

# THE RIGHT ORDER OF THINGS: PEELING THE ONION OF CHRONIC DISEASE

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*"The well-meaning are often ill doing."*

—Herbert Benson, MD, Benson-Henry Institute for Mind Body Medicine

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In the practice of medicine, healing depends not only on doing the right things but doing them in the right order. The shift from linear reductionism to holographic thinking is essential to understand the nuanced collage that is the story of a patient's illness. From that story, the right place to push or pull on the web of biologic dysfunction emerges, along with the right order of pushing and pulling to restore balance.

Medical education teaches us to funnel clinical information gathered from medical history, physical exam, laboratory, and imaging into a disease label and matching ICD-9 code. As William of Occam said in 1320, "What can be done with fewer assumptions is done in vain with more." Unfortunately, medicine in the 21st century is bleeding as a result of Occam's razor. The complex web of physiology and patterns that link apparently disparate biologic systems are increasingly more relevant in formulating notions of health and disease. It is the lens through which we can understand the whole story of a patient's illnesses without discarding facts or findings that seem unrelated. The inevitable conclusion of systems medicine is that everything is related, and we ignore any detail at our peril. Functional medicine is an evolved clinical map that uses scientific tools for understanding this web.

Illness is never simply one discrete process or dysfunction. It is a bundle—a patient's whole life, from genetics to beliefs and how those influences are layered to create the thing we call disease. Sorting out the proximal causes from the downstream effects and determining how the illness is woven into a patient's story and biology helps the practitioner know where to start and which layer to peel away in the web of physiologic dysfunction.

Doing the right things in the wrong order often will result in

a failure to treat or exacerbation of the illness. There are often many things to do, and it is difficult to choose which to do first. But after years of thinking, sorting, trying, failing, and sometimes succeeding, a few things seem apparent. And fortunately, though human biology is infinitely complex and beyond anyone's capacity to fully grasp, there are some principles and well-traveled routes to healing that are accessible to primary care practitioners.

## BEFORE YOU BEGIN

The practitioner's first task is to ascertain the cause (or causes) of the illness. There are essentially 5 proximal causes of all illness: infections, allergens, toxins, stress (physical or psychological), and poor diet.

The second task is to identify the 7 "ingredients" needed for optimal biologic function—real food; nutrients, and hormones; a healthy environment (water, air, light); deep relaxation; rhythm (including sleep); movement; and love, community, meaning, and purpose. We must also become experts in assessing deficiency of these "ingredients" and helping to provide the conditions for thriving.

The presence of any of the 5 etiologic factors and the absence of any of the 7 essential ingredients creates imbalance in the basic biologic systems and processes—hormonal/neurochemical, immune, digestive, detoxification, energy metabolism, structural, and mind-body. And imbalances in any one or combination of these systems result in the manifestation of disease. With this map and process of thinking, the names of the diseases we see become increasingly less important.

When faced with multiples causes—toxins, infections, allergens, poor diet, and stress—which often occur together in varying patterns and degrees, the question is what to do first. The simplicity of this clinical approach belies the underlying biological complexity. Fortunately, the body knows how to heal if we remove the impediments and provide the proper conditions.

## WHAT IS THE RIGHT ORDER?

### Start With Food

Start with whole, real foods. As Michael Pollan writes in his 2008 book, *In Defense of Food: An Eater's Manifesto* (Penguin Press), "Eat food. Not too much. Mostly plants." A refinement is what I have termed the "nutrigenomic index" (Table). Food is by far the most powerful clinical intervention in chronic disease. Learn to apply it, and use it skillfully.

**TABLE** Nutrigenomic Index

A whole, unprocessed, predominantly plant-based diet provides the highest nutrigenomic index based on the following properties:

- Low glycemic load—the overall balance of the meal
- Proper fatty-acid composition—high level of healthy omega-3 fats vs omega-6 fats, low in saturated fats and no trans fats.
- High phytonutrient density—high level of phytonutrients and antioxidants
- Healthy protein—lean, healthful, predominantly plant-based proteins or pasture-raised animal products
- High micronutrient density—high amounts of vitamins and minerals
- Low allergenic burden—low in foods that are highly allergenic (gluten, dairy, and others based on personalized prescription)
- Low toxic burden—minimizes toxic burden of food, (eg, no/few added hormones, pesticides, antibiotics, or other artificial additives)
- Healthy PH balance—provides proper balance between acidity and alkalinity
- Healthy salt:potassium ratio—low in salt and high in potassium
- High fiber content—high in fiber to help slow the insulin response and optimize digestive health

### Remove Food Allergens

Delayed type-3 hypersensitivity IgG-mediated food responses are among the most potent triggers for chronic symptoms and immune system upregulation.<sup>1</sup> A trial of a comprehensive elimination diet for 2 to 3 weeks with systematic food reintroduction is a powerful therapeutic and diagnostic tool. After introducing a whole-foods, low-glycemic-load, phytonutrient-dense diet, food elimination/provocation is the least expensive and most powerful diagnostic and therapeutic tool available to primary care practitioners. Becoming familiar with the manifestations of gluten intolerance and the continuum of gluten-related disorders is a neglected and powerful therapeutic tool in medicine.

### Fix the Gut

Health starts in the gut. The digestive tract has an independent nervous system, the enteric nervous system, and contains 60% of our immune system. Skill in assessment based on history and appropriate diagnostic tests (celiac panel, metabolic, immune, and microbiological analysis) and in treatment of the primary gut dysfunctions—including increased intestinal permeability, delayed food allergy, small intestinal bacterial overgrowth (SIBO), yeast overgrowth, parasites, and worms—is essential. Antibiotics, antifungals, and antiparasitic and antihelminthic medications or botanicals are the first step in eradicating triggers for intestinal dysfunction. Repair and healing of the gut requires use of digestive enzymes, prebiotics, probiotics, and nutrients needed for epithelial repair, including zinc, omega 3 fats, gamma-linolenic acid, glutamine, and antiinflammatory botanicals such as quercetin and curcumin.

### Optimize Nutrient Status

Nutrient deficiencies affect up to 92% of Americans.<sup>2</sup> Learn

the clinical manifestations and therapeutic treatment for the most common nutrient therapies. These are magnesium (think anything that is tight, irritable, or crampy—muscles, bowels, lungs, moods); zinc (for immune function); vitamin D (for anyone who lives in the upper northern and lower southern hemispheres and is not on supplementation); methylation (B<sub>6</sub>, folic acid, B<sub>12</sub>) necessary for detoxification, cognitive function, and DNA repair; and omega-3 fatty acids (EPA and DHA), the stuff of which we are made. Become an expert in the diagnosis of these common deficiencies and their treatment.

### Balance Hormones

Dietary disruption of hormones (sugar and refined flour), endocrine disruptors or xenobiotics (petrochemicals and heavy metals), and chronic stress are rampant. Four categories of hormones are the most important to learn to assess and treat: insulin resistance, hypothalamic-pituitary-adrenal (HPA) axis dysfunction and subclinical adrenal insufficiency, thyroid dysfunction, and sex hormone dysfunction. Diet, exercise, stress management, bioidentical hormone replacement, nutrient support, and herbal therapies are among the most effective tools, along with oriental medicine.

### Support Energy Metabolism

The end result of many nutritional, toxic, allergic, infectious, and dietary insults is injury to the mitochondria, unchecked oxidative stress, loss of energy, and ultimately, apoptosis or cell death.<sup>3</sup> Mitochondrial dysfunction has led to epidemics of obesity, diabetes, fatigue, developmental and neurodegenerative disorders, and accelerated aging. Understanding how to assess mitochondrial dysfunction using organic acid analysis and supporting and protecting mitochondrial function through the use of phospholipids, essential fatty acids, acetyl-L-carnitine, coenzyme Q<sub>10</sub>, D-ribose, magnesium/potassium aspartate, alpha lipoic acid, NADH, riboflavin, niacin, and n-acetyl-cysteine (NAC) are important steps in supporting health and recovery from chronic illness.

### Enhance Detoxification

Detoxification is one of the most important and metabolically demanding functions of our physiology. The toxic burden of 2.9 billion pounds of petrochemical toxins and 6 million pounds of mercury unloaded into our environment every year has put undue stress on our capacity for detoxification.<sup>4</sup> Identifying heavy-metal toxicity, particularly mercury and lead, through provocation challenge testing is an advanced skill worth learning.

Becoming skillful in strategies for upregulating endogenous phase 1 and phase 2 detoxification enzymes through phytonutrients, amino acids, and vitamins and minerals is essential in treating chronic disease. The twin intersecting pathways of methylation and sulfation are central to detoxification and near the center of all chronic diseases. However, mobilizing toxins must be done after all other aspects of our biologic systems have been optimized and pathways for detoxification are working at full speed.

## HELP TO ACHIEVE MIND-BODY BALANCE

*We are obliged by the deepest drives of the human spirit to make ourselves more than animated dust, and we must have a story to tell about where we came from, and why we are here. . . . It is our nature to put all knowledge into context in order to tell a story, and to re-create the world by this means.”*

—E.O. Wilson, *Consilience: The Unity of Knowledge*

Helping patients find meaning and connection in the context of illness and within the tapestry of their lives, relationships, and beliefs is one of our primary roles as physicians. Supporting the patient to develop skills in self-care and nourishment are both the first and last steps in healing.

## Look for Hidden Infections

If a patient is resistant to treatment or has an elevated high-sensitivity C-reactive protein, testing for hidden infections often identifies unsuspected triggers: viruses (HHV-6, EBV), atypical bacteria (chlamydia, mycoplasma, ureaplasma), tick-borne illness (Lyme disease, ehrlichiosis, babesiosis, *Bartonella*), and dental infections (root canals). If no infection is found, consider mold in the home or workplace, particularly black mold or *Stachybotrys*.

## THE RIGHT ORDER OF THINGS

Despite the complex world of systems biology and medicine, the way into the web of dysfunction and healing is often simple and effective for patients with chronic disease. The puzzle of chronic illness is not so difficult if we start with food, address food allergens, fix the gut, optimize nutrient status, balance hormones, support energy metabolism, enhance detoxification, teach self-care and nourishment of mind and soul, and if we get stuck, dig around for hidden bugs. This model works for most patients most of the time. It is based on a clear framework for understanding the impediments to optimal function, the necessary conditions for thriving, and the essential physiologic systems that are at the root of the more than 12 000 different “diseases” that are only the effects of these causes. Keeping in mind the right order of things will get us from effect to cause and from illness to health.

## REFERENCES

1. Wilders-Truschning M, Mangge H, Lieners C, Gruber HJ, Mayer C, März W. IgG antibodies against food antigens are correlated with inflammation and intima media thickness in obese juveniles. *Exp Clin Endocrinol Diabetes*. 2008;116(4):241-245.
2. Fairfield KM, Fletcher RH. Vitamins for chronic disease prevention in adults: scientific review. *JAMA*. 2002;287(23):3116-26. Review.
3. Short KR. Introduction to symposium proceedings: the emerging interplay among muscle mitochondrial function, nutrition, and disease. *Am J Clin Nutr*. 2009;89(1):453S-454S.
4. US Environmental Protection Agency. *Toxics Release Inventory Program*. Available at: <http://www.epa.gov/tri/>. Accessed February 4, 2009.