 2005, p. 227). Following Pfeiffer's death in 1988, his work was continued by Dr. William Walsh and Dr. Hugh Riordan, among others (Hoffer, 2005, p. 262). These physicians acknowledged the educational

value of case studies and regularly wrote and presented both their laboratory research and clinical findings in the *Journal of Orthomolecular Medicine* (Hoffer, 2005, p. 263). Dr. William Philpott brought clinical ecology and environmental medicine under the orthomolecular umbrella (Hoffer, 2005, p. 263). Following this path, physicians began to explore the roles of food allergens and other environmental inputs in precipitating disease (Hoffer, 2005, p. 263). More clinical research strengthened the links between nutrient deficiencies and allergen toxicities as biological causes of mental conditions such as autism and depression (Hoffer, 2005, p. 264).

In response to orthomolecular theory's foothold in the practice of psychiatric medicine, representatives of the American Psychiatric Association (APA) orchestrated several attempts to discredit orthomolecular medicine (Hoffer, 2005, p. 251). The 1973 APA Task Force Report on *Megavitamin and orthomolecular therapy in psychiatry* pronounced that the claims about high dose vitamin therapy, including niacin and vitamin C, treating mental illness were unsubstantiated, particularly because of a lack of controlled, randomized, blind studies that assess the treatments' measurable efficacy (American Psychiatric Association). The report portrayed Hoffer, Osmond, Pauling, and other researchers and practitioners of orthomolecular psychiatry as frauds in the world of psychiatric medicine (Hoffer, 2005, p. 252). Pauling gave a detailed lecture, later published in the *American Journal of Psychiatry,* addressing the report's misrepresentations of orthomolecular medicine and rebutting the arguments that claimed a lack of evidence to support the validity of orthomolecular theory and the value of its practice (Pauling, "Orthomolecular Theory," 1977). Vitamin therapy's advantages include its safety, low financial cost, limited side effects, and clinical efficacy, provided a knowledgeable practitioner properly assesses the biochemical needs of the individual patient. Pauling defended the

importance of clinical evaluation of orthomolecular treatments, as organizing controlled studies that provide identical treatments to a given subject group contradicts the essential tenets of biochemical individuality and proves fruitless and unethical (Pauling, "Orthomolecular Theory," 1977). Pauling felt so strongly about the importance of implementing orthomolecular therapy, with or without the support of controlled study evidence, that he replied to his detractors in the ASA newsletter, "I believe that a physician who refuses to try the methods of orthomolecular psychiatry, in addition to the usual methods, is failing in his duty as a physician" (Hoffer, 2005, p. 209). Despite Pauling's and others' best efforts at justifying the megavitamin approach, this Task Force report succeeded in discouraging many psychiatrists from joining in vitamin research (Hoffer, 2006, p. 253). While this disparagement halted the momentum of the orthomolecular psychiatry movement, it triggered an expansion of interested practitioners' focus from primarily mental illness to all types of physical disease (K. Emonds, personal communication, September 5, 2018).

Orthomolecular Medicine: Expansion and Pushback

Members of the Academy of Orthomolecular Medicine regularly discuss the interactions among clinical nutrition, environmental and ecological factors, and illness (Hoffer, 2005, p. 260). The field has evolved from focusing on general "megadose" vitamin therapy to a more individualized "optidose" approach. Orthomolecular physicians increasingly incorporate the essential elements of food, chemical, and environmental allergies and sensitivities in diagnosis and treatment. They prioritize uncovering biochemical imbalances over producing diagnoses and strive to eliminate the "trial and error" imprecision of drug administration (Hoffer, 2005, p. 277). They do not discriminate between psychological and physical diseases, with psychiatrists

treating somatic aspects of illness and general practitioners addressing psychosocial health (Hoffer, 2005, p. 278).

As orthomolecular medicine reached a broader array and greater number of patients through complementary and primary medical practices, allopathic doctors continued to express doubts about its efficacy. Every step of the journey towards researching and disseminating information about orthomolecular treatment has been met with resistance by the mainstream medical establishment. Physicians and research scientists like Hoffer, Osmond, Pauling, and Cameron have had to fight against the tide of misrepresentation and blind dismissal of their work (Pauling, 2006, p. 247). Studies often fail to accurately replicate pioneering work on the effects of high dose vitamin administration because of significant deviations in treatment length, dose, and mode of administration, as well as other confounding factors (Pauling, 2006, p. 187). Data may not lie, but results depend on the methodology, type of data collected and ignored, and the statistical measures used to analyze them (Pauling, 2006, p. 249). This makes assessing conflicting reports on the efficacy of high dose vitamin therapy complicated and sometimes emotionally charged. Physicians repeatedly fail to produce favorable clinical results with vitamin therapy because of using incorrect, most often too small, doses (Hoffer and Saul, 2008, p. 63). Some medical doctors practicing orthomolecular medicine have lost their medical licenses for their use of unconventional vitamin therapies that do not meet narrow standards of practice, despite the absence of harm done by the treatments (Hoffer, 2005, p. 268; Pauling, 2006, p. 247). The continuous harassment and threats from the medical boards frighten many physicians away from implementing orthomolecular therapies (Hoffer, 2005, p. 268). Modern mainstream physicians may dismiss the widespread benefits of orthomolecular treatment and vilify its

practitioners for many reasons. Doctors' reliance on medical authorities' statements rather than the primary literature, medical schools' and textbooks' disregard of unorthodox knowledge in the classroom, physicians' fear of ridicule by the medical establishment, and bias against anecdotal and clinical evidence all contribute to the general hostility (Hoffer, 2005, p. 249; Levy, 2002). The capable orthomolecular physician is rewarded by helping patients and seeing them recover, not by his popularity or prestige within the medical profession (Hoffer, 2005, p. 313). Ultimately, good doctors are motivated by compassion in their search for truth.

Orthomolecular treatment requires the patient to make substantial and long-term lifestyle changes, which make it less preferable to the immediate and less apparently obtrusive gratification of pharmaceutical medicine. Many people dismiss the orthomolecular philosophy through a reluctance to give up a well-established way of life. In the modern world, the pharmaceutical and food industries support this attitude, constantly asserting that taking a pill will cure our ills and allow us to eat the nutrient-poor foods we enjoy (Hoffer and Prousky, 2006). The adoption of a new lifestyle of optimal nutrition often changes patients' fundamental understanding of health and medicine. They realize that while they may have considered themselves healthy (eating a "balanced" diet, never needing to visit the doctor, etc.), they never actually understood what "healthy" felt like. Not only do those who consume the optimal doses of nutrients through diet and supplementation have more energy and capacity to live a fulfilling life, they also develop an awareness of the subtleties of health. They find that they can adjust their intake of certain foods and nutrients in response to their state of wellness or illness, without the physician's explicit instruction (Levy, 2002, p. 38). These patients proclaim that they have received a great gift: the knowledge and ability to enhance their own well-being.

Fundamental Causes of Chronic Ill Health

To preface his discussion of the uses of optimal doses of vitamin C to prevent, treat, and cure "incurable" diseases, physician Thomas Levy, MD, JD first explains why this vitamin is essential to human life. Biochemist Szent-Györgyi proposed a theory that the living state is characterized by electron desaturation in the organic molecules of the body's cells, and that the ongoing electron exchange constitutes the organism's most important type of cellular communication (Levy, 2002, p. 34). Put simply, Levy defines life in the molecular sense as "a state in which an optimal degree of electron interchange among cells can take place" (2002, p. 34). Diseased states arise from poor or obstructed electron flow from any number of causes, and cessation of electron exchange results in death. Antioxidant compounds directly aid the flow of electrons among and through the body's cells by donating protons to oxidized molecules (Levy, 2002, p. 34). Placing the north pole of a bio-magnet against the skin brings electrons into the cell, producing a comparable antioxidant effect (K. Emonds, personal communication, September 5, 2018). This electron flow throughout the body maintains subtle electromagnetic fields present in all living organisms (Levy, 2002, p. 34).

Promoters of cellular oxidation (lipid peroxidation, oxidative stress, etc.) cause inappropriate protein molecule cohesion, DNA damage, and other deleterious effects. Oxidizing substances include infectious agents (endotoxins) and their secreted toxic substances (exotoxins) (Williams, 1971, p. 143). Presence of these pro-oxidants correspond with the rapid consumption of antioxidant compounds. This reduction weakens the antioxidant response to additional toxins already present or introduced. Other oxidative toxins include heavy metals such as lead, mercury, and cadmium; pesticides; and cellular byproducts generated by high-energy radiation

(Pfeiffer, 1975, p. 137). Disease pathology from nearly any etiology involves oxidative compounds damaging the body's cells. Levy asserts that vitamin C can treat virtually any illness because it acts as the body's most abundant and available antioxidant, constantly donating electrons to neutralize, destroy, and chelate toxic substances (Levy, 2002, p. 34). Replenishing the body's depleted supply of vitamin C is one of the most important steps in preventing and curing almost any disease.

Before determining a patient's supplemental nutrition program, orthomolecular physicians consider how the patient's diet contributes to their illness. Food toxicities, sensitivities, and allergies constitute primary contributing factors in chronic disease, and without addressing these, supplemental nutrients will not have the intended therapeutic benefits. As Dr. Hoffer and other naturopathic nutritionists describe, humans are adapted to eat food that is whole, alive (or recently alive), nontoxic, variable, indigenous, and scarce (Hoffer and Saul, 2008, p. 20). Many of the Western world's health problems emerge from consuming a diet that instead is artefact (fractionated and reconstituted), dead (preserved and stored), toxic (with chemical additives), monotonous (dependent on a few staple items), exotic, and surplus (Hoffer and Saul, 2008, p. 23). Overconsumption of the wrong foods may generate food sensitivities and metabolic disorders. People regularly consuming foods to which they are allergic often use up certain nutrients at a higher rate, lowering levels of vitamins B_3 and C compared to those who avoid allergens or do not experience allergies (Hoffer and Saul, 2008, p. 75). Hoffer advises the general population to follow the simple rules of eliminating "junk" (e.g. heavily processed) food, and any food that makes you feel sick (Hoffer and Saul, 2008, p. 23).

Much ill health arises from the dependence on refined and processed foods, including the "sugar metabolic syndrome," described by Surgeon-Captain Thomas Cleave, M.R.C.P (Hoffer and Saul, 2008, p. 28). This refers to all the disorders, spanning every organ system, related to the overconsumption of refined carbohydrates. Today, the British eat about 125 pounds of sugar per person per year, 110 pounds more than in 1815 (Hoffer and Saul, 2008, p. 28). This number continues to climb, as members of the industrialized world attempt to satisfy a powerful sugar addiction (Hoffer and Saul, 2008, p. 29). Reliance on refined carbohydrates as dietary staples affects nearly every part of the body: The high concentration of calories with less bulk compared to whole foods leads to overconsumption and overweight and obesity (Hoffer and Saul, 2008, p. 32). Excess simple sugars absorbed into the bloodstream (with a corresponding lack of other nutrients) leads to insulin resistance, hypoglycemia, and diabetes mellitus (Hoffer and Saul, 2008, p. 32). Excess sucrose consumption predicts high cholesterol and cardiovascular diseases more strongly than fat intake (Pauling, 2006, p. 41). The disaccharide's fructose component breaks down into acetate, which the liver converts to cholesterol that enters the bloodstream (Pauling, 2006, p. 43). Absence of vitamins and trace minerals that have been extracted from food lead to micronutrient deficiencies and dependencies, which cause metabolic disorder in any tissue system. Prolonged deficiencies, such as those of the B vitamins, trigger a wide array of mental disorders, including anxiety and depression (Hoffer and Saul, 2008, p. 31). Chronic lack of dietary fiber in combination with excess simple carbohydrates leads to constipation, disruption of healthy gut flora, diverticular disease, and other colon problems (Hoffer and Saul, 2008, p. 31). Absence of sufficient dietary protein to neutralize stomach acid secretions causes damage to stomach lining, increasing susceptibility to peptic ulcers (Hoffer and Saul, 2008, p. 33). Millions

of people likely suffer to one degree from this systemic saccharine disease, for which a dietary shift to whole, nutrient-rich foods provides a solution (Hoffer and Saul, 2008, p. 24).

Orthomolecular physicians recognize that adverse responses to particular foods may manifest in a broad array of physical ailments and such dramatic mental disorders as neuroses and psychoses (Hoffer, "Supernutrition," 1977). Without addressing the patient's food allergies, the treatment for any of the "symptoms" will not benefit him. Out of a collection of sixty psychiatric patients in Hoffer's practice who did not respond permanently to any treatment, including megavitamin therapy, over two-thirds had significant symptom relief after a four-day fast (Hoffer, "Schizophrenia," 1977). Hoffer found that the vast majority were allergic to dairy products, and Pfeiffer and psychiatrist Dr. Philpott have discovered a large number of cereal grain allergies in their mentally ill patients (Hoffer, "Schizophrenia," 1977). Dr. Kenneth Emonds, Ph.D. an orthomolecular specialist in immunology, has found that virtually all of his chronically ill patients, especially cancer patients, have sensitivities to a large quantity and variety of foods, especially gluten-containing grains, cow dairy products, corn, soy, and refined sugar (K. Emonds, personal communication, September 5, 2018). Optimal nutrition, as well as eating a wide variety of foods, decreases the formation of allergies and intolerances (Hoffer, "Supernutrition," 1977).

There are several known etiologies of food sensitivities and allergies that concern the orthomolecular physician. These include the IgE- or IgG-mediated fixed food intolerance, genetically acquired; frequent consumption or redundancy of exposure; cross-reactivity with another environmental allergen; metabolic dysfunction (e.g. dysfunctional sulfuration pathway in the liver or absence of the lactase enzyme); and iatrogenic (drug induced) allergy, related to gut

dysbiosis (microbial imbalance) caused by xenobiotic substances (K. Emonds, personal communication, September 5, 2018). Other immune system malfunctions, including autoimmune disorders, often predispose one towards developing adverse reactions to foods via one or more of these etiological pathways (K. Emonds, personal communication, September 5, 2018). Food allergy often causes widespread and severe illness through the complications of excessive and chronic inflammation. Food that is poorly broken down by faulty digestive enzymes in the gastrointestinal tract contributes to gut dysbiosis, which perpetuates poor digestion. Food particles crossing the gut epithelial layer to enter the bloodstream trigger local inflammation (Gonzalez *et al.*, 2018). This immune system activation leads to continued allergic responses reaching as far away as the brain. Resulting damage to the intestinal walls can cause nutrient malabsorption, nutrient dependencies, and systemic symptoms (Gonzalez *et al.*, 2018).

People may discover sensitivities to foods they hate, as they trigger immediately noticeable unpleasant symptoms such as nasal congestion and intestinal pain (Hoffer and Saul, 2008, p. 36). However, frequent consumption allergies usually comprise foods one loves to eat, which cause less distinct symptoms such as fatigue and depression (Hoffer and Saul, 2008, p. 36). Austrian endocrinologist Hans Selye uncovered the explicit link between food addiction and "masked" allergy, explaining the body's stress response to prolonged exposure to toxins (Selye, 1946). As with any stressor, an individual may become acclimated to the allergic substance. At this point, he no longer exhibits the original acute symptoms, but still accrues damage from increased toxin load (Selye, 1946). With continued consumption, the body's defenses eventually wear down, and another triggering stressor may precipitate full-blown illness (Selye, 1946). Following the acclimation stage, the individual may exhibit an addiction to the

allergic food, experiencing withdrawal symptoms that reinforce the pattern of consumption (Hoffer and Saul, 2008, p. 271). Identifying an allergic substance often requires avoidance for a period to reverse the acclimation, and then reintroduction to demonstrate acute symptoms (Philpott, 1977).

This sequence of alarm, resistance, and exhaustion applies to other environmental and chemical triggers, or incitants, of chronic disease. Allergist Dr. Theron Randolph expounded upon Selye's theory to form an ecological view of medicine that accounts for people's maladaptation to specific materials (Randolph, 1977). Rather than study allergies by isolating particular antigenic molecules and pinpointing minute mechanistic responses, he applied the evolutionary and ecological principles of dynamic human adaptation. "In contrast to the vogue for over-generalization of concept and over-analysis of medical investigation, it must not be forgotten that the whole living body is actually exposed to and reacts to specific foods, chemically-derived products, and other environmental agents as these are encountered in their intact form" (Randolph, 1977). The theory of biochemical individuality helps explain the wide range of susceptibility to incitants and the differential responses based on exposure dose, frequency, and progress of adaptation (Randolph, 1977). Treatment includes avoiding known incitants and correcting metabolic defects that contribute to the maladaptive response (Philpott, 1977).

Orthomolecular Approach to Chronic Diseases

While somewhat incompatible with the view of the body as a highly integrated system, characterizing disease states by affected organs or tissues sometimes provides a practical starting point for diagnosis and treatment. Here, I describe a few categories of chronic disease that afflict

vast numbers of citizens in modern society, the biochemistry associated with their progression, and the orthomolecular substances used to treat them. This brief summary of some existing knowledge about orthomolecular substances only scratches the surface of the capacity (both known and unknown) of nutrients to heal disease and promote wellness.

General Deterioration and Aging

Chronic stress placed on the body, from disease, nutritional, or social factors, increases its allostatic load. This "wear and tear" comes from the endocrine and neural systems' reaction to repeated stressors, inability to habituate or adapt to stressors, delayed cessation of the stress response, or an insufficient response that triggers other systems to compensate (Brown, 2018). While the body's normal acute stress response is advantageous, disease states reflect breakdown in the healthy response pathways to promote widespread cellular deterioration (Brown, 2018). Research has demonstrated that supplementation with B vitamins, vitamin C, magnesium, or omega-3 fatty acids modulates hypothalamic-pituitary-adrenal (HPA) axis function (Brown, 2018). This regulation involves lowering elevated cortisol levels after instances of physiological stress, thus limiting the stressor's long-term impact on the body (Brown, 2018).

The general public has come to identify low energy, decreased mobility, cognitive impairment, and any number of chronic degenerative conditions, from overweight, to heart disease, to diabetes, with aging. While many consider this degenerative process natural and unavoidable, these conditions usually indicate underlying, sub-clinical malnutrition, often in conjunction with other pathologies, such as chronic infectious disease. Scientists attribute much of the cellular damage blamed on "aging" to the attack of reactive oxygen species (ROS), which damage all cellular components, from DNA to lipids to proteins (Hoffer and Saul, 2008, p. 236).

Free radicals, highly reactive uncharged molecules with an unpaired valence electron, generate ROS in the absence of sufficient intracellular antioxidants (Pauling, 2006, p. 239). ROS damage to key molecules (e.g. enzymes involved in DNA replication, or DNA itself) may cause somatic mutations responsible for decreased cellular functionality and the extensive symptomology of aging (Pauling, 2006, p. 239).

The body relies on a host of antioxidant molecules, including vitamin C, vitamin E, Vitamin A, ubiquinones, sulfhydryl compounds, selenium, N-acetyl cysteine, alpha lipoic acid, glutathione, inositol, and others (Hoffer and Saul, 2008; Pfeiffer, 1975). In addition to the direct ROS damage, depletion of these antioxidants causes malfunctions in the hundreds of other biochemical pathways in which these molecules participate. Recent research shows that ascorbic acid counters cellular hypoxia, which interferes with mitochondrial function, a key factor in the process of aging (Demeda, 2018). High concentrations of vitamin C facilitate the production of hydroxyl radicals, which help oxidize NADH, maintaining the 700:1 NAD^+ to NADH ratio critical for proper mitochondrial function (Demeda, 2018). The resulting Krebs cycle augmentation increases the formation of intracellular antioxidants, decreases oxidative stress, and increases aerobic respiration efficiency in every tissue system (Demeda, 2018). In order to minimize the mental and physical symptoms associated with increasing age, a person must avoid the known causes of oxidative stress, mainly, poor diet, toxin exposure, and infection. When necessary a person must supplement with antioxidants and other micronutrients. Bioflavonoids, a class of plant secondary metabolites, have a variety of cellular and systemic properties, including anti-inflammatory, antioxidant, immune stimulating, LDL cholesterol lowering, and anti-coagulating effects (Hoffer and Saul, 2008, p. 146). Consuming a diet rich in a variety of

unadulterated edible plants is an important component of the orthomolecular treatment of any illness. Disease stress and comorbidities gradually reduce cellular functionality over time, decreasing overall life expectancy and quality (Pauling, 2006, p. 241). It may take decades of continued oxidative damage and low-grade inflammation for symptoms and complaints of aging to arise. Proper nutrition, through diet and supplementation can reduce the stress placed on the body and extend the period of well-being, even allowing people to die relatively healthy in old age (Pauling, 2006, p. 242).

Cardiovascular Diseases

A healthy cardiovascular system is essential for transporting nutrients to all cells, and when it loses functionality, tissues across the body may become nutritionally depleted (Hoffer and Saul, 2008, p. 189). Severe deterioration of the heart or vasculature is one of the primary causes of death in the United States (W. Raghupathi and V. Raghupathi, 2018). The orthodox treatments of cardiovascular diseases, including surgical implants, drugs (beta-blockers, statins, anticoagulants, diuretics, and others), and vague dietary recommendations, neglect to account for biological variability and the cellular nutritional environment (Williams, 1971, p. 69). Excess cholesterol in the blood comprises a primary component of plaques that form and contribute to atherosclerosis, or hardening of the arteries (Pfeiffer, 1975, p. 72). Concentrated in the brain and adrenal glands, cholesterol is a component of myelin nerve fiber sheaths and a precursor to the adrenal steroid hormones (Pfeiffer, 1975, p. 72). Enzymes in the liver convert saturated fats and monosaccharides such as fructose into acetate and then cholesterol (Pfeiffer, 1975, p. 72). Excess cholesterol is transformed into bile acids that are excreted into the small intestine (Pfeiffer, 1975, p. 72). While a high level of low-density lipoprotein (LDL) cholesterol in the

blood has a strong correlation with atherosclerosis, dietary intake of cholesterol and saturated fat has shown a much weaker connection, indicating the involvement of other biochemical factors (Pfeiffer, 1975, p. 75). Adequate levels of lipotropic substances (e.g. choline, inositol, lecithin, vitamin B_{12}, biotin, and pangamic acid) prevent accumulation of fat in the liver and play crucial roles in cholesterol metabolism and plasma levels (Pfeiffer, 1975, p. 79; Williams, 1971, p. 74).

Low blood levels of vitamin C are associated with cardiovascular diseases, including coronary heart disease and stroke, and increased intake of the vitamin is linked with decreased incidence of heart disease (Pauling "Congress," 1977). Dr. William McCormick determined that vitamin C deficiency leads to a large number of chronic diseases, including cardiovascular disease ("Vitamin Channel," 2016). He found that 80 percent of cardiovascular patients at various hospitals were deficient in the vitamin ("Vitamin Channel," 2016). McCormick estimated that smoking one cigarette neutralizes about 25 mg of vitamin C, verifying smoking as a causative factor for a large spectrum of illnesses, including heart disease (Pauling, 2006, p. 237; "Vitamin Channel," 2016). In the 1990s, Linus Pauling and Dr. Matthias Rath reported evidence that vitamin C deficiency causes cardiovascular disease and that administration of ascorbate mitigates the condition (Hoffer and Saul, 2006, p.88). Vitamin C may protect the cardiovascular system through its indispensable function in collagen synthesis. Collagen, the most abundant protein in the human body, is the primary component of connective tissue (Pauling, 2006, p. 73). Deficiency in ascorbate diminishes the collagen in veins and arteries, decreasing blood vessel wall integrity, which leads to leakages, lesions, and accumulation of fatty deposits (Hoffer and Saul, 2006, p.89; Pfeiffer, 1975, p. 128). Vitamin C's insufficiency is correlated with weakened vessel walls, bleeding, clotting, and risk for stroke (Hoffer and Saul,

2006, p.89). Ascorbic acid is necessary for the conversion of cholesterol into bile acids in the liver and steroid hormones in the adrenal glands (Pfeiffer, 1975, p. 80). These functions relate to its positive effects on cardiovascular health, as well. High intake of vitamin C increases the ratio of high-density to low-density lipoprotein cholesterol and lowers total levels in hypercholesteremic patients (Cameron and Pauling, 2018, p. 116). Also, Vitamin C may complex with calcium to dissolve plaques and increase the solubility of cholesterol in the blood serum (Pfeiffer, 1975, p. 80).

Other nutrients often lacking in patients of heart disease include folic acid, vitamin B_3, vitamin B_6, vitamin D, and vitamin E. The B vitamins function as coenzymes in fatty acid metabolism, modulating blood lipid levels (Pfeiffer, 1975). In animal studies and clinical trials, administration of high doses of niacin decreased elevated blood cholesterol levels and raised initially low levels (Hoffer, 2005, p. 125). It has dramatically decreased the death rate of cardiovascular patients, as described in a 1986 article in the *Journal of the American College of Cardiology* (Hoffer, 2005, p. 128). Like vitamin C, Vitamin B_3 has been shown to enhance tissue repair, such as in those with bleeding gums (Hoffer, 2005, p. 124). Pyridoxine is a coenzyme in unsaturated fatty acid synthesis, and excess fat consumption generates deficiency in this vitamin (Pfeiffer, 1975, p. 78). Staples of the modern Western diet like high temperature-treated foods such as pasteurized milk and canned foods, and highly milled (i.e. white) flours lose this vitamin in the processing, throwing off the proper proportions of fatty acids to pyridoxine (Pfeiffer, 1975, p. 79). Vitamin D_3 deficiency may cause congestive heart failure, and its supplementation may prevent and treat hypertension (Hoffer and Saul, 2008, p. 137). Canadian physicians and brothers Drs. Wilfred and Evan Shute used high doses (about

800-1,600 IU) of vitamin E (d-alpha tocopherol) to treat and cure atherosclerosis, thrombosis, phlebitis, and claudication for several decades, beginning in the 1940s (Hoffer and Saul, 2008, p. 108, 113). Large clinical studies published in the *New England Journal of Medicine* found that subjects who supplemented with at least 100 IU of vitamin E per day decreased their risk of heart disease by about 60% or more (Hoffer and Saul, 2008, p. 113). In addition to protecting cell membranes, and preventing blood clotting and plaque development, vitamin E inhibits the oxidation of LDL cholesterol by free radicals and increases the heart muscle's efficiency (Hoffer and Saul, 2008, p. 114).

Several minerals play important roles in cardiovascular system function, as well. Deficiency in magnesium has been implicated as a factor in heart disease, and animal studies and clinical evidence show that supplementation significantly improves angina pectoris, coronary thrombosis, and lipoprotein levels in patients (Pfeiffer, 1975, p. 79). Chromium deficiency leads to abnormal sugar and lipid metabolism, disrupting glucose and cholesterol homeostasis (Pfeiffer, 1975, p. 79). Resulting changes in mucopolysaccharide synthesis contribute to sub-endothelial arterial lesions that may become filled with lipid deposits (Schroeder, 1977). Higher zinc blood levels also correspond with decreased blood fat levels, and zinc supplementation has improved patients with hardened arteries (Pfeiffer, 1975, p. 80). As with the vitamins, refining procedures strip these trace minerals from the foods that naturally contain them.

Overweight and Obesity

Excess weight is a primary symptom of the sugar metabolic syndrome, and other genetotrophic factors likely contribute. Some physicians have theorized that obesity results

principally from a dysfunctional midbrain appestat mechanism, which produces appetite signals, due to a combination of genetic predisposition and poor cellular environment (Williams, 1971, p. 93). Animal studies show that depleting B_1 levels disrupts the appestat mechanism, and animals lacking the vitamin refuse to eat (Williams, 1971, p. 106). Perhaps another vitamin imbalance promotes an opposite response. Exact hormonal (e.g. pituitary, thyroid, adrenocorticoid, pancreatic, and sex) contributions are poorly understood, though physicians have observed that vitamin D_3 utilization is severely inhibited in overweight individuals (Williams, 1971, p. 107; Hoffer and Saul, 2008, p. 136).

Arthritis

Joint health depends on adequate synovial fluid, composed of water, mineral salts, and mucoprotein produced by synovial membrane cells, and a sufficient supply of nutrients to these cells (Williams, 1971, p. 124). Toxicity from microbial pathogens or allergens inhibits lubrication and causes the inflammation and pain associated with arthritis (Williams, 1971, p. 124). Physician William Kaufman's clinical study found that supplementing with niacinamide (400-2,250 mg per day for two months) significantly improved arthritic patients' joint range index and subjective reports of arthritis (Williams, 1971, p. 125). High dose vitamin C treatment has prevented and reversed many cases of arthritis. High ascorbic acid serum levels correspond with more viscous synovial fluid and greater joint mobility, but traditional treatments for arthritis, adrenocorticotropic hormone (ACTH) and cortisone, deplete the vitamin (Klenner, 1977). Other vitamins inversely correlated with arthritis severity include vitamin A, pantothenic acid, and riboflavin (Williams, 1971, p. 126-127). Arthritis is linked with impaired tryptophan metabolism and anemia, usually a B_6 deficiency (Williams, 1971, p. 127). Physician Dr. John

Ellis found that B_6 shrinks synovial membranes lining joint surfaces, increasing mobility and decreasing pain, and the vitamin also serves as a treatment for carpel tunnel and edema (Pauling, 2006, p. 223). Pyridoxine's action as an antihistamine and prostaglandin synthesis regulator relates to its efficacy (Pauling, 2006, p. 225). The synovial environment is also influenced by nearby bone enlargement and cartilage mineral deposits, implicating involvement of mineral disproportions, as well (Williams, 1971, p. 128). Isolated vitamin supplementation has yielded notable but unsustained improvement in many cases, but physicians continue to improve the synergistic combinations of nutrients with substantial clinical efficacy (Williams, 1971, p. 126-127).

Infectious Diseases

Vitamin C is necessary for proper immune system functioning, and subclinical anascorbemia, in which levels of the vitamin fall below tissue saturation, predispose one to the infection (Klenner, 1977). Ascorbic acid stimulates both the production and phagocytic ability of neutrophils, phagocytes, and lymphocytes (Pauling "Congress," 1977). Leukocytes use ascorbic acid to generate the hydrogen peroxide breakdown products that destroy microbial pathogens (Klenner, 1977). As stated previously, stress on the body causes it to expend vitamin C at a higher rate, lowering available amounts unless replenished through increased supplementation. People with a higher intake of vitamin C produce more antibodies (IgG and IgM), as demonstrated in a 1977 study that isolated human subjects from nearly all sources of new infection and supplemented them with different amounts of this vitamin (Cameron and Pauling, 2018, p. 109). In guinea pigs, vitamin C supplementation also increases the amount of C1 esterase, the first component of the immune complement system (Cameron and Pauling,

2018, p. 109). Low vitamin C levels heighten skin graft tolerance in guinea pigs, presumably by lowering circulating, active lymphocyte levels (Cameron and Pauling, 2018, p. 109). In the 1970s, Dr. Yonemoto's team studied five healthy human adults and found that supplementing with 5 g of vitamin C for a few days doubled new lymphocyte formation, and intake of 10 g and 18 g tripled and quadrupled the control rate, respectively (Cameron and Pauling, 2018, p. 110). The manufacture of some immune-regulating substances, such as prostaglandin E1, require several dietary micronutrients, including vitamin C (Cameron and Pauling, 2018, p. 110). Ascorbic acid promotes parts of the inflammatory response, but it also protects against sepsis by strengthening vascular structure and regulating histamine release and breakdown and normal thrombosis (Demeda, 2018). Supplementation with high levels of vitamin C during a viral illness not only treats the acute infection, but it also helps prevent secondary infections that may arise within a vitamin-depleted environment (Pauling, "Congress," 1977). Investigators such as Irwin Stone, Linus Pauling, and Thomas Levy provide copious evidence that vitamin C acts as a potent antiviral and antibacterial substance at gram level doses. The vitamin inactivates viruses both *in vitro* and *in vivo,* possibly through the generation of free radicals that damage viral nucleic acids (Klenner, 1977). In a 450-page volume, Dr. Thomas Levy assembled reports on high dose vitamin C treating and curing infectious diseases including polio, hepatitis, measles, mumps, viral encephalitis, herpes, influenza, tetanus, streptococcus, and staphylococcus, and significantly improving such formidable diseases as AIDS, malaria, and tuberculosis (Levy, 2002).

In the middle of the twentieth century, Frederick R. Klenner, MD demonstrated that vitamin C is an ideal agent for killing viruses, bacteria, and other microbial pathogens. He also

recognized vitamin C's ability to neutralize and eliminate most toxins, including microbial products, chemical pollutants, and other poisons (Levy, 2002, p. 21; "Vitamin Channel," 2016). Klenner was perhaps the first physician to inject patients with high doses (ranging from 350 mg to 1,200 mg per kg body weight) to treat illness ("Vitamin Channel," 2016). He treated and cured acute poliovirus with frequent injections of ascorbic acid, using body temperature (measure of fever) as a dosing guide (Levy, 2002, p. 53). He cured all 60 cases in a 1948 polio epidemic in North Carolina by administering doses of 6 to 12 g per day, typically over three days (Levy, 2002, p. 54). After the initial dose, he applied the same dose every two hours until the patient's temperature dropped and then increased intervals between doses over the next days. He reported all patients as clinically well—absent of symptoms, including fever; headache; limb, neck, and back pain; nausea; and vomiting, and expressing a general feeling of wellbeing—after 72 hours (Levy, 2002, p. 54). When three patients experienced clinical relapses, Klenner placed all of the patients back on the treatment (with doses given at longer time intervals) for another 48 hours, until all patients achieved complete, permanent resolution of symptoms (Levy, 2002, p. 54). No patients developed deformities associated with the disease, and even two advanced cases were reversed (Levy, 2002, p. 54). Klenner further refined and used this treatment method of building up doses until symptom relief (usually within 72 hours) and then weaning off over several days to two weeks. He would then prescribe a continued oral vitamin C regimen to prevent relapse (Levy, 2002, p. 56). Klenner implemented variations of this method to cure many other viral illnesses, including herpes simplex, viral encephalitis, mononucleosis, and measles (Klenner, 1977). He often found that patients responded favorably to doses in the tens of grams within a couple of hours (Klenner, 1977). Klenner emphasized the necessity of

maintaining tissue saturation levels of vitamin C through continuous administration until the complete eradication of disease (Klenner, 1977).

Other physicians discovered the value of high dose vitamin C treatment both during and following Klenner's career. Claus Jungeblut, MD also studied vitamin C as a treatment for the poliovirus in the 1930s ("Vitamin Channel," 2016). Experimentally, he inactivated the virus *in vitro* by administering vitamin C and determined that polio-infected monkeys receiving vitamin C treatment avoided paralysis significantly more than control animals ("Vitamin Channel," 2016). Clinically, he found a low vitamin C status in polio patients and that adequate doses of the vitamin cured the disease ("Vitamin Channel," 2016). In the 1960s, Robert Cathcart, MD also successfully used the vitamin as an antiviral and described the difficulty, faced by most of these clinicians, of obtaining permission from ethics, university, pharmacy and other committees to use large doses of vitamin C in research studies ("Vitamin Channel," 2016). Cathcart first described the titration of patient doses to bowel tolerance, writing, "The amount of oral ascorbic acid tolerated by a patient without producing diarrhea increases somewhat proportionately to the stress or toxicity of his disease" ("Vitamin Channel," 2016). As with all optimal doses of vitamins, the bowel tolerance amount is highly dynamic. For individuals in good health, this amount falls roughly in the range of 4 to 15 g per day, which can increase to more than 200 g during viral illness (Pauling, 2006, p. 129). William McCormick, MD pioneered the use of gram dose vitamin C injections in the middle of the century. He declared ascorbic acid a "specific antagonist of chemical and bacterial toxins" and advocated its use as an antiviral and an antibiotic ("Vitamin Channel," 2016). In his discussion on using vitamin C to treat the common cold, Pauling wrote, "I am convinced by the evidence now available that vitamin C is to be

preferred to the analgesics, antihistamines, and other dangerous drugs that are recommended for the treatment of the common cold by the purveyors of cold medicines" (Pauling, 2006, p. 129). It amazes any orthomolecular practitioner that the medical community continues to promote these palliative medications at the expense of public health and ignores the overwhelming evidence supporting vitamin C's preventive and curative power.

Other vitamins also influence immune system function through a variety of chemical and physical mechanisms. Short term, high dose supplementation with vitamin E leads to an increased ratio of helper T (CD4) cells to killer T (CD8) cells and enhanced production of pro-inflammatory cytokines (Hoffer and Saul, 2008, p. 116). The body requires vitamin A, or beta-carotene, to maintain healthy mucous membranes and epithelial tissue, including skin, mouth, respiratory membranes, gastrointestinal tract, and genitourinary tract (Hoffer and Saul, 2008, p. 121). These tissues and membranes form the primary physical barriers to infectious agents. Vitamin D_3 acts as an immune system regulator, combating infection and preventing autoimmune conditions such as multiple sclerosis, lupus, and thyroiditis (Hoffer and Saul, 2008, p. 136). Niacin releases histamine from mast cells, causing temporary vasodilation (Hoffer and Saul, 2008, p. 78). However, niacin supplementation does not trigger a drop in overall blood pressure and it ultimately inhibits the continued release of pro-inflammatory molecules and sepsis (Hoffer and Saul, 2008, p. 78).

Cancer

Healthy cells may become cancerous when they suffer from prolonged insufficiency of required nutrients (Williams, 1971, p. 182). In one rat study, dietary choline restriction induced cancer development, and in another, injections with liver extracts, rich in B vitamins, prevented

tumor growth (Williams, 1971, p. 181). Vitamin C-supplemented guinea pigs also experienced reduced tumor growth (Williams, 1971, p. 183). Animal studies and clinical observations continue to correlate poor nutrition with cancer development and progression, and high dose nutrient supplementation with cancer prevention and tumor regression. The cellular chemical environment determines the likelihood of error-prone cell replication that results in uncontrolled proliferation (Hickey and Roberts, 2018).

Local cellular oxidation stimulates redox signaling and free radical damage, and without sufficient antioxidants and the removal of the pro-oxidant sources, carcinogenesis may result (Hickey and Roberts, 2018). Traditional cancer treatments— surgery, chemotherapy, and radiotherapy—have serious health costs that sometimes outweigh their benefits (Cameron and Pauling, 2018). While cancer cells are slightly more vulnerable to some chemical poisons and ionizing radiation, their susceptibility is usually only slightly higher than that of normal cells (Hickey and Roberts, 2018). Treatment administered as prescribed by an oncologist may kill the patient before it kills the cancer (Hickey and Roberts, 2018). Treatments that avoid directly poisoning all exposed cells include immunotherapies, which take advantage of the body's natural defense system to target malignant cells using tumor-specific antibodies (Cameron and Pauling, 2018, p. 78).

Dr. Pauling and Dr. Ewan Cameron, MD, collaborators in the search for effective orthomolecular cancer treatments, suggested another way to enhance the body's ability to resist and fight cancer. In their comprehensive book on the subject, Pauling and Cameron clearly state: "The simplest and easiest way to enhance immunocompetence in these [cancer] patients and to ensure their molecular and cell-mediated defense systems are working at maximum efficiency is

to increase their intake of vitamin C" (Cameron and Pauling, 2018, p. 111). Vitamin C's immense usefulness comes in part from its ability to act as an antioxidant in healthy cells and as a pro-oxidant in cancerous cells (Hickey and Roberts, 2018). At concentrations only achievable through IV administration, vitamin C produces significant amounts of hydrogen peroxide, which damages DNA, mitochondria, and other cellular structures, causing cancer cell death through apoptosis or necrosis (Cameron and Pauling, 2018, p. xxix). While hydrogen peroxide is damaging to all cells, healthy cells produce significantly more catalase, the enzyme that breaks down hydrogen peroxide, than cancerous cells (Cameron and Pauling, 2018, p. xxix).

In 1971, these two scientists produced independent but related theories about vitamin C's anti-cancer mechanisms. Pauling built off a hypothesis by physician Dr. William McCormick that cancer is directly related to vitamin C deficiency (Cameron and Pauling, 2018, p. 101). Dr. McCormick observed similarities between the tissue alterations in scurvy and the stromal changes near neoplastic cells, and he thought that ascorbic acid may prevent cancerous cell spread in the same way it prevents the onset of scurvy (Cameron and Pauling, 2018, p. 101). By mid-century, research showed that cancer patients have a much lower plasma vitamin C concentration (about half) than non-cancerous individuals (Pauling, 2006, p. 177). In mice susceptible to breast cancer development, dietary supplementation with ascorbic acid was significantly negatively correlated with tumor emergence, with the highest percentages of added ascorbate significantly lengthening cancer lag time and life span (Pauling, 2006, p. 180). Using his knowledge of ascorbic acid's necessity in collagen synthesis, Pauling hypothesized that vitamin C resists the expansion and outgrowth of malignant cells by strengthening the collagen-rich ground substance, or intercellular "cement" that keeps cells in place (Pauling,

2006, p. 183-184). Dr. Cameron found that vitamin C inhibits hyaluronidase, an enzyme secreted by tumor cells that breaks down glycosoaminoglycans, polymers that make up much of the ground substance (Cameron and Pauling, 2018, p. 90). By stimulating the normal cells' production of a hyaluronidase inhibitor, vitamin C decreases hyaluronidase activity, thereby increasing ground substance integrity (Cameron and Pauling, 2018, p. 90). Pauling and Cameron observed that scar tissue, comprising intercellular molecules such as collagen, encapsulates tumors, provided the patient has sufficient vitamin C and other necessary nutrients (Cameron and Pauling, 2018, p. 113). Working together, Pauling and Cameron proposed that abnormal proliferation of cells is prevented in part by the physical and chemical restrictive effects of the ground substance, and that vitamin C is an important regulator of the natural feedback mechanism that controls the spread of cancer (Cameron and Pauling, 2018, p. 91).

Careful preliminary clinical trials at his clinic, the Vale of Leven Hospital in Scotland, convinced Dr. Cameron that most of the advanced cancer patients benefited from high doses of vitamin C. Pauling and Cameron proceeded to conduct vitamin C clinical studies at the same hospital in 1976 and 1978 (Cameron and Pauling, 2018, p. xii). Cameron treated each of the 100 cancer patients under his care with about 10 g of sodium ascorbate daily, using the other 1,000 cancer patients in the hospital as controls (Cameron and Pauling, 2018, p. xii). He and Pauling found that the ascorbate-treated patients survived an average of ten months longer than controls matched by age, sex, cancer type, and clinical state (Cameron and Pauling, 2018, p. xii). Twenty-two percent of terminal patients lived longer than a year, compared to 0.4 percent of controls (Cameron and Pauling, 2018, p. xii). The two scientists were astounded by patients' dramatically improved quality of life upon taking the vitamin (Cameron and Pauling, 2018, p.

130). Almost immediately, many exhibited improved appetite, increased mental alertness, greater optimism, and decreased requirement for pain-controlling drugs, with an absence of withdrawal symptoms (Cameron and Pauling, 2018, p. 131). These studies assessed patients in late stages of cancer, and in the following years, Cameron and Pauling saw much greater improvements supplying early-stage patients with the vitamin, often in larger intravenous doses (Cameron and Pauling, 2018, p. xiii). Like Dr. Cameron, many physicians who recognize the benefit of high dose vitamin C therapy refuse to perform blind, randomized trials that deny a control group of patients access to the treatment (Murata *et al.,* 1982). These physicians continue to witness substantial clinical improvements, including complete remission, in cancer patients of all types on IV and oral vitamin C (Stoute, 2018).

Orthomolecular scientists and doctors have adopted approaches similar to Pauling's and Cameron's to research and use the body's methods for resisting cancer. Dr. Hugh Riordan evaluated and implemented many orthomolecular theories, pioneering IV vitamin C cancer treatments, among others ("Vitamin Channel," 2016). In the 1993 updated edition of his and Cameron's book, *Cancer and Vitamin C,* Pauling recommends that every cancer patient follow some variation of Dr. Hoffer's nutritional regimen, which consists of 1,200 mg vitamin C, 1,500 mg niacin, 800 IU vitamin E, 25-50 times the RDA of the other B vitamins, 0.20 mg selenium, and other minerals including calcium and zinc for some patients (Cameron and Pauling, 2018, p. xxiii). Of course, a competent physician assesses relevant recommendations and then tailors the therapy to the individual patient, ideally by determining his or her needs for a wide variety of nutrients that work synergistically to mitigate the complex causes and progression of cancer. Mechanical tissue damage increases the risk of cancer development, so avoiding injury and

perhaps more importantly, providing the necessary nutrients the body needs to heal damaged tissue, plays a preventive role (Cameron and Pauling, 2018, p. 13). Vitamin A helps maintain healthy epithelial tissue, which is especially susceptible to cancer development, and vitamins C and B_3 function in tissue repair (Williams, 1971, p. 183). Vitamin C's anti-viral and anti-bacterial properties prevent infections that produce mechanical damage and intracellular toxicity. Furthermore, vitamin C acts as a detoxifying agent, working with oxygen and enzymes to convert toxic molecules into derivatives bound for excretion in the urine (Cameron and Pauling, 2018, p. 117). Carcinogenic substances removed with the help of vitamin C include toxic hydrocarbons and nitrosamines (Cameron and Pauling, 2018, p. 117). The body's natural mechanisms of keeping cancerous growth in check display greater complexity and efficacy than any synthetic treatment. The orthomolecular physician assumes the responsibility of finding the right nutritional keys to unlock this potential.

Nutrient Network

Assessing disease through the lens of biomolecule imbalances dispels false distinctions between diseases based on the afflicted organ or tissue system. Any nutrient performs multiple (sometimes hundreds or thousands) functions across the body that differ based on setting and circumstance, and no nutrient works in isolation to maintain homeostasis. A single nutrient deficiency may advance poor cellular function in multiple tissue systems simultaneously, producing several separate diagnoses. But a deficiency seldom arises singly. Any environmental factor that reduces the presence of one nutrient directly or indirectly depletes or augments another. The human body, like all other ecological systems, abides by the first rule of ecology: everything is connected to everything else (K. Emonds, personal communication,

September 5, 2018). Because multicellular organisms developed their complex biochemical pathways from simpler reaction sequences, it makes sense that all bodily substances function in multiple pathways. The body can acclimate to reductions in essential substances by rearranging their roles to a certain extent, but prolonged failure to feed the cells what they need and the contamination with toxic substances instead leads to inefficiencies, misfires, malfunctions, and ultimately, death.

Nutrients are seldom effective as treatments in isolation, but must work in concert to produce noticeable effects in the body (Williams, 1971, p. 212). The absorption of calcium into blood and then bones depends on vitamin D_3, vitamin K_2, magnesium, and phosphorous (Hoffer and Saul, 2008, p. 156). Vitamin C reduces oxidized vitamin E into its active state, and active vitamin E protects vitamin A from oxidation (Hoffer and Saul, 2008, p. 108). Severe deficiency in vitamin A reduces the effectiveness of vitamin C against infections (Hoffer and Saul, 2008, p. 122). In transmethylation reactions, vitamin B_{12} requires the presence of folic acid (Hoffer and Saul, 2008, p. 129). While many physical and mental diseases involve an increase in the ratio of copper to zinc, zinc supplementation decreases copper levels (Hoffer and Saul, 2008, p. 153). Zinc acts as a coenzyme for at least eighty metalloenzymes, and copper is required for a variety of enzymatic reactions and hemoglobin synthesis (Hoffer and Saul, 2008, p. 152, 153). While depletion of the former element is relatively common, deficiency in the latter is rare (Hoffer and Saul, 2008, p. 153). These codependences limit the ability of controlled scientific experiments to accurately describe the functions and therapeutic effects of individual orthomolecular substances. The administration of a single nutrient affects individuals differently, even producing opposite effects, depending on the levels of other nutrients already present. Research continues to

illuminate how different vitamins, minerals, and coenzymes depend on each other. This inherent interdependence differs fundamentally from the mechanism of a pharmaceutical (Pauling, 2006, p. 213). The chemist formulates the drug molecule to exhibit a pronounced and measurable effect on its own when introduced into any human body with a certain diagnosed disease (Pauling, 2006, p. 214). Drug trials assume general homogeneity of the study population, disregarding the confounding effects of patients' diet and nutritional status. In reality, the xenobiotic substance interacts with the particular cellular environment of the patient, so its function varies according to biochemical individuality (Pauling, 2006, p. 214). Formulating an effective treatment regimen requires employing nutrients, along with xenobiotic substances, in the proper combinations and ratios. This requires a deep reservoir of biochemical knowledge and intuition.

Importance of Administration and Dosing Methods

When formulating or assessing the efficacy of any orthomolecular treatment, the physician must carefully consider the factors that influence its assimilation and functionality in the target cells. These include the chemical form of the substance, the mode of application, the dose, the frequency of application, the length of treatment, and its interactions with other treatments (Levy, 2002, p. 21). For a single oral dose of 1,000 to 2,000 mg of ascorbate, roughly 25% is lost in the urine, though this value varies greatly depending on the physical condition of the individual (Cameron and Pauling, 2018, p. 122). Spreading oral intake over several hours decreases this loss. Intravenous administration has hugely greater efficacy at raising blood and tissue levels of vitamin C (Cameron and Pauling, 2018, p. 126). Blood ascorbate concentrations

may reach levels 100 times higher through IV administration than oral (Cameron and Pauling, 2018, p. xxviii).

Making dramatic and sudden changes in vitamin dose can cause a patient harm by over- or under-loading enzymes in its metabolic pathways. Intermittent injections of vitamin C can produce a rebound effect, whereby suddenly stopping or significantly reducing administration causes the cells to rapidly consume existing stores, manifesting an acute deficiency (scurvy) state (Cameron and Pauling, 2018, p. 117). This occurs as a result of induced enzyme production, a well-documented phenomenon in bacteria. Following increased ascorbate intake, production of enzymes involved in its oxidation reaction increases (Cameron and Pauling, 2018, p. 117). In this way, the body may use oxidized ascorbate products in addition to the ascorbate itself, rather than excrete excess vitamin in the urine (Cameron and Pauling, 2018, p. 117). If the person then suddenly and drastically decreases ascorbic acid intake, nearly all of the remaining vitamin is processed by the abundant enzymes, which decreases blood ascorbate to dangerously low levels (Cameron and Pauling, 2018, p. 118). It takes a few days for the breakdown of excess enzyme, and the individual is more susceptible to infection and other medical complications during this time (Cameron and Pauling, 2018, p. 118). This example highlights the importance of working with a knowledgeable practitioner to administer large doses of any vitamin, and always decrease high doses gradually.

The Search for Exact Dose Therapy

Since the inception of orthomolecular medicine, determining the appropriate doses of substances for each patient has proved a substantial challenge. While reference to previous studies and clinical experience and sequences of trial and adjustment has worked passably,

physicians strove to match the theory of biochemical individuality with the practice of vitamin dosing (Hoffer and Saul, 2008, p. 52). Traditional blood and urine testing used today only provides valuable information about some nutrients and does not indicate what levels would promote optimal health for a given patient (Hoffer and Saul, 2008, p. 52). Next-generation, high-throughput gene sequencing methods are increasingly accessible and sometimes used by orthomolecular physicians to detect genetotrophic disorders, such as genetic vulnerabilities to cancer or methylation disorders (Huemer, 2015). Genetic testing allows for targeted nutrient therapy, but it still cannot inform precise dosing (Huemer, 2015). In his autobiography, Hoffer wrote, "I envision a future in which simple laboratory tests will be available which will advise which nutrients are lacking and how much of each nutrient patients need to regain and maintain their health" (Hoffer, 2005, p. 314). Pauling similarly predicted, "In the course of time it should be possible to develop a method of diagnosis (measurement of concentrations of vital substances) that could be used as the basis for determining the optimum molecular concentrations of vital substances for the individual patient and for indicating the appropriate therapeutic measures to be taken" (Pauling, 2001, p. 1401). Dr. Kenneth Emonds, Ph.D., Diplomate of the American Psychotherapy Association and Fellow of the Academy of Environmental Medicine took on this challenge and developed a solution that has radically improved the effectiveness of nutrient therapy.

Since the 1970s, Dr. Ken Emonds has integrated orthomolecular, environmental, and energy medicine to treat chronically ill patients with cancer, autoimmune disorders, and severe environmental illness ("About Us"). Emonds draws inspiration from Dr. Maynard Murray, the physician who drew attention to agricultural soil demineralization and the impact of

re-mineralized food on health, Hoffer's and Osmond's "megavitamin" research, and of course, Pauling's work on orthomolecular psychiatry (American Academy of Environmental Medicine, 2010). Emonds' doctoral degree combined the study of psychology, orthomolecular biochemistry, and immunology ("About Us").

A miraculous path led Emonds to meet and train with Dr. Pauling. Like Hoffer, Emonds was disenchanted with Freudian psychoanalysis and the blind trial and error methodology used to select drug type and dosage for psychotic conditions (K. Emonds, personal communication, September 5, 2018). Wanting to make a difference in the world, Emonds traveled to East Africa and worked as a physician's assistant in a bush clinic. While there, he contracted malaria, which progressed to tissue stage (end stage) with a prognosis of death (K. Emonds, personal communication, September 5, 2018). Emonds refused to accept this death sentence, and he returned to the U.S. and consulted physicians who offered no hope and refused to support his own unorthodox treatment ideas. Aware that all organisms have a pH window, outside of which they cannot survive, he devised and implemented his own treatment regimen. With the goal of exceeding the protozoa's pH threshold, he hooked himself up to an IV tube, pumped a weak acid, ascorbic acid, into his blood until nearly passing out, and then switched the IV solution to sodium bicarbonate (baking soda) solution (K. Emonds, personal communication, September 5, 2018). By repeatedly shifting back and forth from acidosis to alkalosis, he killed the pathogen in his body. After three months of pulsing this treatment, his symptoms had improved, and Emonds visited the infectious disease specialist he had previously consulted. Microscopic analysis and biopsy showed no remaining *Plasmodium* in his blood or tissues (K. Emonds, personal communication, September 5, 2018). The physician was amazed that Emonds was still alive and

had done this on his own, and he contacted Dr. Pauling about this remarkable young man. Impressed with Emonds' ingenuity, Pauling invited him to pursue a doctoral degree under his mentorship in California (K. Emonds, personal communication, September 5, 2018).

During their time working together, Pauling articulated a paradox permeating medical practice: as good as chemists and biochemists are at finding patterns in molecular structure and function, you cannot apply scientific formulas to the human condition (K. Emonds, personal communication, September 5, 2018). The bell-shaped curve upon which deficiencies and dosages are determined is an unachievable statistical ideal, where the average human actually represents no human at all (K. Emonds, personal communication, September 5, 2018). Pauling tasked Emonds with figuring out a testing method for administering vital substances at optimal, individualized amounts. After Emonds completed his doctoral degree and began a fellowship in environmental medicine, his supervisor Dr. James O'Shea, M.D. reiterated Pauling's charge to find a way to scientifically measure what an individual body needs (K. Emonds, personal communication, September 5, 2018).

In the meantime, Emonds became particularly interested in allergies and clinical ecology, a field advanced by allergist Dr. Theron Randolph. In the 1960s, when many allergists began to define allergy strictly as an IgE-mediated reaction, Randolph separated from his colleagues to form the Society for Clinical Ecology, later renamed the American Academy of Environmental Medicine (AAEM) (American Academy of Environmental Medicine, 2010). He pioneered the concept that immunoglobulins are only one of many, perhaps hundreds, of existing allergy mediating molecules (American Academy of Environmental Medicine, 2010). Allergy testing methods vary in their efficacies and the mediators they detect, from intradermal testing (i.e.

scratch test), pulse testing, and kinesiology (muscle testing), to the Radio-Allergo-Sorbent Test, a serum test detecting IgE presence for particular substances, and the Lymphocyte Response Assay (American Academy of Environmental Medicine, 2010). Elimination diets may reveal food allergies, either through removing suspected foods for several weeks and reintroducing them one by one to identify the reaction triggers, or by four-day fasts (Hoffer and Saul, 2008, p. 305).

In 1979, Emonds received a request from Dr. O'Shea, AAEM president, to develop a safe form of allergy testing that would not cause anaphylaxis in extremely sensitive patients (K. Emonds, personal communication, September 5, 2018). Emonds also sought a way to prevent adverse responses to the clinic's tri-flu vaccine, used to stimulate a patient's immune system prior to allergy skin testing. Some patients had developed subcutaneous benign tumors at the site of vaccine injection (K. Emonds, personal communication, September 5, 2018). Emonds solved this problem by degrading the proteins in the vaccine, leaving the polysaccharides to serve as antigens to activate the immune response without causing permanent tissue damage (K. Emonds, personal communication, September 5, 2018). Using the same principles, Emonds formulated an oral allergy extract by combining over 1,000 diluted and deproteinized antigens (inhalants, foods, and chemicals), preserved in a solution of nearly 80 trace minerals (American Academy of Environmental Medicine, 2010). This extract did not produce an acute, life-threatening reaction in allergic patients, and it simultaneously helped remedy mineral deficiencies, but Emonds had no accurate way of determining the neutralizing dose for each patient (American Academy of Environmental Medicine, 2010). His following investigation integrated Pauling's earlier charge for him to develop a reliable method for determining patients' exact nutrient needs (K. Emonds,

personal communication, September 5, 2018). Here, Emonds delved into the field of energy medicine.

In addition to the physical and chemical aspects of an organism, the body contains a subtle energetic system. The empirical success of Chinese acupuncture therapy for over 3,000 years demonstrates the existence and clinical importance of this network of energetic pathways throughout the body (Kaptchuk, 2000, p. 132). In pursuit of a way to measure the body's state of health, Emonds adopted an electro-acupuncture technology developed by German doctor and engineer Dr. Reinhard Voll (American Academy of Environmental Medicine, 2010). Voll's electro-acupuncture machine indirectly measures the subtle flow of energy through these pathways using an input of electricity. Voll found that levels of electrical conductivity varied at certain points on the skin, many corresponding with traditional acupuncture points, and others with nervous system pathways (American Academy of Environmental Medicine, 2010). He calibrated his machine based on the normal skin resistance of healthy people. Following electromagnetic principles similar to electrocardiography (EKG) and electroencephalography (EEG), Voll's machine runs a low voltage electrical current through the patient's body. When a practitioner completes this circuit by pressing a metal pointer onto an acupressure point on the patient's finger, the skin resistance value signifies the energy flow through the organ or tissue system that corresponds with that specific energy pathway (American Academy of Environmental Medicine, 2010). The ten identified physiological pathways accessible on one hand are the lymphatic system, lung, large intestine, peripheral nervous system, circulatory system, central nervous system, immune system, endocrine system, heart, and small intestine (American Academy of Environmental Medicine, 2010). A resistance measure lower than the

calibrated optimal value reflects high resistance, indicating degeneration in that anatomical system, and a measure higher than this middle value reflects low resistance, indicating inflammation (K. Emonds, personal communication, September 5, 2018). Voll had discovered an amazingly practical indicator of health, applying the simple principle that life reflects an unobstructed flow of electrons within and among cells.

Emonds refined this technique into a powerful and sensitive diagnostic tool, calling it electro-dermal titration. In addition to measuring "baseline" values for each of the ten points, Emonds tests the body's response to any substance (nutrient, medication, toxin, food, chemical, etc.) or combination thereof, placed upon the metal tray situated on top of the instrument. The substance on the tray alters the electrical current to provide the body with its electrical "signature." He uses the machine to test for food allergies and doses of dietary supplements, drugs, and his proprietary allergy extract. If a substance on the tray does not test optimally on all ten points, then he concludes that it is either the wrong substance or the wrong dose, and he keeps trying different doses and combinations to achieve optimal readings (American Academy of Environmental Medicine, 2010). At the end of a visit, a patient receives an extensive, integrated regimen to follow at home. This includes a list of supplementary vitamins, minerals, probiotics, and other orthomolecular substances, each at the dose titrated with all other substances present, accompanied by lists of foods to avoid and foods tolerated with the neutralizing dose of allergy extract. Emonds' electro-dermal titration method combines his understanding, through decades of research and clinical experience, of how every substance affects every other in the body with the ability to determine objectively the exact dose required by the body at a given moment in time.

Dr. Emonds' development of exact dose therapy using electro-dermal titration has supplied a crucial link to the practice of orthomolecular medicine. Physicians no longer need search for the optimal therapeutic doses for their patients using time and resource consuming trial and error using vague "average" recommendations. This method honors biochemical individuality and addresses the fluctuations of a person's nutrient needs. However, its efficacy depends not only on the machine's "hardware," but also, and more importantly, on the practitioner's "software," an extensive knowledge of cellular life and complex nutrient interactions. Through nearly forty years of practicing exact-dose orthomolecular medicine as founder and clinical director of the New England Center for Orthomolecular Medicine in North Hampton, New Hampshire, Emonds has uncovered patterns and surprises in deficiencies, dependencies, and toxicities. He has improved the lives of thousands of suffering people and has enabled his patients to achieve near-miraculous recoveries from devastating illness (K. Emonds, personal communication, September 5, 2018).

Orthomolecular Medicine Now

Other orthomolecular physicians in the twenty-first century continue to confirm and build upon the discoveries of their predecessors. They have uncovered more reasons for biochemical individuality in vitamin utilization, cultivated a better understanding of nutrition's role in degenerative diseases such as dementia, added more pieces to the puzzle of micronutrient networks, and identified common nutrient ratio imbalances present in various disease states (Demeda, 2018). Even the mainstream scientific community has begun to acknowledge the underlying metabolic component of many chronic diseases. In 1971, Dr. Roger Williams made a prediction about advancing technology's effects on nutritional therapy, saying, "Computerized

information will be increasingly valuable in diagnosing diseases, and one of the outgrowths will be the recognition that many diseases that are considered as single diseases will be found to include those with several different etiologies" (Williams, 1971, p. 225). Indeed, physicians now acknowledge multiple causes of faulty glucose regulation that lead to the single diagnosis of diabetes mellitus, and more psychiatrists have adopted Carl Pfeiffer's replacement of "throw-away" diagnoses with biotype identifiers of mental illness. Medicine is slowly moving away from the assembly line model to greater integration and personalization.

Most importantly, the developments of orthomolecular medicine over the past 50 years has advanced a philosophy of disease, seemingly new, but actually as old as medicine itself. The staples of allopathic medicine, drugs and surgery, may mask or alter the problem, but nutrients heal. Only nutrition can restore optimal health, as faulty nutrition is the root of ill health. In order to accommodate this philosophy, medicine has diverged into new fields, called naturopathic, functional, holistic, and integrative medicine. These branches strive to replace the existing reductionist approach that isolates body systems, symptoms, etiologies, and treatments with a unified perspective of the body systems involved in illness (Gonzalez *et al.*, 2018).

The founder of orthomlecular theory espoused the enduring values of this movement. Linus Pauling was not just a brilliant laboratory scientist, but also a humanitarian, endlessly generous to his students and compassionate towards humanity. He understood that everybody has a unique role to fill in this world, and that no other will play it the same way (K. Emonds, personal communication, September 5, 2018). He taught Dr. Emonds that regardless of your perspective, you are always going to have critics and naysayers, and you have to ignore them. You have to move forward with what you believe is the right thing to do (K. Emonds, personal

communication, September 5, 2018). With continued perseverance, the courageous community of orthomolecular scientists and physicians will keep spreading the message of hope and healing to wounded bodies, minds, and spirits.

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References

About Us: I^3H_2C – Dr. Kenneth Emonds, Ph.D., D.A.P.A., A.F.A.E.M. The International Institute for Integrated Health and Higher Consciousness. Retrieved from https://www.i3h2c.org/meet-dr-kenneth-emonds.php

American Academy of Environmental Medicine (Producer). (2010). *30 YRS of Voll's Electro Dermal Titration Using OPRE By Kenneth Emonds, PhD, DAPA, AFAAEM.* [DVD]. USA: Insta-Tapes Digital Media.

American Psychiatric Association, Task Force on Megavitamin and Orthomolecular Therapy in Psychiatry. (1973). *Report of the APA Task Force on Vitamin Therapy in Psychiatry*. Retrieved from https://www.psychiatry.org/psychiatrists/search-directories-databases/library-and-archive/task-force-reports

Ames, B. N., Elson-Schwab, I., and Silver, E. A. (2002). High-dose vitamin therapy stimulates variant enzymes with decreased coenzyme binding affinity (increased K_m): relevance to genetic disease and polymorphisms. *The American Journal of Clinical Nutrition*, *75*(4), 616–658. https://doi.org/10.1093/ajcn/75.4.616

Andrew W. Saul's Vitamin Channel. (2016, December 7). Andrew Saul - High Dose Vitamin C Therapy for Major Diseases [Video file]. Retrieved from https://www.youtube.com/watch?v=W5Bgdqsorg0

Brown, B. I. (2018). Stress, HPA Axis Dysfunction and Personalized Nutrition. *Journal of Orthomolecular Medicine, 33*(6).

Cameron, E., & Pauling, L. (2018). *Cancer and Vitamin C: A Discussion of the Nature, Causes, Prevention, and Treatment of Cancer with Special Reference to the Value of Vitamin C* (3rd ed.). Philadelphia, PA: Camino Books. Originally published: (1979).

Demeda, P. (2018). Highlights from the 46th Orthomolecular Medicine Today Conference. *Journal of Orthomolecular Medicine, 33*(6).

Gonzalez, M. J., Miranda-Massari, J. R., Mora, E.M., Jiménez, I. Z., Matos, M. I., Riordan, H. D., Casciari, J. J., Riordan, N. H., Rodríguez, M., and Guzmán A. (2002). Orthomolecular Oncology: a Mechanistic View of Intravenous Ascorbate's Chemotherapeutic Activity. *Puerto Rico health sciences journal*, *12*(1), 39-41.

Gonzalez, M. J., Olalde, J., Rodriguez, J. R., Rodriguez, D., and Duconge, J. (2018). Metabolic Correction and Physiologic Modulation as the Unifying Theory of the Healthy State: The Orthomolecular, Systemic and Functional Approach to Physiologic Optimization. *Journal of Orthomolecular Medicine, 33*(6).

Hickey, S. and Roberts, H. (2018). Vitamin C and Cancer: Is There A Use For Oral Vitamin C? *Journal of Orthomolecular Medicine, 33*(6).

Hoffer, A. (2005). *Adventures in Psychiatry: The Scientific Memoirs of Dr. Abram Hoffer*. Caledon, Ontario: KOS Publishing.

Hoffer, A. (1977). Supernutrition. In R. J. Williams & D. K. Kalita (Eds.), *A Physician's Handbook on Orthomolecular Medicine* (15-23). Elmsford, NY: Pergamon Press. Originally published: (1974). Canadian Schizophrenia Foundation. Regina, Saskatchewan, Canada.

Hoffer, A. (1977). Treatment of Schizophrenia. In R. J. Williams & D. K. Kalita (Eds.), *A Physician's Handbook on Orthomolecular Medicine* (83-89). Elmsford, NY: Pergamon Press. Originally published: (1974). *Orthomolecular Psychiatry, 3*(4), 280-290.

Hoffer, A., & Prousky, J. (2006). *Naturopathic Nutrition: A Guide to Nutrient-Rich Food & Nutritional Supplements for Optimum Health*. Toronto, Ontario: CCNM Press.

Hoffer, A., & Saul, A. W. (2008). *Orthomolecular Medicine for Everyone: Megavitamin Therapeutics for Families and Physicians*. Laguna Beach, CA: Basic Health Publications.

Huemer, R. P. (2015). Genomic Tools for Precision and Personalized Medicine. *Journal of Orthomolecular Medicine, 30*(1), 8.

Kalita, D. K. (1977). Orthomolecular Medicine. In R. J. Williams & D. K. Kalita (Eds.), *A Physician's Handbook on Orthomolecular Medicine* (1-3). Elmsford, NY: Pergamon Press. Originally published: *Journal of the International Academy of Metabology, 5*(1), 54-57.

Kaptchuk, T. J. (2000). *The Web That Has No Weaver: Understanding Chinese Medicine*. New York, NY: McGraw-Hill.

Klenner, F. R. (1977). Significance of High Daily Intake of Ascorbic Acid in Preventive Medicine. In R. J. Williams & D. K. Kalita (Eds.), *A Physician's Handbook on Orthomolecular Medicine* (51-59). Elmsford, NY: Pergamon Press. Originally published: (Spring 1974) *Journal of Preventive Medicine*.

Levy, T. E. (2002). *Vitamin C, Infectious Diseases, and Toxins: Curing the Incurable*. Bloomington, IN: Xlibris.

McCarrison, R. (1936). Nutrition in Health and Disease. *British Medical Journal. 2*(3951), 611–615.

Murata, A., Morishige, F., and Yamaguchi, H. (1982). Prolongation of Survival Times of Terminal Cancer Patients by Administration of Large Doses of Ascorbate. *International Journal for Vitamin and Nutrition Research Supplement, 23*, 101-113.

Nutrient Recommendations: Dietary Reference Intakes (DRI). National Institutes of Health: Office of Dietary Supplements. Retrieved January 6, 2019, from https://ods.od.nih.gov/Health_Information/Dietary_Reference_Intakes.aspx

Pauling, L. (2006). *How to Live Longer and Feel Better*. Corvallis: Oregon State University Press. Originally published: (1986). New York: W.Y. Freeman.

Pauling, L. (1977). "Linus Pauling before Congress." In R. J. Williams & D. K. Kalita (Eds.), *A Physician's Handbook on Orthomolecular Medicine* (45-50). Elmsford, NY: Pergamon Press. Originally published: *Healthline, 1*(2).

Pauling, L. (2001). *Linus Pauling: Selected Scientific Papers, Volume 2*. P. J. Pauling and B. Kamb (Eds.). River Edge, NJ: World Scientific. Retrieved from https://ebookcentral-proquest-com.ezproxy.middlebury.edu

Pauling, L. (1977). On the Orthomolecular Environment of the Mind: Orthomolecular Theory. In R. J. Williams & D. K. Kalita (Eds.), *A Physician's Handbook on Orthomolecular Medicine* (76-82). Elmsford, NY: Pergamon Press. Originally published: (1974). *American Journal of Psychiatry, 131*(11).

Pauling, L. (1968). Orthomolecular Psychiatry. *Science, 160*(3825), 265-271.

Pfeiffer, C. C. (1975). *Mental and Elemental Nutrients: A Physicians Guide to Nutrition and Health Care*. New Canaan, CT: Keats Publishing.

Pfeiffer, C. C. (1987). *Nutrition and Mental Illness: An Orthomolecular Approach to Balancing Body Chemistry*. Rochester, VT: Healing Arts Press.

Philpott, W. H. (1977). Maladaptive Reactions to Frequently Used Foods and Commonly Met Chemicals as Precipitating Factors in Many Chronic Physical and Emotional Illnesses. In R. J. Williams & D. K. Kalita (Eds.), *A Physician's Handbook on Orthomolecular Medicine* (140-150). Elmsford, NY: Pergamon Press.

Raghupathi, W., & Raghupathi, V. (2018). An Empirical Study of Chronic Diseases in the United States: A Visual Analytics Approach. *International journal of environmental research and public health*, *15*(3), 431. doi:10.3390/ijerph15030431

Randolph, T. G. (1977). Ecologic Orientation in Medicine: Comprehensive Environmental Control in Diagnosis and Therapy. In R. J. Williams & D. K. Kalita (Eds.), *A Physician's*

Handbook on Orthomolecular Medicine (121-129). Elmsford, NY: Pergamon Press. Originally published: (1965). *ANNALS OF ALLERGY, 23*, 7-22.

Robinson, M. H. (1977). On Sugar and White Flour…the Dangerous Twins. In R. J. Williams & D. K. Kalita (Eds.), *A Physician's Handbook on Orthomolecular Medicine* (24-30). Elmsford, NY: Pergamon Press. Originally published: *Executive Health, 11*(6).

Schroeder, H. A. (1977). Micronutrient Deficiencies in Major Sources of Calories. In R. J. Williams & D. K. Kalita (Eds.), *A Physician's Handbook on Orthomolecular Medicine* (36-39). Elmsford, NY: Pergamon Press. Originally published: (1971). *Medical Counter-point, 3*(7), 54-57.

Selye, H. (1946). The general adaptation syndrome and the diseases of adaptation. *Journal of Allergy and Clinical Immunology*, *17*(4), 231-247.

Shenkin A. (2006). Micronutrients in health and disease. *Postgraduate medical journal*, *82*(971), 559-67.

Stoute, J. O. (2018). The Use of Vitamin C with Chemotherapy in Cancer Treatment: An Annotated Bibliography – 1. *Journal of Orthomolecular Medicine, 33*(6).

Walsh, W. J. (2014). *Nutrient Power: Heal Your Biochemistry and Heal Your Brain*. New York, NY: Skyhorse Publishing.

Williams, R. J. (1971). *Nutrition Against Disease: Environmental Prevention*. New York, NY: Pitman Publishing.

Williams, R. J., Heffley, J.D., Yew, M. L., and Bode, C. W. (1977). A Renaissance in Nutritional Science is Imminent. In R. J. Williams & D. K. Kalita (Eds.), *A Physician's Handbook on Orthomolecular Medicine* (4-10). Elmsford, NY: Pergamon Press. Originally published: (1973). *Perspectives in Biology and Medicine, 17*(1).