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WEB-LIKE INTERCONNECTIONS OF PHYSIOLOGICAL FACTORS

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Introduction

Understanding the scientific basis and clinical applications of functional medicine and a "whole patient" approach to health care requires that clinicians fully appreciate the interconnectedness of organ system function with biochemical and physiological processes. Simplistic models of health and disease developed decades ago may no longer be accurate or clinically useful insofar as they fail to reflect the more recently discovered complex and multifaceted interrelationships. (Figure 10.2 uses the functional medicine matrix to depict some of this complexity.) Numerous mechanisms mediate these interrelationships, including, but not limited to, those that can be described as biochemical, hormonal, neurological, immunological, piezoelectric, and physical or mechanical. Ultimately, we are forced to dissolve the artificial intellectual boundaries we have created between organ systems and expand our appreciation of individual molecules, cellular messengers, and the physiologic mechanisms that mediate intercellular communication and coordinate interorgan function.

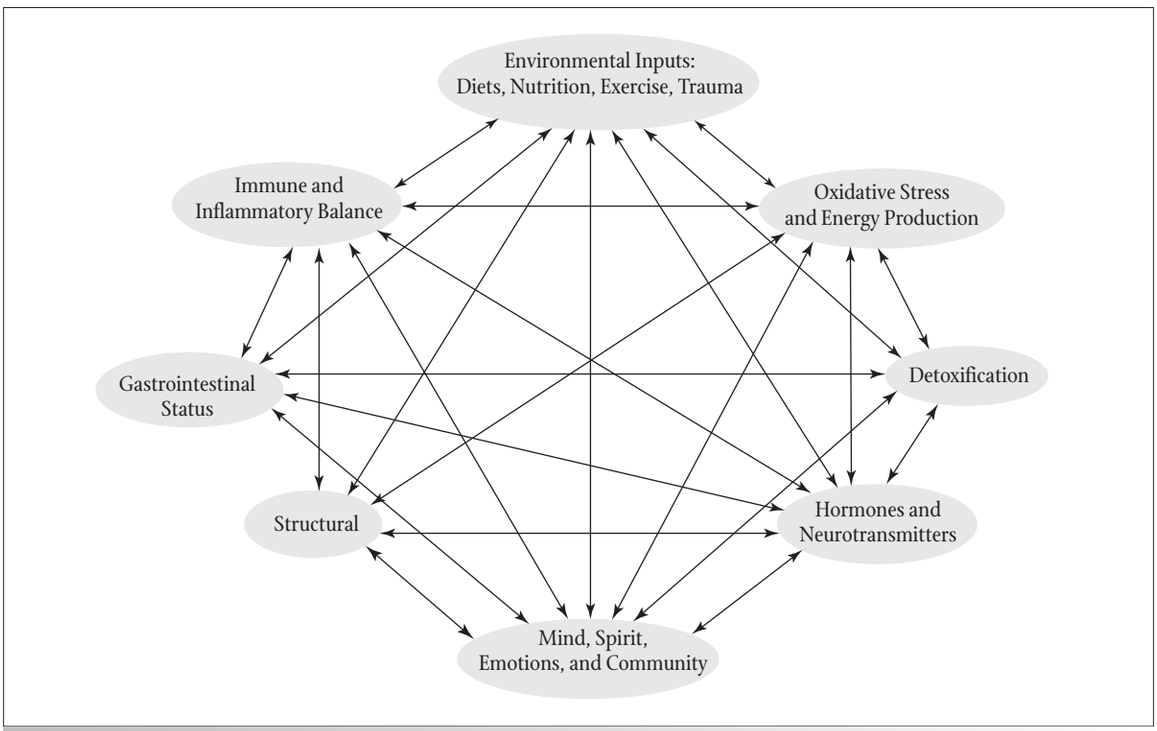

FIGURE 10.2
FUNCTIONAL MEDICINE MATRIX

Web-like Interconnections of the Functional Medicine Matrix

The following discussion provides some specific examples of this profound interconnectedness that is a foundational principle of functional medicine. We will survey current research literature documenting the interconnected nature of some key organ systems and disease processes. With these examples, clinicians will better appreciate how the gastrointestinal, immune, cardiac, neurologic, and other systems interact with and depend upon each other for optimal physiologic function. Likewise, clinicians will understand more completely how essentially any dysfunction or lesion in the body can have clinically significant implications and distant adverse effects. From this perspective, individualized clinical interventions can be designed and employed to deliver better health outcomes.

Gastrointestinal Tract and Liver

While the liver and the gastrointestinal tract share an obvious anatomic connection via the portal circulation, the functional clinical implications of this connection are often not fully appreciated. Not only is the gastrointestinal tract the recipient of massive amounts of "external information" in the form of nutrients, toxicants, and allergens that weigh in at more than 1,538 pounds (700 kilograms) per year, but the gastrointestinal tract is also a reservoir for the several hundred species and subspecies of yeast, bacteria, and other microbes with the potential to modify hepatic function (e.g., detoxification) and overall health (e.g., immune response) by numerous mechanisms and with positive effects or negative consequences.

The various organs and tissues of the gastrointestinal tract perform the complex functions of digestion, absorption, exclusion, excretion, immunologic defense, antigen sampling, and temporary storage of food residues and other substances that have been ingested. The mucosa is selectively permeable and allows the absorption of nutrients and other molecules via transcellular and paracellular routes. Compromise of mucosal integrity due to injury from antigens, infection, systemic inflammation, or toxicants such as ethanol or nonsteroidal anti-inflammatory drugs, increases absorption of potentially harmful substances that are normally excluded when mucosal integrity has not been breached. Materials that are harmless when rejected by the selectivity of the intestinal mucosa can, when inappropriately absorbed, serve as a source of inflammatory and immunogenic stimuli for the embedded macrophages in the liver (Kupffer cells) and also for the systemic immune system and the brain's embedded astrocytes and microglia. This phenomenon is clearly demonstrated by the neurological complications and focal white-matter lesions seen in the brains of patients sensitized to the dietary antigen gluten; in this scenario, it appears that dietary antigens cross a damaged mucosal lining and escape filtration by the liver to produce a systemic inflammatory response that manifests clinically as neurologic disease.[23,24] It seems likely that other antigens are also capable of inducing a systemic inflammatory response in susceptible individuals.

The two most voluminous substances in the gastrointestinal tract are food antigens and microbial metabolites and debris, notably lipopolysaccharides (LPS, endotoxin) from gram-negative bacteria. These foreign substances normally excluded by an intact mucosa can serve as mediators of physiologic disruption (hence the importance of their exclusion), and indeed this is what has been observed in experimental and clinical data. For example, in patients with autism, increases in inflammatory mediator production are seen following exposure of monocytes to dietary allergens and LPS.[25] We also note that LPS is a potent inhibitor of numerous cytochrome P450 biotransformation pathways, thus leading to impaired drug metabolism as demonstrated in recent clinical trials.[26,27] The implications of these data are profound and correlate closely with phenomena observed in clinical practice, namely that patients with irritable bowel syndrome—a condition causatively associated with both food intolerance and bacterial overgrowth of the small bowel—commonly report environmental sensitivity and medication intolerance. One plausible answer to the conundrum of the chronically unwell patient—typified by the patient with chronic fatigue or environmental illness—now becomes clear: overgrowth of the small bowel with LPS-producing bacteria leads directly to the gastrointestinal symptoms of gas and bloating, with immune system activation,[28] and also reduces hepatic clearance of metabolites, toxicants, and xenobiotics to which the patient eventually becomes sensitized (immunologically and/or non-immunologically). This explains, at least in part, the rationale for and impressive clinical efficacy associated with the implementation of clinical therapeutics that simultaneously improve intestinal microecology, improve mucosal integrity, and provide biochemical/nutritional support for the processes of detoxification.[29,30]

Gastrointestinal Tract and Immune System

Any discussion of the role of the gastrointestinal tract in relation to the immune system must include a view of the gut that is inclusive of its contents of food antigens, intraluminal microbes, and their debris and metabolic products. When the gut is simply pictured as a passive semi-sterile tube with food entering one end and feces exiting the other, then it would appear an unlikely locus of immunogenic stimulation and neurogenic inflammation that can have systemic health consequences.[30-35] Conversely, appreciation of the manifold quantitative and qualitative variables that can exist hidden from both the clinician's external view and the endoscopist's internal

camera enables practitioners to have a more realistic perspective on the influence that gastrointestinal function, dietary antigens, and microflora can have on extra-gastrointestinal processes and overall health.[36,37]

The combination of a hypersensitive/dysregulated immune system and exposure to dietary antigens sets the stage for the clinical phenomenon commonly described as "food allergy." Diverse in frequency, duration, severity, and quality, these immune-mediated adverse reactions to foods can precipitate or exacerbate a wide range of clinical manifestations including rhinoconjunctivitis, chronic sinusitis, dermatitis, epilepsy, migraine, hypertension, joint inflammation, and mental depression.[38,39] The immunopathogenesis generally includes multiple mechanisms and is not limited to mediation via IgE antibodies and histamine. Indeed, the pathophysiology of "food allergy" is commonly seen with numerous (not singular) aberrations in physiologic function, including responses mediated by or resultant from antibodies (including IgE, IgG, and/or possibly IgA classes of antibodies), cytokine-mediated responses (e.g., TNF-α), increased intestinal permeability, occult gastrointestinal inflammation, and alterations in gastrointestinal microflora.[40] To be more complete, our conceptualization of "food allergy" must also include awareness of enterometabolic disorders (i.e., the inter-connections between food, intestinal flora, and systemic health[41]) as well as contributions from neurogenic inflammation (i.e., the translation of immunogenic inflammation to a neurologic signal with systemic proinflammatory effects[42]).

Aberrations in gastrointestinal microflora can provoke a cascade of physiologic responses that may lead to widespread physiologic imbalances and result in a variety of clinical manifestations that may or may not conform to a recognized pattern or named disease even though the patient is highly symptomatic.[43] Furthermore, we can conclude from recent literature that the concept of molecular mimicry is now well established and that it provides us a model with which to apprehend the induction of immune dysfunction (especially autoimmunity) by microorganisms with immunogenic epitopes that are structurally similar to those in human tissues.[44] Thus, the link between "dysbiotic" gastrointestinal flora such as *Klebsiella pneumoniae* and systemic immune-mediated inflammatory disorders such as ankylosing spondylitis and chronic uveitis has a biological and scientific basis. Individualized assessment and treatment of such dysbiotic loci, whether in the gut, genitourinary tract, or nasopharynx, are likewise supported by current research and offer the hope of cure rather than an endless and additive cycle of anti-inflammatory and anti-rheumatic drugs. For example, evidence now shows that the systemic autoimmune disease Wegener's granulomatosis may be triggered and perpetuated by molecular mimicry with occult respiratory infections caused by *Staphylococcus aureus*, and that eradication of the infection can result in clinical improvement and reduced need for ongoing anti-rheumatic medication.[45-47] In addition to molecular mimicry, microbes (i.e., occult infections and environmental exposures) can also alter immune regulation by serving as a source of superantigens, which cause widespread and multifaceted immune dysfunction with resultant proinflammatory effects contributing to the exacerbation of allergy and autoimmune disease.[48]

Immune System and Cardiovascular System

The role of subclinical inflammation in the etiopathogenesis of atherosclerosis is no longer an issue of conjecture, as it has become a well-established aspect of the disease process. Even slight elevations in high-sensitivity C-reactive protein are associated with a significantly increased risk for cardiovascular morbidity and mortality in otherwise "apparently healthy" individuals.[49] With the increasing irrefutability of these data, pharmaceutical companies have scrambled to develop and sell drugs that can reduce this low-level inflammation, while physicians with a broader perspective have directed their energies toward intensifying their patient-centered search for the source(s) of inflammation in each individual patient. For example, subclinical inflammation can result from dietary indiscretion,[50] disturbed sleep,[51] and vitamin D deficiency;[52] in any of these situations, addressing the underlying causes of the inflammation with multicomponent nutritional/lifestyle interventions may deliver more effective health improvement than can the long-term use of inflammation-suppressing medications.[53-55]

Gastrointestinal Tract, Liver, and Neurologic Systems

The last several years have witnessed an increased appreciation for the influence that the gut and liver have on the brain, and advancements in functional assessments are now documenting analytically what was at one point known only clinically—that the status of the gut and liver have profound effects on the functioning of the brain. Evidence supporting the existence of a clinically important gut-brain interconnection has been published consistently over many decades and in major journals. Today, among the most poignant examples are Parkinson's disease and the autistic spectrum disorders. Indeed, the strength of evidence supporting the hepatogastrointestinal link with these "neurologic" conditions is so strong that it could be logically argued that any treatment of these conditions that does not address the hepatic and enteric aspects of these diseases is therapeutically incomplete.

Although Parkinson's disease was once considered idiopathic, we now recognize it as being a multifaceted

disorder associated with defective mitochondrial function, impaired xenobiotic detoxification, and occupational and/or recreational exposure to toxicants, particularly pesticides. These associations align to create a new model for the illness based on exposure to neuro-toxicants such as pesticides,[56] which are ineffectively detoxified[57] and then accumulate in the brain,[58] inducing mitochondrial dysfunction[59] and oxidative stress,[60] and leading to the death of dopaminergic neurons. Therefore, from the perspective of both prevention and treatment, the clinical approach to Parkinson's disease must include pesticide avoidance and optimization of detoxification to prevent the neuronal accumulation of neurotoxic mitochondrial poisons. The plan must also include optimization of nutritional status, antioxidant capacity, and mitochondrial function.[61]

The view that autism is a behavioral problem unfortunately continues to permeate present-day medical treatment of this condition, and many pediatricians and psychiatrists still advise only behavioral therapy and medicalization with psychoactive pharmaceuticals, particularly selective serotonin reuptake inhibitors (SSRIs).[62,63] While these interventions produce modest improvements over those seen in control groups, neither intervention remotely addresses the complex underlying physiology nor offers the possibility of cure, and SSRI use in children is highly controversial due to the association with increased incidence of suicide.[64] We now know that autism is a multifaceted disorder associated with gastrointestinal inflammation, nutritional deficiencies,[65] multiple food allergies and intolerances,[66] impairments in liver detoxification and resultant accumulation of xenobiotics, the majority of which have neurotoxic and/or immunotoxic effects.[67] Thus, autism is not a behavioral disorder *per se*; rather, it is a gastrointestinal-allergic-immunological-toxicant-nutritional-environmental disorder, and the behavioral/cognitive abnormalities are symptoms of the underlying complex and interconnected pathophysiology.

Musculoskeletal System, Neurologic System, Immune System

The adverse effects of a dysregulated immune system upon the musculoskeletal system are well known for their contributions to autoimmune diseases such as rheumatoid arthritis. In this classic scenario, the immune system is the effector, and periarticular structures, synovium, and joint surfaces are the targets of inflammatory and destructive processes that result in joint destruction and pain that affect the musculoskeletal and neurologic systems, respectively. This model holds that the direction of events flows from the immune system (autoimmunity) to the musculoskeletal system (target site) to the nervous system (perception of pain). This popular model must be updated in light of current research.

The phenomena of neurogenic inflammation and neuronal plasticity demonstrate the active, effector functions of the sensory nervous system and exemplify the extent to which the Cartesian model of the sensory nervous system (i.e., as exclusively afferent and passively receptive) is no longer valid.[68,69] Much of the musculoskeletal inflammation seen in clinical practice appears due, in large part, to inflammation that originates from and is mediated by the sensory nervous system through the release of proinflammatory mediators from sensory nerves in periarticular tissues.[70,71] Furthermore, evidence is accumulating that neurogenic inflammation can result from a heterogenous group of diverse stimuli, including allergens, environmental chemicals, and pain distant from the site of arthritis.[72,73] Likewise, evidence that intentional relaxation[74] as well as acupuncture[75] can modulate inflammatory pathophysiology indicates that psychoemotional variables and nonbiochemical therapeutics are important clinical considerations for patients with inflammatory diseases.

Evidence also suggests that musculoskeletal therapeutics such as spinal manipulation may influence immune responsiveness. Brennan et al.[76,77] showed that chiropractic spinal manipulation resulted in an acute increase in phagocytic capacity of polymorphonuclear neutrophils, and that this result was seen only following authentic (versus sham) manipulation, and that the effect was proportional to the increase in serum levels of substance P, a multifunctional molecule that acts as a neurotransmitter as well as a proinflammatory messenger. While the clinical implications of these data are yet to be clarified, they clearly demonstrate that the immune system is sensitive to mechanical stimuli.

Beyond Biochemistry and Neurophysiology: Piezoelectricity as a Mechanism for Intersystem Connectedness

Piezoelectricity, the continuum between mechanical stress and bioelectric conduction, is a well-established aspect of organic matter, affecting all vertebrates and, therefore, humans. Notably, the nervous system in general and the spinal cord in particular demonstrate an intrinsic dipole moment that is demonstrable across species of vertebrates.[78,79] In 1977, Lipiski from Tufts University School of Medicine[80] summarized the current research of the day and speculated on the effects of spinal manipulation, yoga, and acupuncture as mediated via the body's inherent pyroelectric and piezoelectric properties. Lipinski's literature review (particularly including the work of Bassett[81]) suggests that "piezo-electricity present in many biological systems may theoretically control cell nutrition, local pH, enzyme activation and inhibition, orientation of intra- and extra-cellular macromolecules, migratory and proliferative activity of cells, contractility of permeability of cell mem-

branes, and energy transfer." With these concepts and possibilities considered, we can construct a conceptual bridge linking mechanical stimuli such as massage, manipulation, exercise, and yoga, and (neuro)electrical stimuli such as acupuncture, meditation, prayer and intentionality, to plausible biochemical/physiological effects that translate into observed clinical benefits. This integrated model helps to explain the effects of "energetic" therapeutics such as moxibustion, acupuncture, and yoga that may be mediated by nonbiochemical physiologic mechanisms. Furthermore, this model also helps us to understand hitherto unexplainable phenomena such as the well-reported sensitivity that some people display to changes in the weather and the positioning of their bodies in relation to electromagnetic fields of the planet, electrical equipment, and power lines. Piezoelectricity may also be the physiologic conduit that transmits the effects of "distance healing," prayer, and intentionality.[82-84]

Summary

Human physiology is complex and treatment plans must be multifaceted to reflect this complexity. Cells, tissues, and organ systems work in concert—not in isolation—and therefore effective intervention generally requires improvement in numerous organ systems. As the artificial boundaries between organ systems dissolve, a unifying theme emerges, namely that the attainment, preservation, and re-establishment of health must be all-encompassing. Programs and paradigms related to the treatment of disease and the attainment of optimal health must reflect appreciation of environmental, physical, mental/emotional, nutritional, biochemical, hormonal, immunologic, neurologic, and gastrointestinal components of our existence that coalesce without boundaries to make the human body and our experience of life itself. Thus, new frontiers in health care will be reached not solely when new discoveries occur, but also when the integration of these discoveries into a cohesive, multifaceted, unified healthcare model prepares the way for more accurate understanding and more effective interventions. Healthcare providers of diverse backgrounds (e.g., ND, DC, MD, DO, RD, RN, LAc, and others) can and must work together to offer scientifically-based, multifactorial interventions that are adapted to the specific needs of individual patients.

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