January 2000 Issue | Dr. Emanual Cheraskin

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Welcome to *Functional Medicine Update* for the new millennium, January, 2000. We are now in our 18th year of *Functional Medicine Update;* in June we will have our 19th anniversary. I look with pride over the past 18 years of visiting with clinical practitioners and researchers around the world. I have great respect for the way this field has evolved, for its principal contributors, and for the way it is helping to shape a healthcare system for the 21st century that will be vastly different from what we encountered 18 years ago in what was then called *Metabolic Update.* (It later became *Preventive Medicine Update* and now is *Functional Medicine Update.)*

We dedicate this millennium issue to the individuals who made the most significant contributions to the evolution of this field, at least as I perceive it. To pay tribute to them, the theme of this month's *Functional Medicine Update* is Past, Present, and Future—Back to the Future in Functional Medicine.

We can start at the turn of the 20th century with two individuals whose contributions became dominant themes in *Functional Medicine Update* over the years. The first is Dr. Archibald Garrod. In 1902 Dr. Garrod published an article in *The Lancet,* titled "The Incidence of Alkaptonuria: A Study in Chemical Individuality."[1] He discovered the first genetic metabolism disease. He looked at diseases of infancy that were tied to genetics and had metabolic consequences. He started us down the road toward understanding the origin of many diseases. Those diseases, he said, originated in the genes and the exposure of the genes to substances in the environment that ultimately led to these disorders.

He discovered alkaptonuria. From that discovery we can understand phenylketonuria and other genetic metabolism diseases of infancy. Many of these diseases were nutritionally modifiable. Methylmalonic aciduria, which was discovered later in the century, is one example. Vitamin B12 could prevent the retardation of infancy, and individuals could live reasonably normal lives just by increasing their vitamin B12 intake some 100 times the Recommended Dietary Allowance. These genetically unique individuals required 100 times the level of B12 intake for their function.

Dr. Archibald Garrod

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Diathesis of Disease: Chemical Individuality

Dr. Garrod has stated, "It might be claimed that what used to be spoken of as a diathesis of a disease is nothing else but chemical individuality. It is nearly true to say that the factors which confer upon us our predisposition and immunities from disease are inherent in our very chemical structure, and even in the molecular groupings which went to the making of the chromosomes from which we sprang."

In 1902 that was a very modern concept. It was written some 53 years before Watson and Crick published their landmark article on the structure of the chromosomes and DNA in the chromosomes, the biological basis of inheritance. But Archibald Garrod had the prescience to look ahead and see where medicine would be going in the next 100 years. Now, at the turn of the next century, the concept of molecular medicine is becoming integrated into the way doctors will treat their patients into the future.

Dr. Linus Pauling

Dr. Linus Pauling was a close colleague in intellectual lineage with Dr. Garrod. Dr. Pauling, in a period from about 1930 to 1950, made extraordinary contributions to our view of the origin of disease. His first such contribution was a 1949 article on sickle cell anemia.[2] He made us realize there was something about the genes that could contribute to disorder, cut across organ systems, and produce symptoms at a distance. This process was much more complicated and diffuse than we had originally thought. We had formerly adhered to the vector disease model of Pasteur, according to which disease occurs as a consequence of an infectious organism that creates a specific, well defined set of symptoms. If you get over it and experience remission from symptoms you are beyond the disease.

Pauling’s molecular medicine model was very different. Sickle cell anemia was the first disease whose origin he discovered at the molecular level. In this model, a single point gene mutation on the heavy chain of the globin molecule of hemoglobin could contribute to a conformational change in the way the hemoglobin molecule was structured in three dimensions. That conformational change affected the way oxygen bound to the heme portion of the hemoglobin molecule, creating a different kind of relationship between the molecule and its oxygen absorption/desorption phenomenon. The change in shape of that molecule then changed the shape of the red cell, because hemoglobin made up about three-quarters of the volume of a red cell. The shape change of the molecule, which led to packing of these sickle-shaped hemoglobins, resulted in changing the actual shape of the normal bidisgloid red cell to a sickle shape. This sickle would cut its way through the vasculature.

The Origin of Molecular Medicine

The sickling shape change was a consequence of the geometric change of the molecule hemoglobin. That change was caused by a single amino acid within a chain of hundreds of amino acids. This molecule became more hydrophobic, crystallizing and packing with itself. The molecule subsequently formed the crystalline bodies within the red cell that are associated with sickle cell anemia. Along with Charles Itano, a postdoctoral medical student, with this article in *Science* Pauling predicted that the molecular origin of disease would be found to have extraordinary implications. He believed that as we learned more about the origin of diseases, we would be able to find a way to modify the expression and function of these genes to prevent the expression of the disease.

That model was published in 1949. In 1993 in the *New England Journal of Medicine* published a paper showing that by administering sodium butyrate intravenously to patients with sickle cell characteristics one could prevent the hemoglobinopathies associated with the genetic disorder.

Altering Gene Expression

Sodium butyrate had that effect because butyrate alters gene expression and upregulates the expression of fetal hemoglobin. Fetal hemoglobin is not sickled. Therefore, when fetal hemoglobin diluted the sickled hemoglobin in the red cell, it prevented the sickled hemoglobins from packing together, from hydrophobic interactions and crystallizing. The shape of the cell did not change, and it did not cause the damage across the organs related to sickle crisis.

Forty years after Pauling proposed this model, the *NEJM* article provided the clinical proof of the pudding. We have now started thinking there may be agents that could modify gene expression to create a different phenotype. Instead of disease and premature illness, we might prolong health for many decades if we ask the right questions about the genes and can modify their expression and function.

Communication at Many Levels

This profound concept emerged from the Archibald Garrod discoveries of molecular illness at the turn of the century. Linus Pauling and his wife Eva Helen told us about structure and function, complementarity, the concept of fit, and the concept of communication. Communication occurs at the atomic level, the molecular level, the supra-molecular level, the tissue level, the organ level, the organ system level, whole organism level, and the level of individuals, families, societies, nations, and the planet. This communication occurs through the complementary nature of relationships, being good listeners and good transmitters.

That model of medicine is unfolding as we move into the 21st century. We have transmitting messages and receiving messages. Transmitters are the molecules we call mediators. The receivers are the membrane receptor binding and soluble receptor sites that pick up the messages and translate them into altered gene expression and altered function. We can manipulate both the messages and their reception on the basis of things we do every day, the way we think, act, eat, and feel, where we live, the nature of our relationships, how our environment influences the nature of our own spiritual belief systems. All these factors influence the mediating molecules and can lead, as Dr. Candace Pert explained, to an informational rubric within the new, expanding health paradigm. An informational rubric involves communicating the right messages, receiving the right messages to be in synchrony with our genes to give rise to function.

That concept has been an underlying theme in *Functional Medicine Update* for the past two years. This theme has caused a transformation in healthcare sciences as we move into the new millennium. It is the concept of modifying the way genes express their phenotype to create a different message, and the communication of that message to the outside and inside environment.

Dr. Roger Williams

In the late 1940s, Dr. Roger Williams was a biochemist at the top of his game. He was president of the American Chemical Society. He was the discoverer of a number of the B-complex vitamins, including pantothenic acid. He was a person who by all rights might be locked into the myopic vision of a pure scientist looking at molecular structures and biochemical function. He published a book on biochemical individuality, however, that caused us to think about biological diversity beyond difference in eye and hair color. (That book was reissued in the 1990s, because it was such a classic.)

Few differences in phenotype are outwardly apparent in the human population relative to the wide-ranging differences Dr. Williams brought to our attention at the level of anatomy, physiology, and biochemistry. The range of function there was far greater than we could have guessed on the basis of differences in physiognomy, hair, eye, or skin color.

Nutrition against Disease

Dr. Williams's book, published in the early 1970s, was *Nutrition Against Disease*.[4] It modified my own thinking and changed the way I conducted research as a professor of biochemistry. *Nutrition Against Disease* made us think about the role of various nutrients in preventing what Williams called genetotrophic disease. Genetotrophic diseases are those for which genetic uniquenesses cause need for specific nutrients beyond what the average, midline individual might require to promote optimal function and prevent premature disease.

He included all the major chronic degenerative diseases of aging in the genetotrophic disease category. He believed heart disease, cancer, diabetes, and arthritis were related to genetotrophic imperfections. The genes called for different levels of nutrition and lifestyle that were not delivered by the individual's selection. The discrepancy expressed itself, over the course of several decades, as degenerative disease "of unknown origin." He even included in the genetotrophic category diseases of mental illness, childhood diseases, behavior disorders, and alcoholism. He thought they all were related to the mismatch of genes and environment. At the genetic level, the person's body was asking for different levels of nutrients to promote proper phenotypic function. Failure to meet that need led to the undernutrition seen as chronic disease in midlife.

Genetotrophic Disease Model

This powerful concept revolutionized our thinking about the origin of age-related diseases. It was not just the vector disease model of Pasteur, not just the model of injury. It was the model of matching the uniqueness of the person to his or her diet and lifestyle to promote optimal function. It took Archibald Garrod's concept to the next level. The genetotrophic disease concept combines well with Dr. Pauling's concept of orthomolecular medicine, using substances that are natural to human physiology to modify or normalize function.

In 1968 in *Science* magazine, Dr. Pauling published a landmark paper titled "Orthomolecular Psychiatry."[5] In that paper he explained how nutrients taken at much higher doses than the Recommended Dietary Allowances can promote improved function in people with metabolic uniquenesses or biochemically individual characteristics. He pointed out that Le Chatelier's principle comes into play. Le Chatelier, a French chemist aristocrat who was beheaded during the French Revolution, said that if you apply stress to an equilibrium the equilibrium will move in the direction that minimizes the stress. (Perhaps if Le Chatelier had heeded his own principle he might not have been beheaded.)

Applying Le Chatlier's Principle

Dr. Pauling explained a way to promote the function of a genetically imperfect enzyme, to clear a metabolic block if there is a coenzyme imperfection. (Coenzymes come, basically, from nutrients like the B vitamins or minerals). To clear the block, you increase the level of that specific coenzyme to try to drive that sluggish equilibrium to completion. A baseball glove analogy helps explain this process. Every kid with a baseball glove knows the value of having a good pocket in that glove. When you have a good pocket, the ball will stick much more easily into the glove. (When I was a little leaguer, I oiled my new glove, put a ball into it, and slept on it under my mattress for a week to get a good pocket.) That would be like an enzyme that is very tightly bound to its coenzyme and can produce an active form of the enzyme that catches the ball every time it comes near.

If your baseball glove is warped, however, and the pocket isn't quite right, you can miss a lot of balls. You may catch some, but you will miss a lot more. This is the kinetic molecular theory related to metabolic function. Pauling said that by increasing the frequency of the hit of the ball against the glove (i.e., the apoenzyme against the enzyme) the probability increases that you will get an active enzyme that can participate in metabolic function. This wasn't built around idle speculation. In this article he pointed out binding constants, transference rates, Kms of enzymes with different genetic states of control of their velocity. By increasing the concentration of the coenzyme vitamin or mineral he was able to demonstrate improved velocity of substrate going to product.

Nutrition for Genetically Unique Individuals

That is a very scientific way to explain why a nutrient requirement for one may be different from that for another. In some cases of genetic uniqueness, it may be vastly different. As Roger Williams said in a talk I heard him present 20 years ago when he was asked how he could support this concept of biochemical individuality, "Nutrition is for real people. Statistical humans are of little interest." Everyone in the audience realized he or she had spent years studying statistical humans but had never seen one of them in real practice. People are unique facets on the diamond of life. Each has different characteristics. As a consequence, we need to treat real people with respect to their biochemical uniqueness; that was the Roger Williams' contribution

Dr. Abram Hoffer

In the same rich period of the 1950s, Dr. Abram Hoffer, with a PhD in chemistry and an MD in psychiatry, helped us recognize that the molecular milieu of the brain can influence the outcome of function. Working with Humphrey Osmond, he produced the extraordinary concept that schizophrenia and other types of mental illness may be associated in certain people with brain chemistry defects that are

modifiable by changing the molecular milieu of the brain. They showed that vitamin B3 (nicotinic acid), vitamin B6 (pyridoxine), or vitamin C (ascorbic acid), given together or singly in high doses to certain individuals with schizophreniform disorders, produced clearance of their mental illness.[6]

Several years ago I had a personal experience that reinforced the importance of vitamins in schizophrenia. I was traveling to a medical meeting in the 1970s with an esteemed medical school professor. He had become a clinical psychiatrist and a strong supporter of Dr. Hoffer's work, at some risk to his own career. It wasn't considered politic in the 1970s to talk about vitamins and mental health. I asked him how he had taken on this potentially adversarial position with his colleagues about the role of therapeutic doses of vitamins in treating certain forms of mental illness. He explained that he himself had experienced a schizophreniform attack in a mental hospital, where he had been taken for observation.

Application of Orthomolecular Psychiatry

"Once I got in there, I couldn't get out," he explained. "They said I needed to be there for watchful therapy. They tried to give me various drugs I had prescribed myself. I knew the side effects and implications of these drugs, and I refused to take them. We had a battle back and forth. Finally, my wife smuggled in to me vitamin B6 and vitamin B3, and I took them at high dose. Over the course of the next month I had a complete remission, and I have remained in remission ever since. I have had my plasma and urine studied over the years. My urine contains metabolites that are associated with brain disturbances. Those metabolites are resolvable with high-dose B6 and B3. I became a believer and a complete devotee of this principle, and I have dedicated my life as a professional to that field."

Personal experiences like this have caused many people to enter this field. Often it was despite their training, which had told them something different. If you have much experience in this field or listened to the exchange on this topic in our society, you know mainstream medicine has discouraged individuals from considering how nutrients might modify function at doses far greater than the Recommended Dietary Allowances, beyond variety and moderation. We have been discouraged from considering biochemical uniqueness.

Hans Selye

Hans Selye was another extraordinary contributor in the 1960s. He should have been awarded a Nobel Prize in medicine, but he never received that prize. Hans Selye is the father of our understanding of the word *stress*, a concept he borrowed from physics and applied to physiology.[7] In our time-compressed, time-urgent society stress is almost the watchword of being a successful survivor of this generation.

Selye conducted research on adrenalectomized animals and was able to make the connection between the adrenal glands and stress and physiological function in these animals. Although he was reputed to be a very poor experimentalist, he was obviously a keen observer and wise enough to use these observations to put together a theme that represents a cornerstone of the way medicine will be practiced in the 21st century. That is the endocrine/environmental interrelationship and how our nociceptor and propioreceptor systems respond to our environment through perceptions of stress or distress.

The General Adaptation Syndrome

The hypothalamus/pituitary/adrenal axis represents the antennae of our body that are out there sampling the energy of our world. These antennae are trying to see if that energy is in coincidence with our body. Is it harmonic friendly energy, or dysfunctional energy that is outside the range of harmonic coordinated function that we call dis-energy or distress? With this model of stress, Selye described the general adaptation syndrome (GAS). GAS has three stages. First is arousal, in which the adrenal glands are stimulated to action, such as when a zebra tries to escape from a lion. The adrenal glands pour out cortisol, and the zebra has an adrenaline reaction throughout the metabolic pathways. (Dr. Robert Sapolsky described this process in his book, *Why Zebras Don't Get Ulcers.*[8] A stress physiologist at Stanford Medical School, he has helped us understand the physiology of stress and how hypercortisolemia over long periods of time can lead to more rapid brain aging.)

We learned from the work of Dr. Selye that the stress response first goes through arousal and then adaptation. The person says, "I'm not under stress; everything is fine." The adrenal glands are still hypertrophied, and they are getting different physiological function, different messenger molecules. They are living in a state of hyperadrenaline and hypercortisol.

Adrenal Exhaustion

Finally, if we push too hard, too long, and too intensely, we get what we used to call a nervous breakdown. Selye called it adrenal exhaustion. Exhaustion is the third stage of the GAS. We might say that people in our culture are running out of GAS in our physiological response to our lifestyle. Dr. Selye helped us understand how our environment and our perception of that environment through our sensory systems can be translated into physiological function.

A Web of Physiological Function

Selye's work led, in the later part of the 20th century, to that of people like Candace Pert, who found neuropeptides on the surface of white cells membrane binding sites, the substances secreted by our nervous system in response to perceptions of how our environment is influencing us. We now see that the immune system is a brain, and the brain is an immune system. An immune system and a brain travel through our cells. The mediators that come from our nervous system communicate with the immune system, and the immune system signals through its release of mediators called cytokines and chemokines messages that are communicated to and received by the nervous system.

A web of physiological understanding has emerged in the last 30 or 40 years. We cannot consider each organ individually, like a chapter in a textbook, as though each is separated from all the others. They are all part of one; it is a holographic system. That is one of the fundamental underpinnings of functional medicine. Every organ reflects every other organ. In this holography the gut is a brain; the brain is a gut; the immune system is a liver; the liver is a brain. Communication is interrelated, and to understand dysfunction we have to understand function at this level of weblike interaction. We can credit Dr. Selye with those contributions.

INTERVIEW TRANSCRIPT

Dr. Emanual Cheraskin

Dr. Emanual Cheraskin was both a medical doctor and a dentist who got his training at the University of Alabama, Birmingham. He was a professor and one of the first people to do controlled studies on the influence of nutrition on function. I have known Dr. Cheraskin for many years, and I have used his presentation as a model for what I wanted to do as an educator. His book, *Predictive Medicine*, was at least 20 years ahead of its time.[9] As a prolific author, a good investigator, and an excellent communicator, Dr. Cheraskin helped us understand that health is more than the absence of disease. Lifestyle and nutrition can promote healthy function. If we ask the right questions we get different answers. He helped us ask those different questions about function.

I spoke with him late in his professional career. He said he had written about 14 books for health professionals, none of which was well received, because they advanced a precept that was outside the norm. Neither medicine nor dentistry was ready to accept the concept that health is more than the absence of disease.. When Dr. Cheraskin wrote a book for the general public, however, it became a best-seller. He said the best way to deliver a message might be not to the sclerotic brains of health professionals but to the general public, which is more receptive to change and to factual information. We are just beginning to see a transformation in the thinking of healthcare providers about how they can better serve their patients, be more effective in their jobs, get away from being pill counters and prescription writers, and become true healers. Dr. Cheraskin contributed to that transformation.

During the 1960s and 70s, Dr. Cleave had a great influence on this field. He wrote an extraordinary book, *Saccharine Disease: The Master Disease of Our Time*.[10] In this book he pointed out that when cultures underwent a transformation from eating whole, unrefined foods to consuming white products, the products of processing (white sugar, white flour, white fat), an array of new diseases began to develop. It is uniform and reproducible in the world no matter where you look. He called these the "saccharine diseases." They included heart disease, diabetes, cancer, and hypertension related to stroke. Dr. Cleave was a well respected scientist, esteemed in the British medical community. For him to talk about these diseases as a serious part of medicine again opened the door for us to start looking differently at the origin of disease.

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Dr. John Yudkin

Dr. John Yudkin wrote a book called *Sweet and Dangerous*,[11] in which he caused us to examine our use

of white sugar. The magnitude of white sugar in the diet, much of it coming as hidden sugars, has had an increasing effect on health. Sugar is hidden in foods and beverages that continually increase our simple carbohydrate exposure and create altered metabolic function.

This was a profound change in thinking. In the past it was thought that carbohydrate was carbohydrate, and there was not much difference between types. People who thought sugar was dangerous were thought of as health-food fanatics who were prone to exaggerate and had no scientific understanding of the effect. Not so, said Dr. Yudkin. Simple carbohydrate sensitivity in some individuals was a real basis for this concern.

Dr. Dennis Burkitt

Dr. Dennis Burkitt, a public health physician, worked in South Africa for many years. He was a tremendous investigator and no doubt a high-quality doctor. He and I were roommates at a medical meeting 22 years ago that changed my thinking. Dr. Burkitt not only discovered Burkitt's lymphoma and did a lot of epidemiological work around this virus-induced cancer, but he also was the person who first studied seriously the dietary fiber connection to health and disease. He recorded the fecal remnants of individuals who ate wild, natural diets in Africa and those who were on the transition, processed, or white diets, described as saccharine type diets by Dr. Cleave. He found a very close correlation between bulk in the diet, called roughage, and disease. He showed that fiber had an impact not only on digestive diseases like hernia, diverticular disease, and appendicitis, but also on risk of other systemic diseases, such as cardiovascular disease. Low-fiber diets increased risk of cardiovascular disease.

Dr. Burkitt made this observation and was the first to publish it in serious medical literature.[12] He got us thinking in a much broader way about the natural diet versus a highly purified diet. He believed that "space food sticks," which were the rage when I was a kid in the 50s, might not be the best way to live in terms of complete nutrition. For optimal function we need to consume substances present in whole-foods, such as those with which we evolved through our Paleolithic ancestors.

Dr. Melvin Konner and Dr. Boyd Eaton wrote an extraordinary article in the late 1980s in the *New England Journal of Medicine*, called "Paleolithic Nutrition."[13] They talked about the anthropological work that had been done on diet and health over a period of our Paleolithic ancestors. They found that Paleolithic diets were a balance of vegetable and animal products. As gathering animals we used a grasping thumb. We weren't very good as hunters, because we didn't have telescopic sites and high-powered rifles. We had to find young, diseased, or old animals and try to catch them. But our grasping thumb allowed us to pick and gather things. As a consequence, we ate a lot of vegetable products in their unrefined state, along with lesser amounts of lean muscle meat.

When we ate meat we consumed the whole animal, including the bone marrow, which gave us calcium. The meats we ate had high omega-3 fatty acid content, because the animals foraged on natural vegetables that were rich in omega-3, cold-weather vegetable oils. The meat we eat today, by contrast, is rich in omega-6 linolenic acid and arachidonic acid, because animals are fed corn, which is a warm-weather plant. As a consequence, we have changed both the composition and the quality of the foods we eat. Konner and Eaton's article follows closely from what Dr. Dennis Burkitt and Yudkin and Cleave were talking about. Populations that continued to eat this unrefined diet had much lower incidence of various types of Western diseases.

This major change in our thinking has affected the last four decades in the evolution of a healthcare paradigm. In the future, we will view diet as a way of improving function and getting the most out of our genes. It will become a primary tool in health promotion, disease prevention, and therapeutics. Only three or four decades ago nutrition was taught almost exclusively in land-grant colleges in the department of home economics and food and dietetics. The setting was an agriculture school. People who went on to the university to become medical doctors didn't get that training. It was thought of as women's work. It had no value if you were going on to undertake male-centered medical school training in the university. That was where all the action was, and you didn't want to be bothered with this nutrition stuff, which was not high tech or good science.

We are coming full circle, to the recognition that the ways we eat, think, act, and believe manipulate the phenotypic expression of our genes through the course of living. Those factors are much more important than the medicine we take or the surgery we have. Communication between our diet and our genes gives rise to the expression of function. Micronutrients, macronutrients, and conditionally essential nutrients in our diet play continuous roles in washing over our genes to give rise to their function. This concept emerged from the observations of people like Dr. Cleave, Dr. Yudkin, and Dr. Burkitt.

Dr. Fredrick Klenner

Dr. Frederick Klenner was a pioneer in the therapeutic applications of vitamins. During the polio era of the 1930s and 40s, before the Sabine and Salk vaccines, he observed that administering high doses of intravenous vitamin C to polio patients could bring about considerable improvement in their function and remission of the neuropathology of polio. Although this thinking was considered heretical, Dr. Klenner was committed to this concept. He wrote and spoke about it but did not receive much medical support for his concepts. He considered vitamin C a virucidal agent in the treatment of and management of polio infection.

Dr. Irwin Stone

Dr. Irwin Stone helped explain the vitamin C connection to physiology by tracing its genetic history. He showed that our ancestors had the ability to manufacture their own vitamin C through L-gluconolactone oxidase, an enzyme that converts glucose through glucose 6 phosphate into vitamin C.[15] Humans are one of the few animals that have lost that enzyme activity. A few birds, fruit-eating bats, and the guinea pig have also lost that ability. Most other animals, including the goat, can make their own vitamin C. A goat weighs about the same as a human. As Dr. Pauling pointed out from conversations with Dr. Stone, the goat normally makes about 200 milligrams of vitamin C a day in its adrenal glands through this biochemical process.

When the goat is under stress, however, it will make 1000 or more milligrams of vitamin C. As Dr. Stone pointed out, we lack the ability to upregulate vitamin C synthesis during stress. (By definition it is a vitamin for us, a life-giving substance that helps prevent scurvy, its deficiency disease). Vitamin C's importance extends far beyond scurvy prevention. Dr. Stone described it as a stress vitamin. It is manufactured in nearly all other animals during stress, but it cannot be made in higher quantities by humans under stress. Vitamin C intake, therefore, becomes increasingly important during times of stress, but the RDAs are doses that are adequate to meet the needs of practically all healthy people to prevent scurvy, with a margin of error. The 30 mg vitamin C RDA was considered to be more than enough,

because scurvy can be prevented in most people at 10 mg a day. Thus there was a margin of error in the RDA over the MDR, the minimum daily requirement.

Vitamin C Intake and Optimal Function

A difference exists between preventing a deficiency disease and optimizing physiological function of the approximately 100 biochemical reactions that depend on vitamin C and its related dehyrdoascorbate for their function. According to Dr. Stone, if you look carefully at animal studies you see that even animals that make vitamin C require much higher levels of it to promote function under different physiological or chemical stresses than what they can get readily in their diet. Therefore, the need exists for conditionally essential supplementation. This does not even take into consideration biochemical diversity or biochemical uniqueness, as discussed by Dr. Roger Williams.

Dr. Stone influenced Dr. Linus Pauling considerably. Unfortunately, late in his career, some people inappropriately labeled Dr. Pauling the vitamin C guru. Certainly, he had a lot to say about vitamin C, and he helped to raise the understanding of vitamins and their relationship to health to a higher level than before, but he was much more than the vitamin C guru. His use of vitamin C was built around this whole model of biochemical individuality and matching the need to the physiological condition of the individual.

Dr. and Mrs. Weston Price

Dr. and Mrs. Weston Price provided cultural supports for this discussion from the turn of the 20th century up to the 1930s. Dr. Price was a dentist from Baltimore, Maryland. He and Mrs. Price traveled around the world at a time when much of the world was beginning to become industrialized or Westernized. Countries were undergoing a transformation from the cultural habits they may have had for centuries to new habits. The Prices photographed and recorded their observations in Eskimo villages, landlocked Swiss villages, African tribes, and Australian aboriginals.[16] They repeatedly returned to these same places in the world, saw individuals evolve over 15 or 30 years, and recorded the changes in photographs.

The Prices saw what they considered to be the physical degeneration of these people as their diets became saccharine type diets—white sugar, white-flour, high-alcohol, fat-rich diets. No matter where the culture was or what the previous diet had been, when they started making the transition to this highly refined diet the changes were dramatic. The Prices concluded that the bones of the face changed shape, the jaw changed shape, the teeth became crowded, the nose flattened, and the nasal pharynx changed so individuals got rhinitis and sinusitis. They became more allergic. Their vitality went down. It wasn’t a gene change; it was the expression of the genes into their phenotype as a consequence of the altered diet, according to Dr. Price.

Dr. Francis Pottenger

Dr. Pottenger’s work focused on the treatment of tuberculosis. He used adrenal extracts in the sanitarium where he worked. Prompted by the high rate of mortality among laboratory cats that had been adrenalectomized, he conducted a feeding experiment between 1932 and 1942 to determine the effects of heat-processed food on the cats.[17] Cats fed a diet of market-grade raw milk, cod liver oil, and cooked meat scraps began to show signs of deficiency, including a decrease in their reproductive capacity

resulting in skeletal deformities and organ malfunction in their offspring. Within a few months, raw meat scraps fed to a segregated group of cats resulted in better health than in animals being fed cooked meat scraps. At the third generation of cats on the cooked meat scraps, Dr. Pottenger produced what he considered the first allergic cat. It had sinusitis, rhinitis, and all the inflammatory, histamine- and cytokine-driven phenomena we might associate with asthma. He went on to do many other good studies, feeding animals raw meat and raw milk, cooked meat and raw milk, and cooked meat and cooked milk. He observed that as the diet became more highly processed, something was lost, and the vitality of the cats declined significantly. Again, this was in the early stages of understanding the implication of the full complement of food on function.

Dr. Lucille Hurley

Dr. Lucille Hurley, at the University of California at Davis, examined zinc nutriture in animals. She showed that by the third generation of zinc depletion in mice she could produce animals whose immunological function was so compromised that they were open to opportunistic infections.[18] Just by depleting one nutrient over three generations, the phenotype of the immune defense of the animals continually declined. By the third generation she produced hyperimmune or immune-compromised animals. It took three generations of zinc repletion to build them back up to their original state.

We are not talking about changing the genes. We are talking about changing the expression of the genes. We are talking about the expression of the genes in the phenotype that is modified by exposure. The gene does not adapt as a consequence of altering the environment, as Lysenko, the Russian physiologist, believed. It is the phenotype that changes.

A number of historical contributors have taken us to this extraordinary threshold in the new millennium in health sciences. They have helped forge a new healthcare system that will cause a paradigm shift comparable to any in human history.

Dr. Benjamin Feingold

Dr. Benjamin Feingold is in the same category as Dr. Price and Dr. Pottenger. During the 1950s, 60s, and 70s, based on his observations about diet and hyperactivity, he founded the Feingold Movement. This movement featured a diet low in food coloring, food additives, and salycilate for children with hyperactivity.[19] This diet was considered very controversial. During the 1950s, as a result of the development of the supermarket and shelf-stable foods that were sweet, colorful, and bursting with synthetic flavors, kids were being raised on these artificial foods. These foods represented an experiment for which we had no precedent in the history of the human species.

Feingold had the audacity to say that some of these food materials and ingredients might be producing neurochemical changes in children with genetic susceptibilities and causing behavior disorders. That created a groundswell of antagonistic response from individuals with vested interest in the status quo.

In the 30 or 40 years since Dr. Feingold's hypothesis, we have learned more about brain biochemistry, NMDA receptor sites, and glutamate sensitivity and neuroexocytotoxicity. We are starting to see genetic variants that can respond to some of these substances that are slipping into our diets. These chemical agents can induce functional changes. This is not even to mention glutamate and monosodium glutamate

(MSG), with its potential effect.

Dr. Denham Harman was a professor of medicine at the University of Nebraska School of Medicine in the 1950s. He published a paper on the role of free radicals in aging.[20] He later showed that vitamin E could help prevent free radical damage in animal systems. Dr. Harman could be called the father of the free radical theory of aging and oxidant stress-related aging. Denham Harman, MD, PhD, had been a student of Dr. Pauling in his undergraduate days.

Dr. Henry Biehler

Dr. Henry Biehler worked with a group of colleagues in Southern California who were health advocates. He wrote a book called *Food Is Your Best Medicine*, in which he explained that food contains constituents that help promote function.[21] This work was fairly unsophisticated relative to where we are today in understanding the constituents that could promote health, but he observed there was something about whole foods that, when they were used appropriately, could promote health and actually treat certain kinds of diseases.

Dr. Evan Schute

Dr. Evan Schute was a cardiologist at London, Ontario, Canada, who stepped out of his discipline and created a backlash that almost got him dismissed as a cardiologist. He had the audacity to suggest that vitamin E, tocopherol, might be useful in treating certain kinds of cardiovascular problems. In the 1950s and 60s Dr. Schute observed improvement with vitamin E in patients with cardiac problems, burns, and wounds. He was an incredible clinical investigator. He and his brother Wilford published a report for over 30 years demonstrating that vitamin E has a profound effect on healing and recovery and the prevention of scarring.[22]

Unfortunately, this observation did not get picked up by the medical community. Instead, it was picked up by the health food industry. Therefore, it was considered not to be reputable information. If it were authentic information, it would have ended up in medicine and not in the health food industry. Over the past 30 years, however, the vitamin E story has woven its way through science to a point where now medicine has discovered it. Epidemiological studies and intervention trials are being published showing that people who consume higher-than-RDA amounts of vitamin E have lower cardiovascular disease risk and lower cancer risk. There is something about the ability of vitamin E to serve as a gene response messenger and controller of redox potential within cells that is very important for the overall function of the cell, tissue, or organ. The RDAs for vitamin E may not be adequate to meet the needs for optimal function in a population that expects to live seven, eight, or nine decades without disease.

Establishing the RDA for Vitamin E

You might be surprised to learn how the RDAs for vitamin E were established. The Food Nutrition Board assumed that because no acute diseases were associated with vitamin E deficiency (such as the association of vitamin C deficiency with scurvy), individuals who were considered to be primarily healthy must be getting adequate vitamin E in their diet. Therefore, they evaluated the common vitamin E intake in this country in the 1950s and 60s (about 15 to 30 IUs a day), assumed that must be adequate, and established the RDAs on that basis.

We might ask how that relates to function and promotion of physiological reserve. That is a different question that only within the last 20 years has been seriously considered.

Dr. Max Horwitt

Dr. Max Horwitt was a principal investigator at Saint Louis University Medical School. He made some extraordinary observations on the importance of increasing vitamin E intake as polyunsaturated fatty acid intake increases in our culture. Vitamin E is necessary for helping to protect against oxidative damage.[23] If we strip vitamin E from our diet and increase vegetable oil consumption, which was the trend in the 50s, 60s, and 70s, we may be increasing our risk of oxidative injury.

Dr. A.L. Tappel

Dr. A.L. Tappel, at the University of California at Davis, was one of the first people to look at the role of antioxidants in the prevention of oxidative stress in cells, as seen in lipofuscin bodies or seroid pigment that is deposited in the nervous system. He observed that antioxidants, at the biochemical level, could influence these clinkers, this damaged debris that is formed during oxidative stress reactions.[24] He opened up and expanded the free radical theory of aging and age-related diseases that was initiated by Dr. Denham Harman.

Dr. Theron Randolph

In speaking of food and the information it contains that it is able to communicate to the body, we must consider Dr. Theron Randolph. He was an extraordinary discoverer of the ecology of food and how some foods and particular genotypes can produce untoward effects.[25] The food for one may be the poison of another. This is a powerful concept. Some foods that we consider good for most people, such as wheat and dairy, may for other people produce an adverse message, related to alpha gliadin in wheat or caseimorphins found in dairy protein, which create an adverse physiological response. The field of ecological and environmental medicine emerged from the observations of Dr. Randolph. He emphasized the use of food elimination diets to manage these individuals.

Jack Lalane

As a member not of the medical community but of the general public we pay tribute to Jack Lalane, who raised our level of awareness. I recall when I was a child he was featured on television, doing his exercise and talking about nutrition and yeast and liver. This seemed strange to the average person at the time, and the medical community ridiculed him. Now in his 80s, he is still quite fit and has outlived many of his critics. There was something about him as a spokesperson, a devotee, and as a committed individual that got our attention.

The books of Adele Davis created the groundswell of what has now become the resurgence of medical nutrition and nutritional pharmacology. Certainly much of what is in her books today does not stand the test of scrutiny, but they contained an important theme. They made us understand the role nutrients play in promoting physiological function.

Paul Bragg was a fundamental contributor to this field whose exercise and nutrition commitment to health

featured low-fat, high complex carbohydrate, unrefined diets for cardiovascular disease and for diabetes. He foreshadowed the Pritikin Revolution, which we will discuss later.

Carlton Fredericks was an educator, communicator, guide, and model for nutrition and health. *Low Blood Sugar and You*, one of his many books, is a classic.[26] He was one of the first people to discuss the higher-protein, lower carbohydrate diet for normalizing insulin through the blood sugar connection that was called reactive hypoglycemia.

Nathan Pritikin

Nathan Pritikin was a brilliant electrical engineer who in his early 40s had serious health problems and was not expected to live long. He sought the care of a physician at the University of California Los Angeles. Dr. Lester Morrison was a cardiovascular researcher who had developed a dietary program and lifestyle called the high complex carbohydrate, low-fat, modest protein, high-fiber dietary approach.

Lester Morrison was a real heretic. Cardiologists didn't talk about dietary intervention using this very unusual fat restriction approach. But Pritikin went to the Morrison clinic at UCLA and entered that program with great commitment. His health was rescued, and the rest is history. Pritikin was an excellent communicator and synthesizer of information. He took that concept to a much higher level of understanding and created a groundswell that helped shift the medical paradigm, although the medical community resisted it for many years. It is now incorporated into the foods and the recommendations of the American Heart Association and the American Diabetic Association.

For the exercise component of functional medicine, we give credit to Dr. Kenneth Cooper, the father of the word *aerobics.*[27] He made us recognize how exercise and the activity of even a simple walking program could have a remarkable effect through the transduction of messages into the gene expression of function. Kenneth Cooper, as Selye did with stress, made aerobics a common parlance of understanding and discussion. He built an industry of fitness. Our heart, vasculature, immune system, and nervous system depend in part on our activity patterns.

Covert Bailey helped us understand how exercise relates to body composition, through the *Fit or Fat* approach.[28] You could be a thin fat person. Your body fat percent could be high even if you look reasonably thin, because you have been on repetitive restriction diets with no exercise and you have been eating up muscle and replacing it with body fat. The whole concept of body composition and fitness and their relationship to heart function and overall body function can be attributed to Covert Bailey.

Dr. Dick Passwater published books, beginning in the 1970s, that extended the work of Adele Davis to the next level of science.[29] He explained how vitamins and minerals could be used therapeutically to promote function. He was one of the first people in the health food industry who raised the level of science and got us to think more about mechanisms. He caused studies to be done and more science to underpin claims and explain the mechanism of the way these nutrients work.

Dr. James Fries

n 1980 Dr. James Fries, professor of medicine in the Department of Preventive Medicine at Stanford University, wrote a landmark paper on aging, natural death, and the compression of morbidity.[30] He

originated the concept of organ reserve and how we can preserve it by health-promoting practices. That reserve could be worked upon and used throughout the aging process to lower biological age. This powerful concept was a departure from the prevailing belief that a person was well until proven sick.

In 1998, Dr. Fries published a 17-year follow-up study in the *New England Journal of Medicine*, in which he demonstrated that people who did elect to maintain a proper body weight-to-height ratio, exercise regularly, and avoid smoking not only lived longer but also lived healthier lives.[31] They compressed morbidity into a shorter period at the end of their lives. They didn't just live longer with more sickness. They lived longer without sickness. He introduced the powerful concept that one could take charge of his or her genes and seize the locus of control.

Dr. Derrick Lonsdale

In the *American Journal of Clinical Nutrition* in 1980, Derrick Lonsdale and his colleague Raymond Shamberger from the Cleveland Clinic reported that children who have low transketolase activities, which suggest inadequacy of vitamin B1, had behavioral problems and learning disabilities.[32] Even though they were consuming what would be considered the RDA levels of vitamin B1, they had lower metabolic functions of vitamin B1 and subclinical manifestations of this inadequacy that affected brain function. Increasing their B-vitamin intake to greater-than-RDA levels brought about improvement of their clinical function and their biochemical indices of B-complex adequacy and intracellular adequacy. This work represented a different perspective on measuring nutrient needs based upon functional testing rather than just on serum levels.

Dr. Richard Pryor at the University of Louisiana helped us understand free radical aging and its relationship to nutrients.

Dr. Helmut Sies

The term oxidative stress emerged from the work of Dr. Helmut Sies in Germany. Together, the work of Dr. Pryor and Dr. Sies created a new chapter in the field of medicine. That chapter concerns oxidative stress and antioxidants, redox control, intercellular signaling, cell messaging, signal transduction, and NFk B, AP-1.

In the 1980s Dr. Pryor wrote a paper in which he demonstrated the effects of antioxidant supplementation in rats. Some members of a litter of rats were exposed to oxidants in the form of ozone and received no increase in antioxidants. Their littermates, exposed to the same level of ozone, received high levels of antioxidants. The group of animals under oxidative stress with no antioxidant support looked ragged and aged, and their fur was coming out.[33]Those that received antioxidants while they were under oxidant stress, on the other hand, appeared much younger and healthier.

Irvin Fridovich and Chuck McCord are two primary investigators at Duke and Stanford Universities, respectively. They discovered superoxide dismutase as an agent produced in cellular physiology.[34] The enzyme superoxide dismutase is there to suck superoxide up before it creates damage. They explained how that process relates to the Fenton reaction, the iron catalyze reaction, in which superoxide is converted to hydroxyl radical, and the role of antioxidants in preventing this free radical pathology.

Dr. Edward Schneider

Ed Schneider, MD, PhD, deputy director of the National Institutes on Aging, wrote a landmark paper in the *New England Journal of Medicine.* In this article, titled "RDAs and the Elderly," Dr. Schneider pointed out that the Recommended Dietary Allowance levels probably don't meet the needs for nutrients to promote proper healthy aging.[35] There are specific needs for biochemical function in aged individuals that are not met by the RDAs. He was another scientist who chipped away at the fundamental paradigm of the RDAs as a standard of good nutrition. He challenged the Standard American Diet (SAD) and the belief that a diet of moderation and variety from our foods of commerce, asserting that such a diet would not lead to optimal function.

Dr. Irwin Rosenberg, at Tufts University Medical School in Boston, was one of the founders of the Human Nutrition Center on Aging. He was editor and founder of the journal *Nutrition Reviews,* which was instrumental in the 1970s in causing me to consider how these things fit together in a scientific perspective. The Human Nutrition Center on Aging is at the forefront of understanding how nutrition can influence the biological aging process.

n the early 1980s AIDS was identified, and the immune system came onto the radar screen. Investigator Dr. Rajit Chandra was a primary authority on nutrition and immunity. He helped us understand how nutrition could influence the immune system.

Dr. William Beisel

In a paper in the *American Journal of Clinical Nutrition,* Dr. Beisel discussed single-nutrient effects on immunological function.[36] He raised the bar in medicine to see the implications of nutrition, fatty acids, minerals, and vitamins on various immunological parameters. Inactive or altered immune systems were caused by factors other than just protein/calorie malnutrition.

Dr. Norman Shealy

If any individual helped doctors get together to discuss areas of integrative medicine it was Dr. Norman Shealy. A neurologist and pain specialist, he felt there was more to managing pain than just uncoupling the message with analgesic and narcotic medications. He founded the American Holistic Medical Association back in the late 1970s and early 80s, and provided a place for physicians to get together and talk responsibly about how to form a more complete and integrated healing system.

Those discussions led to a generation of doctors in the 1970s and 80s who have reformed the practice of medicine from this integrated medicine perspective. Many of those clinicians have been featured on previous issues of *Functional Medicine Update* and its precursors *Metabolic Update* and *Preventive Medicine Update.*

As a young physician, Dr. Jonathan Wright came out of Group Health in Seattle knowing there was more to the practice of medicine than treating crisis illness. He began utilizing the principles of medical nutrition and molecular medicine in his practice. Investigators and clinicians, including Dr. Alan Gaby, came through his clinic in Kent, Washington, and became experts in the field of nutritional medicine.

Dr. Leo Bolles

One of my intellectual forefathers is Dr. Leo Bolles. Now in his 80s, he is still practicing in Bellevue, Washington. One of the first nutrition-focused doctors in Washington State, he was under tremendous scrutiny by medical advisory and licensure boards for more than 25 years because he chose to march to a different drummer. With his patients he has always had the highest level of integrity and has focused on healing. He has been fearless about what he knows is right.

Dr. Richard Kunin started the Orthomolecular Medical Association and brought together scholars and clinicians who were followers of Linus Pauling. In San Francisco he started this whole field moving through a different paradigm of molecular medicine applied to chronic health and disease problems.

Dr. Garry Gordon

In the 1970s, Dr. Garry Gordon was a student of chelation therapy. He later started looking at minerals and the relationship to nutrition. He created an academy focused on chelation therapy, which was more recently called the American College for the Advancement of Medicine. It provided an underpinning of quality education for individuals in this field, bringing in investigators from many disciplines.

During the 1970s and 80s, the International Association of Preventive Medicine provided a place where doctors could meet to study these concepts in greater applications in their practice.

Warren Levin, another New York physician, was a pioneer who provided a model for his patients and other doctors about how these concepts could be applied.

Dr. Sidney Baker

Dr. Sidney Baker is a former Yale Medical School professor and the 1999 recipient of the Linus Pauling Award in Functional Medicine. Dr. Baker is helping us understand how physiological function interrelates with personal experience in the environment and the inside/outside communication. He came up with the "Tacks Rule," an interesting way of looking at the body. According to this rule, if you are sitting on two tacks and you remove one of them, you don’t have 50 percent reduction in pain. His concept was that if you only treat one part of a person’s problem and don’t look at the underlying cause, which compares to having more than one tack, you are not likely to get as good a response as you would if you looked at the overall system. You have to remove all the tacks by looking at the underlying principle. Dr. Baker helped us understand the science and reasonableness of what he calls "good medicine."

Dr. Leo Galland

Dr. Leo Galland is a physician/internist who is a brilliant synthesizer of information. He draws from the history and tradition of science-based medicine and has brought it into better understanding in the field of nutrition and integrated medicine. It was he who coined the term *dysbiosis* and studied gut parasitology at a time when we were told people in the Western world didn’t have parasite problems. He believed that was not true; you don’t see what you don’t look for. As people began to look for parasites, they found them. Now we find numerous articles about difficulties with *Giardia, Cryptosporidium, Entamoeba*

histolytica, *Coccidioidesmycoses immitis* organism, and other organisms that are producing the parasitic infections Dr. Galland helped us understand.

Dr. Robert Cathcart

Dr. Robert Cathcart was a renowned orthopedic surgeon who had developed prosthetic devices used for orthopedic surgery. He was an innovator and leader in that field. He was so convinced of the Pauling hypothesis and the benefits of vitamin C that he started administering what he called bowel-tolerance doses of vitamin C, bringing about remission of hepatitis and other viral infections.[37] Ascorbyl radical at high doses of vitamin C intake could be a very important virucidal agent. He started to look at this clinically. Dr. Cathcart, a good observer and a good doctor, demonstrated that vitamin C had effects at different doses in the same way as aspirin. Baby aspirin may help prevent colon cancer or heart disease; two adult aspirins may ward off a headache; multiple aspirins may be taken throughout the day for arthritis. Aspirin has different physiological effects at different levels. Dr. Cathcart helped us understand this principle applied to vitamin C.

Dr. Donald Rudan

Dr. Donald Rudan, a psychiatrist, helped us understand essential fatty acids. His work on omega-3 fats was at the forefront of our education. Lecturing to a group of physicians on the East Coast during in the 1970s, he introduced the concept that fats were not just bad. Friendly fats, essential fatty acids, could modulate physiological function and influence brain biochemical function. As he pointed out, much of the architecture of the brain is made up of phospholipids with essential fatty acids like DHA (docosahexaenoic acid) at the su2-position in the glycerol moiety of phospholipids.[38] These are essential fats that must be obtained in the diet. Diets containing more warm-weather plant oils, partially hydrogenated vegetable oils, and saturated animal fats may lead to temporal insufficiency or even deficiency. Of course, more recently we have found through clinical trials that insufficiency of these omega-3 fats may be associated with ADHD (attention deficit hyperactivity disorder) in children, particularly boys, who have bed-wetting, thirst, and skin problems as manifestations of essential fatty acid insufficiencies.

Dr. David Horrobin

Dr. Horrobin was a physician, experimentalist, synthesizer, and creative individual in the field of medicine. Coming from the pharmacological model, he transitioned through his own experience to nutritional medicine through his understanding of the role of gamma-linolenic acid (GLA). GLA is a desaturated, chain-elongated derivative of linoleic acid, the 18:2 omega-6 essential fatty acid. Dr. Horrobin helped us understand the relationship of GLA to promotion of the 1-series eicosanoids, the PGE-1 family, which are anti-platelet adhesive antiinflammatory, and anti-cell proliferative. He explained that the balance between the 1- and 2-series eicosanoids can determine inflammatory or cell replicative or platelet adhesive effects.[39] The use of GLA for multiple sclerosis and immunological problems of arthritis and even problems of schizophrenia was extraordinarily important.

Dr. William Rea

Dr.William Rea expanded on the themes of Theron Randolph in environmental and ecological medicine.

Dr. Rea is a surgeon who is an expert on the effects of detoxification and environmental sensitivities. A polluted environment, he explained, influences individuals we might call the "yellow canaries" of our world.[40] These individuals have detoxification defects in their cytochrome P450 and conjugase enzyme systems. The activities of their nervous and immune systems were considered atypical and have typically been overlooked in medicine.

Dr. Rea has spent more than 20 years studying and writing a three-volume series on environmental medicine with thousands of references. It defines the implications and origin of this field. The biochemical individuality of Roger Williams and the genetotrophic disease concept and the orthomolecular medicine of Dr. Pauling weave their way into the interrelationship of the patient to his or her environment. Lifestyle and diet can modify these risk factors to an imperfect environment, an environment in which tens of thousands of different chemicals outside us impact our nervous and immune systems, and resistance to them depends on our own detox system.

As author of *The Yeast Connection*, Dr.Bill Crook made the world aware of the importance of understanding the role of *Candida albicans* in a great number of health problems.

Dr. Truss is responsible for the Truss discovery concerning *Candida*.[42] He worked together with Bill Crook for 20 years in helping us understand the *Candida* connection to chronic health problems.

Dr. Jean Munro

Dr. Jean Munro, a physician in England, has helped spread the word about environmental medicine. In collaboration with Glenn Steventon, a neurologist at Birmingham University Medical School, she has looked at detoxification enzyme profiles. She has helped us understand how to modify and modulate the detox pathways of individuals. That has led to the development of pharmacogenetics, a new field within pharmacy.

Different people have different responses to medications, depending upon their own detoxification uniquenesses. Atypical adverse drug reactions may not be atypical at all. They may be typical and reproducible if we ask a different question about the person’s detoxification machinery. A person may not be able to detoxify a specific drug, or he or she may have an antagonism to that drug with something else that vies for the same detox pathway. In this case, the dose of the drug that might be therapeutic for most patients may build up to super-physiological levels in that individual. He or she could have an adverse response due to the buildup of intermediary molecules, biotransformed intermediates that could be more toxic than the initial drug. That understanding is now forcing drug companies to undertake pharmacogenetic testing to know whether that drug is metabolized by cytochrome 2D6 or 1E2 or 1A1. This theme, which has been part of our discussion in *Functional Medicine Update*since 1990, is now becoming part of the paradigm of medicine for the new millennium.

Dr. John Bastyr

Dr. John Bastyr showed us how to integrate natural medicine into this fabric. Natural medicine will play a major role in healthcare delivery in the new millennium. In Washington State Dr. Bastyr was a leader who gathered a group of intelligent, capable, and dedicated people group around him for training on the tenets of naturopathic or natural medicine.

Dr. Joseph Pizzorno

Dr. Joseph Pizzorno was a student of John Bastyr in the 1970s. Together with Dr. Les Griffith and Dr. William Mitchell, Dr. Pizzorno founded a college of natural medicine they called Bastyr University. It became the first college in the United States accredited in natural medicine and is now turning out competent and capable naturopathic physicians who are seeding the whole country. Bastyr University, the Natural College of Naturopathic Medicine in Portland, Oregon, the Toronto College of Naturopathic Medicine in Canada, and the Southwest College of Naturopathic Medicine in Arizona are producing high-quality graduates who integrate natural medical therapies within the field.

Several new colleges are beginning to provide naturopathic education, including the New England College of Naturopathy. More states now have naturopathic physicians who are grounded in the concept of natural medicine based upon the science of proper anatomy and physiology. They are educated and accredited to provide these services in integrated medical system in which outcome-based medicine will be the watchword. No one person can know it all, but integrating one discipline with another can produce a better system, a weblike medical system.

Dr. Robert Buist, a chiropractor in Australia with a PhD in nutrition and biochemistry, has been an excellent educator and communicator over the last 20 years to the Australian medical and pharmacy communities about the role of natural and nutritional medicine.

Dr. Steven Davies is the founder of the British Association of Nutritional Medicine. He has been a primary researcher, clinician, and text writer in the field of nutritional medicine.

The Future of Medicine

The list goes on. Together these extraordinary individuals have laid the groundwork for a paradigm shift, as Thomas Kuhn described in his book, *The Structure of Scientific Revolutions*.[43] We are at the threshold of a paradigm shift that is drawing from the rich, 100-year tradition of these investigators, clinicians, communicators, educators, commentators, and contributors to this changing thought pattern about the origin and remediation of disease.

Where will this field go? Will we enter an era of gene splicing and genetic engineering? Or will we discover how to manipulate the genetic capability of the individual by optimizing his or her function in the phenotype? Does cloning represent the future of medicine? Or will we discover that within our genetic polymorphic and pleomorphic capability as a human population we have tremendous adaptability, and we just have to promote proper function from that variegated set of opportunities that exists within our genes?

he deterministic model of Gregor Mendel, which was passed to us from the 19th century, tends to tell us that our genes are what they are. They are static, determined, rigid, and locked in place. Therefore, our disease patterns are a consequence of flawed genes, and the goal of medicine is to save us from our genes. That model is dying as we move into the new millennium. The current model is that our genes are certainly there, but they represent the potential for function. There are many "we’s" locked into our genes. The ones that are expressed are the consequence of our experiences of living, starting from the moment of conception and continuing throughout our lives to the present. Those experiences, washing

over the genes, give rise to the upregulation of certain functions, downregulation of others, and the expression of what we are at any given moment.

Each of us is the result of a non-blinded, non-crossover, non-controlled experiment called our life. If we don't like the results of that experiment, if the outcome is not good, we can change the experiment, according to this new paradigm. Find the right way to match the communication of your lifestyle and your environment to resonate with your genes to give rise to the energy of function that improves outcome. That is the new paradigm.

Genes and Environment

In their landmark book *Genome*, published in 1993, Bishop and Waldholz talked about the importance of environment in gene expression.[44] They say it is not unmasking the genes in and of themselves that will determine the ultimate outcome for a patient. Rather, it is the recognition that when those genes are plunged into a harmful environment based upon that old individual uniqueness, the expression of the gene that causes the poor processing of cholesterol, for example, may exhibit heart disease. That concept is very important in defining where we are heading in medicine. As we start the new millennium we are reworking the view of how and why we get sick and what we can do about it.

Regina Hertzlinger, author of the book *Market-Driven Health Care*, is another person we have interviewed on *Functional Medicine Update*.[45] A professor of business at Harvard Business School. she predicted that in the next 10 years, health care will be framed not by the third party reimbursers but by the consumers of health care. The recognition by consumers that they control the healthcare system and their rising advocacy for improving their health will continue to work with the newly developing science of how genes can be promoted to optimal function to create this new paradigm. The old models, although there is an inherent inertia to overcome, will die because truth has its own vector. Truth will out.

A Modern Renaissance

We are living through a renaissance. I always wondered how it was back in what we call the Renaissance in Europe, whether people knew they were living through a great period of human history. Or did they just hear some different music, see some different art, experience different architecture and literature? Did they know they were in this epic period of human history until historians wrote about it years later?

If we look back at the 18 years of *Metabolic Update*, *Preventive Medicine Update*, and *Functional Medicine Update*, we have to conclude that a truly remarkable shift in thinking is taking place regarding how and why we get sick and what to do about it. Our new understanding emerges through recognizing the underlying mechanisms of some of the degenerative diseases we used to think were "of unknown origin."

Understanding the Origin of Disease

Now we know something about the origin of these diseases. We know there are underlying, fundamental processes that have to do with intercellular signaling problems, dysinsulinism, dysglycemia, oxidative stress, mitochondrial uncoupling, chronic inflammatory mediation by the upregulation of various components within the immunological system that trigger action at a distance and then alter physiological

function. Methylation defects occur as a consequence of inadequacies of B6, B12, folic acid. Alteration in gut floral integrity, with the gut-associated lymphoid tissue, creates immunological alterations and cell signaling to distant sites from the gut, saying foreigners on board. Detox pattern irregularities cause imbalances in detoxification that produce biotransformed intermediates.

Acetominophen Toxicity

The authors of an article in the *New England Journal of Medicine* in 1998 reported on the prevalence of acetaminophen toxicity in an urban county hospital.[46] They observed that those who died of acetaminophen toxicity were unlikely to be individuals who took abusive doses and committed suicide. They were generally people who took lower doses but had uniquely poor detoxification patterns for acetaminophen because they had been fasting, drinking alcohol, or consuming poor-quality diets, or because they had a unique genotype of altered detoxification of acetaminophen.

Acetaminophen is detoxified by cytochrome P450 into an intermediary molecule called NAPQI, a napthaquinone that is very hepato- and neurotoxic. If it is not properly conjugated in the liver with glutathione to form a mercapturate, that intermediary compound can be very damaging to the liver and the brain. People who consume poor-quality diets or excess alcohol or are fasting are those whose livers may lack sufficient glutathione to detoxify that intermediate. Therefore, they are many times more susceptible to toxicity. This is a new theme. It was only in the early 1970s that the first cytochrome P450 molecule was discovered. We are talking about medicine that is only 25 to 30 years old from its fundamental first research understanding, and from which a new paradigm in medicine around genes and environment is being born. We are learning of the plasticity of gene expression, not the determinism of a Mendelian model of rigidity.

Functional Medicine Update of the Future

In *Functional Medicine Update* for the new millennium a dominant theme will be factors that are modifiable by matching genes and environment. This theme will extend to the Applying Functional Medicine in Clinical Practice training programs we offer in Gig Harbor. It will echo in our outreach, the symposium we offer every year, and our individual training programs in applied nutritional biochemistry and cell physiology from a functional perspective. How do we use a patient’s antecedents and create an environment so that the person’s triggers do not produce the mediators associated with specific signs and symptoms of chronic illness? How do we maximize and rectangularize survival, compressing morbidity into just the very last portion of life, and extend both life expectancy and quality of life?

Those are the themes of functional medicine. A small indication of the increasing importance of the field of functional medicine as we move into the new millennium is the fact that the Institute for Functional Medicine, the parent organization from which *Functional Medicine Update* is produced, has been granted accrediting ability by the American College of Continuing Medical Education Accreditation. We can now provide category 1 credit for our courses and our training systems, and even for *Functional Medicine Update.*

Year 2000 Symposium

The Symposium 2000, to be held in May of this year, will be a great celebration. We will be in

Scottsdale, Arizona, talking about energy in medicine and bioenergetics from a functional perspective. I think you will find that gathering with 600 of your colleagues and an extraordinary group of presenters will be an energizing experience that will reinforce the techniques, concepts, and practices that underlie functional medicine. I urge you to be part of that symposium. If you have not gotten the brochure, please call us at 800-843-9660 to inquire about the Year 2000 Symposium for the Institute for Functional Medicine.

For the past 18 years I have had the same colleague sitting by my side as we create this audio program month by month. Mr. Jay Johnson and I have the privilege of communicating this information every month, now to 27 countries around the world, to thousands of health providers. This means we could potentially influence thoughts and actions in millions of patient experiences over the years. We both have felt we have traveled an extraordinary journey in these 18 years. We have seen a principle that relates to the patient being number one and truth, uncomfortable as it sometimes is, has been our watchword. I am proud of our record as we move into the 21st century.

As I go to the stern of the ship and look out, I think the individuals we have described this month in *Functional Medicine Update* are the kind of people you would want to hang out with in the world. They are competent, capable, dedicated people who have tried to make this world a better place. I want to honor all those people, both those we mentioned and the thousands that we didn't have the opportunity to mention. They may labor in small labs, doing their work, trying to connect that work with others, trying to see patients in an imperfect world and do the best they can. They may not be properly rewarded and honored. They may have problems with colleagues who misunderstand them. But they are creating the positive change. It is the collected energy of all of those who strive to improve health, function, vitality, and the opportunity to be fully functional. With that I close our centennial, millennium issue of *Functional Medicine Update.*

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