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the language of functional medicine

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NTRODUCTION: WHAT IS FUNCTIONAL MEDICINE

Functional medicine is a field of medicine that employs assessment and intervention to improve physiological, emotional/cognitive, and physical function. In this context, function is the "kind of action or activity proper to a person, thing, or institution."(1) Functional medicine is science-based health care that demands a systematic, patient-centered approach to understanding the underlying web of physiological factors and effects that influence health and the progression of disease. It incorporates the functional principles that exist in many conventional and alternative practices but focuses, as a special core competence, on the principles of molecular medicine and modern nutritional biochemistry with an emphasis on clinical application.

As the field of functional medicine evolves, so do the useful metaphors for explaining and illustrating to both patients and professional colleagues the principles and methodologies of this field. In what follows, I address the key principles, processes, and metaphors for explaining balanced, dynamic health according to a functional perspective, and explore how these processes, when dysfunctional, lead to the conditions traditionally identified as disease.

SCIENCE-BASED FIELD OF HEALTH CARE: THE PRINCIPLES

Biochemical Individuality Based on Genetic and Environmental Uniqueness
According to a functional medicine perspective, patient care presumes that each person is a unique individual with a singular genetic structure. Our purpose as functional medicine practitioners is to elicit and understand our patients' uniqueness, including their experiences. These experiences are the context of the complex processes where environment merges with their genetic inheritance. We have seen with great anticipation the evolution of thinking and instrumentation that has brought us closer to describing the probabilities and possibilities inherent in our inherited DNA templates.(2) We have come to understand that our DNA does set boundaries on individual performance. However, as the deterministic model of genetics breaks down, research has demonstrated a plasticity to genetic induction not appreciated earlier.(3) Important to functional medicine practitioners is the idea that lifestyle translates into quantifiable effects on health through the energetics of our biochemistry and genetics. These effects can lead to disease. As we more fully understand the web-like relationships between environment and genetic responses, we can develop individual programs that reliably reflect the unique needs of our patients.(4)

Patient-Centered versus Disease-Centered
The individual—not the disease—is the target of treatment. Functional medicine views disease not as an enemy (not even as independent realities) with which to grapple, but as a manifestation of the breakdown of mechanisms that maintain control, resilience, and balance.(5) Dysfunction and disease are rarely organ-specific. Rather, they are an altered systemic physiological malfunction that requires an integrated model of therapeutic intervention. Functional medicine focuses on the interaction between the host and his or her internal and external environment and the processes that can go awry in this relationship. Findings in molecular medicine research have caused a revolution based on the discovery that modifiers of gene expression are not only produced inside the body by different organs, they also exist as agents of change within the diet and environment.

The patient-centered biographic model is a key feature of functional medicine. An early spokesman for this concept was Leo Galland, MD, who wrote:

> Disease is a dynamic event in the life of an individual, determined by disharmonies, imbalances and pernicious influences. The goal of diagnosis is not to identify the disease entity, which has no independent reality, but to characterize the disharmonies of the particular case, so that they can be corrected.(6)

This approach to diagnosis emphasizes the functional pathogenesis of disease in individual patients. It may complement or replace the convention of differential diagnosis, in which diseases are treated as distinct entities existing independently of the patients they inhabit. Patient-centered diagnosis focuses on knowing the mediators, triggers, and antecedents of disease (illustrated below) in each individual patient.

Dynamic Balance of Internal and External Factors
Important to the functional medicine practitioner is the idea that lifestyle translates into quantifiable effects on health and disease through the energetics of our biochemistry and genetics. Different activities and emotions; such as eating, exercising or not exercising, joy, pain, and love, for example; are integral to inducing the homeodynamic mix of molecules that, through the masking and unmasking of chromosome sites, lead to the sum of experiences that our patients identify as their lives. Jeffrey Bland, PhD, describes this balance as follows:

> Environment modifies not only the expression of inducible genes but also post-translational cellular function. After the genes have been expressed and their message has been translated into the manufacture of protein and other cellular materials, the structure and function of these substances can be further altered as a consequence of processes such as oxidation or glycation. Both of these post-translational influences can further alter cellular function in such a way as to be associated with unhealthy aging.
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> The combination of the environmental effects on both gene expression and post-translational modification of cellular materials gives rise to symptoms of aging that are well recognized in clinical medicine. For example, individuals who smoke heavily appear to age faster, and they have higher risk of age-related diseases such as cancer and heart disease. Individuals who consume excessive alcohol also appear to age more quickly, and they have increased risk to liver and heart-related problems. Individuals who consume poor quality diets that are excessive in calories and low in essential nutrients show the signs of over-consumptive under-nutrition with obesity, poor health patterns, and more prevalent age-related diseases. These examples demonstrate how environment and lifestyle influence gene expression and post-translational modification of cellular function. Medicine has focused principally on the diagnosis of these diseases once they occur, and physicians have historically placed less emphasis on understanding genetic susceptibilities and gene expression modifiers.(7)

Web-like Connections of Physiological Factors
Sidney Baker, MD, explains that "people do not get sick from diseases, but rather diseases reflect a disruption in the dynamic balance between themselves and their environment."(8) Fundamental to functional medicine is a profound awareness of web-like interactions among all systems—interactions that have been artificially singularized by disease taxonomy. Robert Heinlein describes the dilemma as follows:

> The greatest crisis facing us is a crisis in the organization and accessibility of human knowledge. We own an enormous ‘encyclopedia’ which isn’t even arranged alphabetically. Our ‘file cards’ are spilled on the floor. The answers we want may be buried in the heap.

Three key notions, first articulated by Leo Galland, MD, help illustrate and organize the web-like thinking that is essential to the success of the functional medicine practitioner. The antecedents of our patients’ dysfunction nest within their biological terrain and genetic susceptibilities. The patient’s dynamic balance has constant perturbations that require adaptation. However, sometimes a force of change such as allergens, xenobiotics, drugs, endotoxins, and emotional stress are strong enough to create a dysfunctional response; Dr. Galland labels these forces triggers. The patient’s response to a trigger consists of complex, web-like effects on the biologic system known as mediators. For example, cytokines, prostanoids, leukotrienes, and lipid peroxides are mediators that cause an inflammatory response.

As futuristic as it may seem, the next step in diagnosis and treatment protocols can incorporate an assessment of the unique risk factors present by virtue of the patient’s DNA interacting with the end-products of his or her lifestyle, diet, environment, and thoughts. For example, we know that the byproducts of tobacco smoke interact with cellular gene structures in the lungs to induce translational molecules. The presence or absence of these molecules affects the detoxifying function of patients’ liver cells. In turn, these cells arbitrate the development of breast cancer. This research regarding the polymorphic expression of inherited detoxification capabilities helps explain contradictions regarding the connection between smoking and breast cancer. The phenotypic expression of breast cancer is controlled by the genetic susceptibility of the patient experiencing the tobacco smoke, which helps define this susceptibility.

This genetotrophic disease and susceptibility model dates back to Roger Williams, PhD,(9) who discovered many of the B vitamins. The year prior, Linus Pauling published pivotal research demonstrating that genetically controlled translational molecules control form and function in sickle cell disease. Today we see clinical applications that decrease sickle cell crisis flowing from the understandings evolved from this model.(10) Rich literature exists on the genetics and epidemiology of aging and chronic illness as well. (11) A model allowing for modifiable factors for achieving healthy aging has been reported by Evans and Rosenberg from their Tuft’s Medical School study on aging.(12)

Health as a Positive Vitality—Not Merely the Absence of Disease
Today medicine is at a crossroads. Although medicine has successfully contributed to the evolution of the science of disease diagnosis and treatment during the past four decades, it has not been as successful in promoting healthy aging. A majority of the aging baby boomer population expects that they will never retire and will continue to engage in multiple activities, travel the world, be physically active, meet exciting new challenges, and be available as catalysts for social change as they grow into their 70s and 80s. This is not a health as the absence of disease model, but rather health as a positive, achievable vitality model.

Fries (Stanford University Medical School researcher in the processes of aging) explains that much of the loss of function associated with disease among older individuals is a consequence of the progressive loss of "organ reserve."(13) When we are young, there is a reserve of organ function beyond that which is necessary for the baseline requirements of most organ systems. As we age, however, we lose organ reserve; stresses that we could have once accommodated now exceed our resilience, which results in health crises. Fries emphasizes that organ reserve is related to biological age. As we lose organ reserve, our biological age increases, making us more susceptible to disease. We can modify how quickly we lose organ reserve and undergo biological aging through changes in lifestyle, environment, and nutrition. It is now recognized that 75 percent of our health and life expectancy after age 40 is modifiable on the basis of such choices. (14),(15)

THE PROCESSES

To add organization and accessibility to this large body of scientific knowledge, we have separated the evaluation phase into six interwoven processes that can cause imbalances. You will find these six processes or categories echoed throughout the training course. These categories also serve as the framework for the Functional Medicine Research Center’s Adjunctive Nutritional Clinical Practice Protocols. In truth, these categories are simply facets of the same stone of dysfunction, intimately and unsolvably interwoven. However, we have separated these imbalanced functional processes into categories to start rethinking and reprocessing our assumptions about diseases.

Nutritional Imbalances
The history of functional medicine has its antecedents in the nutrient deficiency model. This model was characterized by early clinical observations such as the use of limes to protect British sailors against scurvy and whole grains to protect against beriberi in the Far East. As Dr. Sidney Baker has pointed out, the epidemic deficiencies in magnesium and essential fatty acids frequently contribute to the maladies of contemporary patients. However, this early model took a silver bullet approach to both thought and research. Today we see the advantages of having underlying biochemical, molecular biology models of dysfunction. Earlier models were linear. In addition, prisoners were often used in these studies as experimental subjects to whom researchers caused severe deficiencies to unmask diseases of deficiency. The end point markers did not account for differentiated genetic peculiarities. We now know that nutritional imbalances cannot be understood fully when isolated from the person experiencing the imbalance. The required daily allowance (RDA) for any nutrient can vary greatly from person to person.

However, a deficiency in key nutrients can amplify havoc within the web of metabolism. For example, folic acid deficiency can lead to unalterable DNA damage, neoplastic transformation of lung cells in smokers, spinal cord defects in developing fetuses, atypical changes of the cervix transforming to carcinoma-in-situ in susceptible hosts, and atheromatous changes in the coronary arteries in human host environments of homocysteine/methionine imbalance.

Dr. Kilmer McCully has presented elegant and exhaustive research about this topic, vis a vis the relationship among folic acid, B6, B12, and betaine in a presentation about defects in methylation and management of the homocysteine pathway.(16) A recent normative aging study of 70 male subjects, ages 54 to 81 years, illustrated that individuals who had lower concentrations of vitamin B12 and folate and higher concentrations of homocysteine had poor spatial copying skills and reduced cognitive performance. This study suggests that neurodegenerative disease does not happen without precedent but occurs after long-term, cumulative damage, with function potentially declining for decades.(17) One of the most remarkable aspects of this story of nutrient insufficiency is the subtlety of mild forms of homocystemia. This condition can go unrecognized for decades, while neurological and cardiovascular function significantly decline. Thus, nutrient insufficiency can affect immune and oxidative balance.

A complex relationship also exists among nutrients. For example, diet and nutrients impact the modulation of triggers and mediators of inflammation. Dr. Buck Levin writes:

> Synergy between antioxidant nutrients has been clearly established in the clinical literature. An emphasis has been placed on the existence of "redox pairs"—the observation that all nutrients acting as antioxidants have an equally active prooxidant form that is created by removing an electron from the antioxidant (reduced) version. Ascorbic acid, the reduced form of vitamin C, has as its redox couple ascorbyl radical, the oxidized form of the vitamin which has been stripped of a single electron. For antioxidant nutrients to successfully recycle between oxidized and reduced forms and for redox potential to be maintained, additional nutrients are required. For vitamin E recycling, for example, vitamin C, vitamin B3, and carotenoids are required. For vitamin C recycling, vitamin E, flavonoids, and glutathione are required. For glutathione recycling, vitamin C, selenium, and lipoic acid are required. Vitamin B3 is also required for continued recycling of lipoic acid between its oxidized (lipoate) and reduced (dihydrolipoate) forms.(18)

In The Four Pillars of Healing, Dr. Galland explains that three levels of nutrient intervention exist: 1) adequacy of nutritional density by appropriate food and supplement selections; 2) balancing essential fatty acids (EFAs) and antioxidants to normalize the prostanoid messenger molecules and produce flexible cell membranes; and 3) balancing critical nutrient pairs, such as calcium and magnesium, or nutrient families, like mixed antioxidants. In Detoxification & Healing, Dr. Baker asks a variation of Dr. Galland's question: "Is there a need to get something in order to thrive, such as vitamins, minerals, fatty acids, amino acids, accessory nutritional factors, light, rhythm, or love?"(19)

Immunological Imbalances and Inflammatory Response

In recent years, the mechanisms and interactions between immune function and activation of inflammation have become better recognized. As scientists unweave the complex interaction of triggers and mediators that result in the inflammatory process, they recognize that inflammation represents the altered cellular physiology that influences the homeodynamic function of many organ systems, including the musculoskeletal, cardiovascular, nervous, gastrointestinal, hepatic, immune, genitourinary, and endocrine systems. There are three basic events underlying inflammation: 1) increased blood flow to the injured area, 2) increased capillary permeability to give immune-mediating molecules better access to the site of injury, and 3) delivery of white blood cells to the area.(20) Stimuli including trauma, ischemia, toxins, allergens, stress, and microbial byproducts can trigger the release of proinflammatory cytokines from macrophages and T-lymphocytes.

The initial steps of inflammation benefit cellular function with enhanced immune surveillance, microbiocidal activity, and recycling of damaged tissues. However, in the proinflammatory state, the physiology is "shifted" to a new state in which messenger substances reinforce an alarm reaction. Although we often think of inflammation as localized, this alarm reaction is systemic. A new functional state characterized by swelling, infiltration of white blood cells, oxidant release, tissue damage, and patient symptoms can result.(21) However, the excessive production of proinflammatory cytokines and nitric oxide (when high levels of reactive oxygen species are present) results in secondary products such as peroxynitrite. Such secondary products can severely damage cells and result in the tissue pathology seen longterm in inflammatory disorders.

The actions of the proinflammatory state are often experienced by patients as localized phenomena, but a systems approach is necessary to understand the phenotypic expression of inflammation in chronic disorders affecting cardiovascular, endocrine, central and peripheral nervous, gastrointestinal, hepatic, and musculoskeletal systems. A comprehensive approach to inflammation evaluates lifestyle, environment, diet, pharmacology, and stress management. This comprehensive approach assesses four basic triggers: 1) toxic exposures, both endotoxic and exotoxic, 2) allergenic exposure, 3) oxidative stress, and 4) dysglycemia.

Treatment evolves from an appreciation of the factors underlying functional imbalance, rather than an impulse to simply suppress symptoms. For example, if laboratory assessment demonstrates exotoxic or endotoxic exposures, treatment centers on the lifestyle changes that can reduce exposure and enhance detoxification. Sidney Baker calls this the tacks rules: 1) if you are sitting on a tack, it takes a lot of aspirin to make it feel good (suppress symptoms), and 2) if you are sitting on two tacks, removing just one does not result in a 50 percent improvement (web-like relationships)." In Detoxification & Healing, he outlines the need for careful detective work to find the offending triggers (the tacks) while understanding that most chronic illnesses are a complex weave (two or more tacks) of offending factors.(22)

The same conceptual process of functional evaluation and treatment holds true for allergenic, oxidative stress, and dysglycemia triggers. Immunological imbalance and inflammation are key processes underlying the expression of many seemingly diverse and disparate diseases.

Gastro-intestinal Imbalance

The first two categories that we discussed focus on nutrient imbalances, as well as the inflammatory cascade and immune dysfunction. Our discussion now shifts to the digestive tract and how imbalances in digestive processes cause functional disorders. Functional concerns address the following questions: 1) Are there adequate quantities of destructive forces of digestion (23) to strip food substances of their antigenicity and size for absorption? 2) Does the GI mucosa membrane selectively and properly absorb and transport nutrients? 3) Is the microflora balance in the GI tract situated in the proper places, and are the beneficial bacteria present in proper balance without competition from dysfunctional biota (e.g., yeast, parasites)? 4) Is the normal microflora being nurtured properly with appropriate amounts of soluble/insoluble fibers and nutrients? 5) Are the failed responsibilities of the GI tract causing downstream problems with the detoxifying and immunological function of the liver because of endotoxins and exotoxins introduced through the gut mucosa barrier?

Nothing is more intimate between individuals and their environment than the process of introducing food substances into the GI tract and hoping for a nurturing, sustaining relationship. Inadequate digestive capacity in the stomach, increased permeability and/or increased gut associated lymphatic tissue activation in the small intestine, or dysbiotic machinations in the small intestine and/or colon can seriously affect health. The GI tract can become dangerous when: 1) the gut becomes the site for a brewery that produces alcohol as a byproduct of microbiota metabolism; 2) the GI tract experiences yeast overgrowth and becomes a site for weird (psychoactive) molecule production; 3) the small intestine becomes more permeable and allows whole molecules into the systemic blood supply; or 4) the ingested food has associated toxins or bacterial-produced toxins that cross through the mucosal membrane and wreak havoc in the vital tissues. Keeping food and the fecal stream separate from the blood stream but available for nutrient supply is key to balanced health.(24)

The "gut-brain" connection has been brought to our attention by the Defeat Autism Now (DAN) group, (25) which presents research showing the relationship between the production of psycho-active amines from dysbiotic microbiota of the GI tract. These byproducts of GI microbiota metabolism have been associated with altered behaviors in children such as autism. Elaine Gottschall's book, Food and the Gut Reaction, alludes to the investigations in schizophrenia that show that "allergists, GI specialists, and psychiatrists have found that certain types of food, impaired digestion, and faulty absorption or ingestion of vitamins and minerals affect the function of the nervous system, including the brain."(26)

A number of clinical conditions are associated with altered intestinal permeability and consequent immune activation-related symptoms. Seemingly unrelated syndromes relate to these processes including Crohn's disease, ankylosing spondylitis, inflammatory joint disease, HIV infection, dermatitis herpetiformis and other chronic dermatologic diseases, Reiter's syndrome, food allergies, and schizophrenia. Each of these conditions appears to be associated with some combination of food antigenic exposure, altered gut flora, abnormal gut fermentation, or altered GI/liver detoxification function. This partial list shows the connection between gastrointestinal function and the detoxifying processes of the body. This functional relationship can play a significant part in many disease processes.

Alteration of the gut mucosal integrity (i.e., leaky gut) can be assessed with oral lactulose/mannitol challenge testing. Gut dysbiosis, digestive capacity, fiber, and adequacy of beneficial short-chain fatty acids can be analyzed using a comprehensive stool analysis (CDSA) including parasitology reporting. Urinary organic acids studies have also shown promise in defining dysbiosis and the presence of downstream psycho-active metabolites. Modifying the intestinal environment to reduce activation of the gut-associated lymphoid tissue (GALT) can have a significant impact on inflammation. Removing foods and other triggers that activate the GALT can lower the systemic markers of inflammation, such as proinflammatory cytokines.(27) Modifying the intestinal environment through a biotherapeutic approach has been formalized into a program called the 4R gastrointestinal support program.(28) This program is a conceptual "blueprint" for normalizing GI function through nutritional support and related modalities.

The 4R program gets its name from the four steps in the program: remove, replace, reinoculate, and repair. Remove refers to the elimination of any pathogenic microflora and/or parasites which may be in the gut. Replace refers to the replacement of digestive factors and/or enzymes whose intrinsic, functional secretion may be limited or inadequate. Reinoculate refers to the reintroduction of desirable GI microflora, also called "friendly bacteria" or probiotics," such that a more desirable balance of microfloral species is obtained. The two probiotics most commonly used during reinoculation are Lactobacillus species and Bifidobacteria species. Prebiotics, or nutrients designed to support growth of desirable microflora, may also be used in this context. Repair refers to the provision of nutrients or regeneration or healing of the GI mucosa or both.(29)

Impaired Detoxification

Primary detoxification occurs in the liver. The liver cells (hepatocytes) restructure undesirable chemicals so that they can be excreted or eliminated from the body. In most cases, this process involves changing or modifying molecules in such a way that they are biotransformed from less polar, lipid-soluble substances into more polar, water-soluble molecules that can be excreted. Impaired detoxification may diminish the liver's ability to protect against the impact of xenobiotics or toxins on the biochemistry and cellular integrity of the body.(30)

Detoxification is generally divided into two phases. Phase I requires breakdown of a compound. This is a metabolically expensive process that activates the changed molecule(s), which can be highly reactive in the transitional phase. Phase I detoxification involves the cytochrome P450 system. Toxins are burned or oxidized into molecules that can advance to the next phase—elimination or further detoxification by conjugation.

Phase II detoxification differs from Phase I because the liver manufactures new molecules from dangerous ones rather than undergoing further destructive processes (e.g., oxidation) with the molecule. These new molecules, produced by joining the changed molecule with sulfur, specific amino acids, or organic acids are more soluble and ease elimination. The liver secretes these biotransformed molecules into the bile with subsequent excretion in the stools or through secretion into the serum and subsequent excretion in the urine through the kidneys. Excretory mechanisms within the lungs and the skin also serve as pathways of elimination for certain compounds, although this system is not as well understood.

The toxicity of a compound in a given organism is the sum of the effects of many factors. The detoxification systems are highly complex, show a great amount of individual variability, and respond sensitively to an individual's environment, lifestyle, and genetic uniqueness. Individualizing a detoxification program depends on assessing the unique makeup or predisposition (antecedents) of the patient. After evaluating family history and personal past medical history, this discovery process progresses to a diet and nutrient intake history. It also assesses total toxin load or challenge using questionnaires like the Medical Symptoms Questionnaire or the Functional Detoxification Outcome Survey Questionnaire. Additional functional tests assessing detox capacity (e.g., urinary sulfate-to-creatinine ratios, the oral caffeine and acetaminophen challenge tests, whole blood Glutathione test, urinary organic acid panel) can help to determine more specifically unique aspects of an individual's detoxification capacity.

Among apparently healthy people, liver enzyme functions related to detoxification may vary from one individual to another by four- to seven-fold efficacy.(31) Individualized therapy using appropriate nutritional support (e.g., additional antioxidant, phospholipids, medium-chain triglycerides) or additional conjugating nutrients, such as glycine, taurine, and sulfhydryl donors (e.g., glutathione, N-acetyl cysteine, methionine, cystine and cysteine) or both follows from appropriate detoxification assessment.

Examples illustrating the importance of this genetic uniqueness has been illustrated by Steventon and Waring. Their studies suggest that individuals who develop Parkinson's and Alzheimer's diseases often have a number of genetically impaired detoxification pathways, which increase their susceptibility to the neurotoxic effects of certain chemicals.(32,33) Exposure may come from the diet, medications, and bacterial metabolites from within the gut or environmental toxins such as volatile chemicals, including commercial solvents and oil byproducts or both. The story that has emerged from this information and other research demonstrates a combination of genetic susceptibility, reduced xenobiotic detoxification capacity, and increased exposure to neurotoxins play a significant role in patient susceptibility to neurotoxins. The interplay between a patient's predisposition and increased exposure to neurotoxins that are inadequately detoxified create damage to specific regions of the brain. Often biochemical dysfunction accrues slowly over many years with progressive tissue destruction. This progression may later be identified as a specific neurological disease.(34)

The impaired gut with increased permeability, an upregulated immune system mediated through the GALT, can cause hepatic oxidative stress. Leakage of substances across the GI mucosal membrane into the portal circulation can increase the demand on the detoxification systems of the liver. Dr. Bland explains:

> Patients with gut dysbiosis, suboptimal GI mucosal mucin formation secondary to defective sulfation, and decreased gastrointestinal mucosal integrity have greater hepatic toxin loads (i.e., challenge) from gut-derived toxins. This situation can both impair or deplete nutrient-dependent detoxification mechanisms and stimulate the hepatic immunological cascades initiated by liver Kupffer-cell (embedded white cells) activation. This results in increased oxidant stress and further hepatic compromise or injury. Thus, exotoxins can induce an immunological response that then produces immune-activating substances or endotoxins. Increased Kupffer cell activity, with the release of cytokines and the consequent increase of oxidative stress reactions, can be modulated by increasing the dietary intake of specific bioflavonoids such as those found in the herb silybum marianum (milk thistle). (35)

Oxidative Stress

Oxidative/reductive processes occur throughout the body and allow metabolism to proceed and the appropriate inflammatory response to transpire. However, the byproducts of normal and abnormal metabolic processes produce free radicals and reactive oxygen species. When an inadvertent loss of electrons exist, we call this oxidative stress because of the significant effects on the offended tissue. For example, these stressful, reactive species can threaten the molecules of trans-generational information (DNA), the energy-producing organelles of the cell (the mitochondria), the lens of the eye, and the innocent structural bystanders such as cell membranes and arteries. When electron transfers go awry, strange and harmful phenomena quickly result. If these processes occur in critical areas of the body and with sufficient magnitude (e.g., mitochondria, neurons, coronary arteries), morbidity and even death can result.

Respiratory activity within the mitochondria, oxidative phosphorylation, produces the required energy exchange (ATP) for cellular breathing. The mitochondria are the energy powerhouses of the cell, where nutrients (potential energy) are broken down into metabolic energy used for cellular repair, defense mechanisms, nervous system, muscle system function, and all other energy-requiring processes that maintain body organization and resist disease. A dysfunctional system can produce reactive oxygen intermediates that deplete energy reserves with electrons hopping off the hot wire of the electron transport chain. This over-heated oxidative process can lead to exhaustion of antioxidant stores that absorb the wandering electrons and, if conditions are not ameliorated, can contribute reactive oxygen intermediates to the cell itself. As Dr. Buck Levin notes, "Ninety percent of all cellular oxygen uptake in the human body is used to fuel mitochondrial processes." (36)

Examples of how oxidative stress causes critical dysfunction abound. Syndrome X and its associated insulin hyper-secretion is a good example of the interwoven events that lead to excessive oxidation of intracellular components. The physiology of insulin resistance illustrates the dysfunctional processes that occur in a context of excessive glucose in non-insulin dependent tissues (nerves, eyes, and kidneys). Insulin can function as an anabolic hormone. It has regulatory effects on the expression of many genes that regulate steroid hormones and detoxification enzyme systems.

Hyperinsulinemia can produce alterations in metabolic function ranging from hormonal imbalances to hypertension, hypercholesterolemia, hypertriglyceridemia, and alterations in the inflammatory cascade.(37) The combination of high insulin and high intracellular glucose promote advanced glycosylation end products (AGEs). Glycation is the non-enzymatic reaction of glucose with proteins in the extracellular matrix, resulting in the formation of AGEs. This process generates reactive oxygen intermediates that lead to damage in innocent bystander cell components. The increase in free radicals, in turn, results in depletion of endogenous antioxidants such as vitamin E and reduced glutathione. The increase in oxidative stress as a consequence of the accumulation and production of AGE proteins is a hallmark of biological aging and loss of organ reserve in every animal species.

Asthma could also serve as a model for an inflammatory disease mediated through the immune system and expressed as oxidative stress to susceptible tissues. Although asthma and related atopic conditions run in families, the relationship between the expression of the two diseases is not simple. Multiple genes appear to be involved in asthma. It is likely that environmental factors are the triggering agents that initiate the release of mediators like nitric oxide and the proinflammatory cytokines, resulting in the symptoms of asthma. Dietary factors and food allergies as well as deficiencies in intake of magnesium and essential fatty acids have been implicated in asthma risk. The interaction of allergens, pollution, viruses, and genetic susceptibility bring us back to the functional medicine model of evaluation of antecedents, triggers, and mediators.

Evaluation of markers for oxidative stress and glycosylation of proteins include C-reactive protein, fructosamine, and glycosylated proteins such as hemoglobin A1c. Other evaluative tests for oxidative stress are being developed.

Treatment for oxidative stress, both preventive and therapeutic, also brings us back to a previous discussion—nutritional balancing. Working together, the family of antioxidants including vitamin C, beta-carotene and related carotenoids, vitamin E, reduced glutathione, quercetin, CoQ10, N-acetylcysteine, and the flavonoids, including silymarin and the minerals selenium, manganese, copper, zinc and sulfur, provide a buffer against out-of-control oxidation and peroxidation. (38)

Recently, studies suggest that niacinamide therapy may provide a useful general tool for modification of situations of enhanced inflammatory response and oxidative stress.(39) Amino acid and essential fatty acid adequacy (e.g., GLA, EPA, DHA) also plays a part in the treatment of oxidative processes and mitochondrial dysfunction. L-carnitine is required for transport of necessary fatty acids into and through the mitochondrial membrane. Pyruvate dehydrogenate complex of co-factors (B1, B2, B3, B5, phosphorus, sulfur, and lipoic acid) are needed for boarding the merry-go-round called the Krebs cycle. The Krebs cycle alone has eight enzymatic steps requiring vitamins B2, B3, and B5, iron, magnesium, sulfur, and phosphorus.

Also, the connection between mind and body has a critical role in oxidative stress. The emotional and cognitive states of any organism, translated through the hypothalamic-pituitary-adrenal axis, provide important protection or damage consequent to immune, infectious, or inflammatory stress.(40)

Endocrine Imbalances

Endocrine imbalances evolve from over- or under-functioning gland tissue. The antecedents and predisposition of the patient that sets the stages for imbalanced endocrine gland function bring this presentation full cycle. Functional medicine is defined as a field of medicine that employs assessment and intervention to improve physiological, emotional/cognitive, and physical function. Central to this process of assessment are both the principle of biochemical individuality and the uniqueness of each person's internal and external experiences. Endocrine imbalances develop from the processes we have discussed: nutritional imbalances, immunological imbalances and inflammation, gastrointestinal imbalance, impaired detoxification, and oxidative stress.

If we look at the common triggers and precipitating events for illness—physical injury, repetitive activities, severe emotional distress, severe infection, exposure to toxins, drugs, allergens(41) —we can identify processes that provoke changes in endocrine function. For example, loss of libido, testosterone imbalance, hypogonadism, gynecomastia, and reduced fertility has occurred in men experiencing the following conditions: 1) exposure to embalming creams containing estrogen-like substances used by a mortician, 2) recurrent, high-dose exposure to the drug ketoconazole for resistant fungal infection that inhibits both testicular and adrenal steroid synthesis, 3) heavy smoking and alcohol consumption due to upregulation of certain detoxification enzyme activities, and 4) cadmium exposure which selectively impair androgen-synthesis.(42) In each of these examples, sex hormones have become imbalanced as a result of a triggering event mediated by one of the key processes described earlier.

Herman Adlercreutz has explored a web-like relationship between inadequate fiber in the diet and breast cancer. His and others' research suggests that breast cancer develops because of hyper-estrogen stimulation of vulnerable tissue receptors. The intake of appropriate dietary fiber correlates with lower plasma and urinary estrogen and with higher fecal estrogen. In turn, fiber affects the balance and function of bacteria in the GI tract. The relationship between fiber and bacterial metabolism translates into a significant effect on concentrations of lignans and isoflavonoids that have, in a number of studies, been shown to act as cancer-protective substances. The body must successfully excrete estrogen-like compounds into the bile through the hepatic process of conjugation. Problems occur when the intestine-colon excretion of these changed molecules is compromised by dysbiosis. Imbalanced microbiota can deconjugate these hormone byproducts, recirculating them through entero-hepatic circulation and thereby increase the body's sex hormone burden.(43)

Endocrine gland function can be compromised as well through the inflammatory process. Well-documented studies illustrate that endocrinopathies leading to hyper- and hypo-function can be mediated through immune/inflammatory dysfunctional processes. For example, Gaitan et al(44) showed that people exposed to water drawn from oil shale areas experience higher rates of hypothyroidism secondary to inflammatory thyroiditis. Insulin resistance secondary to receptor insensitivity can cause hyper-insulinism. The resultant inflammatory response causes glycation end-products.

THE FOUNDATION SCIENCES— HOW TO ANSWER THE QUESTION?

Molecular Medicine, Nutritional Biochemistry, and Preventive Medicine

Molecular medicine is to functional medicine what physics is to chemistry: the very under-pinning. The amount of basic science that begs for clinical application is truly daunting and requires a rigorous sifting and assimilating. Dr. J. Baker explains, "For example, the discussion of immunodeficiency diseases is no longer a clinical description of arcane disorders but the definition of immune dysfunction based on genetic defects at specific points in the immune response."(45) The fundamental paradigm of molecular biology is succinct: "one gene–one enzyme." The details of how the genetic message specifies the synthesis of proteins and how proteins in turn regulate cell function(46) is core to the functional medicine paradigm.

This genetotrophic disease and susceptibility model dates back to 1909. Amplifying findings from his study of an inborn error in metabolism, black urine, Archibald Garrod(47) developed the concept of chemical individuality. In 1931, he outlined this concept in greater detail: "In the case of every malady there are two sets of factors at work in the formation of the morbid picture, namely, internal and constitutional factors inherent in the sufferer and usually inherited from his forebearers, and the external ones which fire the train."(48)

In his 1950s landmark discussion of genetotrophic diseases, Roger Williams broadened Garrod's concept of chemical individuality. Williams(49) defined genetotrophic disease as the faulty expression of genes resulting

from a diet failing to meet an individual's inherited nutritional requirements. The year prior to Dr. Williams' publication, The Concept of Genetotrophic Disease, Linus Pauling(50) published pivotal research that argued that genetically controlled translational molecules control form and function in sickle cell disease. Recently, researchers have successfully applied high-dose nutrient interventions (cf. butyrate administration) to decrease sickle cell crisis.(51)

However, it should be remembered that preventive medicine and risk factor analysis was the safe harbor within which the vessel of functional medicine first anchored. Primary prevention, or risk analysis and early intervention based on biochemical individuality, are the sine qua non of functional medicine. Secondary prevention or reversal and/or stabilization of disease or dysfunction is another way of conceptualizing functional medicine. Along similar lines, rich literature exists on the genetics and epidemiology of aging, organ reserve, and chronic illness.(52) Evans and Rosenberg(53) offer a model predicated on modifying biomarkers with lifestyle interventions for achieving healthy aging by maintaining organ reserve. Their work is based on research from Tufts University Medical School and the U.S. Department of Agriculture Human Nutrition Center on Aging.

Cognitive Sciences

Information mapping, information dissemination, and making the unconscious conscious are the techniques wrestled from the research in the cognitive sciences (what we know and how we know what we know). Raising the level of awareness, increasing the amount of information available, and thus improving the likelihood of making intelligent decisions together is the primary goal between the functional medicine practitioner and patient.

Healthy Changes is an awareness program for patient-centered choices of lifestyle changes with mental, emotional, and cognitive tools for awareness and change.(54) Healthy Changes formalizes the steps in this evolving paradigm: tools for empowering patients to participate in their unique process of recovering health. Included in this process are tenets that have been gathered from research in cognitive science, behavioral psychology, philosophy, and the neurosciences. The first step in this patient empowering process requires a reversal of the traditional relationship between practitioner and patient. Yes, we do have expertise in creating clarity of the functional processes that has brought illness into our patients' lives. But unless we create a safe environment for this information to be owned and used uniquely by the patient, we have again been trapped within the "victim-expert" relationship that burdens us as practitioners and disempowers our patients.

The Healthy Changes process addresses this dilemma directly. From the beginning of the patient-practitioner relationship, a trust can develop from the belief that humans are not machines: when provided tools for self-nurturing, they can self-organize and heal. Healthy Changes provides these tools. Essential to this process of self-nurturing are tools of self-awareness, a product of the cognitive sciences. In a step-wise process inherent in the Healthy Changes process, patients learn about non-judgmental self-observation. They learn how to create a state of mindfulness. The creation of mindfulness is the simple, but often forgotten, state of being aware of what is going on with one's feelings, body, and perceptions without immediately judging and acting on these observations. Understanding about and compassion towards oneself can grow in a soil emptied of judgments.

Once this non-judgmental state exists, patients can organize their personal context and begin the journey that reveals to them their present state of un-wellness as well as how they reached that state. This process involves two steps. First we need to understand the "functional pathogenesis" of their present physiological state so that patients can begin their journeys with a clear foundation for recovery. Secondly, they need to learn how their present context of un-wellness grew out of their life choices through the technique of telling their personal story through exercises of self-awareness. Their journey of personal clarity and understanding includes exploring their "rules of living" that unconsciously drive their behaviors with their family, friends, at work, society and culture, personal eating and exercise patterns, as well as their priorities of self-care and love.

As part of this journey, the patient learns structured information about food. By learning what is in food that nourishes them, patients can make food choices based on scientifically validated information rather than fad, hearsay, and marketing misinformation. There is also an "Exercise and Health" section that guides the patient to explore the role physical activity can play in the transformation of their metabolism and, even more importantly, the pleasure that physical activity can bring to their lives.

As a partner rather than an expert, we can travel with our patients through this functional process of re-empowerment and genuine self-care where patients again become "Rulers of their own Lives" and configure their activities from their inner curiosity, love, acceptance, and compassion—the most powerful forces we can invoke for our patients' healing and reintegration.

The Marriage of Lifestyle Changes with Molecular and Nutritional Medicine

The time I have spent in clinical practice and with thousands of patients has taught me principles that have become axiomatic in my medical practice. Foremost among these truths is the awareness that each patient is unique. Each person whom I see has distinct qualities and traits. In daily interaction we become most aware of this uniqueness, but it is mirrored throughout their being.

The science behind each person's uniqueness is no longer controversial. At the heart of each cell in our body rests strands of DNA ready to respond and translate our uniqueness throughout our environment. We cannot change the genetic heritage (the gift of life from our parents) transmitted through these strands of nuclear DNA. However, our daily choices of what food we eat, water we drink, rest and sleep we achieve, and emotional responses we sustain have a powerful influence on our cells. These factors induce a vast, pluripotential variety of responses. How we choose to live these unique experiences profoundly affects the biochemical, electromagnetic flux that permeates and prompts direct gene responses.

For example, in 1995 I was shown how researchers in Russia (at the Pavlov Institute in St. Petersburg) have experimentally configured different, artificial, and emotional contexts (e.g., fear, calm, anger). In the lab, they have traced the biochemical cascade of mediators that cause immediate differences in brain chemistry that then have downstream effects, some immediate and other longer acting responses, through gene expression. We are well aware of the vast varieties of lifestyle interventions (nutritional, pharmacological, exercise, etc.) that have been shown to alter basic biochemistry, many of which are now understood to be translated through gene expression. We identify the integration of these genetic responses as our unique lives. This integration defines our own, as well as our patients', overall sense of health or illness.

Boundaries: Self and Nonself

Strict divisions between categories like nature and nurture, heredity and environment, and genetics and experience have little meaning in a functional perspective. Instead, a functional approach encourages exploring the anatomy of functional processes—the connections between "self" and "nonself"—to better recognize the limited division between the "inside" and "outside" factors that influence our health. But where do most of the processes relevant to functional medicine occur? In his lectures at the Second International Symposium on Functional Medicine (1995; Rancho Mirage, CA), Dr. Baker explained that four key interfaces act as settings for the interaction between inside and outside factors. Considering what qualifies as self and nonself among these interfaces helps us understand the action and reactions that trigger essential processes of survival such as active/passive transport, the inflammatory/immunologic cascade, etc. Asking how is each interface working leads to fruitful information about key functional processes.

The Environmental Interface

Where does the outside world (non-self) meet the anatomy and physiology of the inside world (self)? Three main tissues link us to the physical environment: 1) the digestive mucous membrane (the size of a tennis court and thickness of an eyelid), 2) the respiratory epithelium, and 3) the brain (psychoneuroimmunoendocrinological interface). The six processes we have been discussing adjudicate the success at these three tissue boundaries. Without their success, no life exists. With limited success, there are maladaptive processes set in motion. For example, short bowel syndrome in which the digestive mucous membrane of the small intestine stops digesting, transporting, and controlling permeability efficaciously results in debilitating symptoms of fatigue, cognitive dysfunction, and often upregulated inflammatory processes. These symptoms have consequences that affect many organ systems.

The Cellular Interface

Molecular medicine begins at the cellular interface—the cell membrane and its extensions throughout the cellular organelles to the molecular level. Each cell is a world within itself, but each cell is affected by the integrated successes and failures of the first interface of outside/inside. For example, the cellular interface includes the membranes of the organelles, where electrons are at risk of being ripped off by oxidative stresses that challenge dynamic balance within the cell.

The Perceptual Interface

The perceptual interface is a free-flowing anatomical systemic interface. This interface describes our sensory apparatus for perceiving and interpreting the world at-large. Immune recognition for the microscopic and molecular world literally requires the intimate processes connected to the outside world (e.g., ingestion, sampling, and processing by macrocytic white cells of molecules originating from outside).

The Memory Interface
The cellular basis for memory resides exclusively in the central nervous and immune systems, which act as a collective system.

Balance
The metaphor of dynamic balance is especially powerful and intuitive to both practitioners and patients. Illness results from imbalance in individuals who bring particular genetic strengths and weakness to their environments. Asked simply, what key functional process(es) were working well approximately one year ago, yet today manifest themselves as broken or dysfunctional? Taking the metaphor to another level, the questioning continues: Which of the six interwoven processes most likely has gone awry as this system and has lumbered to a new eccentric dysfunctional state?

The same reasoning can be applied to the six functional processes. For example, the joint processes of nutritional and detoxification balance prompts the following two questions: 1) Could this person be failing to get something from his or her environment for which he or she has a special need or deficiency? and 2) Could this person be failing to avoid something from his or her environment for which he or she has a special need to avoid or an inability to detoxify and remove?(55) As you ask yourself these questions, keep in mind Dr. Baker's Tack Laws: 1) if you are sitting on a tack, it takes a lot of aspirin to make it feel good (suppress symptoms), and 2) if you are sitting on two tacks, removing just one does not result in a 50 percent improvement (web-like relationships).(56)

Naming and Blaming
Old medical maps and guides indicated that sickness happens because "disease entities" attack "victims." Along this line of argument, Dr. Baker has noted:

> Those of you who are relatively new to the concepts of functional medicine may be bewildered at first by the need to let go of naming and blaming. Name the illness and then blame the illness for the symptoms. Then look up "the treatment of choice" for the illness and offer it to the patient with confidence that your peers stand with you. The basic error of the map we were given in our professional matriculation is the failure to distinguish between names, notions, and things.(57)

What happens when the functional medicine practitioner abandons the comfort of naming a patient's disease so that the patient has a group membership (the diagnosis) and has been prescribed the group treatment? The practitioner is left with what first feels like an unprotected open space, a foggy landscape, where the patient exists alone among her or his inconvenient individuality, a bewildering assortment of "natural" remedies, and the practitioner. Deprived of the convenience of placing individuals in groups (that have all been attacked by the same entity) and applying the same group treatment, the physician is left blinded by the variety of treatments at hand and doubly blinded if he or she tries to travel this land using the old maps. How does one find the way to becoming a happy doctor with establishing resonance among the patient, treatment, and doctor? The message to remember is that we are treating individuals not diseases. Diseases are not entities. They are ideas that we form about groups of people who have similar health problems. We do not treat conditions, and we do not prescribe for symptoms. The reason we listen to our patients' stories is that those stories give us the best clues about what they may need to get or avoid to achieve better health.

Useful Maps
Logic: Get what is needed; avoid what causes disruption.

Anatomy: Understand the functional interfaces and processes that occur at the interfaces.

Determinants: Investigate the antecedents, triggers, and mediators.

Information: Together with your patient, create a full and rich story of his or her health.

Expectations: List the options based on the information; don't waste effort on labels. Share with patients the maps and the logic of the maps as the information develops.

Short cuts: Understand the common processes of dysfunction in the medical landscape of the patient's life (e.g., the epidemic in our culture of EFA and magnesium deficiency).

Tailoring
While retaining much of the approach to the diagnosis and treatment model that characterizes main stream medicine, functional medicine focuses more on understanding the individual biochemical, immunological, and psychological quirks that influence how illness becomes expressed in each person. It is similar to tailoring in that it requires some measuring and some trying it on to see how each treatment fits.

Detoxification as a Metaphor of Empowerment

John Furlong, ND, explains how detoxification is a useful metaphor of empowerment in the following passage: (58)

> The tenets of naturopathic medicine include prevention of disease and stimulation of the healing power of natural processes...There are multiple syndromes, pathologies and diagnoses with which a person may be labeled...We can be seduced by our capacity for gnosis...(which) can lead to the patient identifying with a pathological persona... Detoxification represents the potential (for patient empowerment) as powerful as the news of a devastating diagnosis. (The process of detoxification) holds out to the patient the possibility of changing the current process their body (and mind) is immersed in. It allows them to paint their own picture of just what exactly they need "detoxified," whether that be an organ system, attitude, relationships with other people or society at large. Detoxification is a term sufficiently general to afford unlimited potential and one that does not prevent physicians from pursing specific–even aggressive–treatments at the same time.

Summary

If, as Dr. Baker suggests, "Illness is a signal to change," then we must help our patients find purposeful and efficacious methods to change. This requires attention to individual peculiarities and searching for the clues to the disharmonies that produce the illness. We need to explore these functional/dysfunctional processes that underlie the many-faceted expressions we have learned to name diseases. Our hope is to separate these functional disharmonies into functional categories or processes to facilitate rethinking and reprocessing our assumptions about diseases. As Dr. David Deutsch describes these changing priorities:

> The science of medicine is perhaps the most frequently cited case of increasing specialization seeming to follow inevitably from increasing knowledge, as new cures and better treatments for more diseases are discovered. . . But as medical and biochemical research comes up with deeper explanations of disease processes (and healthy processes) in the body, understanding is also on the increase. More general concepts are replacing more specific ones as common, underlying molecular mechanisms are found for dissimilar diseases in different parts of the body. Once a disease can be understood as fitting into a general framework, the role of the specialist diminishes. . . . Physicians can look up such facts as are known. But (more importantly) they may be able to apply a general theory to work out the required treatments, and expect it to be effective even if it has never been used before.(59)

As functional medicine providers, we can look forward to a simplified presentation of dysfunction and disease. We can begin to organize our thoughts along core functional processes, understanding why functional medicine views disease not as an enemy (not even as independent realities) with which to grapple, but as a manifestation of the breakdown of mechanisms which maintain control, resilience, and balance.(60)

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