FUNCTIONAL DIAGNOSTICS: REDEFINING DISEASE

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Functional medicine is a disruptive technology that will overthrow the tyranny of the diagnosis.

—Jeffrey Bland

Medical diagnosis has a storied and embarrassing past. The taxonomy of disease morphed as we moved from symptoms to anatomy to molecular biology to genomics and metabolomics. A penchant for naming is intrinsic to the human mind. Hippocrates categorized disease into the 4 humors: black bile, yellow bile, phlegm, and blood. Linnaeus, the 18th-century Swedish scientist known for the naming and classification of plant species, developed 11 categories of disease, including painful disease, motor disease, and blemishes. Tibetans distinguish 404 diseases divided into 4 causes: karmic disease originating in past lifetimes, disease resulting from influences in early life, disorders involving spirits, and superficial disorders resulting from diet and behavior.

In the late 19th and early 20th centuries, doctors and scientists shifted from a symptom-based diagnostic model to an anatomical view of disease, which led to the first international classification of disease in the 1850s and segregated disease into 140 categories, including "visitation from God." The 10th edition of the ICD (International Classification of Diseases) published by the World Health Organization in 1993 contains 12 000 categories of disease. With the advent of the genomic revolution and personalized medicine, the next edition, due in 2015, may need a radically new system of classification.

Our current categorization of diseases has little to do with the meaning, myths, and metaphors we associate with them. Before Robert Koch discovered the "tubercle bacillus," medical textbooks unequivocally defined the cause of tuberculosis: hereditary disposition, unfavorable climate, sedentary indoor life, defective ventilation, deficiency of light, and depressing emotions. The microscope changed all that.

Disease is primarily defined in phenomenological, not etiological, terms. We describe what we see—histology under the microscope or through more refined and sophisticated ways of seeing static pathology: the x-ray, ultrasound, computed tomography, magnetic resonance imaging, or other advanced imaging tools, or gross aberrations in physiology such as elevated glucose or renal or liver function tests.

We struggle to accommodate new scientific understanding by creating new categories of "pre-disease"—pre-diabetes,[1] pre-hypertension,[2] pre-dementia (MCI),[3] pre-autoimmune disease.[4] But what has eluded us until now as we move away from the static, anatomically based categorization of disease divided into medical specialties is a dynamic functional model that can weave a web of genomic, metabolomic, and molecular patterns into a new roadmap for diagnosis and therapy.

The study of metabolomics—the complex interplay of physiology and biochemistry connected to our gene expression, including genomics and epigenomics, allows us to understand the complex ways in which the disruptions in molecular pathways and networks of function cause disease. But this begs the question of how we might use this information clinically. An esoteric discussion of nosology may not seem relevant to a patient who presents with an array of "diseases." However, a new nosology, necessarily transitional, can provide a more effective, specific, and accurate way of getting to the roots of illness.

I suggest we put aside the artifact of medical history that is our current ICD model of illness and replace it with a new framework of interpretation of clinical information. It is based on function rather than pathology, on networks of physiology rather than organ systems, on assessment of more subtle changes on the continuum of dysfunction rather than sharp lines marking the onset of "disease." The anatomical assessment of disease becomes less relevant as we assess the burden of functional illness in the 21st century: the functional somatic syndromes (eg, chronic fatigue and immune dysfunction syndrome, fibromyalgia syndrome, premenstrual syndrome, multiple chemical sensitivity syndrome), obesity, diabetes, cardiovascular disease, depression, autism, attention deficit disorder, allergies, asthma, respiratory disease, autoimmune disease, digestive disorders (gastroesophageal reflux disease, irritable bowel syndrome), migraines, back pain, and more.

In assessing a patient today a new roadmap is available, one based on networks of function and causality, on a new architecture of thinking and evaluation. It is a diagnostic medicine focused on patterns and disruptions in molecular pathways

leading to disturbed function. The declaration of a clinical disease is only a waypoint on the continuum of illness.

How then can we help patients view their symptoms through new lenses? What questions must we ask? How can we deduce proximal causes from diverse symptoms and measurements of physiology and biochemistry? How can we systematically reduce impediments to health and restore optimal function and the capacity for self-regulation and healing?

Ultimately, all the conditions classified by the ICD as "diseases" can be viewed through the prism of 2 questions, 5 causes of illness, and 7 key concepts (Table 1). This 2/5/7 model of illness may shift with the tides of scientific understanding to 2/5/6 or 8 or 9. While the interior landscape is yet to be fully discovered, the shoreline is mapped and the topography can be traversed with a new compass. It is the compass of functional medicine, or the clinical application of molecular systems biology.

TABLE 1 The 2/5/7 Model of Illness

The 2 Questions

1. Does this person need to be rid of something, such as toxins, allergy, infection, poor diet, or stress?
2. Does this person have some unmet individual need that must be filled for optimal function, such as food (protein, fats, carbohydrates, fiber), nature-made molecules (vitamins, minerals, accessory or conditionally essential nutrients, hormones), light, water, air, sleep, deep relaxation, movement, rhythm, love, community, connection, meaning, and purpose?

The 5 Causes of Illness: The Environment

1. Toxins (biologic, elemental, synthetic)
2. Allergens (food, mold, dust, animal products, pollens, chemicals)
3. Microbes (bacteria, yeast, parasites, worms, prions, etc)
4. Stress (physical or psychological)
5. Poor diet (standard American diet, or SAD)

The 7 Core Physiologic Systems and Clinical Imbalances

The environment (the 5 causes of illness) interacts with genes to influence 7 core physiological systems.

1. Hormonal and neurotransmitter imbalances
2. Oxidation-reduction imbalances and mitochondropathy
3. Detoxification and biotransformational imbalances
4. Immune and inflammatory imbalances
5. Digestive, absorptive, and gut microbiological imbalances
6. Structural imbalances from cellular membrane function to the musculoskeletal system
7. Mind-body/body-mind imbalances

What then is the 2/5/7 model? And how can it be used as a clinical map for solving the puzzle of chronic illness?

In a patient encounter in this new territory of illness, data are analyzed differently. Rather than a reductionistic differential diagnosis where confounding variables are eliminated, inclusion of all variables allows an etiologic evaluation by discerning the patterns and connections that define the mosaic of illness. Symptoms are not viewed as the disease. Symptoms are the body's homeodynamic response to underlying functional imbalances. Symptoms are the body's attempt to reestablish balance and restore function and health. Laboratory and other diagnostics are focused on assessing causes and mechanisms of illness rather than confirming pathology. Treatment is directed at removing causes and restoring normal function and not suppressing symptoms.

FUNCTIONAL DIAGNOSTICS: FINDING YOUR WAY THROUGH IMBALANCE

A new framework for diagnostic evaluation might be called "functional diagnostics." Rather than assessing pathology, functional diagnosis assesses genetic predisposition, functional reserve, metabolic capacity, variations in physiologic functioning, diurnal and cyclic variation, and early tissue injury. Inquiry into the dynamic processes of the "metabolome" allows personalization of therapy. Questions of sensitivity and specificity break down under the light of a continuous, web-like network of function. Disease is not a discrete phenomenon, on or off, defined by this or that test or this or that descriptive disease definition (eg, "meets 2 major and 4 minor criteria").

The matrix of functional clinical physiologic systems provides a filter for gathering data on the "metabolome." A comprehensive history and physical conducted through the lens of these systems, supplemented by "functional diagnostics," allow the clinician to answer the 2 questions essential for guiding therapy. For each physiological system, answers to the questions of what are the root causes (toxins, infections, allergens, stress, poor diet) and what is lacking for optimal function (food, nutrients, air, water, light, sleep, rhythm, movement, connection, love, meaning, and purpose) guide both diagnosis and therapy. The aim is to restore balance in each system by removing impediments to health and providing the "ingredients" needed for optimal function. Much of this story can be gleaned from the patient history; however, selective use of functional diagnostic testing can refine the clinical approach (Table 2).

DEPRESSION OR IMBALANCE? A CLINICAL CASE HISTORY

Abstractions are rarely helpful in clinical medicine when one is faced with a suffering patient. I present here a complex medical case illustrating this model of functional diagnostics and therapy based on a new clinical compass.

JP was an 18-year-old man who presented with fatigue, depression, anxiety, a 27-pound weight gain, and acne worsening over the 4 years prior to his visit. His symptoms included cold intolerance; early morning fatigue; canker sores; chelosis (cracking at the corners of the mouth); acne on his face, chest, back and shoulders; and seasonal allergies. He also complained of trouble falling asleep, increasing anxiety, and depression worsening during the winter, for which he had been on Paxil for 4 years, when he gained 27 pounds and had increased refined carbohydrate and sugar cravings. Other symptoms included itchy ears and white spots on his nails.

TABLE 2 Functional Diagnostics Through the Matrix of Functional Medicine: A Sampler*

Core Imbalances	Conventional Diagnostics	Emerging Diagnostics
Nutrition	Methylation: homocysteine, methylmalonic acid (folate and B_{12} status) Iron status (transferrin saturation, ferritin, serum iron, total iron binding capacity) 25-hydroxy vitamin D Red blood cell magnesium Plasma zinc Alkaline phosphatase (zinc status) MCV, MCH (folate, B_{12} status) Genomics: MTHFR (methylation), VDR (vitamin D) polymorphisms	
Hormone	Insulin response (glucose tolerance with insulin) and hemaglobin A1C Cardiovascular risk: lipids and particle size, triglyceride/HDL ratio, fibrinogen, lipoprotein-a Thyroid: TSH, free T3, free T4, thyroid peroxidase antibodies, anti-thyroglobulin antibodies Hormone analysis: male, female, IGF-1, adrenal DHEA-S 24-hour urinary cortisol Osteoporosis assessment: PTH, ionized calcium, serum protein electrophoresis	Adrenal stress index (saliva cortisol) Estrogen metabolism and detoxification urine, blood, saliva Salivary sex hormone assessment Bone resorption assays RMR testing DEXA body composition and bone density Heart rate variability—autonomic function
Immune/ inflammatory	High sensitivity-C-reactive protein Fibrinogen CBC with differential Celiac panel: IgG, IgA anti-gliadin antibodies, IgA tissue transglutaminase, total IgA HLA DQ2/8 (celiac genes) Autoimmunity: anti-nuclear antibodies, sedimentation rate, rheumatoid factor, anti-cyclic citrullinated peptide antibodies, etc Infection screening (serology, polymerase chain reaction) Natural killer cell function Immunoglobulins Lymphocyte analysis	Vitamin and mineral assessment Essential fatty acid analysis Amino acid analysis (blood, urine) Organic acids (B vitamin status, etc)
Digestive	*Helicobacter pylori* serum antibody or stool antigen *Helicobacter pylori* breath test Small bowel bacterial overgrowth breath test Stool for ova and parasites CBC with differential (neutrophil:lymphocyte ratio)	Allergy testing: IgG and IgE antibodies to foods and environmental allergens Gut immunology: EPX, calprotectin in stool
Detoxification	Hepatic function with GGT (NASH, drug reactions) Whole blood or red blood cell metals (mercury, lead, argon, etc) Genomics: GSTM1, apolipoprotein E polymorphisms	Detoxification challenge: Phase 1 and 2 Hair analysis: methylmercury (fish) Provocation/chelation challenge: heavy metals Detoxigenomics: phase 1 and phase 2 Chemical antibody evaluation Mycotoxin antibody assessment Visual contrast sensitivity
Mitochondria/ redox	Muscle biopsy	Organic acids (fat, carbohydrate, and Krebs cycle metabolites) V02 max—cardiometabolic testing Lipid peroxides 8-0H-2DG (DNA adducts)

*MCV indicates mean corpuscular volume; MCH, mean corpuscular hemoglobin; MTHFR, 5,10-Methylenetetrahydrofolate reductase; VDR, vitamin D receptor; HDL, high-density lipoprotein; TSH, thyroid-stimulating hormone; IGF, insulin-like growth factor; DHEA-S, dehydroepiandrosterone sulfate; PTH, parathyroid hormone; RMR, resting metabolic rate; DEXA, dual energy X-ray absorptiometry; CBC, complete blood count; Ig, immunoglobulin; HLA, human leukocyte antigen; EPX, eosinophil protein X; GGT, gamma-glutamyl transpeptidase; NASH, non-alcoholic steatohepatitis; GSTM1, glutathione S-transferase M1; redox, reduction/oxidation reaction.

His history included that he was carried to term and delivered by Cesarean section. He was bottle-fed with soy formula. He had transient synovitis of the hip at 5 years old, intermittent otitis media treated with antibiotics, and acne treated with Bactrim for 2 years. He also had gynecomastia, which was treated surgically, and hyperlipidemia.

His medications were Paxil 15 mg daily, Bactrim daily, Claritin as needed, and a multivitamin.

Family history was significant for depression in father and paternal grandfather, allergies in his mother and sister, and myocardial infarction in maternal grandfather at 54.

He was a nonsmoker, used no alcohol or substances of abuse or caffeine. His diet consisted of no breakfast, fast food for lunch and dinner, and diet and regular sodas. He avoided seafood. He exercised 25 minutes a day on a treadmill and 1 to 2 times a week with a trainer. He slept 10 hours a night.

His exam revealed a moderately overweight teenager. His blood pressure was 110/68, body mass index 26.5 (weight 201 lbs), temperature 95.5 degrees F. Other than severe acne vulgaris and chelosis, his physical exam was normal.

Nutritional laboratory assessment revealed vitamin D deficiency (25-OH vitamin D 17 ng/mL, normal 30-100), severe omega 3 fatty acid deficiency with low alpha-linolenic acid (ALA), eicosapentanoic acid (EPA), and docosahexaenoic acid (DHA), and an omega 6 fatty acid deficiency of gamma linolenic acid (GLA). Organic acids revealed deficiency of B_6 (xanthurenate, kynurenate elevation) and B_{12} (methylmalonic acid) and deficiency markers for CoQ_{10}, biotin, and B vitamins.

Hormonal evaluation revealed "sub-clinical" hypothyroidism with elevated thyroid peroxidase antibodies, thyroid-stimulating hormone 2.55 mIU/L (normal 0.5-3.5), normal free thyroxine (T4) of 1.1 ng/dL, and low free triiodothyronine (T3) of 281 pg/dL (normal 287-455). He also had hyperlipidemia with total cholesterol of 232 mg/dL, low-density lipoprotein of 164 mg/dL, high-density lipoprotein of 42 mg/dL, triglycerides of 130 mg/dL, and an elevated lipoprotein-a of 209 nmol/L (normal <75). A 2-hour glucose insulin response test revealed normal fasting insulin (5 micro IU/mL, normal <5) but severe hyperinsulinemia at 1 and 2 hours post glucose load (242 micro IU/mL and 84 micro IU/mL, normal <30 micro IU/mL). His fasting glucose was 74 mg/dL, his 1-hour glucose was 184 mg/dL, and his 2-hour glucose was 93 mg/dL.

Immune and inflammatory evaluation revealed elevated IgG antigliadin antibodies of 16 U/mL (normal <11) with normal IgA antigliadin and tissue transglutaminase antibodies. He had elevated IgG antibodies to wheat, dairy, and yeast. His high-sensitivity C-reactive protein was normal at 0.3 mg/L. His quinolinate was significantly elevated, indicating cytokine disruption of the enzymatic conversion of tryptophan to serotonin.

Moderate elevation of dysbiosis markers on urinary organic acids indicated digestive imbalances.

Detoxification markers showed low levels of sulfate and alpha-hydroxybutyrate, indicating glutathione deficiency.

Mitochondrial evaluation on organic acids revealed deficiencies of carnitine, riboflavin, lipoic acid, coenzyme Q_{10}, magnesium, and lipoic acid.

What story do the history, exam, and functional laboratory assessment tell?

We asked 2 simple questions: what did this young man need to get rid of that was impeding his health, and what was he missing? By asking how this affected his core clinical physiologic systems we learned the following.

THE CORE CLINICAL IMBALANCES: NETWORKS OF DYSFUNCTION

He was nutritionally depleted of vitamin D (seasonal depression[5,6] and impaired immunity[7]), as well as deficient in omega 3 fats (depression[8] and acne), B_{12}[9] and B_6[10] (depression and fatigue), B vitamins (chelosis, B vitamin deficiency markers on organic acids), and zinc, based on his impaired immunity, acne, and the white spots on his nails.

His hormones and neurotransmitters were out of balance, causing the history of anxiety and depression. He had a low body temperature (95.5 F), elevated thyroid antibodies, and low free T3 (depression, morning fatigue, hyperlipidemia, insulin resistance[11]), he was severely hyperlinsulinemic (acne,[12] depression,[13] weight gain, carbohydrate cravings), and he had dyslipidemia with low HDL, high triglycerides, and high LDL (from insulin resistance).

His immune imbalances included elevation of IgG antigliadin antibodies (fatigue, depression,[14] hypothyroidism,[15] acne) and IgG antibodies[16] to dairy, wheat, and yeast. His canker sores supported the diagnosis of gluten intolerance.[17]

Digestive imbalances were supported by his history of long-term antibiotic use and dysbiosis markers on organic acids.

Mitochondrial dysfunction was inferred from his fatigue[18] and confirmed by significant abnormalities of fat, carbohydrate, and Krebs cycle metabolites. Deficiency of sulfate and abnormal glutathione markers indicated impaired detoxification and oxidative stress.

REMOVING IMPEDIMENTS, REPLACING WHAT IS MISSING

Based on these clinical markers we simply removed impediments to health—gluten, IgG food allergens, and antibiotics—and treated yeast overgrowth with fluconazole. We removed processed food, junk food, and refined carbohydrates from his diet.

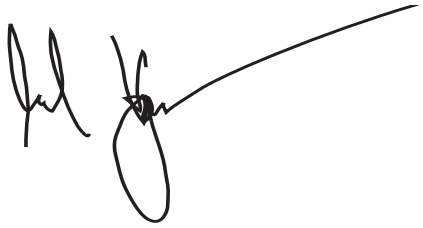
Then we replaced what he was lacking and needed to thrive: a whole-foods, low-glycemic-load, high-phytonutrient, allergen-free diet, thyroid hormone (Armour thyroid), a multivitamin and mineral, vitamin D, zinc, methylation factors (5-methylfolate, pyridoxine, sublingual B_{12}), mitochondrial support (coenzyme Q_{10}, carnitine, lipoic acid), omega 3 fatty acids, detoxification support (N-acetylcysteine), probiotics, protein kinase modulators[19] from hops to improve insulin sensitivity, as well as whole soy protein and plant sterols to improve lipid metabolism.

His clinical response included improved energy, depression, and cold intolerance. His acne, cankers sores, and chelosis resolved. He lost 15 pounds in the first 2 months of treatment and eliminated his carbohydrate cravings.

So what can we say about his "diagnosis"? Were the causes of his symptoms "depression," "acne vulgaris," and "hyperlipidemia"? Did he need antidepressants, antibiotics, and statins? Or was he suffering from a few underlying causes, which triggered imbalance and patterns of dysfunction in his core physiologic systems (gluten, IgG food allergies, poor diet, yeast overgrowth from antibiotic use)? Was he missing a few "ingredients" or raw materials needed to thrive—thyroid hormone, whole foods, omega 3 fats, vitamin D, zinc, methylation support (B_6, B_{12}, folate), mitochondrial nutrients, and probiotics to restore normal gut flora?

Complexity in chronic illness is the norm, but navigating therapy is relatively simple. Using a comprehensive history and exam and reframing diagnostic evaluation to identify impediments to health and assess function and imbalance rather than pathology is a better compass for finding our way through the 21st-century puzzle of chronic illness.

The next era of research might focus on the clinical application of systems biology and generate new models of investigation and data analysis. Our current reductionistic analysis in clinical medicine based on the randomized controlled trial prevents study of multi-interventional approaches. Clinical practice must piece together research into discrete interventions (nutrients, phytonutrients, hormones, lifestyle treatment, and so on). Clinical experience can inform research and research, clinical practice in a fertile cycle. But at the bedside there are inherent limitations for translation of research into clinical protocols. What guides us each day is the art of blending science, theory, and experience into what we hope is the best treatment for our patients.



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CORRECTION

Erdal Gocmen, MD, should have been listed as a coauthor in the byline of the article "Effects of Aqueous Green Tea Extract on Activities of DNA Turn-over Enzymes in Cancerous and Non-cancerous Human Stomach and Colon Tissues" that appeared in the May/Jun issue of *Alternative Therapies in Health and Medicine* (2008;14(3):30-33). The authors of that article regret the error.