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AAPI'S NUTRITION GUIDE TO  
OPTIMAL HEALTH:  
USING PRINCIPLES OF  
FUNCTIONAL MEDICINE  
AND  
NUTRITIONAL GENOMICS



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FUNCTIONAL MEDICINE AND NUTRITIONAL GENOMICS

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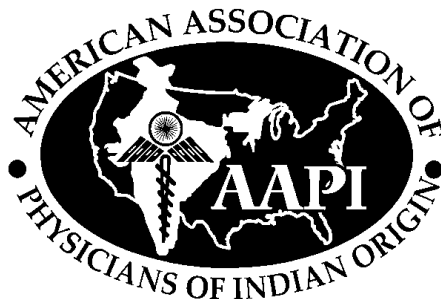
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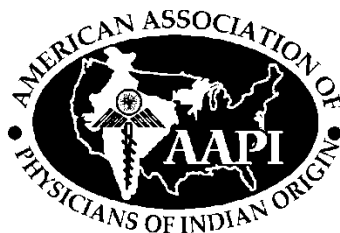
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# Introduction

## Rita Kashi Batheja, MS, RD, CDN



Om Shanti.

Shanti means peace in the Indian language.

“Let thy food be thy medicine and thy medicine thy food”  
– Hippocrates – The founder of Western Medicine.

Nutrition will become the primary treatment modality in the 21<sup>st</sup> century. The term *functional medicine* is a new approach to healing. It is a revolutionary way to treat illness by prevention and looking at the root cause rather than putting a band-aid on symptoms. “Integrative and Functional Medical Nutrition Therapy (IFMNT) Radial: An Emerging Tool for Practice”, written by Kathie Madonna Swift, is the brainchild of Kathie Madonna Swift, Diana Noland and Elizabeth Redmond. Kathie covers personalized nutritional care by going over signs and symptoms; environmental exposures with biomarkers like digestion / absorption, toxins etc.; metabolic pathways / networks like nutrient cofactors; core imbalances like digestion, energy metabolism, and inflammation; nutritional status; and overall lifestyle choice.

“Your genes load the gun, but your lifestyle pulls the trigger”.

The word obesity is all over the media. “Lose weight without dieting”, “The Miracle Plan to boost your metabolism and lose weight”, so on and so forth. In today’s world we want everything instantly, but there are no short cuts! Nationally and internationally recognized colleagues, Registered Dietitians (RDs), Functional Medicine, Mind Body Medicine and Nutritional Genomic practitioners who are members of The Academy of Nutrition and Dietetics ([www.eatright.org](http://www.eatright.org)) and its Dietetic Practice Group of the Dietitians in Integrative and Functional Medicine ([www.integrativeRD.org](http://www.integrativeRD.org)) have contributed to AAPI’s indispensable nutrition guide, along with the finest conventional medical doctors (MDs) who are currently practicing functional medicine and preventive care specialists who are prominent in their field and support scientific evidence.

AAPI’s E book, “AAPI’s nutrition guide to Optimal Health: Using Principles of Functional Medicine and Nutritional Genomics”, has been dedicated as a service to the global community. I encourage every healthcare practitioner and individual worldwide to utilize AAPI’s invaluable nutrition guide which does not have a price attached to it. Read about the contributing authors and get to know them. Their contact information is mentioned at the end of their respective chapter. Kindly contact them directly to use any information from their article.

The idea of AAPI's E book was presented to AAPI president Sunita Kanumury, MD in July 2011. Without the blink of an eye, she graciously embraced the idea to share these concepts not only for AAPI's members, but for everyone else to manage incurable illnesses with less expensive and simpler interventions. Many physicians have been trained by the Institute of Functional Medicine [www.functionalmedicine.org](http://www.functionalmedicine.org). Look into upcoming nutritional genomics and such programs through the Dietitians in Integrative and Functional Medicine, a Dietetic Practice Group (DIFMDPG) of the Academy of Nutrition and Dietetics, formerly known as The American Dietetic Association ([www.eatright.org](http://www.eatright.org)). Another such state of the art tool is the yearly professional training program titled, "Food as Medicine", by the Center for Mind Body Medicine ([www.cmbm.org/fam](http://www.cmbm.org/fam)).

Almost all of the chapters are self-explanatory when you read the title of the chapters mentioned in the table of contents. To increase the understanding of the role of genetic variation and dietary response, it is important to understand the role of nutrients in gene expression. I recommend that you get familiar with nutrition genomic wiz, Colleen Fogarty Draper's chapter on "Nutritional Genomics Research and Practice." In addition, I recommend that you be on a wellness program rather than on a weight-loss program. Micheline Vargas' chapter on "Highly Palatable Foods: Brain Reward Pathways and Connections to Overeating." It covers dopamine and hormones, leptin and ghrelin, that are responsible for hunger and satiety. Dr. David Brownstein's chapter titled, "Iodine: Why You Need it, Why You Can't Live Without it", is an eye opener. Dr. Jay H. Mead touches base on vitamin D, the essential sunshine nutrient responsible in weight management and its many other roles like supporting calcium absorption, which non-healthcare professionals may not be familiar with.

Dr. Gerard Mullin's chapter on probiotics in gastrointestinal disease is profound. "By treating your inside tract and reducing inflammation throughout your body, you set the stage for a lifetime of wellness". I highly recommend you pay close attention to the use of probiotics. Kathie Madonna Swift, RD and Gerard Mullin, MD, director of Integrative GI Nutrition Services at Johns Hopkins, have written a book titled, "The Inside Tract - Your Good Gut Guide to Digestive Health", which is forwarded by Andrew Weil, MD and should be on everyone's desk.

Detoxification is a very popular, but new word to many readers in many countries. Diana Noland has explained detoxification very well; freshly prepared vegetables, like leafy vegetables and roots, optimize the body's ability for optimal gut function. There are a lot of imbalances, like pollution from air and water, that are on the rise. Many people are looking into integrative and functional lab tests to personalize a plan to fit their profile. Elizabeth Redmond has covered these points very well giving case studies, and Dr. Jay H. Mead has as well with a chapter on "Bioidentical Breakdown: Emerging Fields of Hormone Replacement." These tests are not done routinely in conventional medicine. This will open up the reader's mind with the possibilities of being in charge of his or her own health. Eat grandma's diet: whole foods, which include vibrant colors of fruits and vegetables and are full of antioxidants, plenty of fiber and whole grains. The disease process is multifactorial; with an unhealthy lifestyle, we are turning on genes that cause damage and produce inflammation.

Diabetes and obesity is termed "Diabesity" per Dr. Mark Hyman, Chairman of the Institute of Functional Medicine. Brilliantly written, this article states one can reverse diabetes with a functional medicine approach. Sheila Quinn and Dr. David S. Jones, President of the Institute of Functional Medicine, explain this concept



in chapter 1. Dr. Mark Hyman has also contributed a chapter on “Functional Diagnostics: Redefining Disease”; you really do not want to miss it.

Jaime Wright, DO, an anti-aging doctor, and Elizabeth Strickland have written exceptional articles on food sensitivities, basic gut health and integrative nutrition for autism. In this chapter, Elizabeth has done a great job by covering Omega 3 fatty acids, which requires special attention. Both of these articles are written in very simple language for everyone's benefit. Do not miss reading them. Jaime Wright also wrote another article on “Hyperbaric Medicine: Application and Evidence: Multiple Sclerosis, Autism, Traumatic brain Injury.” The word *cancer* is very frightening; Dr. Richard Linchitz, a Cornell graduate from Long Island, New York, is a cancer survivor who has written a chapter on integrative cancer therapy.

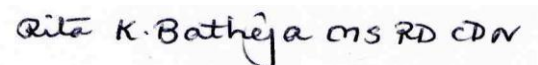
Sheila Dean, known as Dr. Dean, practices functional medicine in Tampa, Florida, and has written a chapter titled, “A Nutritional Genomics Approach for the Management of Crohn's Disease: An inflammatory Bowel Disease.” Even if you are not suffering from Crohn's disease, please share this information with people who have Crohn's disease.

Lighten emotional baggage. Stressful situations and depression are covered in “Getting Unstuck” with spiritualism and gentle care by Dr. James Gordon, founder of the Center for Mind Body Medicine.

AAPI's priceless nutrition guide to optimal health would not have been possible without the cream of the crop contributing authors. My special thanks to Kim Kaur, Executive Committee members of the Dietitians in Integrative and Functional Medicine Dietetic Practice Group of the Academy of Nutrition and Dietetics, and the Institute of Functional Medicine.

I am running out of words for AAPI president Sunita Kanumury, MD. I thank her from the bottom of my heart for her strong support. We are focused on helping to provide healthcare practitioners with the essential tools and resources to help them find clarity in this uncertain environment in the healthcare system. Healthcare practitioners are the backbone of our society and are saving millions of lives. My hope is for MDs and RDs to work in partnership.

Healthy Regards,



Rita Kashi Batheja, MS, RD, CDN  
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# Foreword

## Sunita Kanumury, MD



Friends,

It has been said, *"In the sea of change, it is our responsibility to light the way for others!"* As physicians, we model this statement in the care we provide and the advice on healthy living we give to our patients. I am confident each physician member of AAPI serves as a beacon amidst an ocean of darkness in healthy lifestyle options. Yet, in spite of our best efforts, obesity, many times leading to heart disease and diabetes, is on the rise.

The American Association of Physicians of Indian Origin (AAPI) takes this pandemic seriously, and as such, has developed this guide on proper nutrition and healthy living. At AAPI, we believe *"...it is our responsibility to light the way for others!"* We have compiled this nutrition book to help everybody eat healthier and make better life choices, which in turn will extend the length and quality of our lives together.

This E book is an indispensable guide for the billions worldwide who suffer from many conditions. I suggest making lifestyle changes for a lifetime by utilizing these principles. You are not what you eat, but you are what you absorb. Take charge of your own health. Have a closer look at the chapters like "Food Sensitivities, Basic Gut Health, Probiotics in Gastrointestinal Disease, Emerging Field of Hormone Replacement, and Diabetes (diabetes and obesity), just to name a few. I suggest looking into integrative and functional lab tests. Prevention is the key. Redefine disease through functional diagnostics. Everything ties in with the Integrative and Functional Medical Nutrition Therapy Radial. The word "Detoxification" is in style; see what the author has to say!

I am very thankful to internationally renowned Physicians, Registered Dietitians and Nutrition Scientists who have spent their invaluable time sharing their knowledge.

Another approach is nutritional genomics, where Crohn's disease and Celiac disease are addressed. There may be hope for people suffering from cancer: prevent it through integrative approaches. More and more people are suffering from autism: see an integrative nutrition approach for this condition. Many people are depressed to some extent with their super busy lifestyles in this high tech society. Spiritualism and yoga have been practiced in India since our ancestors and more so all over the world lately. There is a power to

heal in mind-body medicine. Dr. James S. Gordon covers this point in "Getting Unstuck." Also, look into nutrients like iodine and vitamin D, which are among the most ignored nutrients in weight management and several other conditions. I highly recommend you read what experts have to say!

My hearty congratulations to Rita Batheja, MS, RD, CDN, Registered Dietitian, Integrative and Functional Medical Nutrition practitioner, who came up with the idea of this timely E book. With her tireless efforts, she approached prominent experts in the various fields who contributed their articles and put together this E book.

It is my hope that you and your loved ones live long, happy, healthy and productive lives!

Healthy Living to you and yours,



Sunita Kanumury, MD

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# 1

## Introduction to Functional Medicine

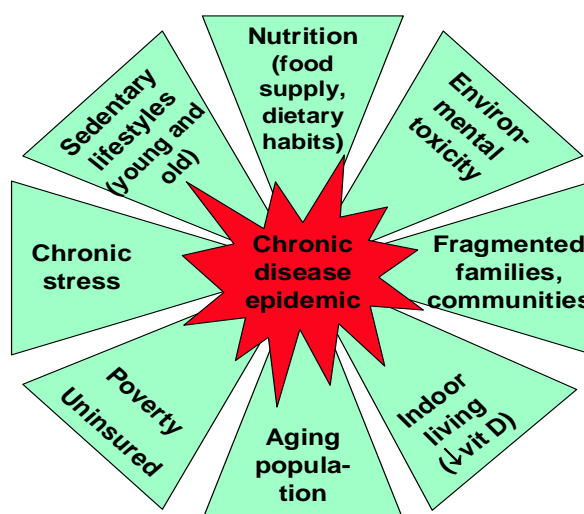
**David S. Jones, MD  
and Sheila Quinn**



The need for a new approach to chronic disease comes from myriad sources, all converging on the same idea. Over the last century, there has been a dramatic shift in prevalence from acute to chronic diseases. By 2020, worldwide deaths from chronic disease are projected to total more than twice the number of deaths from infectious disease (50 million vs. 20 million). It is estimated, for example, that more than half of all Americans suffer from one or more chronic diseases,<sup>1</sup> and that the 8 million Medicare beneficiaries who have five or more chronic conditions accounted for over two-thirds of the program's \$302 billion in spending in 2004.<sup>2</sup> The U.S. spends twice the median per-capita costs calculated by the Organization for Economic Cooperation and Development (OECD),<sup>3</sup> but has extraordinarily poor outcomes for such a massive investment.<sup>4</sup> The \$1.3 trillion estimated to be the cost of chronic disease in the U.S. today is projected to grow to \$4.2 trillion within 15 years,<sup>5</sup> making the cost of care using the current model economically unsustainable.

Given the prevailing evidence, there can be little doubt that 21<sup>st</sup> century health care demands a

different approach than the acute-care, specialist-driven model that emerged during the 20<sup>th</sup> century.



**Figure 1. Major Influences Contributing to the Epidemic of Chronic Disease**

During the last 100 years, such significant advances have been made in conquering or controlling scourges such as tuberculosis and pneumonia, and in the treatment of trauma, that life expectancy and quality of life have both increased dramatically. Unfortunately, over the last

50 years, other influences (see Figure 1) have fueled what is now recognized as an epidemic of chronic disease,<sup>6,7</sup> including heart disease, diabetes, cancer, asthma, multiple sclerosis, Alzheimer's and other dementias, stroke, irritable bowel syndrome (IBS), and inflammatory bowel disease (IBD), to name some of the most common. Assessment, treatment, and prevention of these chronic conditions are not well served by an acute-care, organ-specialty medical model.<sup>8</sup>

Why doesn't the old model work? Because chronic disease is a food- and lifestyle-driven, environment- and genetics-influenced phenomenon. It won't be conquered with drugs and surgery, however helpful those tools may be in managing acute signs and symptoms. It won't be conquered by adding new or unconventional tools (e.g., botanical medicine, acupuncture) to a failing model. It won't be conquered by pharmacogenomics (although advances in that discipline should help reduce deaths from appropriately prescribed medication—estimated to be the 4<sup>th</sup> leading cause of hospital deaths). It CAN be conquered by integrating what we know about how the human body works with individualized, patient-centered, science-based care that addresses the causes of chronic disease, which are rooted in lifestyle choices, environmental exposures, and genetic influences.

The transformation of 21<sup>st</sup> century medicine from the prevailing acute-care model to a far more effective chronic-disease model will succeed only if we attack the underlying drivers of the epidemic—the complex, lifelong interactions among lifestyle, environment, and genetics.<sup>9</sup> In order to be successful, clinicians must pay much closer attention to etiology; taxonomy alone—naming the disease—and prescribing drugs or surgery are no longer sufficient. Achieving a systems-oriented approach to health care requires new concepts, tools, and interventions. We must integrate the science of medicine with the art of clinical practice:

- Take what we know from clinical research about the causes of complex, chronic disease, and change what we do.
- Learn to restore balance in the complex adaptive system that is a human being.

- Develop effective therapeutic partnerships between practitioners and patients.
- Identify the causes of and remedies for each individual's unique expression of chronic disease.

Functional medicine exemplifies just the kind of systems-oriented personalized medicine that is needed to transform clinical practice. The functional medicine model of comprehensive care and primary prevention for complex chronic illnesses is grounded in both science (evidence about common underlying mechanisms and pathways of disease; evidence about the contributions of environmental and lifestyle factors to disease) and art (the *healing partnership* and the search for insight in the therapeutic encounter).

### What is Functional Medicine?

Functional medicine is an approach to health care that conceptualizes health and illness as part of a continuum, in which all components of the human biological system interact dynamically with the environment, producing patterns and effects that change over time. Functional medicine helps clinicians identify and ameliorate dysfunctions in the physiology and biochemistry of the human body as a primary method of improving patient health. Functional medicine is often described as the clinical application of systems biology.

In this model of practice, we emphasize that chronic disease is almost always preceded by a period of declining function in one or more of the body's systems. Returning patients to health requires reversing (or substantially improving) the specific dysfunctions that have contributed to the disease state. Those dysfunctions are, for each of us, the result of lifelong interactions among our environmental exposures, our lifestyle influences, and our genetic predispositions. Each patient, therefore, represents a unique, complex, and interwoven set of influences on intrinsic functionality that have set the stage for the development of disease or the maintenance of health.

To manage the complexity inherent in this approach, functional medicine has adopted practical

models for obtaining and evaluating clinical information that leads to individualized, patient-centered therapies. Functional medicine concepts, practices, and tools have evolved considerably over a thirty-year period, reflecting the dramatic growth in the evidence base concerning the key common pathways to disease (e.g., inflammation, GI dysfunction, oxidative stress), the role of diet, stress, and physical activity, and the effects of environmental degradation (air, water, soil) on health.

In addition, clinicians should keep in mind some basic concepts that have emerged from the prolific research literature. These concepts are altering our view of disease, patients, and all types of health care, including functional medicine:

- **Emergence:** How genes are translated into patterns of health and disease
- **Exposome:** How internal metabolic factors and environment influence gene expression
- **Epigenetics:** The study of heritable changes in gene expression or cellular phenotype caused by mechanisms other than changes in the underlying DNA sequence
- **Nutritional genomics or nutrigenomics:** How different foods may interact with specific genes to increase the risk of common chronic diseases such as type 2 diabetes, obesity, heart disease, stroke and certain cancers
- **Pharmacogenomics:** Prediction of drug response and clinical outcomes, reduction in adverse events, and selection and dosing of drugs based on genotype
- **Proteomics:** The study of the proteome, the complete set of proteins produced by a species, using the technologies of large-scale protein separation and identification
- **Metabolomics or metabonomics:** The study of metabolic responses to drugs, environmental changes and diseases—an extension of genomics (concerned with DNA) and proteomics (concerned with proteins)
- **Sociomics:** How social networks influence health and disease

## Elements of Functional Medicine

The knowledge base—or “footprint”—of functional medicine is shaped by seven core principles:

- Acknowledging the **biochemical individuality** of each human being, based on concepts of genetic and environmental uniqueness
- Incorporating a **patient-centered** rather than a disease-centered approach to treatment
- Seeking a **dynamic balance** among the internal and external factors in a patient's body, mind, and spirit
- Addressing the **web-like interconnections** of internal physiological factors
- Identifying **health as a positive vitality**—not merely the absence of disease—and emphasizing those factors that encourage a vigorous physiology
- **Promoting organ reserve** as a means of enhancing the health span, not just the life span, of each patient
- Functional medicine is a **science-using profession**

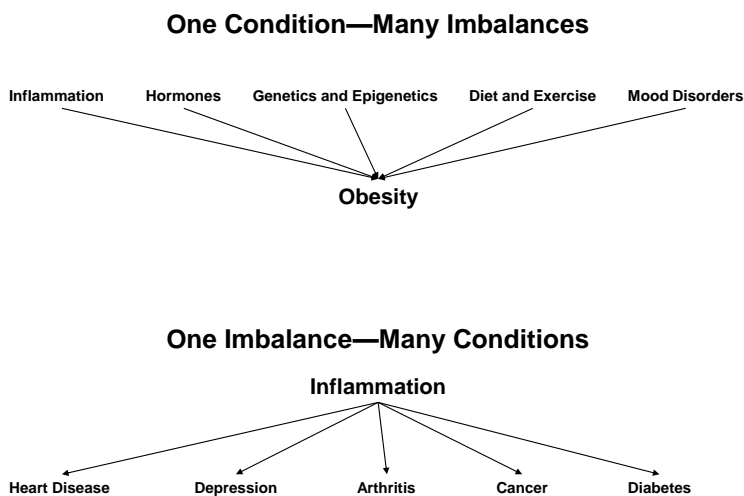
These foundational principles of how the human organism functions—and how its systems communicate and interact—are essential to the process of linking ideas about multifactorial causation with the perceptible effects we call disease or dysfunction. To assist clinicians in understanding and applying this information, functional medicine has adapted and organized a set of seven biological systems in which **core clinical imbalances** are found; these function as the intellectual bridge between the rich basic science literature concerning physiological mechanisms of disease (first two years of medical training) and the clinical studies, clinical experience, and clinical diagnoses of the second two years of medical training. The core clinical imbalances serve to marry the mechanisms of disease with the manifestations and diagnoses of disease. Many common underlying pathways of disease are reflected in a few basic clinical imbalances:

- **Assimilation:** digestion, absorption, microbiota/GI, respiration

- Defense and repair: immune, inflammation, infection/microbiota
- Energy: energy regulation, mitochondrial function
- Biotransformation and elimination: toxicity, detoxification
- Transport: cardiovascular and lymphatic systems
- Communication: endocrine, neurotransmitters, immune messengers
- Structural integrity: subcellular membranes to musculoskeletal integrity

Using this construct, it becomes much clearer that one disease/condition may have multiple causes (i.e., multiple clinical imbalances), just as one fundamental imbalance may be at the root of many seemingly disparate conditions (see Figure 2).

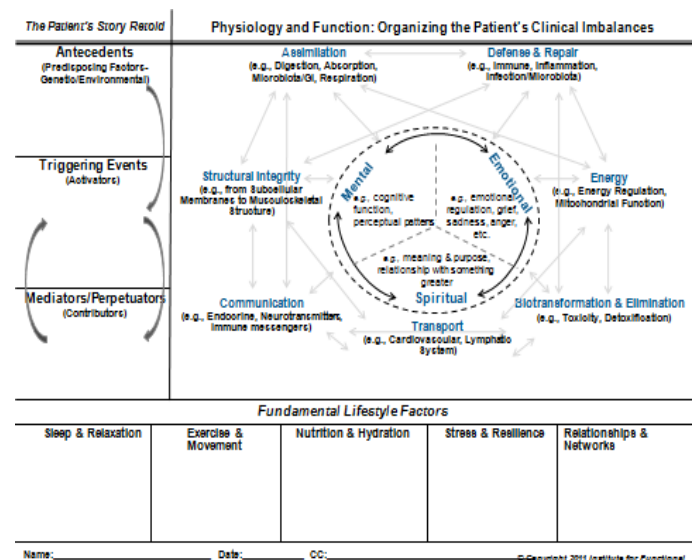
**Figure 2. Core Clinical Imbalances—Multiple Influences**



patient's environmental inputs and in the body's fundamental physiological processes—is the key to restoring health.

### Constructing the Model and Putting it into Practice

Distilling the data from the expanded history, physical exam, and laboratory into a narrative story line that includes antecedents, triggers, and mediators can be challenging. The key to developing a thorough narrative is to organize the patient's story according to the seven clinical imbalances, as shown on the Functional Medicine Matrix Model form (Figure 3). Using this Matrix, functional medicine practitioners evaluate the patient's history, signs and symptoms, physical exam findings, and laboratory results in each of the seven basic biological systems to identify the underlying clinical imbalances (disturbances in physiology and biochemistry). The lifestyle influences are entered across the bottom of the matrix, and the antecedents, triggers, and mediators of disease/dysfunction are entered in the upper left corner. The centrality of the patient's mind, spirit, and emotions, with which all other elements interact, is clearly shown in the figure.



The most important precept to remember about functional medicine is that restoring balance—in the

Within this single complex figure, the most important elements of functional medicine can be seen:



1. identifying each patient's antecedents, triggers, and mediators of disease and dysfunction;
2. discovering the factors in the patient's lifestyle and environment that influence the expression of health or disease;
3. applying all the data collected about a patient to a matrix of biological systems, within which disturbances in function originate and are expressed; and
4. integrating all this information to create a comprehensive picture of what is causing the patient's problems, where they are originating, what has influenced their development, and—as a result of this critical analysis—where to intervene to begin reversing the disease process.

Thus, the Matrix form helps organize and prioritize information, and also clarifies where further investigation is needed. For example, indicators of inflammation on the matrix might lead the clinician to request tests for specific inflammatory markers (such as hsCRP, interleukin levels, and/or homocysteine). Essential fatty acid levels, methylation pathway abnormalities, and organic acid metabolites help determine adequacy of dietary and nutrient intakes. Markers of detoxification (glucuronidation and sulfation, cytochrome P450 enzyme heterogeneity) can determine functional capacity for molecular biotransformation. Neurotransmitters and their metabolites (vanilmandelate, homo vanillate, 5-hydroxyindoleacetate, quinolinate) and hormone cascades (gonadal and adrenal) have obvious utility in exploring messenger molecule balance. CT scans, MRIs, or plain x-rays extend our view of the patient's structural dysfunctions. The use of bone scans, DEXA scans, or bone resorption markers<sup>10,11</sup> can be useful in further exploring the web-like interactions of the matrix. Newer, useful technologies such as functional MRIs, SPECT or PET scans offer more comprehensive assessment of metabolic function within organ systems. It is the process of completing a comprehensive history and physical and then charting these findings on the matrix that best directs the choice of laboratory work and successful treatment.

Once a comprehensive assessment has been made and initial laboratory results have been obtained, the functional medicine practitioner develops a treatment plan that focuses on the areas where the greatest leverage can be found—those sections of the matrix which appear to have the greatest concentration of dysfunctions and which are connected to the most important of the patient's signs and symptoms. A therapeutic plan may involve one or more of a broad range of therapies, including dietary interventions (e.g., elimination diet, anti-inflammation diet, low glycemic-index diet), nutraceuticals (e.g., vitamins, minerals, essential fatty acids, botanicals), lifestyle changes (e.g., improving sleep quality/quantity, increasing physical activity, decreasing stress and learning stress management techniques, quitting smoking), acupuncture, physical medicine (e.g., massage, manipulation), and counseling. Where the clinician does not have the requisite expertise in the prescribed therapy, the patient should be referred to a practitioner who does. Follow-up is done regularly and the patient's progress is tracked and evaluated. (IFM has many tools available for practitioners to use in this complex process; they are provided to attendees at live courses and to IFM members.)

All of this work is done within the context of a therapeutic partnership. The practitioner engages the patient in a collaborative relationship, respecting the patient's role and knowledge of self, and ensuring that the patient learns to take responsibility for his/her own choices and for complying with the recommended interventions. Healing happens in relationship—not in isolation. Learning to assess a patient's readiness to change and then providing the necessary guidance and training and support are just as important as ordering the right lab tests and prescribing the right therapies.

In brief, then, the practice of functional medicine involves four essential components: (1) eliciting the *patient's complete story* during the functional medicine intake; (2) identifying and addressing the challenges of the patient's *modifiable lifestyle factors and environmental exposures*; (3) organizing the patient's clinical imbalances by underlying causes of disease in a *systems biology*



*matrix framework*, and (5) establishing an effective therapeutic partnership between practitioner and patient.

Even using the functional medicine model that has been reviewed here, no single practitioner—and no single discipline—can cover all the viable therapeutic options. Interventions will differ by training, licensure, specialty focus, and even by beliefs and ethnic heritage. However, all healthcare disciplines (and all medical specialties) can—to the degree allowed by their training and licensure—use a functional medicine approach, including integrating the matrix as a basic template for organizing and coupling knowledge and data. So, functional medicine can provide a common language and a unified model to facilitate integrated care. Regardless of which discipline the primary care provider has been trained in, developing a network of capable, collaborative clinicians with whom to co-manage challenging patients and to whom referrals can be made for therapies outside the primary clinician's own expertise will enrich patient care and strengthen the clinician-patient relationship.

This chapter provides a brief introduction to functional medicine. Extensive additional information and training opportunities are available in many forms. The Institute for Functional Medicine encourages all interested practitioners to study the *Textbook of Functional Medicine*, sign up for the 5-day intensive *Applying Functional Medicine in Clinical Practice*, and consider enrolling in IFM's *Functional Medicine Certification Program*. IFM also offers eLearning options, a *Functional Nutrition Course*, and an extensive list of webinars. More information about all of these can be found at [www.functionalmedicine.org](http://www.functionalmedicine.org).



Significant portions of this chapter were excerpted from *21st Century Medicine: A New Model for Medical Education and Practice*, a publication of The Institute for Functional Medicine, and an

excellent source of extensive discussion and references on the development of the acute-care model and the need for a different approach to the chronic disease epidemic. The document is available by download, at no cost, on IFM's website:

[http://www.functionalmedicine.org/ifm\\_ecommerce/ProductDetails.aspx?ProductID=174](http://www.functionalmedicine.org/ifm_ecommerce/ProductDetails.aspx?ProductID=174) .

Other sections have been extracted from the *Textbook of Functional Medicine*, also published by IFM and is available on their website, as well as other materials developed by IFM.

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## 2

# Nutritional Genomics Research And Practice

## Colleen Fogarty Draper, MS, RD, LDN



Nutritional Genomics is the scientific study of the impact of gene polymorphisms on the body's propensity for disease and functional imbalances and nutritional requirements; and the impact of food, nutrients and related, holistic aspects of human lifestyle on gene expression; which also effects gene regulation, transcription, early phase protein production and intermediary markers of metabolism expressed by the metabolome. As this informative area of science progresses, the nutritional genomics term will increasingly encompass nutritional systems biology, including all of the "omics" sciences as they relate to nutrition, lifestyle, life experiences, and other related aspects of the environment that contribute to an individual's wellbeing. This exciting science has tantalized many of us for the last decade providing mechanistic insights which help us better understand impactful nutrition therapies and helps scientists do better research. Although this area of science is still maturing, it is important for the practitioner to start the education process now, to

be prepared for a future in which holistic practice is synonymous with nutritional genomics.

The evolution of nutritional genomics research offers some clues to the root cause understanding necessary to use nutrition therapies in practice to heal, instead of simply treating disease symptoms or prevention of worsening disease. It also holds the potential to fuel the research in practice necessary to design evidence-based intervention strategies. Thus, Western/conventional nutrition practice can be evolved to prevent and heal chronic health issues rather than treat symptoms (e.g., neurodevelopmental disorders are a phenotypic translation of a nutritional catastrophe).

However, in order to promote healing in practice to achieve positive health, we must first agree on a definition of health; particularly since Western medicine is focused on defining disease and this focus has permeated in scientific research efforts and funding. In 1948, the World Health Organization (WHO) ratified a definition of health as the following, "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity"[1].

This definition of health was recently challenged at a conference held in the Netherlands in 2009. The conclusions drawn at that time suggested the definition should be considered more of a concept. Health is really a dynamic state of phenotypic plasticity or resilience and attaining complete wellness is likely un-realistic for many. Thus, the following concept of health was described as, "The ability to adapt and self manage in the face of physical, emotional and social challenges"[2]. In 1985, Antonovsky described a new health term called salutogenesis. Salutogenesis is the study of the origin and cause of health that looks at how to strengthen homeostatic resiliency through creating, enhancing and improving physical, mental and social well-being [3]. So, perhaps, the proposed concept of health could be shortened to "the ability to attain salutogenesis".

In order to understand this salutogenic state of stress resilience and adaptability, it becomes important for us as scientists, researchers and clinicians to be able to assess multiple components of the equation. The first component is genetic susceptibility. Although we know gene polymorphisms, such as single gene polymorphisms (SNPs) only contribute 1% to our knowledge of heritability; and the large number of variants (including approximately 2 million SNPs) identified through genome wide association studies on large numbers of people (as much as 250,000 in some studies) so far explain only 5-10% of heritability for common chronic health issues, such as dyslipidemia, obesity, and diabetes; this offers us a place to start [4].

While it takes millions of years for our genes to change from natural selection, as proposed by Charles Darwin, it takes far less time to impact their expression, either with epigenetic effects that last through generations or accrue over a lifetime, or changes in gene expression which are affected on a daily basis by transcriptional regulation in response to environmental influence. The strongest

environmental influence is diet, however, there are many environmental factors to consider from exercise to stress management to weather and geographic location.

So the first component of the equation is to know an individual's genetic susceptibility. The next step is to understand the mechanistic interactions between this susceptibility, environmental choices (such as, diet and lifestyle) and health plasticity. It is, also, important to know the limitations of this information. That the "missing heritability" in relation to disease risk has not been fully explained due to the need for a better understanding of epistasis (gene x gene interactions – including the newly recognized impact of copy number variants), impact of rare variants, epigenomics interactions, and environmental interactions not yet identified [5].

Ultimately, the outcomes of this equation need to be measured and monitored, which can be done through gene expression analyses (mRNA microarrays), proteomic and metabolomic analyses. For example, urinary metabolite testing is already used by early adopters in nutrition practice to conduct a functional nutrition assessment that identifies early phase markers of metabolic dysfunction that, if left unchecked, will eventually result in a loss of health plasticity and disease will ensue. Recently, researchers have been evaluating the interaction between genes and metabolites. Suhre et al. 2011 identified 25 genetic loci associated with blood metabolite concentrations, accounting for 10-60% of differences in metabolite levels per allele. Disease target associations included cardiovascular disease, diabetes, kidney disorders, gout and Crohn's disease. While those associations discovered were not specifically targeted to particular mechanisms, many new hypotheses for influence of genotype on human metabolic individuality were generated; which hold the potential for future research translatable into practice [6].

Circadian rhythmicity, caloric restriction and gut health are three areas of interest, which hold promise for the future of nutrition therapy in practice. Therefore these areas of research focus will be highlighted in the remainder of this document to give the reader a “taste” of the future potential for scientific applications of nutritional genomics.

### Circadian Rhythms

The human circadian rhythm defines a 24 hour physiological, biochemical, behavioral cycle; affected by availability of light, stress level, eating and sleeping times, temperature and exercise. A greater biological understanding of circadian rhythmicity holds the potential of translatability into clinical practice. However, scientific research is necessary to understand unique, individual, and biochemically different responses to circadian challenges, such as, night shift work or travelling over multiple time zones. These individual differences in response become clear amongst international travelers who seem to vary in their adaptation (i.e., phenotypic resilience) to changes in light, timing of food intake, and geographic location; and shift workers that develop problems with metabolic syndrome and obesity from night eating and excessive caloric intake.

The human master clock resides in the suprachiasmatic nuclei (SCN) located in the anterior part of the hypothalamus in the brain. Every organ/tissue of the body has its own biological clock; and all of these clocks need to be synchronized. In fact lack of synchronization will decrease physiologic adaptability to stress (salutogenesis). The parallel to this would be interconnected train cars which are not moving at the same pace. If this is not corrected, the train will eventually cease to function. In this case, the body can be envisioned as a train.

The United States and many other Westernized countries are now harnessing the power of light

24 hrs/day and could be cause of some chronic disease, particularly in those individuals that are more genetically susceptible to the negative effects of rhythmicity stress.

Major acute health events seem to occur at common times of the day and during particular seasons. For example, according to a study in the Beijing metropolitan area, myocardial infarctions (MI) were found to occur frequently between 8 and 10 AM or 10 and 12 PM[7]. The Second International Study of Infarct Survival (ISIS-2) trial looked at five different geographic regions and found MI incidence increased between 6 AM and 8 AM and peaked between 8 and 11 AM [8]. The Triggers and mechanisms of myocardial infarction (TRIMM) study group found MIs most commonly occurred within 3 hours of waking, between 6 and 9 AM [9]. Another study of medical records from the Beijing Emergency Medical Service found cases of Upper Gastrointestinal bleeding occurred more frequently during the cold months of the year and in the night time hours [10].

Some research suggests insufficient sleep time and shift work negatively affect our circadian rhythms and increase our risk of developing metabolic syndrome, diabetes, heart disease and obesity [11–13]. Additionally, some people are more biochemically sensitive to alterations in their circadian clock than others. The Circadian Locomotor Output Cycles Kaput (CLOCK), gene encodes a transcription factor responsible for modulating human circadian rhythms which affect metabolic alterations. Variations in the CLOCK gene have been linked to binge eating, reduced weight loss success, and the propensity to be a short time sleeper ( $\geq 6$  hrs/day) [14, 15]. The TT genotype of the CLOCK 3111TC variant tends to be more obese, sleep less, with a high saturated fat diet; however, this effect is not seen for those who do not consume a diet high in saturated fat. Also, TT individuals lose less weight

than the alternate genotype [15]. This is related to high ghrelin levels, which seem to translate to excessive food intake during the evening, lethargy in the morning and lower overall physical activity [16]. A sample of 3311 adolescents from 9 European countries reveals adolescents with short sleep duration (less than 8 hours) have higher body mass index values, body fat, waist and hip circumference and fat mass index. Additionally, these adolescents with short sleep duration are more sedentary and watch more TV. Finally, the group ate less fish, vegetables and fruits. While it is difficult to say which issue comes first in the equation, it is interesting that sleep is also playing a role in the overall biochemical wellbeing of the adolescent community [17].

Gastrointestinal motility is, also, rhythmic with most people having bowel movements in the early morning and rarely at night. Gastrointestinal disruptions are common in shift workers and time zone travelers. In fact, the CLOCK gene is expressed in the cells of the colon [18]. Individuals with certain CLOCK gene variations may be more susceptible to gastrointestinal dysfunction because of changes in sleep cycle.

This latest research on sleep calls attention to the importance and opportunity for the holistic practitioner to integrate sleep into the patient/client assessment and treatment plan. It is fundamentally important to understand harmony in the body and its association with nutrition and wellness and the circadian clock; as chronotherapy, an emerging area of personalized practice in which therapy is administered to readjust the circadian clock, becomes a reality.

### Caloric Restriction

Caloric restriction has been shown to delay aging in rodents, extending lifespan by as much as 50%; as well as, enhancing plasticity and

resilience when faced with stress, fitting Machteld Huber's conceptual definition of health [2, 6, 19, 20]. Increased expression of Sirt1 occurs in the presence of caloric restriction and is considered the key controller of the longevity response. Sirt1 is a deacetylase shown to regulate histone modification (an epigenetic effect) and a vast array of physiological functions; including glucose homeostasis, fat metabolism and apoptosis [21, 22]. Nicotinamide adenine dinucleotide (NAD) cofactors play a critical role in regulating CLOCK and Sirt1 gene expression [23]. Sirt1 has also been shown to decrease oxidative stress and increase lipolysis; two pathways that may ultimately prolong life [24–26].

While daily caloric restriction is an effective method to decrease body weight in the short term (and potentially promote longevity in the long-term), many people find it difficult to continue to adhere to a daily restriction. Alternate day diet restrictions offer another option for reducing obesity and risk of other chronic diseases. A 75% energy restriction, on alternate days has been shown to be effective in obese adults, offering a new strategy for weight loss that may promote greater compliance long term. A study of 16 obese subjects who completed a 12-week trial of a 2 week control phase, 4 week alternate day modified fasting (ADMF) "in-house" and a 4 week ADMF, self-selected feeding phase produced an average total of 5.6 +/- 1.0 kg post-treatment; which correlated with expectations in accordance with daily energy restriction. Significant improvement in hunger was seen after two weeks and no compensatory caloric intake was observed on the alternate feed day with participants taking in an average of 95 +/- 6% of calculated energy needs. Significant decreases were also seen in total body fat, LDL cholesterol and systolic blood pressure [27, 28].

The benefits of alternate day diet restrictions do not need to be limited to caloric restriction. In



fact, animal research has shown alternate dietary composition restriction produces benefits to metabolic health. ApoE\*3Leiden mice, considered to be humanized models for atherosclerosis, were used to evaluate and compare the impacts of 4 diet groups: 1) cholesterol free (CON); 2) high cholesterol (HC); 3) an alternate regimen of low cholesterol every other day (ALT); 4) and a daily regimen with cholesterol intake equivalent to the ALT group (MC). The ALT feeding group (low cholesterol diet every other day) experienced most of the beneficial effects of the CON group (cholesterol free daily); including improvements in hepatic and vascular activation and inflammation. Since this study was a cross-over design, cholesterol levels of the ALT group were similar to the HC group during the HC diet, but dropped rapidly after periods of the CON diet, demonstrating an adaptive response to dietary cholesterol intake (i.e., salutogenesis).

Atherosclerosis was reduced by 50% in the ALT group; however, serum cholesterol was still lower in the CON group at study end. Serum Amyloid A (SAA) is a liver-derived inflammation marker, and SAA levels in the ALT group were very comparable to the CON group at study end. NF-kappaB, the inflammatory transcription factor that controls SAA, showed a 4-fold increase in the HC group. However, the NF-kappaB levels of the ALT group were again comparable to the CON group; whereas the MC group experienced a 3-fold increase. These data demonstrate dietary cholesterol has adverse effects on the liver, such as increased inflammation, and alternate cholesterol feeding may reduce or prevent these effects, particularly in the area of inflammation[29]. The obvious next step is to replicate this study in humans to evaluate the realistic effects of these diet strategies. While alternate day diet restrictions produce many benefits and show physiologic adaptability to the positive effects of diet restriction, they are not perfect; but they hold the promise of greater long-term compliance and

success with lifestyle change strategies; and another option for a personalized approach to hyperlipidemia prevention and management.

### Gut Health

The microbiome has its own genome to understand, which needs to adapt to our environment, which affects human gastrointestinal health and wellbeing. Three million genes are present in our intestinal microbiome, which is far greater than the 25,000 genes identified in the human genome [30]! Microdiversity seems to equate to resilience and salutogenesis with less microbial diversity seen at old age. An international comparison of microbiomes was conducted across continents and three enterotypes, groups of microbiota that seem to co-occur, were identified. Further research is needed in order to better elucidate associations between these three distinct groups and clinical and biochemical phenotypes of interest. However, researchers now have a way of grouping the microbiome data to understand how these groups may affect diet response and how other environmental factors interact with these groups to form disease susceptibility phenotypes[31]. Ultimately, we will be able to use enterotype groups in practice to better understand the health trajectory of our patients.

There is a complex and interesting symbiotic interplay between food and nutrition, our microbiota, and its genes. We feed our microbes daily with carbohydrates and, in turn, our microbes facilitate our own carbohydrate digestion and keep our gastrointestinal systems functioning properly. In fact, low carbohydrate intake, including fiber, has been shown to be detrimental to the colonic mucosa, decreasing cancer protective metabolites and increasing hazardous metabolite concentrations, further emphasizing the importance of paying attention to gastrointestinal function in practice[32]. Probiotic supplements and probiotic

enriched foods, such as, fermented vegetables (sauerkraute) and milks (kefirs) are used to improve the status of human microbiota. However, research has shown human microbiota are resilient and may be resistant to change with probiotic supplements having the smallest effect on global microbiota change (1%) followed by specific diet strategies (5%). The largest effect on microbiota composition in the human intestine is through microbial transplantation (up to 100%)[33]. Thus far, gut microbiota seem to be quite stable and are easily restored, so even the small effect of probiotic supplementation has not been shown to last long [34, 35]. Microbial transplantation has shown the greatest effect on restoring gut microbiota. With further research, microbial transplantation may become the therapy of choice to restore a healthy gut [36].

Celiac disease is a partially inherited, life-long intolerance to gluten. The disease was traditionally defined as a gastrointestinal malabsorption disorder but we now recognize that manifestations of the disease are highly variable [37]. It is most certainly an inflammatory-related disorder in which gliadins, toxic peptides in gluten, pass through the epithelial barrier of the intestine generating an immune response that cascades into an inflammatory reaction guided by CD4+T cells bound to HLA DQ2 and HLA DQ8 molecules on antigen presenting cells[38]. The major environmental factor in celiac disease, gluten, found in wheat, barley and rye; was identified 60 years ago when Dr. W.K. Dicke published a paper that described the improvement of symptoms in celiac children when wheat, rye and oat flour had limited availability in the diet, during World War II. Approximately 1% of the global population has received a celiac disease diagnosis (current estimates), for which positive serum antibodies and an intestinal biopsy indicative of villous atrophy are required. However, many celiacs remain undiagnosed; some of whom are likely to have silent disease in which gastrointestinal

symptoms are absent, or other less obvious manifestations; such as neurologic symptoms or dermatitis herpetiformis[38].

Alleles that comprise the HLA DQ2 and 8 phenotypes associated with celiac disease susceptibility were identified over 30 years ago; and celiac disease does not develop unless an individual possesses one of various combinations of these alleles. However, 40% of the population has these genetic markers, and the contribution of the HLA genes to the genetics of celiac disease is less than 50% [39]. The additional contribution to disease manifestation could be additional, unidentified gene x gene interactions or environmental interactions, such as excessive gluten intake over a prolonged period of time.

Genome Wide Association Studies (GWAS) have been conducted to examine additional genetic contributors to disease susceptibility and manifestations. Data have been collected on thousands of celiac patients and controls to compare non-HLA SNP frequencies. Approximately 39 non-HLA celiac disease risk loci have been identified, including multiple genes of obvious immunological functioning [40]. Since individuals with celiac disease are at risk of developing other autoimmune diseases, there is a particular interest in genes shared by autoimmune diseases and celiac disease. Thirty one unique genetic loci have been identified of which 14 are shared between celiac disease and rheumatoid arthritis. These shared genes are also implicated in T cell antigen presentation[41].

It is a common misconception that we wake up one day and have a chronic disease. The body needs to go through a period of progressive dysfunction first, that will ultimately result in disease diagnosis if it is not rectified. For individuals with celiac disease, a life-long, gluten free diet can prevent the development of other auto-immunities, however, quality of life is lower,



despite following a gluten free diet. Thus, it is important we address these issues earlier with better, more comprehensive testing and a greater understanding of some of the changes occurring at an earlier phase of an individual's health trajectory.

Large data sets of genomics, metabolomics, transcriptomics, proteomics, and nutrient biomarker data that crossover ethnicities and geographic regions are needed to account for natural differences in genotype prevalence and environmental influence in order to continue to see scientific progress in nutritional genomics research. Genome wide association studies (GWAS) that cross over continents have been conducted and more are in progress to account for this need. Additionally, researchers such as Jim Kaput are pushing for more international research nodes to participate in and harmonize research protocols to allow for ease of data sharing. The Human Variome Project (HVP) is a worldwide effort to identify all gene variations in the human genome associated with phenotypic variability and human disease risk. Kaput et al., 2010, proposed a collaboration between the HVP and the nutritional genomics research community to harmonize and systematize their research efforts to ensure cross-benefit of novel data and results [42]. Advances in systems biology and genomics research are increasing the feasibility to assess the mechanistic effects of micronutrients on metabolism.

As a result, a central repository of micronutrient data has been developed for scientific researchers to submit and access data, that will aid in further harmonizing and advancing nutritional genomics research efforts [43]. The micronutrient project ensures the environmental impact of nutrition is accounted for consistently on an international level.

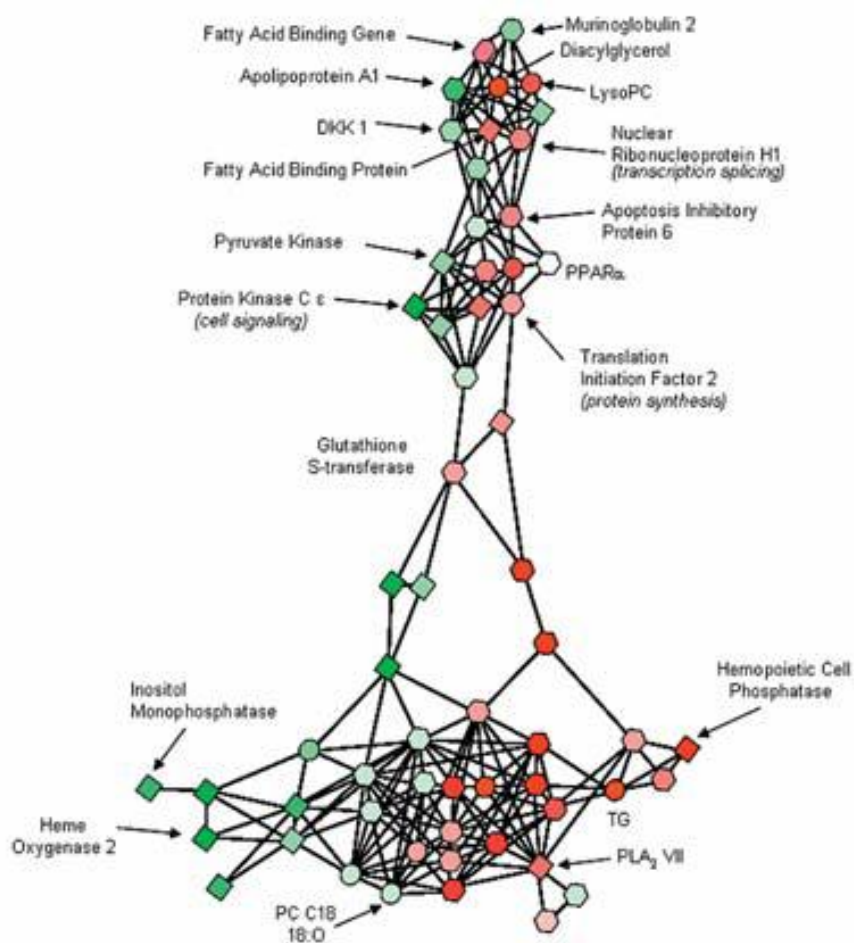
In the near future, data access will change in order to meet the growing needs of nutritional genetics and systems biology research and may

be partially fueled by the wants and needs of individuals with chronic disease desiring the opportunity to get closer to an understanding of the root cause of their health issues. Enterprises, such as Patients Like Me ([www.patientslikeme.com](http://www.patientslikeme.com)), the Personal Genome Project ([www.personalgenomes.org](http://www.personalgenomes.org)), and mandatory data collection in clinical practice, will become part of the health routine and experience for the researcher and the patient.

Is systems biology, of which nutritional genomics is a part, forming a scientific bridge between Western medicine/nutrition and Ancient Eastern traditions? While it is early to formulate this opinion from the scientific literature, there is some evidence to suggest this is the precise direction we are heading. In Chinese medicine, rheumatoid arthritis (RA) fits into the Bi-syndrome grouping, meaning blockage or obstruction. The Bi-syndromes are caused by pathogenic factors categorized as heat, cold, dampness and wind; and are identified by patient inquiry, palpation, pulse and the tongue's appearance. Since RA therapy in Western medicine can lack effectiveness with lots of individual variation present; it can be frustrating for the medical practitioner and the patient. Differences have been identified between RA Cold and Heat patients that can be defined through unique symptomatology (to Western medicine), gene expression and metabolic profiling. Heat patients with RA tend to exhibit more apoptosis, while Cold patients seem to exhibit a better response to biomedical combination therapy. This information will hopefully lead to more personalized therapy [44]. Additionally, common RA symptoms evaluated through Western medical practice (joint pain, swelling, and stiffness) do not contribute to a greater understanding of significant variation amongst patients. In order to categorize RA patients with traditional Chinese medicine Bi-syndromes, significant symptoms include the following: panting, shortness of breath and aversion to cold to define the Cold syndrome; and

restlessness, nervousness, warm feeling, dry mouth and thirst to describe the Heat syndrome [45]. This suggests an alternative method of categorizing this patient population and may provide more personalized, targeted, and effective therapies. Future research in this area should evaluate the use of targeted nutrition therapies to Cold and Heat syndrome associated RA patients as a nutritional genomics approach to strengthen the bridge being built between Western medical research and Eastern Chinese medicine.

right panel is the Neijing Tu, a chart of the body's inner landscape. This picture is found in the White Clouds Taoist temple in Beijing. "The Taoist school of Highest Clarity envisions the body as a complete world onto itself that is also a reflection of the world" [44].



The following is a depiction of systems thinking in Western science and Chinese Taoist traditions. The left panel is a correlation network map. The metabolites, genes and proteins reveal the complex interactions related to atherosclerosis onset. The

In order to present future perspectives on nutritional genomics, this chapter has summarized the definition of health as resilience and salutogenesis, that when applied to practice, can be done so using nutritional genomics scientific

tools. The focus areas of circadian rhythmicity, caloric restriction and gut health and their application to practice have been highlighted, and the approach to and importance of expansive database creation and access has been discussed. Finally, the future expansion of systems biology and nutritional genomics into ancient Chinese medical thinking has been contemplated.

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Colleen is actively committed to the integration of nutritional genomics into dietetics practice as a frequently invited lecturer and writer. Recently, she successfully facilitated the development of a networking relationship between the Dietitians in Integrative and Functional Medicine (DIFM) and Research Dietetics Practice Groups of the Academy of Nutrition and Dietetics (AND) and the International Society of Nutrigenomics and Nutrigenetics (ISNN) in order to strengthen the scientific knowledge base of the dietitian and the integration of practice methodologies into nutritional genomics research. As the Nutritional Genomics Advisor for the DIFM DPG, Colleen is a committee member of DIFM petition for Board Certified Specialty Credentials.

Colleen is experienced in nutrition practice, program/product development, clinical research, and business development and consulting. In private practice, she is passionate about using nutrition therapy to facilitate weight loss, optimize gastrointestinal health, neurologic and hormone functioning and treat food allergies and sensitivities in children and adults. She founded Nugenso

Nutrition and Company, an innovative strategic planning, program development consulting company focused on providing next generation, nutritional genomics solutions for industry, practitioners, and individuals interested in its translation and integration into product portfolio planning, design, and clinical practice. In business, Colleen is passionate about creating products and services that promote and create lifestyle change. The company's recent focus is the development and design of a nutritional healing platform for the spa industry. She also works with the Optimal Health and Prevention Research Foundation to research, design, and direct the Personalized Nutrition and Genomics Program. Colleen has spent several years in biotechnology directing nutritional genomics clinical research and product design. As Program Director of Nutrigenomics at Interleukin Genetics, her experiences ranged from directing the design of a weight management nutritional genetic test to clinical research trials, program leadership and planning/forecasting, and other translational science initiatives.

Colleen is interested in furthering the research necessary to make nutritional genomics in practice a reality. As a result, she is pursuing coursework in preparation for her PhD; and was recently selected as a recipient of the AND Foundation's Mary Swartz Rose Memorial Graduate Scholarship sponsored by the International Life Sciences Institute (ILSI).

Colleen is an alumni member of the Functional Medicine Nutritionist Advisory Board for the Institute for Functional Medicine; an active member of the AND; the Nutritional Genomics Advisor for the Dietitians in Integrative and Functional Medicine Dietetic Practice Group; the Nutritional Genomics Advisor for the Food as Medicine Program of the Center for Mind-Body Medicine; and a member and RD advisor to the (ISNN).

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#### Nutrition and Genomics Glossary of Terms



- **Nutritional Genomics** concerns the effect that changes in our genes have on our risk of disease and dysfunction that can be mitigated by nutritional intervention as well as the impact our food, nutrition, stress, and toxins have on the expression of our genes. It is the umbrella term that includes **nutrigenetics**, **nutrigenomics**, and **nutritional epigenomics**. However, the term is broadening to mean nutritional systems biology which includes all of the “omics” technologies; proteomics, transcriptomics, metabolomics, etc.
- **Nutrigenetics** is focused on the impact that changes in our genes (also referred to as polymorphisms) have on our potential health trajectory, which is strongly influenced by food, nutrition, stress, and toxins.
- **Nutrigenomics** is focused on the impact of diet and lifestyle factors, such as food, nutrition, stress, and toxins, on gene expression and the resulting effects on the human system that can be measured scientifically.
- **Nutritional Epigenomics** concerns changes in gene expression influenced by modifications to DNA and its associated proteins without changing the nucleotide sequence of DNA, where the genetic information is stored. These epigenomics changes affect gene expression and can also be inherited.
- **Allele** – An alternate form of a gene.
- **Phenotype** – The physical, biochemical, and physiological characteristics determined by genotype and environment.
- **Single Nucleotide Polymorphism (SNP)** – The occurrence together in a population of two or more genetically determined alternative phenotypes, each with appreciable frequency (each occurs in >1% of the population).
- **Homozygous** – Two copies of the same nucleotide; CLOCK 3111 TT.
- **Heterozygous** – One copy of each nucleotide; CLOCK 3111 CT.
- **Plasticity** – The adaptability of an organism to changes in its environment or differences between its various habitats.

# 3

## Functional Diagnostics: Redefining Disease

### Mark Hyman, MD

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

*Jeffrey Bland*

The history of 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. Linnaeus, the 18<sup>th</sup> century Swedish scientist known for the naming and classification of plant species, developed 11 categories of disease – painful disease, motor disease, blemishes and so on. Hippocrates categorized disease into the four humors: black bile, yellow bile, phlegm and blood. Tibetans distinguish 404 diseases divided into four 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 late 19<sup>th</sup> and early 20<sup>th</sup> centuries, doctors and scientists shifted from a symptom based diagnostic model to an anatomical view of disease, which lead to the first international classification of disease in the 1850's and segregated disease into 140 categories including "visitation from God". The 10<sup>th</sup> 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, CT scan, MRI; 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,<sup>i</sup> pre-hypertension,<sup>ii</sup> pre-dementia (MCI),<sup>iii</sup> pre-autoimmune disease.<sup>iv</sup> 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 together 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 that we may 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 not pathology; on networks of physiology, not organ systems; on assessment of more subtle changes on the continuum of dysfunction and not 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 21<sup>st</sup> century: the functional somatic syndromes (CFIDS, FMS, PMS, MCS, etc.), obesity, diabetes and cardiovascular disease, depression, autism, attention deficit, allergies, asthma, respiratory disease, autoimmune disease, digestive disorders (GERD, IBS), migraines, back pain and more.

In the assessment of 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 face a patient viewing 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 ICD as “diseases” can be viewed through the prism of two questions, five causes of illness and seven key concepts. 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 remaining topology can be traversed with a new compass. It is the compass of Functional medicine, or the clinical application of molecular systems biology.

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.

## The 2 Questions

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

## The 5 Causes of Illness: The Environment

1. Toxins (biologic, elemental and 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 (SAD or standard American diet)



## The 7 Core Physiologic Systems and Clinical Imbalances

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

1. Hormonal and neurotransmitter imbalances
2. Oxidation–reduction imbalances and mitochondriopathy
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

In a patient encounter in this new territory of illness, data is analyzed differently. Rather than a reductionist 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 homeo-dynamic response to underlying functional imbalances. Symptoms are the body's attempt to re-establish balance, 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 symptom suppression.

### Functional Diagnostics: Finding Your Way Through Imbalance

A new framework for diagnostic evaluation may 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 (for example, 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 through the lens of these systems, supplemented by “functional diagnostics” allows the clinician to answer the two questions essential for guiding therapy. For each physiological system, the questions of what are the root causes (toxins, infections, allergens, stress, poor diet), and what is missing required 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 history, however selective use of functional diagnostic testing can refine the clinical approach. How might we look at the role of testing in this new web like model?

### Functional Diagnostics through the Matrix of Functional Medicine: A Sampler

#### Nutritional Assessment

- Methylation: homocysteine, methylmalonic acid (folate and
- B12 status)
- Iron status (transferrin saturation, ferritin, serum iron, total iron binding capacity)
- 25 OH vitamin D
- RBC magnesium
- Plasma zinc
- Alkaline phosphatase (Zn status)
- MCV, MCH (folate, B12 status)
- Genomics: MTHFR (methylation), VDR (vitamin D) polymorphisms

#### Hormonal Assessment

- Insulin Response (glucose tolerance with insulin) and hemoglobin 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 (insulin like growth factor-1), adrenal (DHEA-S)
- 24 hour urinary cortisol
- Osteoporosis assessment- PTH (parathyroid hormone), ionized Ca, serum protein electrophoresis

### Inflammation/Immune Function

- High sensitivity-C-reactive protein
- Fibrinogen
- Complete blood count (CBC) – 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 (anti-CCP) antibodies, etc.
- Infection screening (serology, PCR – polymerase chain reaction)
- Natural killer cell function
- Immunoglobulins
- Lymphocyte Analysis

### Digestive Function

- Helicobacter pylori serum antibody or stool antigen
- Helicobacter Pylori breath test
- Small bowel bacterial overgrowth breath test
- Stool for ova and parasites
- CBC – differential (neutrophil/lymphocyte ratio)

### Detoxification Function

- Hepatic function (NASH, drug reactions)
- Whole blood or RBC metals (Hg, Pb, Ar, etc.)
- Genomics: GSTM1 (glutathione), ApoE (apolipoprotein E polymorphisms)

### Emerging Functional Diagnostics

#### Nutritional Analysis

- Vitamin and mineral assessment
- Essential fatty acid analysis
- Amino acid analysis (blood, urine)
- Organic acids (B vitamin status, etc)

#### Hormonal Assessment

- Adrenal stress index (saliva cortisol)
- Estrogen metabolism and detoxification – urine, blood, saliva
- Salivary sex hormone assessment
- Bone resorption assays
- RMR (resting metabolic testing)
- DEXA body composition and bone density
- Heart rate variability – autonomic function

### Inflammation/Immune Function

- Allergy Testing – IgG and IgE antibodies to foods, and environmental allergens
- Gut immunology: EPX (eosinophil protein X), calprotectin in stool
- Microbial analysis (virus, bacteria, ticks, parasites, worms, etc.)

### Digestive Function

- Digestive stool analysis
  - Digestive enzyme function, microbiology, absorption, immune function, metabolic function and microbial analysis with culture or PCR
- Intestinal permeability
- Lactulose:mannitol challenge
- Urinary polypeptides (gluteo/caseomorphins)
- Urinary dysbiosis markers (Clostridia, yeast,

small bowel bacterial overgrowth)

### Detoxification Assessment

- Hair analysis: methylmercury (fish)
- Provocation/chelation challenge: heavy metals
- Detoxigenomics: Phase 1 and Phase 2
- Blood and urine testing for pesticides, PCB's, solvents, parabens and phthalates
- Mycotoxin antibody assessment
- Visual contrast sensitivity
- Gamma glutamyl transferase

### Mitochondrial Function/REDOX

- Organic acids (fat, carbohydrate and Krebs cycle metabolites)
- V02 max – Cardiometabolic Testing
- Lipid peroxides
- 8 OH-2DG (DNA adducts)

### Depression or Imbalance? A Clinical Case History

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

J.P. was an 18 year old young 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, and canker sores, cracking at the corners of his mouth, acne on 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 has been on Paxil for 4 years when he gained 27 pounds and had increased refined carbohydrate and sugar cravings. Other symptoms noted included itchy ears, and white spots on his nails.

His past history included full term pregnancy 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 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 non-smoker, 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 min a day on the treadmill and 1-2 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 pounds); his temperature was 95.5 degrees F. Other than severe acne vulgaris, chelosis, his physical exam was normal.

Nutritional laboratory assessment revealed vitamin D deficiency (25 OH vitamin D 17 ng/ml – nl 30-100), severe omega 3 fatty acid deficiency with low ALA (alpha linolenic acid), EPA (eicosapentanoic acid), and DHA (docosahexaenoic acid), and an omega 6 fatty acid deficiency of GLA (gamma linolenic acid). Organic acids revealed deficiency of B6 (xanthurenate, kynurenate elevation), B12 (methylmalonic acid) and deficiency markers for CoQ10, biotin and B vitamins.

Hormonal evaluation revealed “sub-clinical” hypothyroidism with elevated thyroid peroxidase antibodies, thyroid stimulating hormone 2.55 mIU/L (nl 0.5-3.5), normal free thyroxine (T4) of 1.1 ng/dL, and low free triiodothyronine (T3) of 281 pg/dL (nl 287-455). He also had hyperlipidemia with total cholesterol of 232 mg/dL, and LDL of 164 mg/dL, an HDL of 42 mg/dL and triglycerides of 130 mg/dL and an elevated lipoprotein (a) of 209 nmol/L (nl <

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 (nl < 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 Q10, magnesium, and lipoic acid.

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

We asked two simple questions: what did this young man need to get rid of that was impeding his health, and what did he need to get or receive that he was missing? And then from asking how this affected his core clinical physiologic systems we learn the following.

### The Core Clinical Imbalances: Networks of Dysfunction

He was **nutritionally** depleted of vitamin D (seasonal depression<sup>v,vi</sup> and impaired immunity<sup>vii</sup>), as well as deficient in omega 3 fats (depression<sup>viii</sup> and acne), B12<sup>ix</sup> and B6<sup>x</sup> (depression and fatigue), B vitamins (chelosis, B vitamin deficiency markers on organic acids), and zinc based on his impaired immunity, acne, and white spots on his

nails.

His **hormones and neurotransmitters** were out of balance with a 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<sup>xi</sup>), and he was severely hyperinsulinemic (acne<sup>xii</sup>, depression<sup>xiii</sup>, weight gain, carbohydrate cravings) and had dyslipidemia with a low HDL, high triglycerides and high LDL (from insulin resistance).

His **immune imbalances** included elevation of IgG anti-gliadin antibodies (fatigue, depression<sup>xiv</sup>, hypothyroidism<sup>xv</sup>, acne) and IgG antibodies<sup>xvi</sup> to dairy, wheat and yeast. His canker sores supported the diagnosis of gluten intolerance.<sup>xvii</sup>

**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<sup>xviii</sup> 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's Missing

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

Then we **replaced what was missing** that he 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 B12), mitochondrial support (coenzyme Q10, carnitine, lipoic acid), omega 3 fatty acids, detoxification support (N-acetylcysteine), probiotics, protein kinase modulators<sup>xix</sup> 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 two months of treatment and eliminated his carbohydrate cravings.

So what can we say about his “diagnosis”? Was the cause of his symptoms “depression”, “acne vulgaris”, and “hyperlipidemia”? Did he need antidepressants, antibiotics and statins? Or perhaps he was 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)? And was he missing a few “ingredients” or raw materials needed to thrive (thyroid hormone, whole foods, omega 3 fats, vitamin D, zinc, methylation support (B6, B12, 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, exam and reframing diagnostic evaluation to identify impediments to health, assess function, and imbalance rather than pathology is a better compass for finding our way through the 21-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 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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**Mark Hyman** has dedicated his career to identifying and addressing the root causes of chronic illness through a groundbreaking whole-

systems medicine approach known as Functional Medicine. He is a family physician, a four-time *New York Times* bestselling author, and an internationally recognized leader in his field. Through his private practice, education efforts, writing, research, advocacy and public-policy work, he strives to improve access to Functional Medicine, and to widen the understanding and practice of it, empowering others to stop managing symptoms and instead treat the underlying causes of illness, thereby also tackling our chronic-disease epidemic.

Dr. Hyman is Chairman of the Institute for Functional Medicine, and was awarded its 2009 Linus Pauling Award for Leadership in Functional Medicine. He is on the Board of Directors of The Center for Mind-Body Medicine, and a faculty member of its Food As Medicine training program. He is also on the Board of Advisors of Memhet Oz's HealthCorps, which tackles the obesity epidemic by “educating the student body” in American high schools about nutrition, fitness and mental resilience. He is a volunteer for Partners in Health with whom he worked immediately after the earthquake in Haiti and continues to help rebuild the health care system there. He was featured on *60 Minutes* for his work there. Dr. Hyman has testified before the White House Commission on Complementary and Alternative Medicine, and has consulted with the Surgeon General on diabetes prevention. He has testified before the Senate Working Group on Health Care Reform on Functional Medicine, and participated in the White House Forum on Prevention and Wellness in June 2009. Dr. Hyman was nominated by Senator Tom Harkin for the President's Advisory Group on Prevention, Health Promotion and Integrative and Public Health, a 25-person group to advise the Administration and the new National Council on Prevention, Health Promotion and Public Health.

With Drs. Dean Ornish and Michael Roizen, Dr. Hyman crafted and helped to introduce the *Take Back Your Health Act of 2009* into the United States Senate, to provide for reimbursement of lifestyle treatment of chronic disease. He continues to work in Washington on health reform, recently testifying before a Congressional hearing

on Functional Medicine, nutrition and the use of dietary supplements.

Through his work with corporations, church groups, and government entities, such as CIGNA, the Veterans Administration, Google, American Express and Saddleback Church, he is helping to improve health outcomes and reduce costs around the world. He initiated and is a key participant in the ongoing development of a faith-based initiative that enrolled over 14,000 people at Saddleback Church in a healthy lifestyle program and research study. In recognition of his efforts, he was recently awarded The Council on Litigation Management's *2010 Professionalism Award*, citing individuals who have demonstrated leadership by example in the highest standard of their profession. He also received The American College of Nutrition *2009 Communication and Media Award* for his contribution to promoting better understanding of nutrition science. He has been featured on *The Dr. Oz Show*, *60 Minutes*, *Larry King Live*, CNN, and MSNBC.

Dr. Hyman is founder and Medical Director of The UltraWellness Center in Lenox, Massachusetts, where he directs a team of physicians, nutritionists and nurses who utilize a comprehensive approach to health. Before starting his practice, he was co-Medical Director at Canyon Ranch Lenox, one of the world's leading health resorts. While at Canyon Ranch, he co-authored the *New York Times* bestseller *Ultraprevention: The 6-Week Program That Will Make You Healthy for Life* (Scribner) – winner of the Books for a Better Life Award honoring the best self-improvement books each year. He has since written *UltraMetabolism: The Simple Plan for Automatic Weight Loss*, and a companion public television special. His latest book and PBS special, *The UltraMind Solution*, a comprehensive approach for addressing the causes of mental illness and cognitive disorders, was released in January 2009. *The Blood Sugar Solution* book and companion PBS special will be released in March 2012, addressing the global epidemic of obesity, diabetes and cardiovascular disease.

Dr. Hyman graduated with a B.A. from Cornell University, and graduated magna cum laude degree from the Ottawa University School of

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# 4

## The Integrative and Functional Medicine Nutrition Therapy Radial: An Emerging Tool for Practice

**Kathie Madonna Swift, MS, RD, LDN**



The Integrative and Functional Medicine Nutrition Therapy (IFMNT) Radial is a conceptual framework for clinical practice that allows for the evaluation of complex interactions and interrelationships that influence health and healing.

The Personalized Nutrition Care Process, including assessment, diagnosis, intervention, monitoring, and evaluation, is centrally positioned in the Radial. Food is a determining factor in health, as noted by its predominant place in the core. It provides the critical biological information that influences, and is influenced by, the other areas of the Radial, notably genes, lifestyle, environment, and precipitating factors that impact whole systems dynamic balance.

The five spheres of the Radial include: Lifestyle; Systems (signs and symptoms); Biomarkers; Metabolic Pathways/Networks; and Core Imbalances. Surrounding the Radial are triggers that can disrupt dynamic balance, such as food allergens and intolerances; negative thoughts and beliefs; environmental exposures; and pathogens.

**Lifestyle:** Lifestyle medicine honors the multiple factors that affect an individual's health and susceptibility to disease. These factors include culture and traditions, socioeconomic, movement/physical activity, spirituality, natural environment, dietary factors, supplement use, and more. Health-promoting lifestyle practices can reduce the risk of chronic disease development and progression. A thorough assessment should consider the whole foods that are aligned with the cultural practices of the individual. These are important considerations in developing a personalized, meaningful, and transformative eating plan to optimize health and support healing.

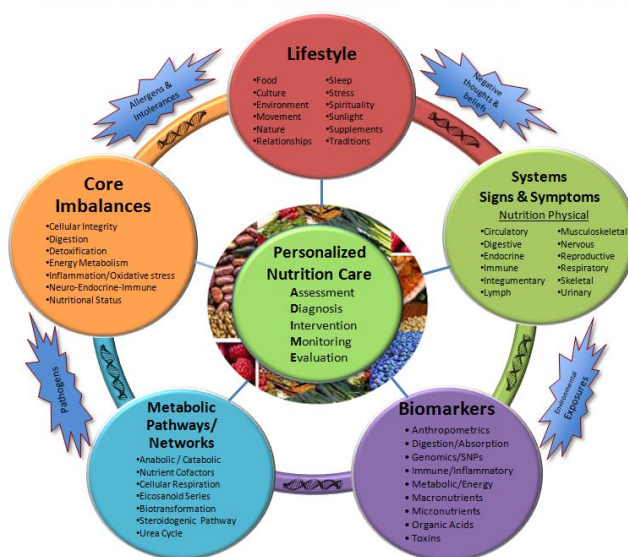
**Systems, Signs & Symptoms:** Nutritional systems biology fosters a deeper understanding of biological



systems and how they interact with each other and the surrounding environment. A systems-level understanding is required to understand the whole person and his or her relationship to health or disease. A “nutrition physical” is used to identify specific signs and symptoms that provide clues to candidate nutrients that may be insufficient in the person’s diet and contribute to compromised health. A full understanding of physical findings and the potential nutrient impairments and how they impact the individual on multiple levels (molecular, cellular, organs, systems and networks) is essential to optimize function and promote well-being.

integrative and functional medicine approach evaluates the function of the pathways and determines, via biomarker analysis, the nutritional support that is needed to improve metabolic performance. Pathways are generally dependent on enzymes, and enzymes have co-factors, which commonly include vitamins and minerals. An IFMNT practitioner evaluates the many repercussions due to impairments in metabolic pathways and targets nutritional therapies accordingly.

Integrative & Functional Medical Nutrition Therapy (IFMNT) Radial



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**Biomarker:** Biomarkers are physiological indicators derived from multiple systems and pathways that impart signals that verify health or reveal functional distress. Nutritional biomarkers can be determined in saliva, blood, urine, stool, or other tissues. Some examples include salivary hormone levels, urine organic acids, stool pathogens, and nutrient levels. Laboratory assessment of biomarkers is helpful to identify functional impairments that may be amenable to nutritional therapies.

**Metabolic Pathways:** A free flow of metabolic pathways is important for optimal human functioning. It is an orchestrated, constant, and collaborative breakdown and rebuilding. An

**Core imbalances:** Core clinical imbalances underlie various disease states. These imbalances include disruptions in cellular integrity, digestion, detoxification, energy metabolism, neuro-endocrine-immune function, and nutritional status and promote inflammation and oxidative stress. Multiple factors, such as pathogens, allergens, infections, nutritional insufficiencies and deficiencies, toxins, negative thoughts and beliefs, and stress, interact with genes and the environment contributing to dysfunction. Signs and symptoms arise that can be detected through a comprehensive nutrition physical and laboratory assessment. Improving balance in the individual’s environmental inputs and in the body’s fundamental physiological processes is essential to restoring health and optimizing healing.

The IFMNT Radial is a valuable clinical tool for 21<sup>st</sup>-century health care. It is a dynamic compass that integrates both evidence-based and practice-based concepts. It allows the clinician to draw from the individual's unique story and offers a whole systems process to prioritize and personalize nutrition therapy.

**Kathie Madonna Swift** is a leading educator, innovator and practitioner in the field of integrative nutrition and founder of SwiftNutrition.com. She was recently named by Today's Dietitian as one of the top Registered Dietitians in the country who are "making a difference". Kathie was also featured in the ebook, Top 10 Nutrition Pros Share Their Secrets because of her significant accomplishments in holistic nutrition.

Kathie has been the core curriculum consultant and co-designer of Food As Medicine since the programs founding in 2001. She is the Chief Nutrition Advisor for [www.myfoodmyhealth.com](http://www.myfoodmyhealth.com), an online program that provides customized meal plans for individuals with various health conditions, and created [www.myfoundationdiet.com](http://www.myfoundationdiet.com), a gluten and dairy free food plan and a FODMAPs friendly eating plan available through [www.myfoodmyhealth.com](http://www.myfoodmyhealth.com).

Kathie also shares her passion for the power of food as a teacher of Healthy Living Programs at Kripalu Center for Yoga and Health in Stockbridge, MA. She is the Senior Nutrition Advisor for the Optimal Health and Prevention Research Foundation in San Diego, California.

Kathie spearheaded the pioneering functional medicine program at Canyon Ranch in the Berkshires, where she served as Nutrition Director for more than a decade and created the "Nutritional Intelligence" dietary guidelines which were presented at the White House Commission on Complementary and Alternative Medicine Policy. In 2005, Kathie joined Dr. Mark Hyman to help establish the UltraWellness Center, where she was the Nutrition Director for three years and continues to practice today, working with individuals with chronic, complex health problems.

Kathie is on the faculty at Saybrook University as an Instructor in the country's first graduate

program in Mind Body Medicine. She also teaches for the graduate program in Nutrition and Integrative Health at Tai Sophia Institute.

Kathie sits on the Scientific Advisory board for Free and Clear Mind Body Program for Corporate Wellness, the Advisory Board for the Integrative Healthcare Symposium, Martha Stewarts Whole Living Magazine and is an alumni of the Nutrition Advisory Board of the Institute for Functional Medicine. She served as the inaugural Chair of Dietitians in Integrative and Functional Medicine (DIFM), a dietetic practice group of the Academy of Nutrition and Dietetics representing dietitians in holistic, complementary and alternative medicine. Kathie also served as a member of the Standards of Practice/Standards of Professional Performance (SOP/SOPP) for Integrative RDs. She has participated in Nutrition Roundtables at the Harvard School of Public Health and participated in medical school education programs at Georgetown University Medical School and Johns Hopkins University School of Medicine.

Kathie serves on the editorial board for *Integrative Medicine: A Clinician's Journal* and has been a scientific reviewer for *Alternative Therapies in Health and Medicine*. Her articles and interviews have been published in *Nutrition in Clinical Practice*, *Experience Life*, *Yoga Journal*, *Healing Lifestyles and Spas*, *Body + Soul*, *Alternative Medicine*, *USA Today*, *Martha Stewart's Whole Living*, *Epicurious*, *CNN*, and others.

Kathie recently co-authored a chapter on adverse food reactions in Krause's Food and the Nutrition Care Process, Elsevier, 2012. She is also the co-author of *The Inside Tract: Your Good Gut Guide to Great Digestive Health* with Gerard E. Mullin, MD, Rodale Press, 2011.

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## 5 Integrative And Functional Lab Tests

### Elizabeth Redmond, PhD, MMSc, RD, LD

Integrative and Functional Medicine is patient-centered and health-oriented, and embraces the use of all appropriate therapeutic approaches whether they originate in conventional or alternative medicine [1]. Functional laboratory testing, which is an essential part of integrative and functional medicine, helps to identify core physiological and metabolic issues that may appear decades before disease symptoms. Advances in clinical laboratories and medical science have brought tremendous growth in laboratory testing that goes beyond standard markers [2]. Functional laboratory assessments involve the evaluation of even the most minor symptoms, which can indicate the beginning of a more serious cascade. This can be thought of as a 'snowball' effect in which seemingly minor imbalances within the body produce a cascade of biological triggers that can eventually lead to chronic illness. Functional laboratory assessment can catch the snowball before it leads to a diagnosed disease, when it can be treated early in the process. Core



nutritional imbalances are an essential part of integrative and functional medicine and include digestion, detoxification, energy metabolism, inflammation, neuro-endocrine-immune, nutritional status, oxidative stress and structural integrity. Testing can provide biomarkers that identify impairments in metabolic pathways, and clarify findings of a nutrition focused physical that can be an early warning of core imbalances [1].

The Triage theory as proposed by Bruce Ames, proposes that DNA damage and late onset of disease are a consequence of a triage allocation response to micronutrient scarcity [3]. Natural selection favors short-term survival at the expense of long-term health [4, 5]. For example, with limited vitamin K, the body will ensure the blood does not clot and will then only use vitamin K for bones once its priority has been taken care of. The theory also proposes that micronutrient triage is done in part through an adjustment of the binding affinity of proteins for required micronutrients. Thus an evaluation of nutrient status, vitamins, minerals, fatty and amino acids, as well as functional assessments, are all

considered to be a part of a full integrative and functional laboratory assessment [1]. While diet records can provide estimates of mean and median intakes of nutrients, actual levels can be altered due to many factors, including nutrient quality of food or supplements, digestion and absorption, disease states, age, medications, activity level, genetics, biological differences, environment or stress. Any of these can lead to insufficiencies even in the face of perceived adequate intake, which can result in changes in cellular function before clinical symptoms develop. In later stages, physiological function can be impaired, resulting in symptoms or a diagnosed pathology. Utilizing functional laboratory testing can help identify insufficiencies before they progress.

Another nutrient effect is that the binding affinity of enzyme responsiveness to co-factors can be adjusted by the level of co-factors within the system. An example is that all newborns get tested for inborn errors, including phenylketonuria (PKU; phenylalanine hydroxylase deficiency). The test is done to identify frank deficiencies of the enzyme, not optimal function. Thus there may be infants who have an impaired enzyme function, but who are not identified as having an issue [6]. These enzymes may become impaired later in life. Let's use the example of a patient with an impairment of the phenylalanine hydroxylase (PAH) enzyme which can result in an elevated concentration of L-phenylalanine in serum, but not an official diagnosis of PKU [7]. Such a person would not experience the frank clinical symptoms of PKU, although they may experience symptoms due to the impairment of the pathway, especially as a result of physiologic stress or environmental exposures. Research has found co-factor responsiveness forms of this condition which are more prevalent than previously thought, particularly in patients with mild hyperphenylalaninemia [8–10]. It would be rare for conventional medicine to relate specific symptoms back to an impaired enzyme. Functional laboratory assessment generally

throws a wide net and may include the serum amino acid precursors phenylalanine and tyrosine, nutrient cofactors iron, vitamin B6 and copper, and precursor end-products, such as vanilmandelate (the product of epinephrine and norepinephrine catabolism) and homovanillate (the product of dopamine catabolism). Targeted supplementation of co-factors has been shown to increase the function of the enzyme and enable it to complete its hydroxylation reaction. Thus assessing all markers of a metabolic pathway can help to identify possible enzyme impairments.

Functional laboratories have taken the lead in offering tests to clinicians practicing integrative medicine. This includes offering many non-invasive tests, such as finger sticks, urine, saliva and stool tests. Finger stick capillary whole blood or blood spot testing on dried filter paper is a well-established technique that has been used for more than 40 years. The filter paper is manufactured to give accurate and reproducible absorptions and consistent chromatographic effects. The most common blood spot test of course is glucose, but there are also tests for HIV, amino acids, celiac, vitamin D, and immune reactions to foods. A specific example of a blood spot tests and its use is the blood spot fatty acid test which helps give clinicians a summary of their patient's predominant fatty acids. Research has found a correlation ( $r=0.82$ ) of fatty acid levels of eicosapentanoic acid (EPA) and docosahexaenoic acid (DHA) in cardiac cells to those in red blood cells (RBC) from a finger stick. The sum of the EPA+DHA in a blood spot finger stick has been termed the Omega-3 index and serves as a surrogate marker for cardiac omega-3 fatty acid levels and aids the clinician in regulating EPA/DHA supplementation or diet changes [11, 12]. Fatty acid assessments and supplementation has also been used in monitoring maternal and infant DHA levels, and in patients with ADHD, depression, learning disabilities, irritable bowel syndrome and fibrocystic disease.

Urine is another specimen type that is easy to collect. There are more than 100 different tests that can be done on urine. Urinary organic acids are frequently used by functional and integrative clinicians to reveal nutritional and metabolic impairments. Organic acids include markers of oxidative damage, neurotransmitter breakdown products, intestinal microbial activity, and may identify impairments related to specific nutrients [13, 14]. Organic acids are metabolic intermediates that may be able to be used to evaluate the function of metabolic pathways. Canada's government has started the Human Metabolome project [www.metabolomics.ca](http://www.metabolomics.ca), which is the next step following the U.S. Human Genome project. The Human Metabolome project is a significant tool in the use of metabolomics. Metabolomics is a new-born cousin to genomics and proteomics.[15]

Salivary assessments are another tool used in integrative and functional medicine; they are used to evaluate stress markers, antibodies, drugs and hormones [16]. While conventional laboratory assessment is used to diagnose Cushing's syndrome, functional laboratory tests are used to evaluate adrenal function. Salivary measurements of cortisol and dehydroepiandrosterone (DHEA) can help to evaluate level of demand of cortisol. An increased level of cortisol and a decreased DHEA-S, or a decrease in the DHEA-S/cortisol ratio can be an indicator of chronic stress or increased fight or flight. Integrative clinicians would then use varying interventions to help ameliorate the stress-induced fatigue [17].

Integrative and functional clinicians additionally rely on stool testing to identify over-all gastrointestinal function. The tests can evaluate status of beneficial or predominant bacteria, SCFAs, pathogens, parasites, yeast/fungi, digestive enzymes and immune status [18–21]. Stool tests are easily collected by the patient; newer DNA tests make only a single sample necessary and

are considered more accurate. The stool test can be a great addition for patients undergoing a colonoscopy for specific GI symptoms. In patients who are found to have a clean colonoscopy, the assessment done in a stool test often helps to guide further clinical treatment. The case study below illustrates such a case.

#### Case Study



RT is a 58 year old female who presented with fatigue. The patient noted she had been taking an OTC PPI (proton pump inhibitor) for acid reflux for several years. Diet and health history evaluations found that the patient ate adequate amounts of protein, vitamins and minerals. Conventional laboratory tests revealed the patient had a low albumin, vitamin B12, ferritin and hemoglobin. Functional laboratory testing showed low and low-normal levels of individual amino acids and minerals. Stool testing also identified low fecal elastase 1, a marker of impaired exocrine pancreatic function. Adequate stomach acid is needed for the breakdown and digestion of proteins into amino acids, as well as minerals and B12. Inadequate stomach acid can lead to impaired absorption. The IOM currently recommends older adults take extra B12 because stomach pH becomes higher as people age.

#### Significant Laboratory Results

Hemoglobin 10 % – low and considered a marker of anemia  
 Albumin– 2.8 g/100ml – indicates poor nutritional state – from inadequate protein intake  
 Plasma amino acids: The majority are low: methionine, tryptophan, phenylalanine, histidine and threonine are below the reference interval. (see table below)

Minerals: All the nutrient elements are low-normal, except selenium. Mineral absorption requires an acidic environment. (see table below)

Amino Acid-Plasma	Results	95% Reference Range
Lysine	114 - low normal	94-277
Methionine	10 - low	12-47
Tryptophan	23 - low	30-75
Isoleucine	39	29-111
Leucine	99	59-197
Valine	172	128-373
Phenylalanine	29 - low	36-85
Histidine	39 - low	52-108
Threonine	37 - low	57-208
Arginine	25 - low normal	25-140
Taurine	37	32-149
Glycine	118 - low normal	73-177

Mineral-RBC	Result	95% Reference Range
Potassium	1380 - low normal	1099-2492
Magnesium	18 - low normal	18-40
Zinc	4.5 - low normal	4.2-9.3
Copper	291 - low normal	275-534
Manganese	26 - low normal	22-43
Chromium	1.6 - low normal	1.3-7.5
Selenium	0.21 - low normal	0.15-0.41



## Intervention

Spread out 4 meals and 2 snacks per day  
 Spread protein intake through-out the day  
 Decrease intakes of processed and fast foods  
 Keep a food/symptom diary

### Supplementation:

- Discontinue PPI (proton pump inhibitor) stop eating 2-3 hours before bed
- Short term use of free-form amino acid supplements (morning and afternoon dosing)
- Digestive enzymes with meals (not snacks)
- Consider a shot glass of apple cider vinegar after large meals to lower stomach acid
- Good quality multi-vitamin mineral supplement
- Iron supplement with vitamin C

### Follow-up:

The patient felt better after 10 days of treatment, and back to normal after 3 months. The patient stopped the free-form amino acids and apple cider vinegar shots with large meals after 6 weeks. She continued with the digestive enzyme and iron supplement. She worked to make sure she got adequate protein sources and spread out her protein intakes. It is not uncommon for patients to eat good diets but due to impaired digestion, age or medication not have adequate nutrient status.

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**Elizabeth Redmond** is the current Professional Advancement Chair and incoming Chair Elect of the Dietitians In Integrative and Functional Medicine (DIFM) a practice group of the Academy of Nutrition and Dietetics [www.IntegrativeRD.org](http://www.IntegrativeRD.org). Additionally she was a member of Standards of Practice (SOP) and Standard Of Professional Practice (SOPP) working group for DIFM, as well as a board member of the credentialing application. Dr. Redmond received her Master of Medical Science in Clinical Nutrition from Emory University in Atlanta, and her doctorate in Nutrition from the University of Georgia. She has worked in public health, research, and private practice. Her research interests have included dietary effects of cancer,

and diabetes translation, though she has worked, written and spoken on a variety of nutrition subjects. She currently works at Metamatrix Laboratory as the Education Coordinator, and has a private practice in Atlanta, GA. Her private practice focuses on clinician education and mentoring,

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## 6

# Diabetes: The Causes of Our Modern Plague

**Mark Hyman, MD**



### Epidemiology

The global prevalence of overweight and obesity of 1 billion people now exceeds that of malnutrition. In 1980 there were no states with obesity rates over 15%. In 2008 there were no states with obesity rates under 15%, and all except Colorado have obesity rates over 20%.<sup>i</sup> Recent NHANES data show that nearly three quarters of Americans are now overweight.<sup>ii</sup> Childhood obesity has increased 3-4 fold since the 1960's.<sup>iii</sup> The prevalence of type-2 diabetes in America has tripled since the 1980s. From 1983 to 2008, the number of people in the world with diabetes increased seven-fold, from 35 to 240 million. The problem is expanding globally. In China 92 million have diabetes, 60% of which are undiagnosed and 148 million have metabolic syndrome, 100% of which are undiagnosed.<sup>iv</sup> In just three years, from 2008 to 2011, we added another 110 million diabetics to our global population.

Obesity also places a large economic burden on our society. Direct health care costs in the U.S. over the next decade attributable to diabetes and

pre-diabetes will be \$3.4 trillion, or one in every ten health care dollars spent. The direct and indirect costs of diabetes in America in 2007 amounted to \$174 billion. The cost of obesity is also significant, and amounts to \$113 billion every year. From 2000 to 2010, these two conditions have already cost us a total of \$3 trillion. That's three times the estimated cost of fixing our entire health care system!<sup>12</sup>

Overweight and obesity are for the majority, markers of a single unifying metabolic dysfunction – insulin resistance. Rather than discrete risk stratification based on ideal body weight, overweight (BMI <25), obesity (BMI >30) or diabetes (fasting glucose < 126), it is more useful to consider the metabolic dysfunction as a continuum of dysfunction from optimal insulin sensitivity to end stage diabetes. Risk increases progressively with increasing BMI, even below the overweight level of 25. This spectrum has been referred to as “diabesity” and is a more useful clinical concept focusing on mechanism rather than phenotype for obesity.

### Mortality and Morbidity

Obesity will take nine years off the life of the average person,<sup>v</sup> and obesity in adolescents creates the same risk of premature death as heavy smoking.<sup>vi</sup> Diabetes, along the entire continuum of metabolic dysfunction, is the main driver of cardiovascular disease,<sup>vii</sup> diabetes, dementia,<sup>viii</sup> cancer<sup>ix</sup> and most chronic disease mortality,<sup>x</sup> and our decreasing life expectancy. A recent 40-year prospective study of 4857 Pima Indian children found that the most important predictor of premature death was insulin resistance, not hypertension or hyperlipidemia. Those in the highest quartile of glucose intolerance had a 73% increased death rate compared to those in the lowest quartile.<sup>xi</sup>

### Risk Factors or Causes: Changing the Focus of Clinical Intervention

Focus has been on pharmacologic or bariatric surgical approaches to correct downstream risk factors to address this epidemic and its chronic disease sequelae (heart disease and diabetes) at great cost and little or no benefit. The recent ACCORD<sup>xii</sup> and NAVIGATOR trials documented that aggressive pharmacologic intervention for lipids,<sup>xiii</sup> glucose<sup>xiv</sup> and blood pressure<sup>xv</sup> did not decrease cardiac or overall mortality, and in some cases increased adverse cardiac events and mortality. Surgical approaches of cardiac bypass<sup>xvi</sup> or angioplasty<sup>xvii</sup> fared no better. However despite a rich evidence base,<sup>xviii</sup> little attention has been placed on the lifestyle, biological, social and policy drivers of obesity and overweight.

Network or systems medicine, of which the best clinical model is Functional Medicine, provides a new framework for addressing the causes, rather than the risk factors of this epidemic. The dynamic interaction of the social, business and policy systems, lifestyle and environmental toxins drives our expanding phenotype.

Chronic disease and obesity is the result of a complex network of biological disturbances driving systemic neuroendocrineimmune dysregulation induced by the effects of diet, levels of stress, our social environment, physical activity and exposure to environmental toxins affecting gene expression. Isolating one risk factor, or even separately treating multiple risk factors, will fail until it is

done in the context of addressing the upstream drivers of disease. Distinguishing between risk factors and causes is necessary for effective primary prevention and treatment of chronic disease.<sup>xix</sup>

Treatment must focus on the **system, not the symptom**. Obesity and its chronic disease consequences, commonly referred to as “risk factors”, dyslipidemia, hyperglycemia and hypertension are only downstream symptoms of upstream biological causes. They are the smoke, not the fire. Unless medicine refocuses on treating the system rather than symptoms (risk factors) through a comprehensive clinical and social systems approach that addresses diet, exercise, stress management and treatment of environmental toxic exposures, medicine will fail to stem the impending tsunami of obesity and chronic disease.

Whole systems approaches of lifestyle interventions reduce incidence of cardiovascular disease<sup>xx</sup> and diabetes by over 90%.<sup>xxi</sup> These studies are part of a large evidence base documenting how lifestyle intervention is often more effective in reducing cardiovascular disease, hypertension, heart failure, stroke, cancer, diabetes, and deaths from all causes than almost any other medical intervention.<sup>xxii</sup>

Despite the difficulty of behavior change and lifestyle and environmental treatment, it is the only proven model for preventing chronic disease. Risk factor treatment must be replaced with elimination of the drivers, triggers and causes of chronic disease based on the network model of disease and obesity. Metabolic, disease and social networks predict disease and outcomes more effectively than risk factors.<sup>xxiii</sup> A person's chances of becoming obese increased by 57% if he or she had a friend who became obese in a given interval. Among pairs of adult siblings, if one sibling became obese, the chance that the other would become obese increased by 40%. If one spouse became obese, the likelihood that the other spouse would become obese increased by 37%. Newer tools supporting behavior change with regular feedback metrics and social networks have proven successful and should be widely adopted in policy and medical practice.<sup>xxiv</sup>

## Etiology and Pathophysiology

### Social Etiologies

Structural violence<sup>xxv</sup> has driven the obesity epidemic through an obesogenic environment. Policies and practices in agriculture, transportation, education, advertising, technology, health care, environment and the food industry promote obesity. These policies and practices have created limited access to whole fresh foods, but unlimited access to calorie dense, nutrient poor foods consumed mostly outside the home, or made in a plant, rather than grown on a plant. The built environment and adoption of technology limits physical activity. Hours of television watched are second only to consumption of liquid sugar calories as a risk factor for obesity.<sup>xxvi</sup> Environmental toxins also promote obesity.<sup>xxvii</sup> *Obesogens* are implicated in the 73% increase in obesity in six-month-old infants since 1980.<sup>xxviii</sup> Growing awareness of the obesogenic environment is driving changes in social, media, business and government policies including limiting sweetened beverages in schools, science rather than industry based nutrition guidelines from the USDA<sup>xxix</sup> and Michelle Obama's *Let's Move* campaign.<sup>xxx</sup>

### Biological Etiologies

Emerging evidence points to obesity as more than simply genetics or a thermodynamic problem of calories in/calories out or eating less and exercising more. Contributing etiologies include poor quality food, nutritional deficiencies, hormonal dysfunction, inflammation, food allergens, chronic infections, gut-derived endotoxins, environmental toxins, oxidative stress, defects in energy metabolism and mitochondrial function, and chronic stress. These factors all interact in a dynamic network of dysfunction that leads to insulin resistance and obesity better described as diabetes.

Systematic focus on diagnosing and treatment of each and all of the underlying causative factors in the network of metabolic dysfunction will result in more successful clinical outcomes and improved gene expression.

## Nutritional Factors: Sugar, Fiber, Micronutrients, Macronutrients

*Nutrigenomics*, the effect of macronutrients, micronutrient, phytonutrients, and glycemic load on gene expression provides an important lens in understanding the impact of nutrition on obesity and insulin resistance.<sup>xxxi,xxxii</sup>

The single biggest contributor to obesity is the increased consumption of refined sugar and carbohydrates. Our Paleolithic ancestors ate 22 teaspoons of sugar per year<sup>xxxiii</sup>. Sugar consumption increased from 10 pounds in 1800 to 150–180 pounds per person per year. In the last 30 years, the sugar calories we consume from high-fructose corn syrup have increased from 0 percent to 66 percent, mostly in the form of liquid calories from soft drinks and other sweetened beverages. Liquid calories increase obesity more than calories from solid food.<sup>xxxiv</sup>

Glycemic load and nutrient density is also controlled by fiber content of food. Our Paleolithic fiber consumption decreased from 100 grams a day to less than 8 grams per day.<sup>xxxv</sup> Lack of fiber promotes heart disease, diabetes, obesity, cancer and many other chronic diseases.<sup>xxxvi</sup> Consumption of 50 grams of fiber per day lowers hemagloblin A1c as effectively as diabetic medication.<sup>xxxvii</sup>

Obesity is often associated with malnutrition. Obese children are increasingly diagnosed with scurvy, B vitamin deficiencies and rickets. Nutrient poor, calorie dense diets promote a society of overfed and undernourished citizens. A number of nutrients are particularly important in the prevention and treatment of diabetes, including vitamin D,<sup>xxxviii</sup> chromium,<sup>xxxix,xi</sup> magnesium,<sup>xli</sup> zinc,<sup>xlii</sup> biotin,<sup>xliii</sup> omega 3 fats,<sup>xliv</sup> and antioxidants such as alpha lipoic acid.<sup>xlv,xlvi</sup> These nutrients regulate glucose metabolism and insulin sensitivity.<sup>xlvii,xlviii</sup> Supplementing with nutrients is necessary because modern food-growing and processing practices have greatly diminished the quality of our diet.<sup>xlix</sup>

Shifting from a nutrient-poor diet to a nutrient-dense diet that is abundant in plant foods such as fresh, whole fruits, vegetables, nuts, seeds, beans, and whole grains improves the function of

hundreds of genes that control insulin function and obesity. An optimal diet to prevent and treat diabetes includes healthy fats such as olive oil, nuts, avocados, and omega-3 fats, along with modest amounts of lean animal protein. This is commonly known as a Mediterranean diet.<sup>i,ii</sup>

### Hormonal Dysregulation: Insulin, Thyroid, Adrenal and Sex Hormones

Obesity results from and drives neurohormonal immune dysregulation.<sup>iii</sup> Impairment in insulin sensitivity, thyroid metabolism, adrenal function and sex hormones, neuroendocrine appetite regulation are common features in diabetes.

Undiagnosed thyroid disease worsens insulin resistance,<sup>iii</sup> and insulin resistance worsens thyroid function.<sup>iv</sup> Chronic stress drives chronically elevated cortisol which promotes insulin resistance, central adiposity, dyslipidemia, depression even dementia.<sup>iv</sup> Elevated cortisol also promotes muscle loss, interferes with thyroid and growth hormones, and negatively impacts sleep, all of which leads to problems with weight gain. Sleep deprivation or impaired sleep, in turn, increases appetite and increases sugar and refined carbohydrate cravings. In a study of healthy young men deprived of just 2 hours of sleep, their blood levels of *ghrelin* (the hunger hormone) increased and *PYY* (the brake on appetite) decreased.<sup>lv</sup>

Diabetes also drives sex hormone dysregulation. Insulin resistance underlies infertility<sup>lvii</sup> and polycystic ovarian syndrome.<sup>lviii</sup> In men, insulin resistance results in androgen deficiency and impaired sexual function.<sup>lix</sup>

### Inflammation: Refined Sugars and Food Sensitivities

Silent inflammation is a final common pathway in most chronic diseases, including heart disease, cancer, Alzheimer's, and diabetes.<sup>lx</sup> Elevated C-reactive protein confers a 1700% increased risk of developing diabetes.<sup>lxi</sup> Inflammation from any source (allergen, infection, toxin, diet, stress) promotes obesity and obesity drives further inflammation. Anti-inflammatory medications do not address the most important question, "What is

causing the inflammation, and how do we treat it most effectively?"

Sugar, refined carbohydrates, artificial sweeteners, food allergies and sensitivities, chronic infections, environmental and metabolic toxins, stress, and a sedentary lifestyle all promote inflammation. Each of these underlying causes of inflammation has to be addressed if diabetes is to be treated effectively.

### Dietary Sugars, Refined Flours, and Artificial Sweeteners

Dietary sugars and refined flours are the single biggest triggers of inflammation driving hyperinsulinemia leading to a biochemical cascade that alters gene expression promoting inflammation,<sup>lxii</sup> and downward spiral into further inflammation and insulin resistance. Lack of fiber and too many inflammatory omega-6 fats (soybean and corn oil) and not enough anti-inflammatory omega-3 fats (fish oil, flax seeds) also contribute to the development of systemic inflammation.

#### Special Note: Artificial Sweeteners

Artificial sweeteners promote obesity through increasing hunger, food consumption, and reductions in body temperature and thermogenesis.

In a recent study, rats were fed yogurt sweetened either with sugar or artificial sweetener for 14 days. The rats that consumed the artificially sweetened yogurt increased their total food consumption, but not total calories, and yet body fat and weight increased, while body temperature and *thermogenesis* decreased.<sup>lxiii</sup>

### Food Sensitivities and Allergies

Delayed or Type 3 IgG food sensitivities or allergens also may play a role in the development of insulin resistance and diabetes through promotion of systemic low-grade inflammation. In a study that compared obese children to-normal weight children, the obese children had three-fold higher levels of C-reactive protein and a two-and-a-half-fold higher level of IgG antibodies for the 277 different foods tested.<sup>lxiv</sup> In addition, these



obese children had increased carotid intimal thickness.

### Special Note: Gluten, Inflammation and Obesity

Another growing problem is gluten intolerance or celiac disease, which triggers systemic inflammation and has been linked to autoimmune diseases, mood disorders, cancer, and cardiovascular mortality. In a recent study comparing blood samples taken from a cohort of 10,000 people 50 years ago to a modern cohort of 10,000, researchers found a 400 percent increase in celiac disease based on antibody testing (tissue transglutaminase).<sup>lxv</sup>

In a 30-year study of over 30,000 people, hidden gluten sensitivity, even without biopsy proven celiac, was shown to increase risk of death by 35 to 75 percent, mostly from cardiovascular and cancer mortality, both known to be driven by inflammation.<sup>lxvi</sup>

Damage to the gastrointestinal tract and impaired intestinal permeability from overuse of antibiotics, NSAID's, and proton pump inhibitors and H2 blockers, combined with our low-fiber, high-sugar diet, combined with genetic alternations in gliadin proteins<sup>lxvii</sup> leads to the development of celiac disease and gluten intolerance or sensitivity and the resultant inflammation.

### Other Factors Driving Chronic Inflammation: Infections, Toxins, Stress, Sedentary Lifestyle, Nutrient Deficiencies

Chronic infections can also trigger inflammation and cause persistent weight gain. New studies show that chronic infections, such as adenovirus, may be linked to obesity and insulin resistance.<sup>lxviii</sup> The increasing load of persistent organic pollutants (like PCBs and pesticides) and heavy metals (such as arsenic, mercury, and lead) has been linked to both diabetes<sup>lxix</sup> and insulin resistance,<sup>lxx</sup> in part through increased cytokine production. Chronic stress is yet another cause of chronic inflammation.<sup>lxxi</sup> Lack of regular exercise promotes low-grade inflammation while regular exercise reduces inflammation.<sup>lxxii</sup> Low-level nutrient and antioxidant deficiencies promote inflammation. Taking a multivitamin and

mineral supplement is as effective for lowering inflammation as is statin medication, at less expense with fewer side effects.<sup>lxxiii</sup>

### Digestive Dysfunction

Metabolic dysfunction and insulin resistance has recently been linked to disturbances in intestinal ecology or the *microbiome*.<sup>lxxiv</sup> Shifts from our Paleolithic diet to a highly processed, high-sugar, high-fat, low-fiber diet has dramatically altered gut microflora.

When the microflora is altered, the homeodynamic balance shifts from *symbiosis*—a mutually beneficial relationship to *dysbiosis*—a harmful interaction between microflora and host. These altered flora create *metabolic endotoxemia* through an increase bacterial endotoxins or *lipopolysaccharides* (LPS) binding to lymphocytes releasing *tumor necrosis factor alpha* (*TNF-α*) which blocks the *PPAR* (*peroxisome proliferator activated receptor*) family of nuclear receptors that control inflammation, insulin sensitivity and mitochondrial function. This triggers a cascade of inflammation, insulin resistance, and weight gain.<sup>lxxv</sup> Improving diet quality and normalizing gut flora with probiotics can reduce the burden of systemic inflammation.

### Toxic Burden and Impaired Detoxification

Environmental toxins interfere with glucose and lipid metabolism and cause insulin resistance.<sup>lxxvi</sup> In 2006, scientists at Harvard School of Public Health found that rates of obesity in infants less than six months old have risen 73 percent since 1980. The Environmental Working Group study found the average newborn has 287 chemicals in the umbilical cord blood, 217 of which are neurotoxic.<sup>lxxvii</sup>

Bisphenol A, a petrochemical that lines water bottles and canned food containers, increases a person's risk of diabetes, heart disease, and abnormal liver function.<sup>lxxviii</sup> Data from the government's National Health and Nutrition Examination Survey 1999–2002 found a very striking correlation between blood levels of six common persistent organic pollutants (petrochemical toxins) and diabetes.<sup>lxxix</sup> Those people who had the highest levels of pollutants in



their blood had a dramatically higher risk of diabetes. Studies of Air Force veterans of the Vietnam War found that those who had been exposed to Agent Orange (dioxin) had a much higher risk of diabetes.<sup>lxxx</sup>

Environmental toxins alter normal thermodynamics making weight regulation simply a matter of calories in/calories out obsolete. New evidence shows that weight gain can occur in the absence of excess calorie intake. Rats given toxic chemicals gained weight and increased their fat storage *without* increased caloric intake or decreased exercise. In six months, these rats were 20 percent heavier and had 36 percent more body fat than rats unexposed to those chemicals.<sup>lxxxi</sup> A large population study published in *Environmental Health* found higher levels of organochlorine pesticides in diabetics.<sup>lxxxii</sup> Heavy metals such as mercury, lead, and arsenic also cause diabetes. Arsenic exposure increases the risk of diabetes.<sup>lxxxiii</sup>

Toxins promote obesity through multiple well-documented mechanisms.<sup>lxxxiv</sup> Toxins are PPARs (*peroxisome proliferator-activated receptors*) antagonists, receptors which regulate insulin sensitivity, inflammation and mitochondrial energetics.<sup>lxxxv</sup> Using new techniques of genetic and metabolic analysis, scientists have shown how toxins cause increases in glucose, cholesterol, and fatty liver.<sup>lxxxvi</sup>

This opens a whole new area of potential treatment for diabetes and obesity. A comprehensive detoxification program for petrochemical and heavy metal toxins can be an effective addition to the treatment of diabetes.

### Mitochondrial and Redox Dysfunction

Obesity and diabetes is linked to defects in mitochondrial function<sup>lxxxvii</sup> and oxidative stress.<sup>lxxxviii</sup> Even thin otherwise healthy first-degree relatives of diabetics have mitochondria that are 50 percent less active than those of people without a family history of diabetes.<sup>lxxxix</sup>

Impaired mitochondrial function and oxidative stress results from calorie-rich, high-sugar, nutrient- and antioxidant-poor foods. Toxins, infections, and any

inflammatory trigger further damage mitochondria through increasing *oxidative stress*, which alters gene expression that drives insulin resistance.

A plant based, low glycemic load, phytonutrient rich, nutrient dense diet enhances mitochondrial function and reduces oxidative stress. *HIT or high-intensity interval training* also significantly improves mitochondrial function and leads to enhanced weight loss and improved cellular metabolism.<sup>xc</sup>

Newer treatments are also being developed to address mitochondrial dysfunction, including one based on *resveratrol*, the antioxidant compound in red grapes.

Resveratrol affects mitochondrial health through its impact on a master class of genes called *sirtuins* that regulate insulin sensitivity and mitochondrial function and helps reverse diabetes and increase longevity.<sup>xcii</sup>

Calorie restriction also helps improve mitochondrial function.<sup>xciii</sup> However, modifying lifestyle, engaging in interval training and exercise, eating a nutrient-dense diet, and appropriate use of dietary supplements can enhance mitochondrial function and reduce oxidative stress.<sup>xciii</sup>

### Psychosocial/Spiritual Imbalances

Stress promotes central obesity,<sup>xciv</sup> insulin resistance and diabetes through elevations of cortisol, insulin and *cytokines*. Mice bred to be obese and diabetic had improved metabolic function and lost weight through adrenalectomy, not an optimum strategy for weight loss.<sup>xcv</sup> However stress management including relaxation therapies, meditation, breathing exercises, yoga,<sup>xcvi</sup> group support, biofeedback, massage, exercise, saunas, dancing and laughing reduce the stress response and help normalize adrenal function and neuroendocrine signaling. Depression and diabetes are linked<sup>xcvii</sup> and may be interactive. A comprehensive psycho-spiritual approach to obesity is necessary.

Obesity and diabetes is a complex, multi-factorial, multi-gene disorder embedded within a complex psycho-social-cultural fabric. Systematic attention, review and treatment of each factor and

fundamental clinical imbalance are essential to address the modern plague of diabetes.

The causes of diabetes are not the same for every person. For some, diabetes may be simply a result of poor diet. For others, it may be due to environmental toxins, chronic inflammation, digestive imbalances, chronic stress, or even food sensitivities. This is why we must take a comprehensive approach to understanding, diagnosing, and treating these fundamental clinical imbalances that drive diabetes, insulin resistance, and most chronic diseases.

### Functional Medicine Approach to Diabetes: Case Studies

Obesity (diabetes) is a complex, multi-factorial, multi-gene disorder with dynamic web-like physiological imbalances affecting gene expression and phenotype. A systemic approach directed at removing the impediments to optimal function (diet, toxins, allergens, infections, stress) and providing the “ingredients” for optimal health (whole foods, micronutrients, light, air, water, movement, rhythm, sleep, connection, community, meaning and purpose) based on the model of Functional medicine<sup>xviii</sup> provides a roadmap for diagnosis and treatment of the underlying clinical imbalances at the root of obesity and chronic disease. The functional clinical imbalances are influenced by the environment including diet and nutritional status on core functional systems – hormonal/metabolic, immune/inflammatory, digestive, detoxification, mitochondrial energetics and redox status, structural and psycho-spiritual.

These diagnostic and treatment principles are illustrated in the following cases.

#### Case 1: Inflammation, Obesity and Diabetes

S.R. is a 67-year-old woman with a 10-year history of type 2 diabetes. Her weight was 233 pounds with a BMI of 36 and waist to hip ratio 0.91. Her past medical history was significant for hypertension, angina, reflux, rheumatoid arthritis and lupus, hypothyroidism, chronic allergies and sinusitis, and depression. Her medications included metformin, benazepril, fluoxetine, pravastatin, bio-identical hormone replacement,

cetirizine, lansoprazole, levothyroxine, naproxen, a multivitamin glucosamine, and calcium with D. She is a widow who lives alone and is estranged from her family. She is a recovering alcoholic with a history of childhood sexual abuse. Her diet consisted predominately of refined carbohydrates including bread, pasta, muffins and ice cream. She does no exercise. Her medical symptom questionnaire (MSQ) was 86.

Functional diagnostic assessment revealed hyperinsulinemia of 23 (nl < 5), glucose of 140 mg/dl and HbA1c of 6.8. Her high sensitivity C-reactive protein was elevated at 10.6 (nl < 1) and her sedimentation rate was 20. Her anti-nuclear antibodies were 1:80 speckled pattern. On a statin her total cholesterol was 198 mg/dl, LDL-C 119 mg/dl, HDL-C 54 mg/dl and triglycerides 199 mg/dl. She had a fatty liver with an elevated gamma glutamyl transferase (GGT) of 40. Organic acid analysis revealed impaired fatty acid and carbohydrate metabolism, and mitochondrial dysfunction as well as impaired detoxification and dysbiosis with small intestinal bacterial overgrowth (SIBO).

Treatment consisted of low glycemic load, high fiber, phytonutrient rich, allergen elimination (gluten and dairy), whole foods plant based diet and moderate exercise of 30 minutes of walking daily. Digestive imbalances were treated by stopping NSAID, proton pump inhibitor, herbal anti-microbials, probiotics, glutamine and an anti-inflammatory rice based medical food for treating dysbiosis. Oral estrogen was changed to vaginal to reduce fat deposition and inflammation. Anti-depressant was changed from fluoxetine to bupropion to improve appetite control. In addition to her multivitamin, she was treated with coenzyme Q10 and alpha lipoic acid (antioxidants and mitochondrial co-factors) as well as B-complex and milk thistle for fatty liver and enhanced detoxification. After 2 years of treatment, she lost 45 pounds. Her medical symptoms score (MSQ) reduced from 86 to 6. Her C-reactive protein reduced from 10.6 to 2.8, total cholesterol from 198 to 171, triglycerides from 199 to 88, and HDL-C increased from 57 to 65. Her insulin reduced from 23 to 11, fasting glucose from 140 to 103 and hemoglobin A1c from 6.8 to 5.7 and GGT from 40 to 17.

Organic acids showed normalization of fat and carbohydrate metabolism and citric acid cycle normalized as did the markers of impaired detoxification and dysbiosis.

## Case 2: Treatment Resistant Obesity and Diabetes

J.L. was a 59-year-old African American female college dean with obesity and diabetes. She had a history of hypertension, obstructive sleep apnea, and hyperlipidemia. She presented with severe fatigue unable to drive, watch television, exercise or cook for herself. Her BMI was 35 at 190 pounds. Despite maximal intensive medical therapy, she remained hypertensive with a blood pressure of 160/104 and was about to start insulin therapy and retire because she could no longer fulfill her work obligations. Her hemoglobin A1c was 10.1.

She was on atorvastatin, metformin, glyberide metopropol, aspirin, lotrel (amlodipine and benazepril) and a multivitamin. She was single, a non-smoker, exercised irregularly and ate prepared and microwavable foods and sweets at night.

Her laboratory evaluation revealed urine 3+ glucose, fasting glucose 312, hemoglobin A1c 10.1. Her 25 OH vitamin D was 17 ng/ml (normal 45–100). She had elevated liver function tests with an ALT of 56. Urine microalbumin was negative. On a statin, her total cholesterol was 186 mg/dl, HDL 54 mg/dl, LDL 122 mg/dl, TG 101 mg/dl. However, on nuclear magnetic resonance spectroscopy, she had predominately small LDL (1320/1608) and HDL particles. Her cardio C-reactive protein was 0.7, homocysteine 6.4, fibrinogen 311, and her Lp(a) was elevated at 423 (normal < 30). She had elevated lipid peroxides of 2.2 nmol/mL (nl <1.5).

Her organic acids revealed an elevated lactate and beta-hydroxy butyrate indicating impaired carbohydrate metabolism, abnormal krebs cycle metabolites and coenzyme Q10 and B vitamin deficiencies.

A functional assessment suggested hormonal imbalances with uncontrolled type 2 diabetes,

hypertension, hyperlipidemia with small LDL and HDL particles and obstructive sleep apnea. Fatty liver or NASH indicated impaired detoxification. Mitochondrial and redox imbalances were indicated by abnormal carbohydrate and krebs cycle metabolites and elevated lipid peroxides. Nutritional evaluation revealed severe vitamin D deficiency.

Addressing the underlying causes of her metabolic dysfunction focused on diet, exercise and nutritional supplementation. Dietary recommendations emphasized protein in morning and with each meal, only WHOLE grains, no flour or sugar, 50 grams of fiber, an increase in omega-3 fats intake, a reduction of red meat, smaller, more frequent meals and no processed food, junk food, trans fats, juices, or sodas or high fructose corn syrup.

The oral hypoglycemic (glyberide) and beta-blocker were eliminated because they increase hyperinsulinemia and weight gain. To improve particle size, atorvastatin was reduced and high dose niacin was added. She exercised 30 minutes daily with interval training three times a week.

Nutritional supplementation focused on addressing the underlying clinical imbalances. She was treated with a whole soy protein shake with plant sterols, glucomannan (konjac root), a multivitamin with extra biotin, chromium, alpha lipoic acid, omega-3 fatty acids, protein kinase modulators (from acacia), and cinnamon. She was also treated with vitamin D3 5000 U daily and a mitochondrial support supplement including coenzyme Q10, n-acetylcysteine, acetyl-L-carnitine, creatine, magnesium malate, phosphatidylcholine and sodium succinate.

After one year her BMI reduced from 35 to 31 with a 20 pound weight loss and resolution of sleep apnea. Her energy increased and she was able to resume a full workload and travel schedule. Her blood pressure reduced from 160/104 mmHg to 127/79 mmHg, her hemaglobinA1c from 10.1 to 5.9, her fasting glucose reduced from 321 mg/dl to 111 mg/dl and LDL from 122 mg/dl to 71 mg/dl (small particles from 1320 to 615) and her vitamin D increased from 17 to 62 ng.

**Mark Hyman** has dedicated his career to identifying and addressing the root causes of chronic illness through a groundbreaking whole-systems medicine approach known as Functional Medicine. He is a family physician, a four-time *New York Times* bestselling author, and an internationally recognized leader in his field. Through his private practice, education efforts, writing, research, advocacy and public-policy work, he strives to improve access to Functional Medicine, and to widen the understanding and practice of it, empowering others to stop managing symptoms and instead treat the underlying causes of illness, thereby also tackling our chronic-disease epidemic.

Dr. Hyman is Chairman of the Institute for Functional Medicine, and was awarded its 2009 Linus Pauling Award for Leadership in Functional Medicine. He is on the Board of Directors of The Center for Mind-Body Medicine, and a faculty member of its Food As Medicine training program. He is also on the Board of Advisors of Memhet Oz's HealthCorps, which tackles the obesity epidemic by "educating the student body" in American high schools about nutrition, fitness and mental resilience. He is a volunteer for Partners in Health with whom he worked immediately after the earthquake in Haiti and continues to help rebuild the health care system there. He was featured on *60 Minutes* for his work there. Dr. Hyman has testified before the White House Commission on Complementary and Alternative Medicine, and has consulted with the Surgeon General on diabetes prevention. He has testified before the Senate Working Group on Health Care Reform on Functional Medicine, and participated in the White House Forum on Prevention and Wellness in June 2009. Dr. Hyman was nominated by Senator Tom Harkin for the President's Advisory Group on Prevention, Health Promotion and Integrative and Public Health, a 25-person group to advise the Administration and the new National Council on Prevention, Health Promotion and Public Health.

With Drs. Dean Ornish and Michael Roizen, Dr. Hyman crafted and helped to introduce the *Take Back Your Health Act of 2009* into the United States Senate, to provide for reimbursement of lifestyle treatment of chronic disease. He

continues to work in Washington on health reform, recently testifying before a Congressional hearing on Functional Medicine, nutrition and the use of dietary supplements.

Through his work with corporations, church groups, and government entities, such as CIGNA, the Veterans Administration, Google, American Express and Saddleback Church, he is helping to improve health outcomes and reduce costs around the world. He initiated and is a key participant in the ongoing development of a faith-based initiative that enrolled over 14,000 people at Saddleback Church in a healthy lifestyle program and research study. In recognition of his efforts, he was recently awarded The Council on Litigation Management's *2010 Professionalism Award*, citing individuals who have demonstrated leadership by example in the highest standard of their profession. He also received The American College of Nutrition *2009 Communication and Media Award* for his contribution to promoting better understanding of nutrition science. He has been featured on *The Dr. Oz Show*, *60 Minutes*, *Larry King Live*, CNN, and MSNBC.

Dr. Hyman is founder and Medical Director of The UltraWellness Center in Lenox, Massachusetts, where he directs a team of physicians, nutritionists and nurses who utilize a comprehensive approach to health. Before starting his practice, he was co-Medical Director at Canyon Ranch Lenox, one of the world's leading health resorts. While at Canyon Ranch, he co-authored the *New York Times* bestseller *Ultraprevention: The 6-Week Program That Will Make You Healthy for Life* (Scribner) – winner of the Books for a Better Life Award honoring the best self-improvement books each year. He has since written *UltraMetabolism: The Simple Plan for Automatic Weight Loss*, and a companion public television special. His latest book and PBS special, *The UltraMind Solution*, a comprehensive approach for addressing the causes of mental illness and cognitive disorders, was released in January 2009. *The Blood Sugar Solution* book and companion PBS special will be released in March 2012, addressing the global epidemic of obesity, diabetes and cardiovascular disease.

Dr. Hyman graduated with a B.A. from Cornell University, and graduated magna cum laude degree from the Ottawa University School of Medicine. He completed his residency at University of San Francisco's program in Family Medicine at the Community Hospital of Santa Rosa. Contact Mark Hyman at [info@drhyman.com](mailto:info@drhyman.com) or 413-637-9991.

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# 7

## Highly Palatable Foods : The Brain Reward Pathways and Connections to Overeating

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For decades we have been taught that the key to losing weight is a matter of energy balance; eat less and exercise more. Yet more and more people continue to gain weight. In fact, in the United States two thirds of adults are overweight and more than 72 million of them are obese.<sup>i,ii</sup> The global picture of overweight and obesity is sobering, and the number of overweight people now surpasses the number of undernourished by several hundred million.<sup>iii</sup> In 2005, over 20 million children under five years of age were overweight, and the World Health Organization has predicted that by 2015, approximately 2.3 billion adults will be overweight and over 700 million will be obese.<sup>iv</sup>

Obesity rates have climbed in unison with the availability of inexpensive highly palatable foods, i.e., processed foods rich in fat, salt, and refined sugars.<sup>v</sup> Eating behaviors characterized by food

cravings and bingeing have increased concomitantly with the increased exposure to these highly palatable foods.

Research in both animal models and human imaging studies shows that high calorie, highly palatable foods are directly associated with addiction and loss of control.<sup>vi,vii</sup>

Emerging science has revealed that excessive food consumption involves the brain's pleasure centers. Neuroimaging studies have shown that food, like substances of abuse, leads to increased dopamine release in the pleasure center of the brain.

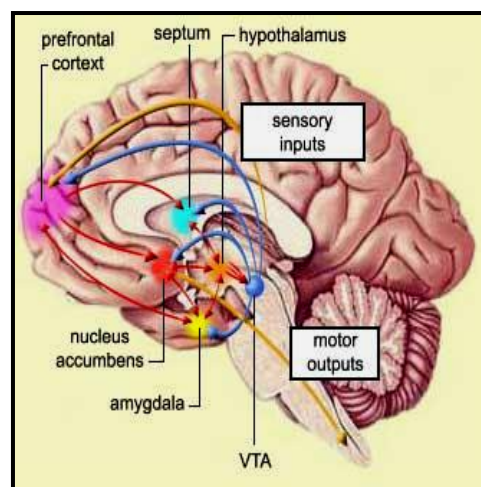
Positron emission tomographic (PET) imaging studies have shown that obese individuals, like drug abusers, have lower levels of dopamine D2 receptors.<sup>viii</sup> Lower dopamine D2 receptors make the obese individual less sensitive to reward stimuli. This, in turn, may make the obese individual more

vulnerable to excessive food intake as a way to satisfy a reduced reward signal.

This new research is important because it helps explain the reason why obese individuals either fail to succeed with weight loss efforts or regain lost weight. Few diet products or programs address the reward pathways that drive eating behaviors. A truly effective approach to weight management should encourage strategies aimed at improving dopamine functioning in the brain's reward circuitry. This article will review emerging science that describes a direct link between the activation of the reward/pleasure pathways in the brain and eating behaviors.

### The Brain is Reward Driven

In order to better understand the drive to overeat and food addiction, we must first understand the basics of the brain's "pleasure or reward center". The nucleus accumbens (a collection of neurons found in the striatum) was first identified as the brain's pleasure center in the 1950s.<sup>viii</sup> A reward circuit (**figure 1**), which includes the ventral tegmental area (VTA), nucleus accumbens, septum, amygdala (involved in emotion), and prefrontal cortex (thinking part of the brain), was later identified. When the brain receives a sensory stimulus that is positive (i.e., highly palatable food), signals are sent to the VTA. The VTA, in turn, releases dopamine into the nucleus accumbens, septum, amygdala, and prefrontal cortex. Dopamine leads to feelings of exuberance, desire, and positive emotions.<sup>ix</sup> The pleasure associated with dopamine's release reinforces eating.<sup>x,xi</sup>



**Figure 1. Reward Pathway**

**Source:**

<http://www.bing.com/images/search?q=brain+image+s%2c+reward+centers&FORM=IGRE1#focal=efec84e00fe6465d25e21488f7d9c7f2&furl=http%3A%2F%2Flibrary.thinkquest.org%2F04oct%2F01639%2Fen%2Fhealth%2Fpopup%2Fnucleus.jpg>

### Obesity & Reduced Food Reward:

The dopamine reward pathways influence the fundamental drive to eat. Dopamine is required to initiate each meal, and it is associated with the duration and quantity of a meal.<sup>xi,xii</sup> Weak activation of dopamine-based reward circuitry may increase overeating.<sup>xiii</sup>

Recent research has found lower dopamine D2 receptors in obese subjects.<sup>vii</sup> A genetic variation may be the cause in some of these individuals. An association between the Taq 1 A allele and lower levels of dopamine D2 receptors has been found by some researchers.<sup>xiii</sup> It may be that individuals with reduced dopamine D2 receptors use food to increase dopamine stimulation to a more satisfying level.<sup>xiv</sup>

### Pleasure Pathways, Habits, & Addiction:

The brain is plastic, meaning it can change. If an individual repeatedly engages in an eating behavior (i.e., binging), the nervous system will actually become wired for that behavior. It will strengthen

the neural (synaptic) connections for that behavior. This is known as experience-dependent plasticity.<sup>x</sup> Changes occur at brain synapses as we make choices, exhibit certain behaviors, store memories, and learn. It is thought that most learning occurs in the brain through the process of strengthening or weakening synapses. Therefore, the brain will actually be modified by the repeated act of overeating.<sup>xv</sup>

The brain creates memories about eating behaviors. Glutamate, an excitatory neurotransmitter, plays a role in synaptic plasticity. It is involved in cognitive functions, such as learning and memory.<sup>xvi</sup> It is, therefore, important in storing information about eating experiences, such as pleasure felt when eating. Later cues in the environment, such as a person, a smell (i.e. French fries), or a location, can “trigger” memories of the pleasurable experience. These pleasurable memories can lead to cravings and relapse.<sup>xvii</sup>

When addiction occurs, the pleasure circuits are in a sense “hijacked”. The addiction basically takes over the pleasure and motivational centers of the brain, creating intense cravings. When the craving is satisfied there is a cascade of pleasure neurotransmitters, including serotonin, dopamine, enkephalin, and GABA. With repeated abuse (i.e., bingeing) the amount of neurotransmitter released in response to normal stimuli is reduced.<sup>xviii</sup> Therefore, more substance (i.e., food) is needed to get the same sense of pleasure. In other words, the food addict will need more food to get the same effect.

### Highly Palatable Foods:

People don't binge on broccoli and spinach, they binge on highly palatable foods loaded with refined sugars, fat, and salt. This is at least partly driven by the brain's pleasure center. Using functional magnetic resonance (fMRI) imaging technology Killgore, et al.<sup>xix</sup> examined the brains of subjects showing them images of low-calorie and high-calorie foods. When subjects were shown the pictures of low-calorie foods, they had very little activation in the reward centers of the brain compared to controls. However, when shown

pictures of high calorie food with high reward, subjects had significant activation of the reward circuitry.<sup>xx</sup>

Excessive consumption of highly palatable foods actually alters the brain circuitry involved in sensory processing of food, particularly the lips, tongue, and mouth. Obese individuals have been found to have enhanced sensitivity in brain regions involved in sensory processing. This heightened sensitivity makes the eating experience of these foods more rewarding and might contribute to overeating.<sup>x</sup> These highly palatable foods share certain neural pathways. One such pathway is the mesolimbic dopamine system.<sup>x</sup> Binging on these highly processed calorically dense foods can release excessive amounts of dopamine in the brain which can override satiety signals.<sup>xxi</sup> In addition, certain neurotransmitters (Table 1) that stabilize appetite long term, such as leptin, insulin, and ghrelin, become less effective when the diet is laden with processed foods containing high fat and high sugar.<sup>xxii,xxiii</sup>

**Table 1. Neurotransmitters Involved in Food Intake Regulation**

<b>Stimulate Feeding (usually decrease energy expenditure)</b>	<ul style="list-style-type: none"> <li>• Anandamide</li> <li>• <math>\beta</math>-endorphin</li> <li>• Dynorphin</li> <li>• GABA</li> <li>• Galanin</li> <li>• Ghrelin</li> <li>• Growth hormone releasing hormone</li> <li>• Neuropeptide Y</li> <li>• Norepinephrine</li> </ul>
<b>Inhibit Feeding (usually increase energy expenditure)</b>	<ul style="list-style-type: none"> <li>• Cholecystokinin (CCK)</li> <li>• Corticotropin-releasing factor (CRF)</li> <li>• Dopamine</li> <li>• Insulin</li> <li>• Leptin</li> <li>• Glucagon</li> <li>• Neurotensin</li> <li>• Thyrotropin-releasing hormone</li> <li>• Melanocyte-stimulating hormone</li> </ul>

Processed foods can have dozens of ingredients, so it is not an easy task to determine which constituents in foods might trigger reward pathways and the addictive process. Much of the research thus far has focused on sugar.

### Are We Addicted to Sugar?

Professor Bart Hoebel and his research team in the Department of Psychology at the Princeton Neuroscience Institute have studied sugar addiction in rats for many years. Their early research demonstrated behavioral patterns similar to those seen in addicts—sugar-binging followed by withdrawal when sugar was removed. Hoebel's more recent research found that rats showed signs of craving and relapse, a critical component of addiction. The rats, after learning to binge, worked harder to get sugar when it was reintroduced and they also consumed more sugar than before.<sup>xxiv</sup> In their experiments, binging on sugar triggered a surge of dopamine in the nucleus accumbens. There were fewer dopamine receptors than before and more opioid receptors, suggesting an adaptive response. The dopamine and opioid systems are involved in reward and motivation and are important in controlling wanting and liking something.<sup>xxv</sup>

Animal research suggests that sugar and drugs of abuse act on the brain in similar ways. Behavioral and neurochemical changes in the brain following a sugar-binge resemble those produced when an individual takes a drug such as nicotine, cocaine, or morphine. Because sugar releases opioids and dopamine, it is expected to have addictive potential.<sup>xxvi</sup>

The pleasure from the sweet taste of sugar-dense foods and beverages initially motivates over-consumption. In fact, research is finding that sweet taste may be more rewarding and possibly more addictive than cocaine. Researchers at the University of Bordeaux in France found that when rats were allowed to choose between water sweetened with saccharin and intravenous cocaine, 94% of the animals preferred the saccharin. This same sweet preference was also seen with sucrose. The researchers speculated that supra-normal stimulation of sweet receptors by sugar-rich

diets, such as those seen in modern society, could create a supra-normal reward signal in the brain that could potentially override self-control mechanisms and lead to addiction.<sup>xxvii</sup>

### Does Eating High Fat Stimulate Eating?

According to data from the United Nations Food and Agricultural Organization, the dramatic increase in consumption of fatty foods over the last thirty years may be partly responsible for the growing obesity epidemic.<sup>xxviii</sup>

Eating high-fat (HF) may increase drives to eat more fat. A study conducted by Gaysinskaya et al.<sup>xxix</sup> found that caloric intake was increased throughout the day in animals fed a small HF meal early in the day compared to those fed a low-fat meal. Triglyceride levels increased 2–3 times in the HF group, but there were no changes in leptin or insulin levels. Leptin and insulin are known to inhibit feeding. The expression of orexigenic (appetite stimulating) peptides, galanin in the paraventricular nucleus and orexin in the perifornical lateral hypothalamus, were increased.<sup>xxix</sup> The findings of this research suggest a potential mechanism involving circulating lipids and orexigenic peptides. Hence, eating a HF diet might in turn stimulate eating.

It is not only short-term eating patterns that are affected by fat intake. Long-term eating patterns can actually be predicted by early life experiences. Chang et al.<sup>xxx</sup> found that maternal HF diet exposure lead to changes in rodent offspring following weaning. In as little as two weeks of exposure to a HF diet, both female and male offspring showed increased intake of calories, body weight, a stronger drive for fat intake, and a rise in brain peptides that are stimulated by fat.<sup>xxx</sup>

There appears to be a positive feedback loop in which a fat rich meal stimulates certain brain systems that further drive fat intake. In fact, the brain systems involved in reward and palatability can each stimulate and be stimulated by the intake of diets rich in fat. It may be that this vicious cycle actually starts in utero and continues through adulthood.<sup>xxx</sup>



## Stress, Reward Pathways and Eating

It is well known that stress affects eating behaviors. Brain reward circuitry appears to play a key role in stress related food intake. A theoretical model of Reward Based Stress Eating has been proposed by researchers at the University of California, San Francisco Department of Psychiatry.<sup>xxxi</sup> According to this model, cortisol and the reward circuitry affect motivation for calorically dense food intake. The reward value of food may be influenced by cortisol via neuroendocrine/peptide mediators such as insulin, leptin, and neuropeptide Y (NPY). Hence, the model also emphasizes the relationship between stress, eating, and potential neuroendocrine mediators.<sup>xxxi</sup>

Stress, in addition to highly palatable food, can stimulate endogenous release of opioids. Opioid release appears to be part of the organism's defense mechanism designed to protect from detrimental stress effects. This is done by reducing hypothalamic-pituitary-adrenal (HPA) axis activity and thereby attenuating the stress response. Stimulation of the reward circuits via the intake of highly palatable foods, stress induced stimulation of the HPA axis, or both, may lead to neurobiological adaptations that encourage overeating.<sup>xxxi</sup>

## Treating Obesity by Changing the Brain

Most weight loss programs are not successful long-term. One reason may be due to the lack of attention given to the brain's very powerful reward pathways. To improve success, it may be necessary to change reward circuitry that trigger cravings and drives to overeat highly palatable foods. Behavioral interventions that enhance dopamine function hold potential in the treatment of obesity.

Breakthroughs in neuroscience show us that we can change our brain's circuitry. We can literally choose to increase certain neural networks and reduce others. A comprehensive behaviorally based program designed to "re-wire" the brain's reward pathways can be an effective way to reduce food cravings and overeating. Although detailed program

design is beyond the scope of this article, a few suggestions will be made.

- A variety of professionals might be involved (i.e., dietitian, physician, exercise physiologist, psychologist) and a variety of formats (online and phone support, individual consultations, group classes, etc.) might be incorporated.
- Treatment should be individualized and incorporate a variety of cognitive and behavioral tools. These tools should help the individual: 1) decrease the reward value of the food or behavior; 2) increase the reward of the new positive behaviors; 3) reduce the power of triggers; and 4) strengthen new neural circuits by learning new habits.<sup>xxxi</sup>
- Stress management tools should be incorporated daily to weaken neural circuits that promote stress. Increasing natural pleasures can help reduce stress and may improve dopamine function. Exercise is a well known natural pleasure, stress reducer, and mood enhancer. This may be due to changes in neurotransmitter concentrations and alterations in central neural activity.<sup>xxxi</sup> Techniques such as mindfulness meditation have been found to increase activity in the left prefrontal cortex, which is associated with joy and peace.<sup>ix</sup>
- Analysis of stimuli, situations, and cues that trigger out-of-control-eating is critical. This information can help the patient become aware of the unconscious cues or settings that drive overeating behaviors.<sup>xxxi</sup> Avoidance of certain triggers or foods (i.e., refined sugar) may be necessary at least initially.

Ingrained behaviors will not likely change without a significant amount of repetition. Cognitive and behavioral tools must be practiced repeatedly if they are going to weaken the strong neural circuits that favor overeating.

It is clear that to better treat the obesity epidemic we must unravel the neural mechanisms that process the hedonic effects of highly palatable foods, but also those that govern reward-learning,



reward-value, and decision making in the context of our current economic and social climate.

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Dr. Vargas is a Certified Nutrition Specialist (CNS), Registered Clinical Exercise Physiologist (RCEP), Certified Strength and Conditioning Specialist (CSCS), and an Emotional Brain Training (EBT) provider. She held a certification as a Group Exercise Instructor from the American Council on Exercise for 14 years. She holds professional memberships with the American College of Sports Medicine, the American College of Lifestyle Medicine, the Obesity Society, and the American Society for Nutrition. Aside from her scientific interests she is an avid runner, has participated in triathlon, and loves Pilates and yoga.

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## 8

# Detoxification

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Continuing the theme of this book, it is important to include a chapter on the subject of *detoxification*. Realizing how much the food you eat makes a difference in how your body maintains a “clean” vibrant state of health, it empowers you to take a proactive role with your health and help prevent and/or manage chronic disease. Health of all living organisms depends on having the ability to efficiently detoxify. Detoxification is the metabolic process by which the waste products our body produces on a daily basis, and the environmental poisons or toxins we are exposed to, are bio-transformed and eliminated from our body. For our bodies to have good “detoxifying ability,” we must have three key factors in place: eating a detoxifying diet, optimum gastrointestinal health, and sleep and a healthy lifestyle.

Food is the most powerful medicine available to deter and heal chronic disease. Chronic disease is projected to account for over 50 million deaths and cost the global economy \$47 trillion by 2030. All you need to do is eat your medicine and think of your grocery store and your meals as your pharmacy<sup>i</sup>. Fortunately, the Asian-Indian cuisine has some of the best detoxifying foods and herbs known. By eating the whole-foods, traditional foods of the Asian-Indian diet, one can support detoxification in an excellent way.

*The question may arise, what is the benefit of helping your body detoxify?*

First, in the past decade there has been a rapidly emerging awareness in public health and medicine that the increasing environmental toxin exposures to human, animal and plants on the earth are being identified as disruptors of our metabolism. These disruptions affect primarily the immune and neurological systems. These toxic effects are being recognized as significantly contributing to the development of chronic disease. For example, the toxin *dioxin* is strongly associated with risk of developing diabetes<sup>iii, iv</sup> and cardiovascular<sup>v</sup> disease, and toxic *lead* with hypertension and cardiovascular disease<sup>vi</sup>. For all of us to be able to prevent developing the chronic diseases of heart disease, cancer, neurological, autoimmune, diabetes, and others, each person would benefit from ensuring the food they eat includes those that assist detoxification.

Secondly, it is important to realize that the human body is capable of eliminating most toxins via their stools, urine, outbreath, and sweat. The toxins are constantly being processed primarily by our liver –an amazing organ that filters our blood every two minutes to process toxins in preparation for elimination. Our bodies are made for detoxifying IF they have the right materials available (the materials are primarily NUTRIENTS from food). When you find

out what the root cause of your health issue is, you can improve your ability to get rid of it. Years ago Dr. Sydney MacDonald-Baker, a functional medicine physician, coined the term “Get and Rid”<sup>vii</sup> that captures the basics of how our physiology survives:

- **GET:** Does this person have an unmet individual need?
- **RID:** Does this person need to be rid of something toxic, allergic, or infectious?

“Dr. Sidney Baker begins the journey of understanding preventive medicine by introducing us to detoxification and healing . . . foreshadows an era of looking at health as a balance of internal and external chemistries, signals, and systems.”

--Lloyd R. Saberski, M.D., Director, Yale University Center for Pain Management, and Associate Clinical Professor of Anesthesiology, Yale University School of Medicine

Detoxification in our bodies depends on three factors:

- **INTAKE:** The type of food we put on our fork. Does it have the nutrients we need? Does it contain toxins from processing, preservatives and contamination?
- **DIGESTION:** How our gastrointestinal tract digests and absorbs nutrients, and also works with the liver to eliminate wastes from the body. Does our digestive system have the right function and microflora to digest, absorb nutrients, and eliminate toxins? Does the digestive tract have toxic pathogens and toxic chemicals in it that impair digestion, absorption and elimination?
- **CELLULAR METABOLISM OF OUR MICROENVIRONMENT:** How our cells use the nutrients we absorb. Does our microenvironment have the right hydration, acid-base balance, and structures to allow cell-to-cell communication, transport of nutrients and molecules of metabolism? Are there toxic substances at high levels that interfere with our metabolic function?

These are general factors for all humans, but we must also recognize that each person is an individual and has their own unique genetic makeup.

### Nutrigenomics – Food Speaking Messages to Your Cells

A newer concept in the field of nutrition science is that food contains information that is constantly speaking to our genes. With the emerging knowledge of nutrigenomics, the traditional concept that food was just calories is being replaced with the idea that food functions as a messenger to our body. Diet and lifestyle are moment-by-moment “talking” to our cells and DNA – turning them on and off determining health or disease. What we eat “programs” our body with messages of illness or health.

Nutrigenomics has revealed how individual each person’s ability to detoxify. Food also is messaging our ability to detoxify. Just by ensuring the frequent inclusion of the following table of foods, you can begin to tune-up your body’s ability to detoxify and support all three of the factors. For some people with more genetic difficulty in detoxifying, it is recommended to consult with an integrative or functional medicine practitioner<sup>viii</sup> that is familiar with nutrigenomics and detoxification protocols to individualize your diet and lifestyle plan. And remember, food is your most powerful tool in maintaining your health and preventing chronic disease.



<b>Ayurveda “The science of Life” (Ayur means life and Veda means science).</b>	
<b>FOOD: HERBS</b>	
Curcumin (turmeric) <sup>ix</sup>	Anti-inflammatory, anti-cancer properties
Garlic	Cholesterol balancing, anti-fungal, aids detoxification
Parsley	Diuretic and anti-cancer (Apigenin) effects
Coriander: Ground / seeds	Anti-oxidant/anti-bacterial effects, liver/cholesterol support
Fennel seeds	Anti-oxidant/anti-inflammatory/anti-cancer effects
Cumin	Liver support and anti-cancer effects
Ginger	Anti-inflammatory, blood-thinning & cholesterol-lowering
Rosemary	Antiseptic and many health benefits, can have side-effects
Thyme	Antiseptic, anti-fungal, lung support (tea)
Oregano	carvacrol and thymol-anti-microbial
Saffron	Carotenoid-rich: anti-oxidant, digestive support, etc.
Nutmeg	Antibacterial, fat-soluble antioxidant
Cardamom	Digestive, antiseptic
Kaffir Lime leaves	Gum health, anti-microbial
Peppermint	Gallbladder/Bile/Liver support
<b>FOOD: VEGETABLES</b>	
Bitter Melon	Blood sugar management support, cooked or juiced
Onions, Garlic	Liver detox support, Allicin-rich
Asparagus	Liver support, contains glutathione
Green leafy vegetables	Kale, Swiss Chard, Collards, Spinach, Watercress, Dandelion
Cruciferous	Broccoli, Cauliflower, Brussel Sprouts, Cabbage, Bok Choy
Summer Squash	Zucchini, Yellow Squash, Crookneck,
Yams / Sweet Potatoes	½ to 1 cup serving size
Winter Squash	Butternut, Acorn, Spaghetti, Bitter Melon
Celery	Hi water, hi mineral content
Cucumber	Hi water, cooling, cleansing
Root Vegetables	Carrot, Beet, Parsnips, Turnips, Rutabagas
Cooking Herbs	Parsley, Cilantro, Oregano, Thyme, Rosemary, Lemon Grass



FOOD: PROTEINS*	Recommend 3-4 (2-4 oz.) servings per day
Lentils	Rich in minerals, blood sugar management
Eggs	Liver support with phosphatidylcholine in the yolk
Milk / Cheese (rBGH-free)	Best if cultured like yogurt, kefir, cheeses
Poultry (antibiotic-free)	Stabilizes blood sugar, assists detox
Fish (wild, small)	Stabilizes blood sugar, assists detox
Meats (hormone-free)	Stabilizes blood sugar, assists detox
Nuts / Nut butters	Almond, walnut, pecan, macadamia, pine nuts
<i>*Restricted on Renal Diets</i>	<i>*Protein amount may be restricted by your physician</i>
FOOD: FRUITS	Limit to 1-2 servings daily – eat more vegetables
Lemon, Lime	Potassium-rich (limit if on a Renal Diet Prescription (Rx))
Grapefruit	Lycopene, Potassium-rich (avoid if your Rx has a warning)
Orange, Tangerine	Best to eat fresh, avoid juice high in sugar
Sweet Fruits-limit amount	½ c serving: Watermelon, Pineapple, Peach, Pear, Apple, Banana
Berries: 1 cup serving	Rich in detox phytonutrients, low sugar content
Kiwi: 1 medium	Fiber, phytonutrient and mineral-rich.
FOOD: FATS	
Ghee (clarified butter) rBGH-free	Gastrointestinal support for detoxification, cooking fat
Butter, organic or rBGH-free	Use in small amounts
Whipping Cream rBGH-free	Use in small amounts
Olive Oil, extra virgin	Cold pressed, use in salads, baking
Almond or Macadamia Oil	Expeller-pressed, use in salads, baking
Omega 3 Oils	Flax, raw walnuts, fish, hi-quality fish oils (capsules or liquid)
Omega 6:GLA oil	Evening Primrose, Black Currant capsules-important for Diabetes, Metabolic Syndrome, Allergies, Autoimmune
Coconut Oil	Medium chain triglyceride, cooking oil, skin topical oil
Coconut Milk	Mineral-rich, soups, drinks, baking
Meat (hormone/antibiotic-free)	Eat lean meats to eat small amounts of meat fats
Poultry (hormone/antibiotic-free)	Eat lean poultry to eat small amounts of meat fats/no skin
Egg Yolk (organic/antibiotic-free)	6/week:Am Heart Assoc guidelines, bile/liver/nerve support
Nuts / Nut Butters	¼ cup / 2-4 Tbsp. daily – mineral-rich, good oils

FOOD: DAIRY	
Kefir	Gastrointestinal support / Homemade or “hi probiotic content”
Yogurt (rBGH-free)	Homemade or purchase “hi probiotic content”
Cheese (rBGH-free)	1 oz. = average 7 grams protein
Milk (rBGH-free)	If tolerated - Hi potential for allergy or lactose-intolerant
FOOD: BEVERAGES	
Water	Pure, minimize plastic bottled water
Green / Black / White Tea	Excellent detox support and health promoting
Ayurvedic Herbal Teas	Many different benefits
Coconut Milk / Water	4-8 oz / monitor sugar content
Coffee, organic	If tolerated. DeCaf, Swiss water processing if low caffeine
Fresh Vegetable Juice	Use high water, low carb vegetables with lemon or lime
Milk / Kefir	As tolerated. ½ or 1 cup servings
AVOID: hi sugar/sweet drinks	Upsets blood sugar & insulin levels, increases body fat%

#### Food Groups of Important Nutrient-Rich Detoxifying Foods:

**PHYTONUTRIENTS:** Food is a source of special colorful ingredients that are increasingly being recognized with very powerful anti-inflammatory and anti-cancer properties, in addition to assisting detoxification. These nutrient ingredients are primarily rich in vegetables and interact with your metabolism. They act like switches turning your DNA in the correct position to heal your body. In the modern diet, vegetables are one of the first group of foods that starts to decrease as one starts to eat a richer, high refined carbohydrate, high meat, damaged oil diet representative of the trend in industrialized societies. Restoring traditional diet principles of eating 6-10 servings of vegetables every day will ensure a good intake of phytonutrients in your diet.

**PROTEIN:** Foods rich in protein like eggs, lentils, chicken, and meats are very important when digested and absorbed into the blood. They help in blood sugar and insulin management.

The body also uses protein molecules to carry toxins out of the body, in addition to making enzymes, hormones, immune factors and repairing tissue.

**MINERALS:** Mineral rich foods, like vegetables, fruits, nuts and beans, support detoxification as co-factors – and when insufficient, your body's cells become more vulnerable to toxins that may have entered your body. The minerals most critical for good detoxification are magnesium, selenium, zinc and iodine, found rich in vegetables and nuts, especially when grown in selenium and iodine rich soils.

**VITAMINS:** The B-Complex vitamins, Vitamin D, A, E, K2 are also critical co-factors for detoxification metabolism to function optimally. More information on the specific good food sources is available at the *whole foods* website: [www.whfoods.com](http://www.whfoods.com)

**FATS:** Beneficial fats are foundational for control of inflammation of chronic diseases, assisting good detoxification, and building good body structures. In particular, are the essential fatty acids Omega 3 and Omega 6 (Gamma Linoleic Acid (GLA)) and maintaining a balance between the two types of fats. These are found in fish oil, flax seed, algae DHA (Omega 3), nuts, and evening primrose & black currant oils (usually supplement capsules) for one of the most important Omega 6s found deficient in diabetics, GLA. Monounsaturated fats (MUFAs) contribute to the balance of oils when olive oil, avocados, almonds, etc. are included in the diet and have cardio protective effects. Even some saturated fats are important for healthy cells such as those found in coconut oil, butter (hormone-free), ghee, hearts of palm, hormone-free meats, antibiotic-free poultry and egg yolks. Many beneficial associations with these fats are known with diabetes and cardiovascular health. The downside of fats found in our food supply, are those fats that have been processed and when eaten become damaging to our bodies: margarines, high-temperature processed vegetable oils, partially-hydrogenated oils, hydrogenated oils, and shortenings. Many of these processed oils have trans-fats known to promote cardiovascular, diabetes, and cancer diseases.

**BEVERAGES:** Most important recommendations regarding beverages, is to drink plenty of water daily (2-3 quarts per day) to flush out toxins and allow cells to function optimally. Avoid sweetened drinks, including artificially sweetened, that stress your blood sugar and metabolism. The best beverages on a regular basis are water, unsweetened green and black teas, herbal caffeine-free teas (many therapeutic ayurvedic teas). Use other unsweetened beverages like milk, coconut milk, nut milks and coffee in small amounts (1-2 cups per day). [note: the only recommended sweetener is *Stevia*.]

*"Detoxification promotes wellness by ridding the body of poisons that can lead to a host of health problems ranging from fatigue and depression to cancer and diabetes."<sup>ix</sup>*

## Summary

Food contributes to your experiences of taste, texture, delight, energy and nourishment to maintain your body in optimum health. Along with good sleep (best time of day your body detoxifies!), exercise, and a joy of life – choose from the wonderful selection of clean whole foods in three meals daily to maintain your blood sugar and insulin levels along with giving your body the foods that add an extra boost to your ability to detoxify and keep your body “clean, green and lean”<sup>\*</sup>.

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## 9

# Food Sensitivities and Basic Gut Health: A Primer

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It may be that the gastrointestinal system is the foundation for health and wellbeing.

This “Primer” is intended to serve as an introduction to food sensitivity, enabling the practitioner of any wellness art to identify and help clients understand the interaction between food and the immune system. The clinician and patient then act as a team to employ strategies to reduce disease and improve all aspects of health through gut healing.

As you learn more about wellness, you will find gastrointestinal health a cornerstone concept; it deserves your time and effort to broaden your understanding of this rapidly evolving, and exciting field. Indeed, gastrointestinal health is central to wellness. Understanding food sensitivity includes overlapping concepts with other disciplines, such as neurodegenerative and autoimmune disease, celiac disease, gluten enteropathy, the gut “biome”, dysbiosis, and intestinal disease. These topics are addressed in generality within this Primer and are covered in greater detail in other areas of the text.

Upon completion of this Primer, you will have a greater understanding as to how food sensitivity can impact multiple body systems. Addressing food sensitivity will be a starting point to begin to bring your clients, and yourself, to greater health by healing the gastrointestinal system.

## Introduction

### *What is food sensitivity?*

Food sensitivity is an immune phenomena, not a food problem. The concept of food sensitivity is emerging and not completely characterized due to the complex nature of the individual immune response. Other terms may include food intolerance and nonallergic food hypersensitivity.

Although sensitivity differs from allergy, it is often assumed that sensitivity and allergy are synonymous terms. Therefore, the literature presents varying clinical opinions, expert opinions, and clinical studies regarding food intolerance and its impact on the immune response, disease, and clinical symptoms. (1,2,3,4)

Despite the fact that food sensitivity is an emerging concept, it is a powerful tool for practitioners seeking to aid their patients in wellness, weight loss, and the improvement of chronic disease.(5, 6) It is in fact so clinically relevant that this author proposes that clinicians should not shy away from the application of these concepts while awaiting for “evidence based medicine” to dictate it as a routine standard. Rather, as clinicians use these principles to further the healing of their patients, the robust and beneficial effects will speak for themselves and give credence to the need to understand the pathophysiology.

*Why is gastrointestinal health so important to my patient?*

Gastrointestinal health, often simply called “gut health”, is central to physiologic balance and wellness.(9) The gastrointestinal system is responsible for a wide variety of metabolic, nutritional, and detoxification processes.(10) Furthermore, the bacteria located within the intestines are intimately involved with our metabolic functioning. The 100 trillion bacteria living within our intestinal system contains more genetic material than the human body and performs more metabolic processes than our liver. The gut environment can be viewed as another organ system.

Approximately 70–80% of our immune system cells are located around the gastrointestinal system and there appears to be a close relationship between the immune system and the gut flora. There is evidence that these bacteria play a role in immune modulation and recognition of “self” that occurs during the early years of extrauterine life.(14) Containing over 1000 species of bacteria, yeast, and parasites, the balance of these living organisms can support nutrient synthesis, detoxification, and immune balance or set the stage for inflammation and intestinal hyper-permeability.(11)The food that we eat is also food for the organisms living within our gut and our food choices influence the balance of bacteria.(8)

Eating right is hard. Even people with chronic disease tend to believe that they eat normally; however, few people eat in a manner that is physiologically sound. We often eat highly processed, nutrient poor foods rapidly under higher stress conditions (think drive-thru!) which sets the stage for inadequate digestion, malabsorption, and chronic disease.(12,13) Digestion, although not the focus of this primer, plays such a significant role in gut health, the intestinal biome, and ultimately the function of our immune system that it deserves a brief discussion.

Proper digestion takes time and preparation. This includes eating foods that our body can digest, with reasonable nutrient, fat, fiber, protein, and carbohydrate intake; preparing food properly, in a low stress environment, allowing for production of stomach acid and pancreatic enzyme synthesis. Taking the time to thoroughly chew the food, in reasonable portions, with

plenty of time between bites will allow the bolus of food time to be broken down within the stomach.

As you can see, proper digestion requires real food and time to prepare and eat the food. Food choices, eating habits, digestion, the gut flora, and elimination all influence the integrity of the gut, preventing or setting the stage for food sensitivity, and ultimately immune dysfunction, inflammation, and chronic disease.(10,11)

*How does Food Sensitivity impact gut health?*

The development of food sensitivity is the end result of multiple inter-related chronic problems of the digestive tract, such as poor digestion, abnormal bacterial growth within the gut, and chronic gut inflammation. In other words, gut problems precede the development of food sensitivity. However, determining and removing foods that cause inflammation can be an important part of breaking the cycle of chronic inflammation.

*Isn't Food Sensitivity just an allergy?*

All allergy and most sensitivity or intolerances to food are mediated by the immune system. Lactose intolerance, which is due to an enzyme deficiency, is an example of a non-immune mediated food intolerance.(27)

Most clinicians think about the production of IgE antibody when they encounter allergy type symptoms and when they are considering food as a potential source of disease.

IgE is an antibody produced by the B-lymphocyte, part of the acquired arm of the immune response. IgE is responsible for causing the release of histamine from mast cells and histamine mediates the allergic symptoms of swelling and redness.

IgG is another form of antibody responsible for long term immune memory. For instance, IgG is formed after the acute phase of a viral infection, preventing reinfection upon further exposure.

Immunotherapy (“allergy shots”) can help us understand the function of these antibodies in a practical way. Immunotherapy is an effective means of reducing the symptoms of allergy by chronically



exposing the immune system to the allergen. The allergy reaction is mediated by IgE antibody. After repetitive low dose exposure to the allergen, the immune system can become tolerant to the allergen by shifting immunoglobulin production from IgE (which drives the allergy symptoms) to IgG. As IgG levels increase, allergy symptoms decrease.(1,16) In this setting, it appears that the presence of IgG against an antibody signals that the body does not view the antigen as a problem.

In regards to food allergy and sensitivity, there are many IgG tests against food antigens. In light of what immunotherapy has taught us about the role of IgG in allergy, this calls into question whether the use of IgG testing would actually correlate with clinical symptoms and pathology. In fact, it could suggest that the presence of IgG to a specific food antigen may be protective, or at the very least simply indicate exposure to the food.(35)

Food sensitivity may have more to do with the inflammation that results from activation of the innate immune system, rather than IgG antibody production against food. The blood test called the “antigen leukocyte cellular antibody test” (ALCAT) can determine which specific food antigens activate the immune system, leading to a downstream inflammatory process.(18,19) Studies also suggest that chronic activation of the innate immune system may be an underlying cause of chronic disease, such as Metabolic Syndrome and other degenerative diseases.(2,3,17)

## Basic Physiology

### *Gut structure and Digestion*

The gastrointestinal tract starts at the mouth and ends at the anus. Although it traverses the body cavity, the contents of the intestinal tract remain EXTERNAL to your tissues. Similar to your skin, this serves a similar protective and functional role.

You can literally control what enters your body because you can choose what to place into your mouth. Individuals can have profound control over their health and wellbeing by exerting control over their diet.

As discussed previously, digestion begins at the mouth, requires proper chewing of food, stomach acid,

pancreatic enzyme production and bile acid secretion. Heart burn is often a symptom of poor digestion, not of too much stomach acid production. Proper digestion will minimize the exposure of the lower gut to whole food particles, which may set the stage for the development of food sensitivity.

Mechanical breakdown of the food and aggressive mixing with salivary enzymes within the mouth begin the digestive process. This process also triggers hormone release, signaling the other areas of the digestive tract to prepare their digestive processes. Stomach pH lowers during the process of preparing to eat, typically from a basal pH of 3–4, down to a pH of 1 when food is ingested. This allows for the optimal functioning of enzymes, bacterial killing, and digestion of proteins. The stomach mixes the food and dispenses it into the first portion of the small intestine called the duodenum where pancreatic enzymes and bile are introduced, as well as bicarbonate to neutralize the acid. This substance is called chyme, and nutrients and minerals are extracted from it as it passes through the small intestinal tract.

Chyme passes into the large intestine through a “one-way valve” where water is extracted and large numbers of bacteria act upon it to further digest it. This material acts as a food source for the bacteria as well, promoting the growth and development of the proper balance of gut flora. The foods we eat are a nutrient source for the bacteria that live within our GI tract. They essentially consume what we consume. Proper digestion ensures optimal breakdown for utilization by the gut biome.(7)

## The Immune System and the Gut

### *Innate and Acquired Immunity*

To truly appreciate food sensitivity, we must understand some basics of the immune system and comprehend the complex, multi-layered, neuro-endocrine-immune system.

The “innate” immune system is a branch which reacts to a foreign antigen or substance. It does not require prior education or exposure to that substance. The “acquired” immune system responds to substances previously learned to be foreign.

Two primary arms of the immune system are the cytotoxic (Th-1) and humoral (Th-2) arms, where "Th" denotes thymus, an organ thought to contribute to educating the Tcells.

The cytotoxic arm is involved in cell-to-cell defenses, where the immune cell acts directly against the pathogen. The humoral immune response is antibody mediated.

The immune system is modulated in part by the endocrine system.(23) The balance of the cellular and humoral arms of the immune system is regulated in part by the hormonal environment with testosterone, DHT, DHEA and DHEA-S favoring a shift toward cellular (Th1 immunity) and glucocorticoids, estrogens, and catecholamines favoring a shift toward the humoral, or antibody producing, (Th2) arm of the immune system.

#### *Gut Biome and the Immune System*

70-80% of the immune system cells are located around the gastrointestinal tract. There is evidence that the gut flora act to educate the immune system in self-recognition during the early years of life, as the gut environment changes in relationship to the foods that are eaten.(20) The balance of organisms in the gut therefore influence the immune activity within the gut, setting the stage for health or disease.

The gut biome is very responsive to changes in diet, hormones, and stress and can shift in its balance of flora, the implications of which are not well understood.(22) This is an emerging science and is only included here to bring an awareness to the reader that there is a sophisticated and complex relationship between the organisms living within the gut, the human immune response, and the health of the human organism.(21)

#### **Evolution of sensitivity**

##### *Food Sensitivity as an Immune Phenomena*

Consider that the development of food sensitivity is an evolutionary process; it is not likely a sudden or isolated event. The development of food sensitivity involves the exposure of the immune cells to food antigens, which requires the breakdown of multiple

steps in human anatomy and physiology. You learned about these steps in isolation in the preceding paragraphs. Now we will tie these concepts together to help you understand how the process might develop.

In order for food sensitivity to develop, the immune system must be exposed to food antigen. Food antigen is essentially poorly digested food. When optimal digestion has occurred, food has been broken down into its basic macronutrient components as it passes through the digestive tract. Furthermore, in order for the immune system to "see" a food antigen requires the gut barrier to be permeable to the contents of the digestive tract, a concept referred to as intestinal hyper-permeability. Poor digestion alone may not lead to the development of significant food sensitivity if there is adequate integrity of the enterocyte lining. In contrast, ensuring optimal digestion beginning with the choice of foods and how they are eaten may play a role in preventing or minimizing the development of food sensitivity if the patient has a problem with the barrier of the enterocyte layer, or a "leaky gut."

The bacterial environment within the gut could be a starting point for the establishment of food sensitivity as well. Gut floral imbalances and overgrowth (termed dysbiosis) can lead to a pro-inflammatory environment within the gut. This inflammatory state may increase the degree of intestinal permeability, setting the stage for prolonged exposure of the immune cells to the intestinal contents.

#### *Dysbiosis*

The human microbiota is undergoing intensive study. The Human Microbiota Project which began in 2007 as an extension of the Human Genome Project is intended to understand the role of human microbial communities in human health.(28) The gut biome alone contains up to 100 trillion organisms of approximately 500 to 1000 species. The term dysbiosis refers to an abnormal, or imbalanced, growth of organisms in the digestive tract that may lead to such issues as poor digestion, malabsorption, intestinal hyper-permeability, inflammation, and other problems in various systems of the body.

Dysbiosis may be caused by the growth of a specific pathogen or the overgrowth or absence of a commensal organism. These organisms likely play a

very significant role in our health, the details of which will be determined over time. Some functions of the organisms which live in the human gut include synthesis of vitamins (such as B6 and Vit K), detoxification, and metabolism of fats.

Given the tremendous number of species present within the gut, it is not clear what balance or ratio of certain species is optimally beneficial, or if this concept is even legitimate.(29) Certainly, there are organisms that act pathologically at a certain colony growth number; there may be organisms that are simply present and innocuous, and there may be organisms that act within the host in such a way that even small numbers can create imbalances that lead to symptoms and ultimately disease processes.

#### *Intestinal Permeability*

Understanding food sensitivity is only relevant if there is an impact on the health of the individual. Indeed, it is important to understand that food sensitivity has little to do with helping clients with symptoms such as diarrhea, bloating, and dyspepsia; rather, these symptoms are a reflection of an underlying inflammatory process, originating at the level of the gut, and being mediated by the immune system.

This process can involve both the innate (non-specific) and acquired (educated) arms of the immune system. The innate immune system is designed to recognize and destroy foreign invaders in a general way and does not require previous exposure to the pathogen or antigen. The acquired immune system responds based on its memory of previous exposure to a foreign pathogen.

The endothelial cells and the integrity of the “tight junction” between them is responsible for providing the physical separation between the contents of the digestive tract and the immune cells.(30) It is known that a wide variety of conditions can cause a loss of tight junction control and allow macromolecules and intestinal flora entry into the body. A reduction in tight junction integrity is seen in acute stress, extreme exercise, sleep deprivation, and exposure to gluten.

It is likely that some degree of intestinal permeability is necessary to establish food sensitivity, as this would

be the predominate mechanism to expose the immune system to food antigen.

#### **Gluten can trigger hyper-permeability**

##### *Is Gluten sensitivity the same as Celiac Disease?*

Much media and healthcare attention has focused on celiac disease and sensitivity to gluten, therefore healthcare providers and patients have a higher level of awareness regarding this issue. The following is a brief overview of celiac disease and gluten sensitivity; please see the extensive work of Alessio Fasano, MD for in-depth research on the topic.

Although there is overlap between celiac disease and gluten sensitivity, it is important to understand that current thinking places them as two distinctly different entities, both with clinical implications.(24) Celiac Disease and gluten sensitivity may have overlapping symptomatology, but the immune system likely deals with the environmental trigger gliadin, in a different way, due in part to the underlying physiologic response dictated by the individual's genetics (25), gut flora and metabolic environment.

##### *What is Celiac Disease?*

Celiac disease is an autoimmune enteropathy triggered by gliadin. It is the only treatable autoimmune disease, responding to a gluten free diet.(26) The prevalence of Celiac Disease (CD) has doubled every 15 years since 1974 and it is now clear that Celiac Disease can develop at any age. The prevalence of CD in not-at-risk groups in the US was found to be 1:133; whereas the prevalence was 1:22 in first-degree relatives of CD patients.(25)

There is evidence that in the CD individual, gliadin binds to and triggers a chemokine receptor on the gut enterocyte, ultimately causing the release of zonulin. Zonulin in turn interferes with the skeletal structure of the cell, leading to a weakening of the intercellular tight junctions.(23) This is referred to as intestinal hyper-permeability (“leaky gut”) and may allow passage of gliadin and other antigens access to the body's innate immune system.(26)

The innate immune cells initially respond to this foreign material, creating an inflammatory cascade. Over time,

this can result in the acquired immune system producing antibody against gliadin and tissue transglutaminase (TTG; TTG binds gliadin and presents it to the immune cells) which may lead to damaged enterocytes. A key feature of celiac disease is the blunting of intestinal villi due to autoimmune destruction.

#### *What is gluten sensitivity?*

Gluten sensitivity is considered distinct from Celiac Disease because gluten sensitivity is not accompanied by the development of anti-tissue transglutaminase nor does it appear to be an autoimmune phenomenon.<sup>(32)</sup> Gluten sensitive individuals can test positive for anti-gliadin antibodies. They do not have the characteristic autoimmune damage to the intestinal villi. Both GS and CD can present with similar clinical features. GS is thought to be under-recognized and therefore under-treated. Gluten sensitive individuals will respond to a gluten-free diet and may experience improvements in a wide variety of symptoms.

#### **Tying it all together**

The following is an very complicated clinical case involving a patient struggling with the development and management of autoimmune disease.

Complicated problems require the management of multiple systems, particularly the gastrointestinal tract. It further illustrates the utility of addressing food sensitivity, and the often dramatic clinical improvement seen when inflammatory foods are identified and removed.

#### *Clinical Vignette*

TT is a 33 year old white female G4P4 who presented with worsening fatigue since the delivery of her fourth child three years ago. She had a 12 year long history of peculiar medical problems including flank pain, abdominal pain, pelvic pain, urinary urgency and frequency. Relevant past medical history was positive for atopic dermatitis and asthma for which she used a leukotriene inhibitor. Her pregnancies were complicated by preterm labor symptoms, allergic reactions, hives, and she was admitted to the intensive care unit during two of the four pregnancies due to these reactions. All deliveries occurred after 37 weeks gestation.

After the delivery of her fourth child, her health began a rapid decline, and over the next 2 years she experienced symptoms including fatigue, low grade fever and chills, low body temperature, lower extremity arthritis, nocturia of 4–6 times per night, and frequent urinary tract infection symptoms. Periodic documented positive urine cultures showing *E. coli* and *P. mirabilis*.

TT sought care from specialists in gynecology, nephrology, general surgery and urology during a 6 year period. She received diagnosis, such as kidney stone, cystinuria and appendicitis. Multiple CT scans during this time period were normal with the exception of a small <1mm right renal calculus.

During one hospitalization for rather acute pelvic, right lower abdominal, and right flank pain she was observed and ultimately underwent an appendectomy. This did not alter her course. A nephrologist gave her the diagnosis of cystinuria was given despite two 24 hour urine collections showing normal urine cysteine levels. She took supplemental potassium citrate for approximately one year upon the recommendation that she take empiric treatment of cystinuria. For pain control she used narcotic pain medication up to three times per day.

Finally, TT sought care from a gynecologist who recognized that she had symptoms consistent with interstitial cystitis. She underwent a potassium sensitivity test in the office to confirm the clinical suspicion. An infusion of a dilute solution of potassium chloride was infused into the bladder using a small catheter. This solution reproduced her pelvic pain, urinary urgency, and flank pain immediately. Her bladder was then infused with a dilute solution of lidocaine and sodium bicarbonate which relieved her pain.

She began conventional treatment with the standard cocktail of Elmiron, Vistaril, and Elavil and was instructed in self-administration of bladder rescue therapy using lidocaine, heparin, and sodium bicarbonate. She was placed on prophylactic antibiotics to reduce the incidence of post-coital bladder infection. Over the course of 16 weeks she had modest improvement of bladder pain, nocturia, urgency, and pelvic/flank pain.

However, her arthritis worsened and she periodically needed assistance with crutches, especially during her menstrual periods. Her fatigue and mental sluggishness persisted and she continued to need narcotic pain medication at least once daily. She sought care from a physiatrist specializing in acupuncture and manual medicine and began neuroleptic and anti-depressant medications (Neurontin, Lyrica, Cymbalta, and Celexa). The side effect profile of these medications were not well tolerated.

Approximately one year after the diagnosis of Bladder Pain Syndrome (IC), she return to her gynecologist who recommended a 4 point saliva test and comprehensive thyroid testing. Thyroid labs were suboptimal with a TSH of 3.2, free T4 of 0.8 and free T3 of 1.1 with positive thyroid peroxidase antibodies. Low basal body temperature testing showing follicular phase axillary temperatures below 97F was consistent with subclinical hypothyroidism.(3) Salivary cortisol testing was very low across all four points with a low DHEA and low 17-hydroxyprogesterone, consistent with adrenal insufficiency.

The patient began a nutritional regimen including zinc, copper, and selenium to support thyroid function, herbal adaptogens (Ashwaganda and licorice), multivitamins, Lcarnitine, vitamin D3, and adrenal extracts. She started Armour thyroid 30mg daily.

She saw dramatic improvements in sleep, energy, and mood within a few days. She gradually withdrew neuroleptic medication and reduced her use of narcotic pain medication over the course of a six month time period and was able to begin a modest exercise regimen. Bladder pain improved approximately 50-60% and she reported once per night nocturia.

Follow-up testing revealed a TSH of 1.8, free T3 2.0 and free T4 1.2 with persistently positive thyroid antibody titers. Over the course of the following 6 months she continued to improve in all aspects of her health and wellbeing, however suffered with moderate bladder pain and arthritis.

An ALCAT food sensitivity panel was then ordered. Within 2 weeks of implementation of the diet, she experienced near complete resolution of bladder pain

and arthritis. She continued to improve in all measures and needed pain medication only periodically.

Two to three months after this marked improvement, she began to experience facial swelling which she attributed to accidental exposure to pork, a severe intolerance food. This swelling persisted and was followed by increased energy, sweating, insomnia, and a general shift in her mood toward anxiety. She was seen by an integrative medicine specialist during this time who placed her on a variety of supplements but did not address the facial swelling.

Her anxiety continued to worsen and she developed more profuse sweating and a rapid heart rate; subsequent thyroid testing showed her TSH to be non-detectable with free thyroid hormones in the thirties and by this time she appeared to be in a state of thyroid storm with an exam revealing a resting pulse in the 130s, exophthalmos, and a goiter. Radioactive iodine uptake scan revealed a diffusely active thyroid gland and she was started on methimazole and propranolol by her endocrinologist.

One year later she has continued on this medication regimen to suppress thyroid hormone production and has had persistent thyroid antibodies despite broad nutrient and mineral supplementation, avoidance of inflammatory foods, oral IgG powder, antioxidant treatment, herbal therapy with Moducare, and 10 courses of hyperbaric oxygen therapy. Considerations have been made for radioactive iodine ablation of the thyroid as well as treatment with a disease modifying agent for rheumatoid arthritis which has shown some benefit in Graves' eye disease.

### *Lessons Learned*

In retrospect, this patient has had signs of immune system imbalance since childhood, becoming more overt as she aged with the development of asthma, atopy, and hives.

From this case we may learn that patients with a baseline of immune hyperactivity or imbalance may be at risk for autoimmune disease, especially when they experience multiple stressors to the immune system. Longstanding inflammation, chronic pain, and physiologic stress may have worked to further imbalance her immune system.

In this particular case, one could rationalize that this patient has had evidence of a physiologic environment consistent with longstanding chronic inflammation. Atopy and asthma are obvious. Less obvious was that each pregnancy was complicated by symptoms of preterm labor, which is thought to be mediated in part by abnormal prostaglandin synthesis and degradation, i.e. inflammation. She also experienced unexplained "allergic" type reactions during two of the four pregnancies, one of which required hospitalization. Pregnancy places a tremendous stress on the immune system and hormonal physiology, requiring the host to adapt to a non-self fetus as well as adjusting to the hemodynamic and metabolic needs of the pregnancy.

Pregnancy depletes nutrients as well as causes hormone imbalance and these may have been part of the pathway to the inflammatory responses that ultimately manifest themselves as chronic bladder pain. This chronic pain played a role in poor sleep and certainly "stressed" the adrenal systems production of cortisol.

So, we see a potentially common thread: atopy and asthma since childhood; pregnancy (stress and hormone imbalance) temporarily unmask the patient's underlying immune system imbalance, which creates the symptoms of preterm labor and "allergic" reaction; chronic bladder pain (inflammation) develops which further stresses the physiology; lack of restorative sleep due to pain, which may contribute to intestinal hyper-permeability and development of multiple food and chemical sensitivity; development of subclinical hypothyroidism and autoantibodies; development of autoimmune thyroiditis and Graves' disease.

We know that the balance of the cellular and humoral arms of the immune system is regulated in part by the hormonal environment with testosterone, DHT, DHEA and DHEA-S favoring a shift toward cellular (Th1 immunity and glucocorticoids, estrogens, and catecholamines favoring a shift toward the humoral (Th2) arm of the immune system. In this patient's case, we could argue for a generally estrogen dominant hormone environment to her low cortisol, low 17-OHP, and weight gain; this may have been part of what tipped the scales further towards autoimmune thyroiditis.

Once established, Graves' disease is difficult to treat. There is little in the literature giving clinical guidance to the prevention and treatment of eye disease. Antibodies directed toward the TSH receptor are involved in eye disease, as expression of the TSH receptor has been shown present in the adipocytes and connective tissue of the diseased Grave's orbital tissues. Very recent research has found a human monoclonal antibody which stimulates the TSH receptor and adipogenesis in the human Grave's orbit via a known signaling cascade. Inhibition of this cascade may be a potential treatment strategy for Grave's ophthalmopathy.

I find it fascinating that this patient has such a constellation of disease processes (atopy, asthma, preterm labor, interstitial cystitis, arthritis, and Graves' disease) and the most logical link among these conditions is the immune system and inflammation. Although the etiology of interstitial cystitis is unknown, as is the cause of Graves' and most autoimmune disease, recent interest in the use of hyperbaric oxygen therapy for urological conditions like interstitial cystitis has been reported in the Italian literature. (3)

HBOT has been used in a variety of other inflammatory and autoimmune conditions. HBOT stimulates stem cell mobilization from the bone marrow and decreases oxidative stress in tissues thereby reducing inflammation and may have potential to help IC. IC may indeed be another manifestation of autoimmunity. This patient had undergone 10 hours of HBOT therapy in a mild chamber and had reported improvement in bladder symptoms.

The cornerstone of treatment for this patient will be long term hormone management, nutritional support and anti-oxidant therapy. Periodic re-evaluation of food intolerances and monitoring of gut flora will aid in restoration or prevention of intestinal hyperpermeability.

## Summary

Food Sensitivity is not a "food" problem. Rather, it is an immune phenomena driven by a myriad of variable metabolic imbalances occurring within the gastrointestinal tract, over time, within the unique genetic environment of the host, which culminates in some degree of immune activation. This immune



activation is also manifest in unique, individually determined signs and symptoms culminating in a physiologic state somewhere along the gradient of asymptomatic to severe disease.

It is always important to remember that the signs and symptoms of disease are only the outward reflection of an underlying physiologic derangement. These symptoms are a reflection of underlying metabolic imbalances and compensatory actions of the host; in some individuals the metabolic imbalance cannot be compensated for. This can lead to chronic inflammatory states, anatomic and functional damage, often resulting in the diagnosis of a formal disease process, such as Crohn's, Celiac, or some other autoimmune disease.

Understanding the development of Food Sensitivity is akin to the chicken-and-the-egg problem: which came first? Think, instead, of food sensitivity as an evolving phenomena which affects each individual differently. As an example, in an individual with a clean diet, relatively normal gut flora, and a well nourished and balanced immune system, food sensitivity may be a mild, intermittent process, resulting in inflammation for which their body can completely compensate.

Their only symptom may be a mild headache or gut cramping which they do not even connect to the ingestion of the food. On the other end of the spectrum are those individuals who develop significant symptoms such as abdominal bloating, fatigue, and loose or foul stool after the ingestion of certain foods and those with established inflammatory diagnoses such as Celiac or Crohn's disease.

As an interested practitioner of any healing art, you have the ability to help your clients take immediate action to improve their health and wellbeing by identifying the role that foods can play in symptoms and disease processes.

The patient can be simultaneously educated and treated using a simple elimination diet, allowing them to learn how foods can immediately affect their health. A food sensitivity panel, such as an ALCAT test, can allow your patient to identify a large number of foods that can activate their immune system. Eliminating these foods will reduce downstream inflammation allowing the patient to lose weight and reduce disease symptoms.

Clinicians and patients must understand that the immune system plays a central role in the generation and mitigation of inflammation in the body. The immune system can be activated by undigested food antigens if the intestinal lining becomes permeable; certain food antigens, such as gluten, as well as imbalanced gastrointestinal flora, can contribute to gut inflammation and intestinal hyper-permeability directly. Digestion of natural, minimally processed foods is essential to absorption of nutrients and optimization of the gastrointestinal flora balance. The balance of these unique factors will ultimately dictate the immune response in the host.

The future of wellness lay in part to our understanding of the immune response, foods, and the "invisible world" living within us. We have only seen the tip of the iceberg with regard to our understanding of the interaction between food and disease. Food sensitivity is a key factor in achieving gastrointestinal wellness. There are likely many avenues through which foods can interact within a particular individual to create wellness or disease.

Until we know more, I counsel my clients to take these simple steps.

### Practical Tips For Your Patients

1. Eat a wide variety of "real foods." "Real" foods are those that are as close to their natural source as possible; for instance, boxed cereal is not found growing from a tree!
2. Eat properly for digestion. This involves adequate chewing of food, eating small amounts of food with each bite, and taking time to consume a meal. This will set the stage for adequate stomach acidity, pancreatic acid production, bile secretion, and time to digest the food substance into its macronutrient constituents. These macronutrients are able to be further digested by the gut bacteria and/or absorbed by the intestinal tract.
3. Reduce inflammatory food intake using these options:
  - a. Simple Elimination Trial: Gluten/Wheat, soy, corn, milk products, yeast.

b. Extensive Elimination Diet: Reduce intake of foods to a very low inflammatory diet, then gradually re-introduce foods while documenting symptoms.

c. Food Sensitivity Testing: I have found that the use of the ALCAT has provided my family and my clients significant improvement in all measures of wellness; therefore, it has become the testing method of choice in my clinical practice. The test is designed to measure the innate immune response to food, allowing the patient to eliminate foods that are activating the immune system and causing downstream inflammation. IgG testing, or allergy testing, is used by some practitioners, however, there is question at this time as to whether the presence of an antibody to a food is a reliable predictor of a pathological response.(35,36)

4. Take a robust pharmaceutical grade nutrient regimen:

a. L-glutamine will aid in gut cell regeneration.

b. digestive enzymes may aid the digestive process.

c. broad spectrum probiotics have been found to help reduce the inflammation.

d. multivitamin and multi-mineral.

5. Journal: this process allows your client to discover the wide variety of responses their body has to certain foods, provide objective information about their diet, and understand and change food behaviors that may be driving pathological eating habits.

### Keep It Simple

Consider a paradigm changing thought: Wellness is the NORMAL state. We work hard to get sick. Often, instead of ordering expensive testing, I counsel clients to start their wellness program by eating only what their grandparents would have eaten. Nearly everyone returns feeling significantly better!

### Concluding Thoughts

Food sensitivity is a complicated problem because it is both the end result and a perpetuating factor in a vicious cycle of gastrointestinal dysfunctions. Food

sensitivity is important because it reflects underlying metabolic, immunologic, and anatomic abnormalities. These include various degrees of intestinal flora abnormalities, intestinal hyper-permeability, anatomic damage to intestinal micro-structures, improper digestion and absorption, and chronic activation of the immune system leading to local and systemic inflammation.

The benefit of a vicious cycle is that it can be broken at any point along the chain of events. When dealing with a complicated patient, I recommend looking at gastrointestinal health immediately. This may be as simple as recommending your patient stop milk and gluten products and journal symptoms for 2-4 weeks. This brief time period is not overwhelming and will allow the patient to “feel” the positive effects and establish “buy-in.”

With a motivated or significantly ill patient, it may be appropriate to evaluate the stool for digestion, absorption, and dysbiosis and use ALCAT testing to guide their diet more specifically.

There are no risks to food elimination and the benefits can be tremendous and immediate:

1. promote gut healing
2. reduce inflammation
3. reduce immune system activation
4. improve metabolic processes and reduce chronic disease

Remember, WELLNESS IS THE DEFAULT STATE. From this perspective, complicated problems are simplified because understand that the body will return to a state of health as certain physiologic, psychologic, and metabolic stressors are removed.

So peel back the layers and help your patient discover wellness! Start with gut health; you can't go wrong. I wish you the best!

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Dr. Wright knows that Wellness is the Natural State. He works with clients to help them achieve "LifeChange Through Wellness", a concept that leverages the power of health to create a vital life.

Dr. Wright lectures and speaks to a variety of audiences. He delivers a motivational and educational message, centered around practical wellness principles. He enjoys challenging his audience to create a "Vicious Cycle of Wellness" in their lives, achieving greater satisfaction and performance in all aspects of life.

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# 10

## A Nutrition Genomics Approach for the Management Of Crohn's Disease: An Inflammatory Bowel Disease

**Sheila Dean, DSc, RD, LD, CCN, CDE**



### Abstract

The emerging field of nutritional genomics, defined as the interface between genes and nutrition, is credited with debunking the concept that “one size fits all” as it relates to nutritional management of chronic disease, including inflammatory bowel disease (IBD). Crohn’s disease (CD), a subcategory of IBD, contributes to significant morbidity, particularly in industrialized nations. It is characterized by chronic inflammation and ulceration that can occur in any portion of the intestinal tract. A number of factors contribute to its etiopathogenesis, including genetic, microbial, inflammatory, immune and permeability abnormalities. Several susceptibility genes have been associated with IBD, however this review is focused specifically on three IBD-associated genes that appear to identify major susceptibility loci for CD: 1) CARD15/NOD2 2) DLG5 3) SLC22A4/A5 (OCTN1/OCTN2). Variations of these genes and their potential impact on IBD pathogenesis are discussed. Nutritional

management, including the use of various functional clinical tests, nutritional influences in IBD and a functional medicine systems biology approach referred to as the 4R™ Gastrointestinal (GI) Restoration Program is described. The 4R™ approach, “Remove, Replace, Reinoculate, Regenerate” provides a framework in which to focus clinical assessment and intervention. Future strategies including a discussion of the evolving role of the registered dietitian are offered.

### Introduction to Nutritional Genomics

Nutritional genomics is an emerging field that is now defined as the interface between genes and nutrition. It addresses the concept of one’s biochemical and genetic uniqueness and how that interacts with environmental factors such as diet. This interaction then gives rise to outward, physical traits known as the phenotype. While nutritional genomics continues to develop, the groundwork was established over 50 years ago by pioneers, such as Linus Pauling, Ph.D.

and Roger Williams Ph.D. Dr. Pauling, Nobel Prize winner for Chemistry in 1954 and Peace in 1962, was already teaching about the importance of nutrients in modulating physiological processes at the biomolecular level. Roger Williams, Ph.D is credited with developing the concept of biochemical individuality and has been described as having “contributed to the evolution of the understanding of the molecular origin of disease” (1).

The catalyst for the development of present-day nutritional genomics has been the Human Genome Project, a multinational undertaking that began in 1990. While there were a number of goals, the primary goal was to identify the nucleotide sequence of the human DNA. However, the specific goals have changed over time since the Human Genome Project was completed in 2003, earlier than expected. Current research is focused on identifying the total number of genes, their chromosomal location, and their function (2).

Why is this important to the dietitian? One reason may be because the impact of the Human Genome Project has created new information that is expected to alter the approach to risk assessment of nutritional issues. However, the dietitian's evolving role in the application of nutritional genomics to clinical practice will require a deepened understanding of genomics, gene-diet interactions and its applications to clinical nutrition practice to occur effectively (3).

Fogg-Johnson and Kaput explain that some of the new information of the Human Genome Project is surfacing in areas that are not totally predictable. Through the Human Genome Project, it has been discovered that individual gene variations exist and are referred to as single nucleotide polymorphisms (SNPs, pronounced “snips”). These SNPs result in differential response to environmental factors, such as diet. The science of how naturally occurring chemicals in foods alter expression of genetic information at the molecular level and how this effects the individual phenotype is the essence of what nutritional genomics scientists seek to uncover (4).

As investigators learn how different individuals metabolize substances based on genetic uniqueness, there is an increasing awareness of the important roles specific nutrients can play in modifying the expression

of metabolic patterns in the individual. Diet, lifestyle, and environment have significant influence on the way an individual can metabolize specific substances based upon his or her genetic uniqueness. These discoveries have opened the door for the future of molecular medicine and the development of a personalized medicine that recognizes aspects of diet, lifestyle, and environment and their roles in individual disease causation and the design of specific intervention programs.

The takeaway from these concepts is that one size does not fit all. Diet and nutritional intervention must be personalized to the genetic characteristics of the individual. Gastrointestinal health is particularly important to achieving optimal nutrition and affords several examples of how diet and genes interface and how the field of nutritional genomics can assist the registered dietitian (R.D.) in maximizing nutrition care interventions for the individual.

### The Healthy Gut

The gastrointestinal (GI) tract is the second largest body surface area. The condition of this organ and the maintenance of its uniquely balanced microflora is essential to optimal health (5). The healthy intestinal wall is coated with hundreds of different species of microorganisms, both beneficial and pathogenic bacteria numbering in the trillions (5). This rich protective coating of microorganisms acts in concert with the physical barrier provided by the cells lining the intestinal tract and other factors to provide the body with important filter-like protection. So, in addition to digesting, absorbing and eliminating food substances and nutrients, the normal GI tract functions as a critical semi-permeable (selective) barrier between the internal and external environment. This prevents toxic, antigenic or pathogenic molecules or microorganisms from entering the bloodstream (6). Ultimately, the importance of the intestinal microflora and, more specifically, its composition, in physiological and pathophysiological processes in the human GI is becoming more evident (6).

### Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is a critical and chronic disorder of the intestines. Generally, its complications can be severe, widespread and very



painful. Crohn's disease (CD) and ulcerative colitis (UC) are two forms of inflammatory bowel disease (IBD).

As researchers try to understand the long unknown etiology of CD, there does not appear to be one precise cause of CD. However, it is clear that CD is relapsing in nature and it affects all layers of the intestines from mouth to anus. In comparison, UC is generally limited to the large bowel and does not necessarily affect all layers of the intestine

The anatomical location and behavior of CD can change over time. At diagnosis, the disease is located in the terminal ileum in 47%, the colon in 28%, the ileocolon in 21% and the upper GI tract in 3% of cases, respectively (7,8). "Patches" of asymmetrical intestinal inflammation and ulceration are seen in CD, interspersed between areas of healthy tissue (9). The inflammation and ulceration can potentially extend deeply into the intestinal wall, forming granulomatous lesions. The clinical presentation of patients diagnosed with CD is largely dependent on disease location. It can include some or all of the following symptoms: frequent diarrhea; lower right quadrant abdominal pain appearing soon after meals; bowel obstruction; fatigue; weight loss; low appetite; fever; stomatitis; passage of blood, mucus or both; and perianal fistulae or fissures.

Some patients also present with arthritis and erythema nodosum lesions on the extremities. Failure to thrive is observed in 75% of pediatric CD patients (10).

Approximately 10–15% of patients with disease confined to the colon and rectum present with "indeterminate colitis", in which the clinician is unable to definitively distinguish between ulcerative colitis and Crohn's disease (9). In such cases, blood tests that detect autoantibodies for "perinuclear anti-neutrophil antibody" (pANCA) and "anti-*Saccharomyces cerevisiae* antibody" (ASCA) are used to assist with a differential diagnosis (9). Frequently, those with UC present with the pANCA blood antibodies, while those with CD present with the ASCA antibodies. Although not every individual with UC and CD fits "neatly" into this profile, this approach is often helpful in distinguishing the two types of IBD (9).

In 1932, a group of three scientists, Ginzburg, Oppenheimer and Dr. Burrill B. Crohn, published a paper describing the features of an inflammatory bowel disease that was ultimately named Crohn's disease in honor of Dr. Crohn (9). Several categories of CD have been described, defined by the portion of the digestive tract involved and the presenting symptomatology (Table 1).

**Table 1.** Subcategories and Symptoms of Crohn's Disease (9)

SUBCATEGORY	AREAS AFFECTED
Crohn's (Granulomatous) Colitis	Affects the colon only. Symptoms include diarrhea, rectal bleeding, and disease around the anus (abscess, fistulas, ulcers). Skin lesions and joint pains are more common in this form of Crohn's than in others.
Gastroduodenal Crohn's Disease	Affects the stomach and duodenum. Symptoms include loss of appetite, weight loss, and nausea. Vomiting may indicate that narrowed segments of the bowel are obstructed.
Ileitis	Affects the ileum. Symptoms same as ileocolitis. Complications may include fistulas or inflammatory abscess in right lower quadrant of abdomen.
Ileocolitis	The most common form of CD, affecting the ileum and colon. Symptoms include diarrhea and cramping or pain in the right lower part or middle of the abdomen. Often accompanied by significant weight loss.
Jejunoleitis	Produces patchy areas of inflammation in the jejunum. Symptoms include abdominal pain

	(ranging from mild to intense) and cramps following meals, as well as diarrhea. Fistulas may form.
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Adapted from Crohn's and Colitis Foundation of America, Inc.  
<http://www.ccfa.org/research/info/aboutcd>

### Prevalence of Inflammatory Bowel Disease

The Crohn's and Colitis Foundation of American (CCFA) reports some alarming statistics. CCFA estimates that approximately one million Americans have IBD. This group is split almost evenly between individuals with Crohn's disease and ulcerative colitis. Crohn's disease affects both sexes fairly equally. People of all ages are affected, but the largest group is adolescents and young adults (ages of 15 to 35). Crohn's disease can occur in the 70+ age group and in young children. Only 10% of those affected are age 18 or younger. (4)

A recent review by Head reports that Crohn's disease predominantly affects Caucasians, with a prevalence rate of 149 per 100,000. However, recent trends show that the prevalence of CD and UC is on the increase with African Americans. IBD is largely a disease of the industrialized nations, especially the US and Europe, and is especially in cities and northern climates. Crohn's disease is prevalent in developed countries especially white-collar workers with indoor, sedentary occupations. One theory is that sedentary jobs delay intestinal transit time, allowing increased contact between food antigens and the intestinal mucosa. (11). The incidence of IBD varies by population. Northern European populations such as the Irish, Norwegians, Scots and Fins, have a modest risk compared to those living in lower latitudes (12,13). The prevalence of IBD in Asians, Arabs, Africans and African Americans are absent or low (14-18).

### Risk Factors

There are several risk factors for CD that range from adult appendectomy to the use of various substances, including nicotine (19-21), oral contraceptives, antibiotics and nonsteroidal anti-inflammatory agents (NSAIDs). Even second-hand smoke exposure has

been shown to increase risk for developing CD (22,23). Other demographic factors such as economical, educational, geographical and occupational status can increase the risk of developing CD (24). Despite these risk factors, Ferguson (25) explains that "IBD is considered a genetic disease" as approximately 20% of people with one form of IBD have a blood relative also with IBD and 58% of monozygotic twins share the disease as compared to 4% of dizygotic twins (26,27).

### The Immune-Inflammatory Connection

The gastrointestinal tract contains trillions of bacteria that are ideally in homeostasis with the host immune system (28). The gut contains most of the immune cells in the body and engages in a continuous fight with potentially pathogenic bacteria while leaving symbiotic bacteria largely unscathed (29). The presence of antibodies to microbial antigens in CD supports the theory that one aspect of CD pathology involves an abnormal immune response to otherwise normal intestinal flora resulting in inflammation and impaired intestinal permeability. For example, Crohn's disease is characterized by elevations in anti-*Saccharomyces cerevisiae* (brewer's yeast) antibodies in up to 60% of cases (30). Additionally, levels of antibodies, such as protein-bound IgG, have been found in the intestinal mucosa of patients with active CD to be significantly higher than patients with UC, irritable bowel syndrome, or non-specific IBD (31).

One theory of immune regulation involves homeostasis between T-helper 1 (Th1) and T-helper 2 (Th2) activity (32). "Th1" and "Th2" cells are "important regulators of the class of immune response." (32) Alterations in the host gastrointestinal flora can have a significant influence on the Th1/Th2 balance of the gastrointestinal immune system (gut-associated lymphoid tissue or GALT). (33) Sometimes referred to as the innate immune system or the acquired or

adaptive immune system respectively, balance of Th1/Th2 cytokines produced by the mucosa-associated lymphoreticular system (MALT) and the GALT plays a role in the stabilization of mucosal surfaces in the gut (34). These mucosal surfaces have multiple tasks that include absorption, macromolecule transfer and intestinal barrier and secretory functions. Large mucosal surfaces, such as the 300 square meters found in the human intestinal tract, are continuously exposed to millions of potentially harmful antigens from the environment, food and intestinal microbes. The mucosal surfaces possess a unique immune system that tightly controls the balance between responsiveness and non-responsiveness. Loss of this immunological recognition of “friend vs foe” in the gut can result in activation of the inflammatory process (29). There is growing evidence that chronic inflammatory disorders in the mucosa, such as IBD, are due to the dysregulation of the mucosal immune system leading to a Th1 dominant inflammatory reaction and impairment of the barrier function of the gut. (34)

### Genes/Gene Variants Associated With IBD – What Do We Know?

Knowing the genes and gene variants associated with IBD can be useful for the practitioner once it is understood what genes are involved and how their variations are related to underlying mechanisms of IBD pathogenesis. Furthermore, evidence based nutrition intervention can be used to modulate genetic expression which can ultimately affect phenotypic outcome of the individual.

While IBD appears to be of polygenic etiology, research strongly supports the assumption that susceptibility to IBD, especially Crohn's disease, is inherited. It also indicates that IBD is not inherited as a Mendelian trait, but rather has a complex genetic basis with many contributing genes and at least nine susceptibility loci identified (34, 35). (See Fig 1). Table 2 is a classification of the susceptibility genes, their variants and areas genes affect (12,13,35,37-42).

**Table 2.** Susceptibility genes associated with IBD

Name Of The Gene	Gene Abbreviation	Gene Variants (discussed in this review)	Areas Genes Affect
Caspase-activated recruitment domain 15/nucleotide oligomerization domain 2	CARD15/NOD2	<ul style="list-style-type: none"> <li>Arg702Trp</li> <li>Gly908Arg</li> <li>1007finsC or c.3020insC</li> </ul>	Affects bacterial recognition of the intestinal wall
Autophagy-related 16-like 1	ATG16L1		Affects bacterial recognition of the intestinal wall
Human beta defensins B2, B3 and B4	HBD-2, HBD-3 and HBD-4		Affects bacterial recognition of the intestinal wall
Major histocompatibility complex	MHC		Affects immune response
Interleukin-23 receptor	IL23R		Affects immune response
Toll-like receptors	TLRs		Affects immune response
Sodium dependent	SLC22A4/SLC22A5	<ul style="list-style-type: none"> <li>SLC22A4</li> </ul>	Affects mucosal

organic cation transporters	(also called OCTN1/OCTN2)	1672 C>T • SLC22A5 -207 G>C	transport or polarity of the intestinal wall
ATP-binding cassette subfamily B member 1	ABCB1		Affects mucosal transport or polarity of the intestinal wall
Drosophila discs large homologue 5	DLG5	• DLG5 113G>A • P.P1371Q • P.G1066G • Rs2289308 • DLG_e26 • P.D1507D	Affects mucosal transport or polarity of the intestinal wall

This review is focused specifically on three IBD-associated genes that appear to identify major susceptibility loci for CD: 1) CARD15/NOD2, 2) DLG5, and 3) SLC22A4/A5 (OCTN1/OCTN2).

### CARD15/NOD2

The CARD15/NOD2 gene located on chromosome 16q12 was the first IBD susceptibility gene to be associated with Crohn's disease (35). The CARD15 gene encodes the NOD2 protein, which is thought to provide protection against invasive bacteria by eliminating intracellular pathogens in epithelial cells at the gastrointestinal mucosa barrier (25). NOD2 protein is expressed by monocytes, granulocytes, dendritic cells and by epithelial cells. It functions as an intracellular sensor of peptidoglycan components of bacterial cell walls, known as muramyl dipeptide (25). Muramyl dipeptide (MDP) is a peptidoglycan component that specifically signals throughout the CARD15/NOD2 pathway. It is involved in modulating activity of the immune related transcription factor, nuclear factor- $\kappa$ B (NF- $\kappa$ B) (25).

There are 3 major polymorphisms that induce structural changes in the leucine-rich repeats for the CARD15/NOD2 gene (13,38). They are (see Table 2):

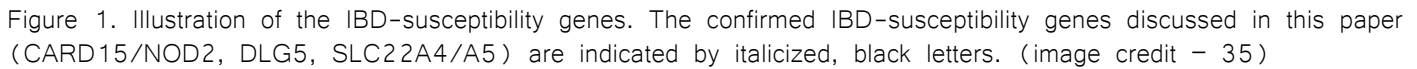
- i. Arg702Trp (35,41)
- ii. Gly908Arg (35,41)
- iii. 1007finsC (35) or c.3020insC (40,42)

The above described polymorphisms in the CARD15/NOD2 gene are all associated with a decreased functional response in stimulating MDP which appears to lead to NF- $\kappa$ B overexpression and inflammation (43,44). In a study by Kobayashi et al., the authors concluded that because the protein Nod2, encoded by the CARD15 gene, is critical in protecting the host from intestinal bacterial infection, variations in Nod2 might promote CD due to a defective response to commensal and/or pathogenic bacteria and may contribute to Th1 skewing (45). Therefore, it appears that defects in the initial innate response and subsequent signaling of the adaptive immune response are associated with increased susceptibility to chronic gut inflammation (46).

The CARD15/NOD2 polymorphisms are more prevalent in individuals with IBD as compared with non-IBD controls, but are not present in all cases of CD, either in humans or in mouse models. Intestinal inflammation is not always present in mice that have CARD15/NOD2 polymorphisms (45) and Hugot et al. (13) reported that 0%-5% of the general Caucasian population are homozygous for CD-associated mutations and 60%-70% of CD patients are heterozygous, in that they do not have both CARD15/NOD2 alleles mutated".

Given these discrepancies, it appears that the presence of CARD15/NOD2 gene variants may be a

immune response, presenting as chronic gut inflammation in susceptible individuals (25).



regulating cell growth and maintaining cell shape and polarity (48).

DLG5 proteins are localized at cell-cell junctions and are thought to be involved in the maintenance of epithelial integrity (47) and, thus, in preserving selective gastrointestinal permeability. Variants in the DLG5 gene are suspected of interfering with this function and resulting in disrupted epithelial barrier

function, which leads to increased gut permeability (49,50).

Six variants of DLG5 have been associated with IBD: p.R30Q (DLG5 113G>A), p.P1371Q, p.G1066G, rs2289308, DLG\_e26, and p.D1507D (35,37). Stoll et al. found that the DLG5 113G>A SNP resulted in an altered scaffolding protein that is involved in the maintenance of epithelial integrity (40). (Scaffolding proteins bring together various other proteins in a signaling pathway and allow for their interaction (51)). They concluded that the presence of the DLG5 gene variant alters intestinal permeability which increases risk for IBD.

Stoll also looked at potential epistatic (gene-gene) interactions. They stratified the study sample according to the presence of risk-associated CARD15 variants. (A gene is said to be epistatic when its presence suppresses the effect of a gene at another locus.) They reported “a significant difference in the association of the 113A DLG5 variant with Crohn's disease in affected individuals carrying the risk-associated CARD15 alleles versus those carrying non-risk-associated CARD15 alleles”, which suggests that there are epistatic interactions between CARD15 and DLG5 (40). This is an important point as it is not always the presence of just one gene variant or another that can lead to increased risk for a condition as much the epistatic interactions influence on disease susceptibility.

Considering that the DLG5 has been shown to be a susceptibility gene in many studies, it was interesting that DLG5 was not a relevant disease susceptibility gene for IBD in German or Hungarian subjects (42). This suggests that DLG5 may be more important as a CD susceptibility gene in some populations than in others. Also, Buning et al. did not find genetic interactions between DLG5 and CARD5 variants. Buning could not even demonstrate that DLG5 variants were associated with intestinal permeability (42). However, Buning states that his results should be interpreted cautiously as the sample size in his study was small (42).

#### SLC22A4/SLC22A5 (OCTN1/OCTN2)

The SLC22A4/A5 genes are located on chromosome 5q31 (39). They function mainly in the transport of sodium-dependent L-carnitine and encode the sodium-independent organic cation transporters OCTN1 and OCTN2 (52) thereby resulting in the elimination of cationic drugs (ie. verapamil, cimetidine, lidocaine, quinidine) in the intestine (25). Several SNPs have been identified, but two variants are SLC22A4 1672 C>T and SLC22A5 -207G>C. (The two are sometimes referred to as the “TC haplotype”(25)). The two-allele risk haplotype was observed with significant frequency in CD patients, however not all studies confirm this (53). The impact of the SLC22A5 -207G>C SNP appears to be to disrupt a heat shock transcription factor binding element (39) resulting in significantly decreased transporter activity compared with the wild-type form and increasing risk for Crohn's disease (41). The presence of the variants associated with the A4/A5 genes seems to reduce carnitine transport in a cell-type and disease-specific manner, thus leading to OCTN expression impairment and ultimately disease. Defects in impaired fatty acid beta oxidation in intestinal epithelium is initiated and is exacerbated by bacterial metabolites, thereby causing colitis (54,55). Alternatively, the effects of the SLC22A5 -207G>C variant on OCTN1 transporter specificity may also diminish uptake of physiologic compounds while increasing uptake of potential toxins, such as putrescine, derived from bacterial catabolism. In either scenario, a role for OCTNs in handling enteric bacteria or their byproducts is consistent with the effects of CARD15 mutations on cellular responses to bacterial products and provides a basis for the genetic interaction between these loci (39).

There is strong interaction among SLC22A4, SLC22A5 and CARD15 in Crohn's disease and a suggested interaction between SLC22A4 and RUNX1 in rheumatoid arthritis (56). These findings suggest that OCTNs participate in multiple pathways underlying chronic inflammation.

#### Summary of Gene Variants and Their Potential Impact On IBD Pathogenesis

CARD 15/NOD2 – Alterations in this gene have been associated with a defective bacterial signal that leads to NF- $\kappa$ B overexpression and subsequent excessive



immune response, which can lead to chronic gut inflammation in susceptible individuals.

**DLG5** – Variations in this gene seem to predispose individuals to what has been coined “leaky gut syndrome”, thus allowing for intestinal permeability and integrity dysfunction.

**SLC22A4/SCL22A5 (OCTN1/OCTN2)** – Functional polymorphisms decreasing OCTN activity and/or expression have been associated with chronic inflammation and contribute to CD/IBD pathogenesis. Specifically, this may be due to reduced carnitine transport function resulting in impaired fatty acid metabolism in the gut and toxic bacterial metabolites generated due to reduced ability for proper clearance of bacterial byproducts.

### Current Medical Management

Conventional pharmacological treatment has been directed towards suppressing inflammation. Typical drugs used to treat Crohn's include aminosalicylates (such as sulfasalazine and mesalamine), corticosteroids (such as prednisone and budesonide), immunosuppressive agents (such as azathioprine, 6-mercaptopurine, methotrexate), and antibiotics (57). More recently, anti-TNF-alpha monoclonal antibodies, such as infliximab and related drugs (Remicade®, Enbrel®, Humira®) are being prescribed since tumor necrosis factor appears to play a significant role in the pathogenesis of CD (58,59). Anti-depressants are typically offered for assisting with stress management as stress can also aggravate CD symptoms (60).

Unfortunately, medications used in the therapy of IBD often contribute to the development of many nutrient deficiencies. For example, sulfasalazine produces folate malabsorption by competitive inhibition of the jejunal folate conjugate enzyme (61). Corticosteroids suppress small intestinal calcium absorption and increase urinary calcium excretion. Cholestyramine,

(which is sometimes used in patients who have undergone post ileal resection in Crohn's disease to prevent diarrhea), produces fat, calcium, and fat-soluble vitamin deficiencies. Sulfasalazine, 5-aminosalicylic acid, or metronidazole may cause

nausea, vomiting, and dyspepsia, which frequently lead to decreased nutrient intake (62,63).

### Nutritional Management

Elemental diets, elimination diets, omega-3 fish oils, high fiber, low fiber, high protein, low residue diets and bland diets have all been used in one form or another as part of the nutritional management of IBD (25,64-67). However, nutritional protocols have been inconsistent from one health care facility to another despite growing research on IBD. Until recently, theories on nutritional management of IBD have been somewhat disunified.

#### *a. Functional Clinical Tests*

A combination of functional clinical testing (i.e. an intestinal permeability assessment, a gut mucosal assessment or even a comprehensive stool analysis) combined with genetic testing (ie. Screening for CARD15/NOD2, DLG5, etc.) could prove to be a prudent way to identify those at risk of IBD. These types of intestinal function tests are often single tests that determine intestinal permeability, imbalances of intestinal microflora, candidiasis, food allergies and immunodeficiencies (68). They can include a sensitive detection of serum IgA, IgG and IgM antibodies using the ELISA method. (The ELISA (e(nzyme)-l(inked) i(mmunoad)s(orbert) a(ssay)) method is a sensitive immunoassay that uses an enzyme linked to an antibody or antigen as a marker for the detection of a specific protein, especially an environmental or food antigen or antibody.) They are recommended for patients who are suspected of suffering from increased intestinal permeability and malabsorption as seen in Crohn's disease, candidiasis, food allergy, chemical hypersensitivity, fatigue, abnormal immune cell count and function and who are at a post-operative stage or at risk for sepsis (68). These tests provide an excellent tool for detection of the most common causes of altered intestinal permeability and poor assimilation of essential nutrients. Various CLIA (clinical laboratory improvement amendments) certified labs offer these types of functional tests, including Metamatrix Clinical Laboratory, Genova Diagnostics (formerly known as Great Smokies Diagnostic Laboratory), and Doctors Data, Inc.

Another possible measure of intestinal permeability in the small bowel is the oral lactulose/mannitol challenge test (69). In this functional assay, a patient consumes a standard amount of a solution of mannitol, a sugar alcohol, and the disaccharide lactulose in a hyperosmolar solution. Individuals with increased gut permeability of the small bowel absorb more lactulose, which is not metabolized and excreted in the urine, than individuals whose mucosa is normal. Mannitol, on the other hand, is translocated at a relatively fixed rate in all individuals. Thus an increased ratio of lactulose to mannitol in the urine indicates enhanced intestinal permeability (69).

Conducting a fecal calprotectin evaluation is another test for measuring intestinal inflammation (70,71). Calprotectin is a calcium-binding protein found in the following types of white blood cells: neutrophilic granulocytes, monocytes, and macrophages (70). Calprotectin resists metabolic degradation and can be measured in the feces. The fecal calprotectin test makes use of the fact that the release of calprotectin in the stool is associated with damage to the GI mucosa and increased inflammatory processes (71).

#### *b. Nutritional Influences in IBD*

A variety of nutrients have been found to be deficient in CD patients. Causes include malabsorption in the small intestine, increased nutrient need because of disease activity, low nutrient intake, nutrient loss due to chronic diarrhea or increased transit time or effect of medications. One study examining multiple nutrient deficiencies found 85% of 279 CD patients had deficiencies. Nutrients most frequently found deficient were iron, calcium, zinc, protein, Vit. B<sub>12</sub> and folate (72).

It has recently been suggested that certain protective nutrients and functional foods can provide protection of the gut mucosa from the CARD15/NOD2 related Th1-dominant inflammatory reactions (73). The amino acids glutamine and arginine, the essential micronutrients vitamin A, zinc, vitamin E and the B vitamin, pantothenic acid are among these protective nutrients. Evidence indicates that chronic H. pylori infection is associated with elevated oxidative stress in the intestinal mucosa, with increased levels of plasma lipid peroxides and other markers of free radical injury

(74). Therefore, supplementation with antioxidants, including ascorbic acid, tocopherol, and food flavinoids like quercetin (found in apples) and epicatechin gallate (from green tea), may be beneficial. Shapiro et al. (75) discusses the addition of polyphenols to artificial nutritional formulas to improve the outcome of patients with IBD. Five polyphenols in particular have shown in animal and human studies to have benefit in IBD by reducing inflammation associated with variations of the CARD15/NOD2 and SLC22A4/A5 genes: Boswellia, curcumin, epigallocatechin, quercetin, and resveratrol (75-84). Prebiotics and probiotics are also important substances that support proper function of the GALT and lead to the repair phase of gastrointestinal restoration (73).

Buddington and Weiher (85) proposed that, in managing functional gastrointestinal disorders, the GI system should be viewed as a flow system or "river". The GI tract is a complex ecological system that flows from top to bottom and requires nourishment to create the appropriate "ecology" within the small and large intestines (85).

#### *c. Putting It All Together With The Functional Medicine "4R™" GI Restoration Program*

There is a slow-moving but growing awareness that understanding the etiology at the genetic-molecular-environmental level may be just as important if not more important than disease classification. "Functional Medicine" – an evidence based systems biology approach addresses this concept of underlying etiology and root cause solutions and is now being encouraged by the National Institutes of Health under the new program NIH Roadmap, a route to accelerate medical discoveries that will improve health (86). In essence, functional medicine assessment is concerned with understanding the antecedents, triggers, and mediators of dysfunction that give rise to molecular imbalances underlying the signs and symptoms of disease (6).

The following is a brief adaptation of the "4R™ GI Restoration Program" that the Institute for Functional Medicine pioneered for the management of gut dysfunction and chronic disease. (6,87). It is a conceptual framework with which to target therapies aimed at improving GI function.

## 1. REMOVE

- What does this patient need to have removed for healthy GI function?

*Remove* focuses on eliminating pathogenic bacteria, viruses, fungi, parasites, and other environmentally derived toxic substances from the GI tract. Dietary modification is important, since foods to which a patient is intolerant or allergic can exacerbate GI dysfunction and stimulate immune and inflammatory responses systemically. Because Crohn's disease is characterized by elevations in anti-*Saccharomyces cerevisiae* (brewer's yeast) antibodies in up to 60% of cases (30), eliminating foods with yeast may prove to be therapeutic.  $\beta$ -glucuronidase is a marker for fecal putrefaction associated with increased risk of the adverse effects of colonic fermentation by bacteria. Interestingly, reduction of  $\beta$ -glucuronidase in the stool was a favorable outcome observed with rice bran supplementation but not with wheat bran (88).

## 2. REPLACE

- What does this patient need to have replaced to support normal GI function?

*Replace*, refers to the replenishment of enzymes and other digestive factors lacking or in limited supply in an individual's GI environment. GI enzymes that may need to be replaced include proteases, lipases, and saccharidases normally secreted by cells of the GI tract or by the pancreas. Other digestive factors that may require replenishment include betaine hydrochloride and intrinsic factor, normally produced by parietal cells in the stomach wall (89).

## 3. REINOCULATE

- What does this patient need to support or reestablish a healthy balance of microflora?

*Reinoculate* refers to the reintroduction of desirable bacteria, or "probiotics," into the intestine to reestablish microflora balance and to limit proliferation of pathogenic bacteria, candida and microbes associated with variation in the CARD15/NOD2 gene. Probiotics

serve a variety of functions in the GI tract: they synthesize various vitamins, produce short chain fatty acids necessary for colonic cell growth and function, degrade toxins, prevent colonization by pathogens, improve epithelial and mucosal barrier function and alter immune-regulation via stimulation of secretory IgA or reduction in TNF-alpha (90-94).

## 4. REGENERATE (also referred to as the REPAIR phase)

- What does this patient need to support the healing of the gastric and mucosal layer?

*Regenerate* refers to providing support for the healing and regeneration of the GI mucosa. Part of the support for healing comes from removing insults that continually re-injure or irritate the mucosa, and from promoting healthy microflora. Zinc-carnosine – Zinc carnosine is a chelate compound consisting of a zinc ion and L-carnosine – a dipeptide of beta-alanine and L-histidine. Studies have demonstrated that zinc carnosate promotes wound healing action, that it has an antioxidant effect in the GI system and that it also seems to have anti-*Helicobacter pylori* activity (95,96).

EPA-DHA – supplementation with omega-3 fatty acid-rich oil (3.24 gm of EPA and 2.16 gm of DHA daily) lowered the inflammatory response associated with variation of the CARD15/NOD2 and SLC22A4/A5 genes (decreased rectal levels of leukotriene B4) and improved remission in patients with IBD (97).

L-glutamine supplementation has also been found useful as part of a repair and regenerate program to restore GI mucosal integrity associated with the variation in the DLG5 gene (98).

A fifth "R" has recently been added (99):

## 5. RELIEVE

*Relieve* addresses acute discomfort in patients while treating the underlying conditions. Lavender oil has been used as an upper GI antispasmodic (100) while Chamomile flower extract and peppermint leaf oil has been studied as lower GI antispasmodics (101).

Additionally Chinese licorice root, tienchi ginseng root, and astragalus root may have a role in addressing heartburn and mild indigestion (100).

Promoting gastrointestinal health through this type of program may have significant impact, not only on localized intestinal inflammatory risk, but also on systemic inflammatory processes associated with the loss of intestinal mucosal integrity.

### Future Strategies

The application of nutritional genomics can create a better understanding of IBD pathology and has focused attention on the interaction between genetic factors and bacteria within the gut.

Whether through any of the above genes discussed, increasing scientific evidence supports the notion that inflammatory bowel disease results from a genetic predisposition to abnormal interaction with an environmental stimulant – most probably part of the normal luminal bacterial flora – which in turn leads to excessive immune activation and chronic inflammation. There are many putative bioactive molecules that are being identified every day that can help modulate genetic expression of inflammation, however, many of these components still need to be further tested with in vivo animal models of human disease. A combination of food fractionation, testing in tissue culture models and validation through animal models has been discussed by Sutton as a rationale for developing “nutrigenomics” based foods (102).

Although there is growing wealth of nutritional and medical information to guide an understanding of which nutrients or nutraceuticals should be used for personalized nutritional recommendations, it is an area that still requires much more intercommunication between various medical disciplines in order to obtain a more holistic and global perspective of a patient's medical and nutritional status and needs. In the past decade, nutrition research has undergone a shift in focus from epidemiology and physiology to molecular biology and genetics. This shift has resulted in a growing realization that we cannot understand the effects of nutrition on health and disease without determining how nutrients act at the molecular level. Muller and Kersten pointed out “There has been a growing recognition that both macronutrients and

micronutrients can be potent dietary signals that influence the metabolic programming of cells and have an important role in the control of homeostasis” (103). As a result, adequately trained health professionals who possess an authentic and experienced understanding of the interconnectedness of the biological systems in the human body, as well as the common underlying mechanisms that cut across many diseases, syndromes, conditions and organ systems, will be required particularly to interpret and communicate this information both to the public and with regulatory officials to responsibly develop, apply and progress this new field.

Additionally, this solid background and training will allow for far more personalized preventative care that incorporates a client centered approach, tailored to the patients' unique needs, (as compared to the current disease centered model which revolves around dissecting the body to arrive to a quick diagnosis, pharmacology and identifying ICD-9 codes), and will help to achieve tremendous success with “healing” our patients rather than just “treating” their symptoms. Searching for root cause solutions will be the focus rather than “band-aid” symptom management. However, the complexity of chronic illness, similar to layers of an onion, will require time, patience and a willingness to ask the questions that will lead us to the answers and understanding of how various human systems function interdependently as well as influence each other.

Nutrition-focused practitioners are at a pivotal point in the history of their practice. Kauwell recently stated, “Armed with the findings of the Human Genome Project and related research, dietetics practitioners will have the potential to implement more efficient and effective nutrition intervention strategies aimed at preventing and delaying the progression of common chronic diseases.” (104)

Additionally, because beliefs, attitudes, and motivations can all play a major role in overall wellness, it will be very important to examine and include not just the physical, but the mental, and emotional aspects, at least to a certain extent, of our patients in order to make a more holistic and accurate assessment and care plan of their nutritional needs.

Vay Liang W. Go (105) explains in an article published in 2005 that “with the advent of the postgenomic era, biological and medical research and clinical practice has witnessed an explosion in strategies and goals. This eventually will revolutionize the classical practice of nutrition from the current evidence-based medicine towards genomic-based medicine.”

But this very explosion can be part of the barrier to realizing the vision for health care professionals. Clinicians today must contend as never before with a massive amount of information emerging from the scientific literature. Furthermore, they must also beware of not falling into the common trap of blindly accepting or rejecting scientific information of any orientation, whether it be Eastern philosophies and/or Western approaches to medicine, or any approach for that matter, just because it is not well understood or because it is someone's opinion. To do so would be the epitome of injustice to the dietetics profession and to the patient.

One thing that can be done now to move this vision ahead will be the unbiased utilization of the already created and available organizational architecture of information that moves beyond the well-established “silos” of organ system medicine. For example, the effects of chronic inflammation of one organ system does not necessarily stop there. The inflammatory process can operate throughout the patient entirely, affecting multiple systems including the brain, the immune system and the endocrine system. Utilizing this type of “functional medicine matrix” will allow for a more precise and clear evaluation, formulation and integration of all the information at our disposal to create a systematic, effective and functional nutrition care plan for our patients that can potentially alter the trajectory of their health status forever.

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# 11

## Probiotics In Gastrointestinal Disease

**Gerard E. Mullin,  
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### What are Probiotics?

Probiotics are “live microbial feed supplements that beneficially affect the host animal by improving its intestinal microbial balance.”<sup>1</sup> There are numerous organisms that meet the criteria established by the WHO in order to be classified as a probiotic.

### Clinical Applications of Probiotics in Digestive Disease

In IBS, the most commonly utilized and studied probiotic species are *Lactobacillus*, *Bifidobacteria*, and *Saccharomyces boulardii*.<sup>2-4</sup> The results of randomized, controlled clinical trials using probiotics to treat IBS symptoms are shown in Table 3. *Bifidobacterium infantis* 35624 (*B. infantis*) has been shown to be associated with improvement in IBS symptoms except stool frequency and consistency.<sup>5, 6</sup> *Lactobacillus GG* was shown in one study to be more likely to have treatment success and reduced frequency of pain compared to placebo.<sup>7</sup> A probiotic mixture containing

*Bifidobacterium breve Bb99*, *Propionibacterium freudenreichii* ssp, and *shermanii* JS was shown to be associated with improvement in IBS total symptom scores.<sup>8, 9</sup> VSL#3 was shown to be superior to placebo for improving bloating, flatulence in patients with IBS.<sup>10</sup> Fermented milk containing *Bifidobacterium animalis*, *S. thermophilus* and *L. bulgaricus* when compared to placebo was found superior for improving symptoms in patients with constipation-predominant IBS patients.<sup>11</sup> A multispecies probiotic formulation used in a smaller study again showed improvement in composite IBS scores, specifically abdominal distension and pain, compared to placebo.<sup>12</sup> VSL#3 was shown to be significantly superior to placebo in the pediatric population.<sup>13</sup>

### Traveler's Diarrhea

Traveler's diarrhea is a condition that disrupts work and vacation and affects many individuals traveling from developed countries to developing countries. The most common causative bacterial

organism is enterotoxigenic *E. coli* (ETEC). Probiotics rather than antibiotics are now among the recommendations for the prophylaxis of traveler's diarrhea. A 2007 meta-analysis concluded a significant benefit in the reduction of diarrhea among travelers who used probiotics.<sup>14</sup> The dose for prevention of traveler's diarrhea varies; the recommended dosing should be started several days before travel to enable adequate colonization and subsequent protection for the initial and riskiest days of the trip.

### ***Clostridium difficile* infection**

*Clostridium difficile* infection is a prevalent and increasingly severe nosocomial infection that presently accounts for 15 to 25% of hospital cases of antibiotic associated diarrhea (AAD). *Clostridium difficile* is a toxin-mediated illness with characteristic clinical and pathologic features.<sup>15</sup> Diagnosis is confirmed by assay of toxins A & B. *Saccharomyces boulardii* has been effective as adjunctive therapy for *C. difficile* infection.<sup>16</sup> The dosage is 250 mg twice daily for prevention and four times daily to prevent recurrent *C. difficile* colitis, in concert with either metronidazole or vancomycin. A meta-analysis has found that probiotics reduced the frequency of acute diarrhea in *C. difficile*-infected patients.<sup>17</sup> *S. boulardii* appears to be effective for recurrent *C. difficile* infection.<sup>18, 19</sup>

### ***Inflammatory Bowel Diseases***

#### ***Ulcerative Colitis***

VSL#3 is a well-studied probiotic preparation that is available in the United States. Each dose contains 450 billion live bacteria per packet. The bacteria included are *Bifidobacterium breve*, *Bifidobacterium longum*, *Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus paracasei*, *Lactobacillus bulgaricus*, and *Streptococcus thermophilus*. A number of well-designed clinical trials have shown that VSL #3 can facilitate both the induction and

maintenance of remission in UC better than when medication was used alone.<sup>20-23</sup> A recent metaanalysis demonstrated that probiotics overall showed superiority to placebo for maintenance but not for the induction of remission.<sup>24</sup> The use of probiotics in ulcerative colitis appear promising.

### ***Crohn's Disease***

There are to date fifteen published trials evaluating the efficacy of probiotics for the maintenance of remission of Crohn's disease. The trials using *Saccharomyces boulardii* appear to be promising.<sup>25</sup> Overall, the results are mixed and thus the use of probiotics as an adjunctive treatment for CD is not warranted. More well-designed trials are needed before *S. boulardii* can be recommended for the therapy of Crohn's Disease.

### ***Pouchitis***

Pouchitis is a non-specific inflammation of the ileal reservoir following ileal pouch-anal anastomosis for ulcerative colitis occurring in about one half of all pouch patients. There are diminished amounts of lactobacilli and bifidobacteria in the pouch contents. Probiotics have been successfully as therapy.<sup>26-28</sup> Overall, VSL#3 appears to be a promising probiotic for the prevention of pouchitis or the maintenance of remission of inflammatory disease.

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### **Summary**

Probiotics play a role in the amelioration of illnesses as *C. difficile colitis*, IBS, traveler's diarrhea IBD and pouchitis. Future research will provide further supporting evidence regarding the value of probiotics in the prevention and treatment of disease and the optimization of health.

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He is an authority in Integrative Gastroenterology and has lectured nationally and internationally on this subject. Dr. Mullin has been awarded a honorary membership of the Academy of Nutrition and Dietetics (formerly known as The American Dietetic Association). He is the editor of the book, Integrative Gastroenterology by Oxford University Press. He co-authored another book, The Inside Tract: Your Good Gut Guide to Great Digestive Health with Kathie Madonna Swift. MS, RD, LDN. He also coedited The Gastrointestinal and Liver Disease Desk Reference by CRC Press.

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# 12

## Getting Unstuck

**James S. Gordon,  
MD**



### Introduction

Depression is not a disease, the end point of a pathological process. It is a sign that our lives are out of balance, that we're stuck. It's a wake-up call and the start of a journey that can help us become whole and happy, a journey that can change and transform our lives.

The approach I use challenges the prevailing "medical model" of depression and the widespread, even epidemic, use of chemical antidepressants. This narrow model of diagnosis and treatment insists that those who feel helpless and hopeless, unhappy and uncertain have a disease, like insulin-dependent diabetes that requires pharmacological treatment. There is evidence that strongly suggests that this model is poorly justified, largely inappropriate, limited and limiting, and, often enough, dangerous to your physical, emotional and spiritual health. The antidepressants that it dictates should be used seldom—as a last resort and generally briefly—not as a form of primary care.

What I'm sharing with you in the case history that follows is a newer, more hopeful and far more comprehensive and effective model for

healing depression—both the clinical depression that is diagnosed in sixteen to eighteen million Americans each year and chronic, low-grade dissatisfaction, unhappiness, and anxiety that affect so many more of us. It's a model you can incorporate into your work now, one that will meet your patients' unique individual needs and give them positive results that they can begin to experience immediately.

This Unstuck approach marries modern science with the perennial wisdom of the world's great psychological and spiritual traditions. It makes use of the remarkable capacity each of us has to recover—physically, emotionally, spiritually—from the hurts and trauma we have experienced, to transform our fears into teachers, and to restore and renew our brain, body, mind and spirit.

Here is how I used this approach with one patient. It will give you a feeling for what is possible, for what you can also do.

Theresa, a 37-year-old African-American civil rights lawyer, tells me in our first session together that she has been miserable for a month. During that time she's dropped weight she can ill afford to lose and has been sleeping only four to five

hours a night. Alternately listless and agitated, Theresa's been unable to concentrate at work. She leaves her office late—feeling guilty for what she hasn't done and anxious that she will have to make up for it the next day. While she used to go dancing with friends in the evenings, now she tells them she's tired. At home, she watches TV and eats frozen dinners. Sometimes she measures her wine in bottles, not glasses. She is feeling increasingly hopeless. Theresa is clearly clinically depressed and her internist and psychotherapist have already urged her to take antidepressants. But she doesn't want to. She has come to me to find “a better way.”

Theresa already knows I view depression differently than her doctor and therapist do—“Depression is not a disease,” as I explained to her on the phone when she called to make an appointment. “It's a wake up call, potentially the start of a journey that can help us become whole and happy, a journey that can change and transform our lives.” Before any patients visit my office or pay me a fee, I make sure to speak on the phone with them, let them know who I am, what my perspective is, how I work, and make sure they want to participate in what I have to offer. I also usually suggest that before the first appointment, they read something I've written about my practice, get to know a little more about the meditative, eclectic, active and engaged “Unstuck” approach I will offer. This kind of conversation feels respectful, clears up misunderstandings and helps ensure that our future time together will be used well.

The congruence, the fit between what I'm offering and what my patient is hoping for, will be the springboard for all our work. It will provide the shared vision on which we can draw in the difficult and challenging times that may come in any therapy. Finally, commitment to an integrative approach – and the urgency that may fuel that commitment – help provide the energy which sustains us in meeting the challenges of our work together.

I begin, as any therapist would, by asking Theresa what happened a month ago right before her

depression. She says that she has just ended another relationship and reminds me that at almost 40, she still doesn't have a man who loves her or a child. I listen carefully as Theresa describes the inhibition and despondency that shadowed her childhood—the recent break up with her boyfriend has plunged her into the same kind of hopeless darkness she remembers from that time. A thousand miles away, she tells me, her mother's arthritis has slowed her to irritated immobility and her father's sight and vigor are fading. Theresa feels she should be with them, but doesn't want to, and she feels guilty about that. “I carry my whole organization on my back, too” she says ruefully, “women's rights for everybody except this woman.”

As I take in what Theresa is telling me, I encourage her to see herself as a student and adventurer, an active participant in our work together. Indeed, she is the one primarily responsible, with my guidance, for helping herself. “Self-care,” I often tell clients, “is the true primary care.” From our first session, I convey to her my belief that she has within her the resources for her own healing. Indeed, I begin to help her recognize what she is already doing that is helpful to her. In Theresa's case, the morning yoga she still sometimes does gives her energy; and phone calls or visits with her best friend, Barbara, dispel, at least for a while, her deepening loneliness. I write these activities down on a prescription pad, as another physician might an antidepressant drug—crafting “a Prescription for Self-Care” at the end of the first session.

I also teach Theresa (and virtually all of my patients), a simple, meditation technique called “Soft Belly,” involving slow deep breathing in through the nose, out through the mouth, with the belly soft and relaxed. I encourage Theresa to close her eyes as she breathes in order to remove distracting stimuli. I suggest that she say to herself, “soft” as she breathes in through her nose and “belly” as she breathes out through her mouth. If thoughts come, I say, let them come, and let them go.

"Soft belly" is, I explain, an antidote to the fight or flight and stress responses, which figure prominently in the development and deepening of depression. Soft belly brings more oxygen to the lungs and stimulates the vagus nerve, which is central to relaxation. Slowly, I tell Theresa, the relaxation of the belly will spread to the other muscle groups as well.

I explain to Theresa that though the research studies are most often done on 30–40 minutes a day of meditation, just a few minutes several times a day will help balance her physiologically, slow her anxious, pressured thought patterns, and give her a little more perspective on her life. Equally important, as she sees she has the capacity to help herself, she will be overcoming the helplessness and hopelessness that are hallmarks of depression. I add "Soft Belly 3–5 minutes, 3–5 times a day" to Theresa's Prescription for Self-Care.

I do Soft Belly along with Theresa and with all my patients. It's of course helpful for me to be as relaxed and open as possible in my sessions. It also conveys an important message to my patients: We are on this journey together. I'm not an observer. I'm here with you, learning as well as teaching, experiencing life, and dealing with my own stress along with you. Dealing with depression and its challenges and with stress, generally is, I am recognizing and admitting, not separate from our lives— an extraordinary response to a pathological situation — but an ordinary and ongoing part of them.

We speak in the weeks ahead about the historical context of Theresa's depression— her mother's coldness; her isolation as a young black girl in a still segregated, white southern community; her tendency to take responsibility for the emotional lives of others— her parents first, then her employees and lovers. Still, I am continually bringing our focus back to what is happening right now — how present feelings reflect past disappointments, and how she can relax with, learn from, and move through them. If she were to ask, I would explain that this is a meditative, present-oriented approach to psychotherapy.

Theresa, significantly more relaxed as well as reassured after our first session, felt encouraged and supported by the Prescription for Self-Care. Each week, I ask her about her progress and express appreciation for what she is doing well, while not being dismayed by what has been too difficult, or what she's ignored or neglected. Our work is not about her "good" or "poor" compliance—what an ugly, condescending word — but about what she can learn from difficulties, avoidance, and defeats as well as from "success."

Sometimes patients who seem originally committed to this Unstuck approach grow discouraged and are reluctant to pursue it. Nagging doubts remain about whether antidepressants might be the best and easiest answer, after all, or at least a necessary precondition for improvement and therapy. I respond with information on the most recent meta-analyses of drug research, which show that when unpublished negative studies are included along with positive, published ones, drugs are little if any better than placebos. I tell patients that I'm not "against" the drugs—I just see them, with their uncertain benefits, significant side effects and potential for habituation, as a last resort, not a first choice.

Like many depressed people, expecting to get a prescription but not much more in the way of attention, Theresa is afraid of being "left alone" with her depression. I assure her that I myself have been on the journey through and beyond depression and that I will be there with her at every step of her journey. I make sure she understands we'll have regular appointments — a usual feature of psychotherapy, but a significant departure for people who are used to seldom seen, drug-prescribing physicians. I also tell my patients they can call me anytime—and find that this reassurance is itself powerful medicine: Knowing they can call me, that I am always there, almost no one does.

I also begin, in our first or second session, to directly address the comprehensive biological dimensions of depression. "Depression is not a disease," I say, "but diseases of a variety of kinds, and imbalances in biochemistry and nutrition

can cause or contribute to depression.” I make sure my patients see a competent primary care physician who can rule out the obvious physical causes of depression--reactions to medication, and conditions like cancer, diabetes, heart disease, multiple sclerosis, etc.

If there are no obvious physical causes, I encourage my depressed patient to find a physician, dietitian or nutritionist who can look for and treat a variety of conditions less commonly diagnosed, which may be implicated in depression, anxiety and chronic fatigue. These include nutrient deficiencies, food sensitivities, subclinical hypothyroidism, heavy metal toxicity, and small intestinal bacterial overgrowth. I sometimes test for these myself. More often, I refer to other physicians who practice “integrative” or “functional” medicine.

Unless you are a physician, dietitian, or trained nutritionist, you shouldn't “prescribe” complex dietary changes. Nonetheless, you can certainly suggest basic guidelines for healthier eating. I always encourage patients to eat whole foods (preferably organic), little or no processed food, less sugar, protein primarily from vegetarian or fish sources and poultry rather than red meat, and increased doses of fiber (we consume about one tenth as much as our Paleolithic ancestors and our indigenous brothers and sisters). Because our food supply is so depleted, and given the ordinary stress of living in modern society, virtually anyone can benefit from a high dose multivitamin/multimineral supplement (without iron, unless anemia is present). People suffering from depression or bipolar disorder will also benefit from supplementation with Omega 3 fish oil (2-6 grams a day). Those with gastrointestinal, as well as emotional upset, may well find relief from both kinds of symptoms by taking supplements with “probiotic” bacteria (*bifidus* and *lactobacillis*) that normally live in a healthy gut.

Exercise is also critical for mood regulation. In fact, next to speaking with an experienced, reliable, and compassionate listener – a good therapist – exercise is probably the single most effective of all the antidepressants. As a therapist

you can provide information about the benefits of exercise from a wealth of studies in peer reviewed journals and also help your patients develop individualized exercise programs. The effectiveness of jogging is well-researched, but if your patient hates doing it, it won't happen. Walking, running, dancing and yoga have also been demonstrated to be enormously helpful. Theresa was already doing yoga, and I encouraged her to continue. Later I suggested that each morning she put on fast music and dance for 15 minutes.

From the first session on, I give my patients detailed instruction in guided imagery, focusing most often on two images: the creation of a “safe place” where they can find calming sanctuary in difficult, stressful times; and consultation with an “inner” or “wise” guide—an emblem of their intuition and imagination on which they can call for advice and counsel. I also often teach “Dialogue with a Symptom, Problem, or Issue (SPI)” –a Gestalt-like exercise in which a rapid, written dialogue between my patient and her physical, emotional, spiritual, social or interpersonal SPI often reveals both its origins and possible solutions. I work too with journaling, drawing and movement to express and reveal feelings and release them. The message to my patients is clear and consistent: You can mobilize your own mind and body to help and heal yourself; I am here to help, to equip you to do it, and to support you as you do.

There may come times, especially when working with very seriously depressed people, when the increased hopefulness and good feelings you have helped stimulate seem to dissolve. Often I find that this is a good time to ask my patient to consult her “wise guide” or to use the dialogue with the SPI to mobilize her capacity for healing. Sometimes I use expressive techniques – fast deep breathing, pounding pillows, and holding yoga postures at length – to bring up suppressed feelings, facilitate emotional release and break up physical rigidity, and mobilize energy.

Occasionally, someone's distress is so great that she insists on what one of my patients called “a



physiological boost” – something beyond the holistic approaches already tried. At this point, I may well use the natural “precursor” supplements that directly increase the levels of the neurotransmitters serotonin, and norepinephrine, including S-adenosylmethionine (SAMe) and tryptophan and the herb St. John’s Wort. While these can also produce side effects similar to those of drugs, they are usually far less severe. I do not regard the use of these precursors as signs of treatment failure, but as necessary, quite often temporary, therapeutic aides. Clearly these are supplements that dietitians and nutritionists can effectively use.

Only when these supplements, together with the rest of my approach, do not work, or if my patient explicitly requests it, do I refer her for pharmacological therapy. And, I continue to work with her while she sees a psychopharmacologist. Except in cases where people have debilitating chronic illnesses that may well become terminal, the time people in my practice spend on drugs is almost always relatively brief.

A spiritual perspective informs my work from my first moments with each person. Not an explicit religious orientation, this perspective encompasses an appreciation for the yet unrevealed potential of each person, a sense of sacred connection within each of us to something larger than ourselves, and moments of inexplicable grace that can transform each person’s work with me and on their own.

Not long ago on a phone call, Theresa reminded me of this dimension of her life and of our work together. She had moved through her depression in two months of weekly sessions with me, without neurotransmitter precursors or drugs. She had continued to see me once every month or two for “refresher sessions” for another three years. Then, two years ago, she moved away to take a position at a law school. I had watched her grow over the years into a peacefulness which she had never before known –meditating regularly, doing yoga, taking time for herself. Now we were catching up and she was looking back on our work together. “My depression and the sad

state of my spiritual life were two sides of the same coin,” Theresa reflected. First, I needed to look at myself psychologically to see that I was depressed, that mine were ordinary human problems. I wasn’t this bad, immoral woman, sleeping with guys who didn’t love me, drinking too much and smoking pot. I just needed to see how what I did and the sad confused way I felt connected to my childhood—to that lonely little girl with her desperate desire to please. And I needed to get my life on a track that worked for me. But, she continued, “I also needed to feel my spiritual side. And by that I mean the heart, or the soul, or the divine in me.”

Through her work with me, as well as meditation, yoga, and dance, Theresa said, she began to develop “some emotional radar...to sense what I was feeling—whether anxious, sad, angry—to know if something was off-kilter. I learned that I didn’t need to fight it, that it was okay just to let myself feel the pain—it was just passing feelings, and not something fundamentally wrong with *me*. I no longer,” Theresa goes on, “have the feeling that I won’t get what I want. I *have* what I want.” Here she emphasizes that wonderful, present tense word, so different from all the past-tense terms of loss and longing that marked her depression, “I feel whole and happy as I am. If I find a ‘significant other’... that would just add to it.

I thank Theresa out loud, and silently, too, for sharing with me what is possible. Freud wrote about replacing neurotic with ordinary unhappiness. Psychopharmacologists praise the restoration of the “pre-morbid personality.” Theresa is showing me, telling us, what it means to move from being terribly, chronically, depressed to feeling blessed every day.

Excerpts from this article are taken from the following book:

Gordon, James S. (2008) [Unstuck: Your Guide to the Seven-Stage Journey Out of Depression](#). New York: Penguin Press.

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Dr. Gordon has created ground-breaking programs of comprehensive mind-body healing for physicians, medical students and other health professionals; for people with cancer, depression and other chronic illnesses; and for traumatized children and families in Bosnia, Kosovo, Israel and Gaza, and Haiti, as well as in post-9/11 New York and post-Katrina southern Louisiana. Visit The Center for Mind-Body Medicine's website at [www.cmbm.org](http://www.cmbm.org) for more info.

Dr. Gordon has also written the books listed below, and has written and edited many other articles, chapters, and monographs and books.

Gordon, James S. (2008) *Unstuck: Your Guide to the Seven-Stage Journey Out of Depression*. New York: Penguin Press.

Gordon, James S. (2000) *Comprehensive Cancer Care: Integrating Alternative, Complimentary and Conventional Therapies* with Sharon Curtin, Cambridge MA: Perseus.

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# 13

## Integrative Nutrition For Autism

### Elizabeth Strickland, MS, RD, LD



There is an alarming increase in the rate of developmental disabilities such as autism spectrum disorders in our young children. Twenty-five years ago, autism was rare; according to the Center for Disease Control, now 1 in 110 children in the United States are diagnosed with the disorder (1). Autism is a developmental disorder identified in the first three years of life and affects the brain's normal development of social and communication skills. First identified in 1943 by Dr. Leo Kanner of Johns Hopkins University, autism remains a puzzling childhood disorder. Treating autism is a challenge and there is no clear cut protocol. Every child is unique and responds to a different variety of treatment approaches. Therefore, it is critical that a multi-disciplinary team work together to create the most effective combination of therapies for the individual child.

#### Autism Treatment

Treatment of autism typically includes medication, special education services, behavioral programs, occupational therapy, sensory integration therapy, speech-language therapy, complementary and alternative medicine, and numerous other therapies such as art, music, and hippo. Another treatment

of autism includes nutrition therapy. Nutrition is the foundation upon which all other treatments are built. We can not expect a child with autism to fully benefit from all his numerous therapies until his nutritional needs are met.

#### Physician's Role in Nutrition Therapy and Autism

More physicians now recognize that treating autism purely as a psychiatric disorder is an outdated model of care. Rather, autism is now seen as a whole body disorder where the brain is affected by biochemistry within the body. For many children with autism, their physiological and behavioral symptoms may stem from or be exacerbated by impaired biochemistry. Physicians play a critical role in ensuring that nutrition therapy is included as a component of the child's comprehensive treatment plan. When physicians emphasize the role that nutrition plays in enhancing a child's brain and body function and refer the child to a Registered Dietitian, it encourages parents to take good nutrition more seriously.

#### Nutritional Interventions Used to Treat Autism

Integrative nutritional interventions are utilized to balance the child's biochemistry and heal the child systemically. Nutritional interventions include removal of certain foods and food additives,

correct nutrient deficiencies, treat gastrointestinal problems, elimination diets, and identify and treat food reactions. Nutritional interventions to help treat autism should be individualized for the child and implemented with the guidance of a Registered Dietitian.

### 1) REMOVAL OF CERTAIN FOODS AND FOOD ADDITIVES

Basic nutrition has become a serious issue for our children over the last twenty years because children's diets have changed dramatically. The food children eat today is nothing like the food children ate in previous generations. Today, children subsist mainly on foods that are highly processed, lacking in nutrients, and loaded with artificial chemicals, preservatives, Trans fats, sugar, and pesticide residues. The repercussions of this shift toward poor nutrition are serious. We've seen a dramatic increase in developmental and neurological disorders in our children. Therefore, the first step in nutritional interventions to treat autism is to transition the child onto a diet that consists of whole, healthy foods and eliminate all unnecessary artificial ingredients.

#### Eliminate Synthetic Food Additives

There are twenty-four different types of synthetic food additives found in the foods we eat. We are consuming man-made chemicals with virtually every bite of food and no one really knows what effect they may be having on our immune, respiratory, endocrine, and nervous systems. There is controversy in the medical community about what the short and long-term impact of these chemicals may be on a growing child's brain and nervous system (2, 3). The autism community is particularly concerned about four of the synthetic food additives: artificial colors, artificial flavors, preservatives, and artificial sweeteners.

**Artificial colors** currently permitted in our foods in the United States (U.S.) include Blue No. 1, Blue No. 2, Green No. 3, Red No. 40, Red No. 3, Yellow No. 5, and Yellow No. 6. There's a growing body of research that indicates some children are sensitive to these artificial colors and that they aggravate the child's Attention Deficit Disorder (ADD) and Attention Deficit Hyperactivity

Disorder (ADHD) symptoms (4). A study published in the November 2007 issue of *The Lancet* concluded that artificial colors in the diets of children resulted in increased hyperactivity (5). Research also indicates that ingesting artificial colors may result in behavioral changes, such as irritability, restlessness, and sleep disturbance (6). Other research indicates that when ingested, some artificial colors may aggravate the symptoms of hives, eczema, dermatitis, rhinitis, and asthma (7). Removing artificial colors from the diet will help relieve a child's physical and behavioral symptoms, though the degree to which it will help will depend on the level of his sensitivity to chemicals.

**Artificial flavors** are chemically synthesized compounds added to foods to either imitate or enhance a natural flavor. There are approximately 1,700 artificial flavors approved by the Food Drug Administration (FDA). An artificial flavor of particular concern in the autism community is monosodium glutamate (MSG). MSG is the sodium salt of an amino acid called glutamic acid and the ionized form of glutamate. It's used commercially as a flavor enhancer and found in many common food products such as canned soups, beef and chicken stocks, flavored potato chips, snack foods, frozen dinners, instant meals with seasoning mixtures, and foods from fast food restaurants. Some fermented products have naturally occurring glutamate, such as soy sauce, steak sauce, and Worcestershire sauce.

Glutamate may also be present in a variety of other additives such as hydrolyzed vegetable protein, hydrolyzed soy protein, autolyzed yeast, hydrolyzed yeast, yeast extract, soy extracts, and protein isolate. MSG is "generally recognized as safe" (GRAS) by the FDA; however, there are health concerns. Glutamic acid is classified as an excitotoxin, and animal studies indicate that ingesting a high level of it causes brain damage (8). While most researchers agree it is unlikely that human adults could ingest enough MSG to create glutamic acid levels high enough to promote neurological damage, there is concern about the unknown long-term neurodegenerative effects of

small to moderate rises of glutamic acid in our systems over time.

Researchers are also concerned about the potential short and long-term effects MSG may have on infants and young children. There appears to be a number of people who are sensitive to MSG and develop acute adverse reactions, such as headache, facial pressure, chest pain, nausea, difficulty breathing, drowsiness, weakness, and aggravation of asthma symptoms. Sensitivity to MSG or other artificial flavors may be causing or exacerbating a physical problem for the child, which in turn may be causing a behavioral problem. Removing artificial flavors from his diet is a critical step toward improving his symptoms.

**Artificial preservatives** are natural or man-made chemicals added to food products to inhibit the growth of bacteria and fungi, inhibit oxidation, and prevent changes in the food's color, odor, and taste. Research shows that artificial preservatives aggravate ADD and ADHD symptoms in some children (4). The autism community is particularly concerned about the effect that the artificial preservatives butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA) may have on children. BHT and BHA are fat-soluble phenol compounds approved by the FDA to be used as an antioxidant food additive. BHT can be found in cereal, chewing gum, and high-fat foods, such as potato chips and shortening. Many countries, such as Japan, Romania, Sweden, and Australia, have banned BHT from use in foods, but the U.S. has not yet followed suit. However, the U.S. has barred it from being used in baby foods. Many food industries have voluntarily eliminated BHT from their foods and replaced it with the preservative BHA, but there also are serious concerns about BHA. After conducting animal studies, the National Institutes of Health (NIH) concluded that it is reasonable to assume that BHA is a human carcinogen (9). Researchers also suspect that people with dysfunctional detoxification systems may have difficulty processing both BHT and BHA (10). Eliminating artificial preservatives, especially BHT and BHA, from the child's diet may help relieve some of his behavioral symptoms.

**Artificial sweeteners** are man-made compounds that are many times sweeter than sucrose. Their safety and potential for health risks, including cancer, has been a longstanding controversy in the medical community (11). The three most commonly used artificial sweeteners in the U.S. are saccharin, sucralose, and aspartame. Saccharin, the first artificial sweetener created, is 300 to 500 times sweeter than table sugar. Saccharin is FDA approved in the U.S., but some countries allow only a restricted level of use and other countries have banned it completely. Sucralose is a chlorinated sugar that is 600 times sweeter than table sugar. It belongs to a class of chemicals called organochlorides, some of which are highly toxic or carcinogenic. However, many researchers suggest that since sucralose is insoluble in fat, it doesn't accumulate in fat as do other organochlorides, which reduces its risk of toxicity (11). Aspartame is derived from two amino acids, aspartic acid and phenylalanine, and is 200 times sweeter than table sugar. Headaches and seizures have been reported in relation to aspartame, making its safety a much-debated topic. In the autism community, the focus is on the impact aspartame may have on a child's brain function (12). Though all of these artificial sweeteners are approved for use by the FDA, there is still much debate surrounding their long-term safety, especially for children who could potentially have decades of continued exposure. It is important to understand that just because a food additive has been approved by the FDA, this does not necessarily mean it is safe for our children. To be cautious, it is suggested to eliminate all artificial sweeteners from the diets of children.

#### **Limit Foods that Contain Trans Fat**

Trans fat is the product of hydrogenation, which is the process by which hydrogen is added to liquid vegetable oil. The fatty acids in the oil then acquire some of the hydrogen, which makes it denser. Typically, the hydrogenation process is only partially completed in order to produce a more malleable fat that is solid at room temperature, but will melt upon baking. Partially hydrogenated fats have replaced natural solid fats

and natural liquid oils in our foods because they are cheaper and they prolong the shelf life and flavor stability of foods. Trans fat can be found in vegetable shortenings, some margarines, crackers, cookies, chips, cakes, pies, bread, snack foods, and foods fried in partially hydrogenated oils. It's also used in some dietary supplements, energy bars, and nutrition bars. In January 2006, the FDA required food manufacturers to list Trans fat on their product labels. Dietary supplement manufacturers are also required to list Trans fat on the product label if it contains more than 0.5grams.

There are a number of reasons why Trans fats should be avoided (13). But the autism community is especially concerned about the negative impact Trans fat has on the liver. Trans fats interfere with the enzyme delta 6 desaturase, which is critical in the process of converting omega-3 and omega-6 fatty acids in foods to the active forms arachidonic acid (ARA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) (14). A deficiency of delta 6 desaturase causes a deficiency of ARA, EPA, and DHA, which are critical for brain development, brain function, brain cell signaling, and vision processing. Research indicates that children diagnosed with ADD, ADHD, dyslexia, dyspraxia, and autism may already have low levels of delta 6 desaturase, so when these children consume foods with Trans fat, it makes their situations worse (15). It is suggested to limit Trans fat in the child's diet.

### **Limit Exposure to Pesticides**

The best way to limit a child's exposure to pesticides is to buy organic foods whenever possible. An organic food has been grown, handled, and processed without the use of artificial pesticides, artificial fertilizers, sewage sludge, artificial additives, hormones, or antibiotics. It does not contain genetically-modified ingredients and has not undergone irradiation or been chemically ripened. The U.S. Environmental Protection Agency (EPA) has established levels of pesticide residues that are considered safe, but these levels were set based on the studied effect pesticides have on adults and do not take children into account.

Children are much more vulnerable to pesticide exposure because of their smaller size and developing brain and nervous system. They may also be more sensitive to pesticides because their detoxification system is less able to adequately process and excrete them. Pesticides disrupt acetylcholinesterase, a key enzyme needed for brain cell communication. Additionally, animal research shows that certain classes of pesticides can affect the developing fetus and impair normal brain development, resulting in hyperactivity, and learning and developmental disabilities (16, 17, 18, 19). A recent research study indicated that children are primarily exposed to pesticides through their diet, and when their foods were replaced with organic foods, their levels of pesticides dropped dramatically (20). While we cannot completely control the amount of pesticide a child is exposed to, we can significantly lower his exposure by purchasing USDA organic foods.

### **Avoid Refined Sugar**

Sucrose, more commonly known as white sugar or table sugar, has typically been the sugar of choice to sweeten food and beverages. Over the last several years, high-fructose corn syrup (HFCS) has begun to replace sucrose in many processed foods in the U.S. Sugar and HFCS can be found in soft drinks, fruit juice, candy, peanut butter, yogurt, snacks, ice cream, and many other foods our children eat on a regular basis. We know that too much sugar is unhealthy for children because it contributes to problems like diabetes, obesity, and tooth decay. Numerous research studies support the belief that sugar has a negative impact on behavior, attention, hyperactivity, aggression, mood, and mental function; however, many other research studies conclude just the opposite, that sugar has no affect (12, 21, 22, 23, 24).

***How does sugar affect children?*** Sugar is a simple carbohydrate that is rapidly digested and broken down into glucose, which is quickly absorbed into the bloodstream. When a child consumes a sugary food or drink, it causes a rapid rise in his blood glucose level (hyperglycemia). This spike in the child's blood glucose level triggers his pancreas to release the



hormone insulin to lower his blood glucose level. This in turn causes his blood glucose level to drop rapidly (reactive hypoglycemia), triggering the release of adrenaline and other hormones to raise his blood glucose level once again. Some children are more sensitive than others to this abnormal, rapid rise and fall of blood glucose levels, and their bodies overreact with a biochemical response that can lead to physical and behavioral symptoms. Symptoms vary from child to child depending on their sensitivity, but some common symptoms include nervousness, shakiness, light-headedness, dizziness, fatigue, sweating, tremors, flushing, confusion, anxiety, headaches, depression, irritability, and craving sweets. Sugar does not directly cause hyperactivity; however, it does set into motion biochemical responses in a child's body that can lead to behavioral problems.

## 2) CORRECT NUTRIENT DEFICIENCIES

If a child is lacking basic nutrients in his diet, his brain and immune, gastrointestinal, and detoxification systems will not function to the best of their ability. Protein, carbohydrate, fat, vitamins, minerals, and water are important basic nutrients the child needs. Getting a child with autism to eat a diet that includes all the basic nutrients is challenging. The majority of children with autism eat a very limited diet accepting less than five or ten different foods. Children with autism often refuse new foods, throw tantrums when offered an unfamiliar food, will only drink fruit juice, or seem to crave carbohydrates. If this is the case, a child with autism will not start eating a healthier diet just because it is offered to him. This child is likely not a "picky eater" rather he is a "problem feeder" that requires feeding therapy to expand his diet. Refer to Chapter 5 in the book "Eating for Autism" by Elizabeth Strickland for detailed information on feeding problems and how to get a child with autism to expand his diet and eat healthier foods.

**Basic Nutrients** are divided into six categories: protein, carbohydrate, fat, vitamins, minerals, and water. These basic nutrients provide a total of 45 essential nutrients, which our bodies are dependent on to sustain life. An essential nutrient is a

substance that your body is unable to make on its own and must be consumed through your diet.

**Protein** is an important basic nutrient, especially during infancy, childhood, and adolescence when children are growing and developing rapidly. The body uses protein to manufacture hormones, antibodies, enzymes, tissue, and neurotransmitters, and to repair body cells and produces new ones. Protein can also be turned into glucose for energy required by the brain when carbohydrates are not available. Lastly, our bodies need adequate protein in order to provide amino acids, which are the building blocks of the body.

When a child eats a food that contains protein, his body breaks the protein down into amino acids that are used throughout his body for various purposes. Protein provides the essential amino acids histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine. Some amino acids are used to produce energy during times of starvation; others are used to produce enzymes that act as catalysts for biochemical reactions, and antibodies to fight off illness. Still others build muscle tissue and generate cell signaling. Several amino acids function as neurotransmitters to generate cell signaling within the brain. Some of these amino acids are involved in activities such as learning, memory, and specification of nerves in the developing brain. If a child with autism eats a poor diet or refuses to eat meats, he may have a protein deficiency. Signs of a protein deficiency include decreased mental alertness, comprehension, and concentration (25).

***How much protein should a child consume?*** The chart below shows the Recommended Dietary Allowance (RDA) of protein children need based on age (26). While the RDA provides a good idea of the minimum amount of protein a child requires, he may need more protein depending on variables, such as illness, infections, stress, and genetics. It is best for a Registered Dietitian to assess the child's nutritional status and determine his individual protein needs and whether he is meeting them in his current diet. The Registered Dietitian may request that the physician order

blood lab tests to assess the child's protein status, such as prealbumin, retinol binding protein, transferrin, and serum albumin tests.

#### RECOMMENDED DAILY ALLOWANCE FOR PROTEIN

Age	Protein (grams/day)
<b>Children</b>	
1–3 years	13
4–8 years	19
<b>Males</b>	
9–13 years	34
14–18 years	52
19 years and older	56
<b>Females</b>	
9–13 years	34
14 years and older	46

*Source: Food and Nutrition Board, Institute of Medicine, National Academies*

When choosing protein-rich foods for a child, the best choices are complete proteins, or proteins that contain all of the essential amino acids. Complete proteins are found in foods such as beef, poultry, fish, pork, game, eggs, milk, yogurt, cheese, tofu, and soy milk.

Also offer child incomplete proteins, or proteins that lack one or more of the essential amino acids. Dietary sources of incomplete proteins include beans, peas, nuts, seeds, and grains. Incomplete proteins can be combined to form a complete protein, meaning together they provide all of the essential amino acids. This combination is called a complementary protein. An example of a complementary protein combination is beans combined with brown rice, wheat, nuts, seeds, or corn; and brown rice combined with beans, wheat, nuts or seeds.

**Carbohydrates** are the body's primary source of energy. Proteins and fats can also serve as energy sources, but the body prefers carbohydrates because they're more easily converted to glucose. Glucose is the only source of energy the brain can use, so it is important that children consume enough carbohydrates to maintain a constant supply of glucose to the brain. This keeps their brains functioning at their optimum level throughout the day. There are two major types of

carbohydrates: simple carbohydrates and complex carbohydrates.

Simple carbohydrates include monosaccharides and disaccharides. Monosaccharides, such as glucose, fructose, galactose, are composed of a single sugar unit whereas disaccharides, such as sucrose, lactose, maltose, are composed of two sugar units. Examples of simple carbohydrates are honey, corn syrup, high-fructose corn syrup, molasses, candy, soda, and sweets. Fruits and milk are also classified as simple carbohydrates, but they are considered nutrient-rich simple carbohydrates because they contain vitamins, minerals, fiber, and important nutrients like calcium and protein.

Complex carbohydrates are polysaccharides, which consist of many sugar units strung together to form long complex chains. Examples of complex carbohydrates include foods such as rice, potatoes, peas, beans, corn, and whole-grains products like flour, bread, and pasta. As with simple carbohydrates, some complex carbohydrates are better choices than others. Refined complex carbohydrates, such as white flour and white rice, have been processed, which removes nutrients and fiber. But unrefined grains still contain their original vitamins and minerals. Unrefined grains also are rich in fiber, which helps the child's digestive system work well.

Unrefined complex carbohydrates and nutrient-rich simple carbohydrates are better choices than simple and refined complex carbohydrates. Simple carbohydrates (with the exception of fruit and milk) are digested, broken down into glucose, and enter the bloodstream rapidly, which causes hyperglycemia and reactive hypoglycemia. On the other hand, complex carbohydrates are digested, broken down into glucose, and enter the bloodstream slowly, which in turn stabilizes the child's blood glucose levels. The protein in milk and fiber in fruit prevent them from triggering the rapid fluctuation in blood glucose levels as do other simple carbohydrates (27).

**Fat** is needed for our bodies to function properly. Besides being an energy source, fat is a nutrient

used in the production of cell membranes, as well as in several hormone-like compounds called eicosanoids. These compounds help regulate blood pressure, heart rate, blood vessel constriction, blood clotting, and the nervous system. In addition, dietary fat carries fat-soluble vitamins A, D, E, and K from our food into our bodies. Fat helps maintain healthy hair and skin, protects vital organs, keeps our bodies insulated, and provides a sense of fullness after meals. It is also critical for brain function, especially in the developing brain of a child. About two-thirds of the human brain is composed of fats. The myelin sheath, which serves as a protective insulating cover for communicating neurons, is composed of 70 percent fat (28).

**Omega-3 fatty acids** in the form of Docosahexaenoic acid (DHA) and Eicosapentaenoic acid (EPA) is the most abundant fat in the brain. EPA works to increase blood flow, which influences hormones and the immune system and affects brain function. DHA is the major structural component of the brain. It supports neurotransmission among brain cells to provide optimal cognitive functioning, which impacts learning and memory. DHA is also a component of the retina of the eye, supporting optimal visual acuity, visual functioning, and vision processing. DHA is also very important during pregnancy, lactation, and infancy because of the rapid brain development of the fetus, infant, and young child. Both EPA and DHA are converted into hormone-like substances called prostaglandins, which help regulate cell activity and healthy cardiovascular function. Clearly, getting enough EPA and DHA is very important, especially for children. DHA and EPA are essential fatty acids, which means that the body can not produce it and therefore it must be consumed through our diet. Good sources include fatty, cold-water fish, such as salmon, mackerel, and herring. A deficiency of essential omega-3 fatty acids will compromise the child's brain function, ability to learn, memory, attention, and behavior. Research studies have linked omega-3 fatty acid deficiencies of DHA and EPA to autism, dyslexia, ADHD, dyspraxia, depression, and anxiety (29, 30, 31, 32).

Research published in the April 2007 *Journal of the Developmental and Behavioral Pediatrics* indicated that supplementing children's diets with omega-3 fatty acids improves poor learning and behavioral problems (33). Another research article published in 2007 in *Biological Psychiatry* found that supplementing with omega-3 fatty acids decreased hyperactivity in children with autism spectrum disorders (34). Many other research studies show that supplementing with omega-3 fatty acids reduces aggression, improves reading and spelling ability, and significantly improves hyperactivity, inattention, impulsivity, anxiety, and cognitive problems (35, 36, 37).

Unfortunately, the typical child's diet is extremely low in both DHA and EPA. The average child in the U.S. consumes only 19 mg of DHA a day, which is a fraction of the recommended amount he should consume. Children may eat a considerable amount of the plant-derived omega-3 fatty acid alpha-linolenic acid (ALA) in the form of flaxseed oil, flaxseeds, canola and soybean oils, and walnuts; however, the body must convert ALA to EPA and DHA to be useful for brain, vision, and body function. The metabolic conversion of ALA to EPA and especially to DHA is very low, even in healthy individuals.

Research indicates that males are less able than females to make the conversion of ALA to EPA and DHA (38, 39, 40). Additional research studies indicate that children diagnosed with ADHD, dyslexia, and dyspraxia have a compromised ability to convert ALA to EPA and DHA even when they consume an adequate amount of dietary ALA (41). Researchers concluded that this was caused by a deficiency of the enzyme delta-6 desaturase, which plays an integral role in the conversion of ALA to EPA and DHA. It is suggested that the best way to compensate for this possible delta-6 desaturase enzyme deficiency in a child is to provide him with a direct dietary source of EPA and DHA. The following chart lists the foods that contain DHA and EPA (42).

## DIETARY SOURCES OF DHA AND EPA

Food	DHA and EPA combined (mg per ounce)
Salmon, Atlantic, farmed	608
Herring, Pacific	602
Herring, Atlantic	571
Salmon, Atlantic, wild	521
Tuna, fresh, blue fin	426
Mackerel, Atlantic	341
Sardines (canned in oil)	278
Trout, mixed species	265
Flounder	142
Halibut	132

Source: USDA, Agricultural Research Service, Nutrient Data Laboratory

**Avoiding Mercury Contamination in Fish** – When adding fish to a child's diet, it is important to consider the health concerns surrounding heavy metals like mercury and fat-soluble pollutants like PCB and dioxins. In the autism community, mercury is a heavy metal of special concern because it is a neurotoxin that harms the brain and nervous system of unborn babies and young children. Mercury naturally occurs in the environment and is also released into the air from coal-fired power plants and municipal and medical waste incinerators. The mercury travels for long distances in the air before being deposited into bodies of water such as lakes, streams, and the ocean. Bacteria in these waters transform the mercury into methylmercury. Fish absorb the methylmercury as they feed in these waters and it accumulates within them. Nearly all fish and shellfish have varying levels of methylmercury, depending on how long they live and how much other fish they eat. Basically, the larger fish and the longer its lived, the higher its level of mercury. When a pregnant woman eats fish, she exposes her developing fetus to methylmercury, which poses a threat to its developing brain. Depending on the level of exposure, methylmercury can cause impairment in language, attention, and memory; gait and visual disturbances; effects on neurological development; and mental retardation.

Below are the FDA and the EPA's recommendations for choosing and eating fish for women who are or may become pregnant and nursing mothers:

- 1) Do not eat shark, swordfish, king mackerel, and tilefish.
- 2) May eat up to 12 ounces a week of a variety of fish and shellfish that are lower in mercury, such as catfish, salmon, pollock, shrimp, and canned light tuna.
- 3) Limit canned albacore "white" tuna to 6 ounces per week due to higher mercury levels.
- 4) Limit tuna steak to 6 ounces per week due to higher mercury levels.
- 5) Check local advisories regarding the safety of fish caught in your local lakes, streams, rivers, and coastal areas.
- 6) If no advisory is available, you may eat up to 6 ounces per week of fish caught from local waters, but don't consume any other fish during that week.

There are currently no recommendations regarding the amount of fish considered safe for young children, so the FDA and EPA suggest following the above recommendations, but serve smaller portion sizes (43).

**Other Dietary Sources of Omega-3 Fatty Acids** –

A new trend has emerged recently in which foods are fortified with omega-3 fatty acids. DHA can now be found in a variety of foods, such as infant formula, yogurt, bread, and juice. Eggs are not naturally a good source of omega-3 fatty acids, but now omega-3 enriched eggs, which contain up to 400mg DHA and EPA, are available in grocery stores. Omega-3 enriched eggs are produced by feeding hens a special diet containing ground flaxseed. The actual level of DHA and EPA will vary depending on the flaxseed composition of the chicken feed. Free-range chickens that eat grass and insects also produce eggs with higher-than-normal levels of omega-3 fatty acids.

**How Much Omega-3 Fatty Acid Does a Child**

**Need?** There is no RDA for omega-3 fatty acids. Instead, the U.S. Food and Nutrition Board set levels of Adequate Intake (AI) for ALA. No specific requirements have been set for DHA and EPA; however the Food and Nutrition Board

indicates that up to 10 percent of the AI for ALA can be in the form of DHA and EPA combined. For example, a child's daily need for DHA and EPA are 70mg for a 1 – 3 year old, 90mg for a 4 – 8 year old, and 120mg for a 9 – 13 year old child (26).

The National Institutes of Health (NIH) recommends we consume even higher levels of DHA and EPA. According to the NIH, 30 percent of our daily calories should be DHA and EPA combined. The chart below lists the amount a child should consume according to these standards (44).

ADEQUATE INTAKE OF DHA AND EPA (Based on 30 Percent of Calories)		
Age	DHA and EPA combined (mg/day)	
1 – 3 years	390	
4 – 6 years	540	
7 years and older	650	

Source: National Institutes of Health (NIH)

Since deficiencies of DHA and EPA are linked to autism, dyslexia, attention deficient hyperactivity disorder, dyspraxia, depression, and anxiety, it is suggested that the NIH's recommendations be used to determine a child's DHA and EPA needs.

***Omega-3 Fatty Acid Supplements for Children with Autism*** – Children with autism and other developmental disorders often have feeding problems, eat a limited variety of foods, and refuse fish, so it may not be possible to get adequate amounts of omega-3 fatty acids into the diet of a child with autism. In this case, the child will need to take an omega-3 fatty acid supplement. A Registered Dietitian can assist parents on selecting a high quality child-friendly fish oil supplement.

Examples of fish oil supplements are listed below:

Fish Oil Supplement	Amount	DHA and EPA
Cod liver oil (liquid)	1 teaspoon	1,035 mg
Coromega™ (original)	1 packet	580 mg
DHA Junior		
(Nordic Naturals)	1 soft gel	52 mg
Omega-3 Gummies	1 gummy	68 mg

(Nordic Naturals)

**Vitamin and Minerals** also known as micronutrients are needed for normal growth, function, and health. Our bodies do not make most micronutrients, so we have to get them from the food we eat or in some cases, from dietary supplements. Vitamins and minerals are critical for brain development and function; regulating cell and tissue growth, processing and eliminating toxins from the body; maintaining a healthy gastrointestinal tract; supporting immune system function; converting protein, carbohydrate, and fat into energy; providing structure to bones; formation of blood; and numerous other body functions. Some vitamins also function as hormones, antioxidants, coenzymes, and precursors for enzymes. Each vitamin and mineral is unique and has its own specific role in the body (45). The most important vitamins and minerals for brain function include:

- **Calcium** is required for the transmission of nerve impulses in the brain and aids in the release of neurotransmitters from neurons.
- **Iron** transports oxygen to the brain and is also needed to produce the neurotransmitter dopamine. A deficiency of iron can cause fatigue, impaired mental function, poor work and school performance, and decreased attention span, learning, and memory.
- **Vitamin B1 (thiamin)** aids normal functioning of the nervous system and a deficiency can result in mental confusion and complications involving the brain.
- **Vitamin B2 (riboflavin)** is required by the body for the production of energy, to form glutathione, and to convert vitamin B6 to pyridoxal 5-phosphate.
- **Vitamin B6 (pyridoxine)** helps the body break down protein, and helps maintain the health of red blood cells, the nervous system, and parts of the immune system. Vitamin B6 is also involved in the production of the neurotransmitters serotonin and dopamine. A deficiency of

B6 may result in depression and confusion.

- **Vitamin B12 (cobalamin)** is involved in the production of certain amino acids, maintenance of the nervous system, formation of the myelin sheath, formation of neurotransmitters, and plays a role in preventing depression and other mood disorders. A B12 deficiency can cause fatigue, confusion, delayed development, poor memory, depression, and neurological changes such as numbness and tingling in the hands and feet.
- **Folic acid** helps the body produce and maintain healthy new cells, especially during periods of rapid growth. A deficiency of folic acid may result in loss of appetite, irritability, forgetfulness, and behavioral disorders.

If a child is deficient in any vitamin or mineral, his brain will not function at its optimum level. This in turn will prevent the child from fully benefiting from his various therapies and special education services. For example, consider how a child is impacted by an iron deficiency. Iron is essential to transport oxygen to the brain and is also involved in the production of the neurotransmitter dopamine. A low iron level could cause a child to experience symptoms such as apathy, short attention span, irritability, impaired memory, and reduced ability to learn (46). Recent studies indicates that iron deficiency interferes with dopamine activity and may contribute to ADHD (47, 48). Correcting the iron deficiency resulted in considerable improvement in these children's ADHD symptoms and cognitive test scores. If just one mineral deficiency can have such a significant impact on

the child's brain function, imagine how several vitamin and mineral deficiencies can affect the child. Children need to eat a variety of foods from all five food groups to get the basic vitamins and minerals required for optimum brain and body function.

The information below can be used as a general guideline to assure a child is consuming an appropriate amount of servings from the different food groups to provide adequate amounts of vitamins and minerals (49).

#### TYPES AND AMOUNTS OF FOOD CHILDREN NEED EACH DAY

Food Group	Number of Servings
Milk, yogurt, cheese	2 – 3
Vegetable	3 – 5
Fruit	2 – 4
Bread, cereal, rice, pasta	6
Meat, poultry, game, fish, eggs, beans, nuts	2 – 3

#### GUIDELINE FOR CHILDREN'S SERVING SIZE

Food Group	2–3 years	4–6 years	7–12 years
<b>Milk</b>			
Milk	½ cup	½–¾ cup	½–1 cup
Cheese	½ oz	½–1 oz	2 oz
Yogurt	4 oz	4–6 oz	8 oz
<b>Vegetable</b>			
Cooked	¼ cup	¼–½ cup	¼–½ cup
Raw	few pieces	several pieces	several pieces
<b>Fruit</b>			



Raw	½ small	½–1 small	1 medium
Canned	1/3 cup	1/3–½ cup	½ cup
Juice	3–4 oz	4 oz	4 oz
<b>Grains</b>			
Bread, buns, bagels	¼–½ slice	1 slice	1 slice
Pasta, rice	¼–1/3 cup	½ cup	½ cup
Cereal, cooked	¼–1/3 cup	½ cup	½–1 cup
Cereal, dry	1/3–½ cup	1 cup	1 cup
Crackers	2–3	4–6	4–6
<b>Meat and Dried Beans</b>			
Meat, poultry, fish	1–2 oz	1–2 oz	2 oz
Eggs	1	1	1–2
Peanut butter	1 Tbsp	1–2 Tbsp	2 Tbsp
Beans	2–4 Tbsp	¼–½ cup	½ cup

Source: *ADA Pocket Guide to Pediatric Nutrition Assessment*

#### ***Daily Multivitamin and Mineral Supplement for a***

***Child with Autism*** – Children with autism tend to eat a very poor diet limited to only a few foods, so they often suffer from numerous vitamin and mineral deficiencies. If this is the case, the child will need to take a daily multivitamin and mineral supplement. Many healthcare professionals believe that vitamin and mineral supplements are unnecessary and that children can get everything they need just by eating a well-balanced diet. This may be true for children who eat a variety of healthy foods from the different food groups, have a properly functioning digestive system that can digest and absorb the nutrients consumed, and whose bodies are able to utilize the nutrients absorbed. Unfortunately, most children with autism do not fall into this category. Children with autism often eat a very limited variety of foods and have mealtime behavior problems that interfere with their food consumption (50, 51, 52). Many have sensory problems that impact their acceptance of certain textures, flavors, and smells of foods, resulting in feeding problems. Some autistic children are on elimination diets that limit their intake of certain nutritious foods. Still, others have chronic gastrointestinal disorders that interfere with their ability to digest and absorb nutrients properly. All of these factors make children with autism far more vulnerable to having chronic vitamin and mineral deficiencies.

Severe vitamin and mineral deficiencies are rare in the U.S.; however, marginal vitamin and mineral

deficiencies are very common. A marginal vitamin or mineral deficiency can result from a chronic poor diet, which impacts the child slowly, over time, with more subtle symptoms. Marginal vitamin and mineral deficiency symptoms include poor attention and concentration, irritability, loss of appetite, mood and behavior changes, depression, anxiety, and sleep disturbances. Marginal deficiencies can affect a child globally, meaning they can prevent both his body and brain from functioning at their best. The child will be physically and mentally unable to fully respond to, participate in, and benefit from his therapies. While vitamin and mineral supplements can not replicate all the nutrients a child would naturally consume from eating a variety of whole foods, a supplement is a good complement to his diet. A Registered Dietitian will advise parents on selecting an appropriate daily multivitamin and mineral supplement for the child.

**Water** is the most basic nutrient our bodies need, and it is also one of the most neglected components of our diet. Our bodies need a certain amount of water each day for proper body temperature regulation, muscle function, absorption of nutrients, transporting nutrients into body cells, transporting waste out of body cells, and the elimination of waste and toxins from the body. We get water not only from drinking it, but also from other liquids like milk and juice and from vegetables and fruits. If we do not have enough water in our diet, we are at risk for dehydration.

For a variety of reasons, infants and children are more prone to dehydration than adults. Symptoms of mild dehydration include tiredness, muscle weakness, lightheadedness, and headache.

In children with autism, these symptoms can be easily missed. Children with autism often have expressive language delays or are non-verbal and unable to express their thirst. Some children with autism do not even recognize the sensation of thirst and therefore never ask for water. These children are especially susceptible to dehydration. Subtle though the symptoms may be, dehydration will have a major impact on how the child feels both physically and mentally, his ability to function normally, and his ability to excrete toxins out of his body. The chart below lists the total amount of water a child should consume daily (26). The amount of total water a child needs will vary according to their level of physical activity, medical problems, and weather environment in which you live. A Registered Dietitian can calculate more exactly the total amount of water a child requires based on their individual needs.

#### ADEQUATE INTAKE OF WATER

Age Group	Total Water	
	Liters/day	Cups/day
<b>Children</b>		
1 – 3 years	1.3	5
4 – 8 years	1.7	7
<b>Males</b>		
9 – 13 years	2.4	10
14 – 18 years	3.3	14
≥ 19 years	3.7	15
<b>Females</b>		
9 – 13 years	2.1	9
14 – 18 years	2.3	10
≥ 19	2.7	11

Source: *Food and Nutrition Board, Institute of Medicine, National Academies*

**Eliminating toxins from drinking water** – It is important to consider the source of the water for a child because safe, uncontaminated drinking water is vital to his health (53, 54). In the autism community, neurotoxins are a major concern and many parents try to eliminate heavy metals from their children's environment as much

as possible. Common sources of water pollutants include:

- Biological agents (bacteria, viruses, parasites)
- Inorganic chemicals (arsenic, lead, mercury, chromium, nitrates)
- Organic chemicals (pesticides, benzene, polychlorinated biphenyls, trichloroethylene)
- Disinfectant chemicals (chlorine, chlorine dioxide, chloramines, haloacetic acid, trihalomethanes)
- Radionuclides (radon)

These pollutants can affect major body organs such as the kidneys and liver; promote certain forms of cancer, leukemia, and anemia; and may affect the neurological and gastrointestinal systems (55, 56). Consider the use of a home water purification system, such as a reverse osmosis water filter, to reduce various contaminants in drinking water.

#### 3) TREAT GASTROINTESTINAL PROBLEMS

Gastrointestinal problems involving the esophagus, stomach, small intestine, and colon are very common among children with autism (57, 58, 59, 60, 61). It appears that GI problems are more prevalent in children with autism than other children. In a study published in the *Journal of the Developmental and Behavioral Pediatrics* in 2006, 70 percent of children with autism were found to have a lifetime history of gastrointestinal symptoms, such as abnormal stools, constipation, frequent vomiting, and abdominal pain (62). A research article released September 2011 by *Williams, Hornig, Buie, et al.* indicated that GI activity of children with autism differs from other children primarily in two ways; intestinal cells show abnormalities in how they break down and transport carbohydrates, and their intestines have abnormal amount of certain bacteria (63). A consensus report published January 2010 in *Pediatrics* stated that problem behavior in children with autism spectrum disorders may be the primary or sole symptoms of gastrointestinal disorders (64).

**Elimination Problems** – One of the most common GI symptoms children with autism have is chronic constipation. Research confirms that constipation is more common in children with autism than other children (65). Abdominal X-rays of children with and without autism who are experiencing stomach pain has shown that autistic children have a significantly higher rate of excess stool in the colon. Children with chronic constipation often associate bowel movements with pain and deliberately hold in their stool to avoid a bowel movement. Due to holding in their stool, over time the child will no longer recognize or respond to the urge to have a bowel movement which exacerbates the constipation. If the child is experiencing chronic constipation, he will feel uncomfortable and may even be feeling severe pain. These children may express their pain as behavioral and feeding problems. Chronic constipation can also result in physical issues such as megacolon and encopresis.

On the other end of the spectrum, some children with autism also tend to have problems with chronic diarrhea, loose stools, non-formed stools, or a combination of all three at different times. Many parents describe their child as never having had a normally-formed stool. Chronic diarrhea is diarrhea that is present for more than three weeks and is not associated with an illness. Many medical professionals refer to it as chronic non-specific diarrhea (CNSD). If a child with CNSD continues to gain weight and grow taller at a normal rate, many medical professionals do not consider it a significant health problem or suggest any specific medical treatment to resolve the bowel issue. Parents, however, are usually very concerned about their child's abnormal loose stools and rightly so. If the child with autism is having difficulty controlling his bowel function, it will impact him in many ways. For instance, having chronic diarrhea, loose stools, and/or non-formed stools will affect his ability to potty train, forcing parents and other caregivers to continue changing diapers beyond the typical age. The child's bowel issues may make him feel uncomfortable which will affect his sensory system and can lead to behavioral problems. He may also encounter nutritional deficiencies because chronic diarrhea

causes malabsorption of vitamins, minerals, and other nutrients. This impedes his body's ability to repair the lining of the GI tract, which only serves to exacerbate his malabsorption of nutrients. This vicious cycle of chronic diarrhea, malabsorption, and nutrient deficiencies can compromise the child's overall health, brain function, and behavior.

**The Gut – Behavior Connection** – Undiagnosed gut problems can cause serious behavioral problems in children with autism, particularly those who are unable to verbally express the pain they are feeling. If a child is nonverbal, he may communicate how he feels through his behavior. Unfortunately, too often these symptoms are dismissed as “typical” autistic behaviors as opposed to attempts to communicate what the child can not put into words. Identifying and correcting the child's gastrointestinal disorder will lead to significant improvement in his behavior. A child with gut problems may suffer from one or more the follow symptoms:

- **Gastrointestinal symptoms** – reflux, vomiting, abdominal pain, bloating, flatulence, loose stool, diarrhea, constipation, infrequent stool, straining to pass stool
- **Vocal behaviors** – clearing of throat, screaming, sobbing, whining, moaning
- **Motor behaviors** – facial grimacing, gritting teeth, grazing, mouthing on clothes, pacing, self-injury, jumping up and down, aggression, puts pressure on abdomen
- **Change in overall state** – sleep disturbances, irritability, oppositional behavior
- **Mealtime behaviors** – food refusal, limited variety of foods, mealtime tantrums, discontinue eating foods he used to eat

#### **Dietary Treatment of gastrointestinal symptoms**

Referral to a Registered Dietitian is important to educate parents on basic nutritional management of GI problems. Often basic nutritional interventions will heal the child's gut and resolve their GI symptoms.

#### **Step 1: Dietary Modifications**

Children with autism tend to eat an excess amount of white refined carbohydrates with their diets lacking in whole grains, protein, healthy fats, vitamins, minerals, and water. As long as the child continues to eat a limited diet consisting primarily of white refined carbohydrates, we can expect the child to have GI problems. So, the first step is to expand the child's diet to include a variety of whole healthy foods. Adequate water and fiber from fruits, vegetables, and whole grains will help promote normal daily bowel movements. The Registered Dietitian will provide specific nutrition recommendations for the individual child to promote normal bowel movements.

**Step 2: Supplements, Herbs, and Nutraceuticals**  
Probiotics, anti-fungals, and digestive enzymes play a major role in healing the child's GI tract. The right combination of these supplements will support and maintain a healthy balance of naturally-occurring microorganisms in the child's gastrointestinal tract.

**Probiotics** – The GI tract contains microflora which must be maintained at an ideal balance in order to support the immune system and the production of certain vitamins and digestive enzymes. Research shows that children with autism have significant imbalances in their upper and lower gut microflora. A study published in the *Journal of Medical Microbiology* in 2005 indicated that severe gastrointestinal problems in children with autism may be due to an imbalance of the gut microflora, and that rebalancing the microflora may help to alleviate gastrointestinal disorders common in children with autism (66). Probiotics, which are live microorganisms that are similar to the beneficial “good bacteria” found in the gut, can help improve the microflora balance in the child's gastrointestinal tract.

Most often, the bacteria used for probiotics come from two groups, *Lactobacillus* or *Bifidobacterium*. Within each group, there are different species (for example, *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, *Bifidobacterium infantis*, and *Bifidobacterium lactis*), and within each species, different strains (or varieties). *Bifidobacterium*, especially *Bifidobacterium lactis*, is the most prevalent bacteria found in breastfed babies,

making it the better supplement choice for infants and young children. *Saccharomyces boulardii* are yeasts that have probiotic properties and are often used in conjunction along with other probiotic supplements.

**Anti-fungal** – Herbs and natural food sources that have anti-fungal properties are often used in conjunction with probiotics. They help support a healthy balance of intestinal bacteria and yeast by keeping *Candida albican* yeast growth under control. Unlike probiotics, the child should not take an anti-fungal product on a daily basis indefinitely. Anti-fungal products are typically taken for a short period of time, 3 – 6 months to assist in healing the gut and then they may be discontinued. Anti-fungal products contain herbs such as pau d' arco and other natural food sources that have anti-fungal properties such as garlic extract, grapefruit seed extract, and caprylic acid. Although most herbs are free of known side-effects, there may be potential contraindications, precautions, and adverse reactions to consider, especially for children.

**Digestive Enzymes** – Digestive enzymes are secreted in the mouth, stomach, and small intestines to break down food so the body can absorb and utilize the nutrients. Studies have indicated that some children with autism have low levels of intestinal carbohydrate digestive enzymes. A digestive enzyme supplement with meals may help these children better digest their food and improve GI symptoms, such as bloating, gas, diarrhea, and constipation.

The body produces different digestive enzymes to break down different types of food, so select a multi-spectrum digestive enzyme product that contains a blend of several different digestive enzymes. This will ensure the child will be able to handle a wide range of foods. Some examples of important digestive enzymes include protease, lipase, amylase, lactase, and sucrase.

### Step 3: Consider Advanced Supplements

**Omega-3 fatty acids** – A significant number of children with autism have inflammation throughout their GI tract. Omega-3 fatty acids have natural

anti-inflammatory properties, and research suggests that omega-3 fatty acid supplements may reduce the pain and inflammation associated with inflammatory bowel diseases. If the child has severe gastrointestinal symptoms or if the gastroenterologist has identified any gastrointestinal inflammation, a therapeutic level of omega-3 fatty acids for a short period of time may be a good option for the child.

**Glutamine** – An amino acid necessary for gastrointestinal function. One of its most important roles is to help protect the lining of the gastrointestinal tract known as the mucosa. Recent research studies have linked glutamine to several other GI health benefits, such as aiding in the maintenance of the gut barrier, promoting intestinal cell growth, promoting healing of the mucosa, inhibiting the growth of “bad bacteria” in the gut, improving diarrhea, and reducing the symptoms of inflammatory bowel diseases (67).

Glutamine is manufactured by the body, but it's also found in many dietary sources, such as beef, pork, chicken, fish, eggs, milk, dairy products, cabbage, spinach, and parsley. If the child has a very poor diet or suffers from certain medical conditions, infections, or prolonged stress, his glutamine level may be depleted and he may benefit from a glutamine supplement.

Glutamine supplements are generally labeled as L-glutamine and are sold as an individual supplement or as part of a protein supplement. There is no RDA for glutamine, so the child's Registered Dietitian will suggest a proper dosage.

#### Step 4: Identify and Eliminate Problematic Foods

Common gastrointestinal symptoms, such as reflux, vomiting, abdominal pain, abdominal distension, gaseousness, loose stools, diarrhea, and chronic constipation, are indications that the child may have an allergy, sensitivity, or intolerance to one or more foods. The most common food allergies among children are cow's milk, wheat, egg, soy, peanuts, and tree nuts. Problematic foods can have a huge impact on a child's overall health, gut function, brain function, feeding, and behavior, so it's crucial to identify and eliminate them from

his diet. The good news is that if the child's GI symptoms are indeed being caused by one or more problematic foods, you'll quickly see a significant improvement in his symptoms once the foods are eliminated.

**Medical Treatment** – If the child still has GI symptoms after trying the basic nutritional interventions, his physician may refer him to a pediatric gastroenterologist. A pediatric gastroenterologist will examine the child for more serious GI disorders, such as gastroesophageal reflux disease (GERD), eosinophilic gastrointestinal disorders (EGID), irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), intestinal inflammation, gastritis, celiac disease, abnormal intestinal anatomy, lactose intolerance, sucrose or fructose malabsorption, fat malabsorption, enteric infection, or parasites. The gastroenterologist may have to perform certain procedures to make his diagnosis, such as a diagnostic trial of proton-pump inhibitor, trial of lactose restriction, pH Probe, abdominal radiograph, lactose breath test, measure lactase-specific activity, stool analysis, esophagogastroduodenoscopy, and colonoscopy. The results of the testing will help the gastroenterologist recommend the appropriate medical treatment, which may include medication and additional dietary interventions. For more detailed information related to identification and treatment of gastrointestinal disorders in children with autism refer to *Evaluation, Diagnosis, and Treatment of Gastrointestinal Disorder in Individuals with ASDs* published in the *Journal of the American Academy of Pediatrics*, January 2010 (64).

**Eosinophilic Gastrointestinal Disorders (EGID)** is a chronic and complex group of disorders characterized by having excessive amounts of eosinophils, a type of white blood cell, in one or more specific places in the digestive system. For instance, if the child has Eosinophilic Esophagitis (EE), he has high amounts of eosinophils in his esophagus. If he has Eosinophilic Gastroenteritis (EG), his stomach and small intestines are affected, and if he has Eosinophilic Colitis (EC), the problem is in his colon. The symptoms of

EGID vary widely, depending on the area affected, and can mimic the symptoms of other disorders like food allergies, IBD, IBS, and GERD. Eosinophilic esophagitis in particular is commonly misdiagnosed as GERD.

**Common symptoms of EGID include:**

- nausea or vomiting
- diarrhea
- failure to thrive
- abdominal or chest pain
- reflux that does not respond to usual therapy
- dysphagia
- food impactions
- gastroparesis
- poor appetite
- bloating
- anemia
- blood in the stool
- malnutrition
- difficulty sleeping

If the child has EGID, it can cause significant pain, which can result in severe feeding problems and refusal to eat foods. EGID can only be diagnosed through an upper endoscopy, colonoscopy, and biopsy. Once the presence of EE, EG, and/or EC is confirmed, food allergy testing is typically ordered by the gastroenterologist. Since reactions to foods can not always be identified with food allergy testing, an elimination/challenge diet is recommended to help identify problematic foods. The foods that are most likely causing EGID are milk, wheat, soy, eggs, and/or peanuts.

#### 4) CONSIDER ELIMINATION DIETS

Elimination diets are very popular in the autism community. The most common elimination diets initiated by parents include the Gluten Free Casein Free Diet, Specific Carbohydrate Diet (SCD), Gut and Psychology Syndrome Diet (GAPS), Rotation, Antifungal, Feingold, and the Low Oxalate diets. Parents have long claimed that many of these diets are effective in relieving their child's autistic symptoms. However, there is very little evidence-based scientific research that supports or refutes

these claims. There are a few studies published with mixed results (68, 69). Currently, there is ongoing research on the Gluten Free Casein Free Diet; the study "*Diet and Behavior in Young Children with Autism*" is sponsored by the National Institute of Mental Health. You may find additional information on this research study at [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

#### The Gluten Free Casein Free Diet (GFCF Diet)

The GFCF diet is the single most common elimination diet recommended for children with autism. Clinical observation over thirty years has shown this to be the most effective elimination diet for children with autism. According to anecdotal reports, the GFCF diet may relieve the child's GI symptoms, increase focus, improve sleep, decrease hyperactivity, and reduce behavioral problems. It is not considered a "cure" for autism, but rather a means to relieve autistic, behavioral, and gastrointestinal symptoms.

Currently, there is no clear explanation of why the GFCF diet is effective for many children with autism. In the early 1980's, the "opiate excess" theory arose suggesting that incompletely digested peptides, gliadomorphine and casomorphine, with opioid activity could precipitate autism (70, 71). The opiate excess theory is still very popular today; however, it remains very controversial.

Another theory, "non-IgE mediated food allergy" theory arose in 2002. Research conducted by Dr. Harami Jyonouchi suggest that children with autism may be predisposed to allergic reactions to the dietary proteins, gluten, casein, and soy, which leads to gastrointestinal inflammation and behavioral symptoms. Jyonouchi's research indicates that while only a small percentage of children with autism tested positive for IgE-mediated food allergies via IgE RAST and skin prick tests for gluten, casein, and soy, a significant percentage of these same children experienced symptom improvement on a gluten, casein, and soy elimination diet. Jyonouchi found that children with autism had an increased proinflammatory cytokine response to gluten, casein, and soy, which indicates that these children have a non-IgE mediated immune reaction



to dietary proteins. The studies concluded that non-IgE mediated immune reactions to gluten, casein, and soy play a role in gastrointestinal symptoms in children with autism (72, 73, 74, 75).

**Gluten** is the protein found in wheat, barley, and rye. It gives flour its elasticity, which allows for leavening and provides texture to baked products. Gluten is commonly found in breads, pasta, cereals, and baked goods. It is not found in oats, but oat is usually eliminated from the GFCF diet because of the high possibility of cross contamination by wheat, barley, or rye during its processing and distribution. Avenin, the protein found in oats, has a peptide sequence that closely resembles wheat gluten, so oat is eliminated.

**Casein** is the protein found in cow's milk and milk products. **Soy**, soybean, also known as soya bean, is a type of legume. Until recently, soy was used as a substitution for dairy products in the GFCF Diet. However, because of the research conducted by Dr. Jyonouchi and the fact that soy is one of the top five common food allergens, it is best to also eliminate soy while on the GFCF diet.

If a parent is interested in trying the GFCF diet for their child with autism, a three month elimination/challenge diet is suggested. A referral to a knowledgeable Registered Dietitian to ensure the diet is implemented properly, effectiveness of the diet is assessed, and parents are instructed on how to replace lost nutrients from eliminated foods so the child's nutritional health is not compromised.

## 5) IDENTIFY AND TREAT FOOD REACTIONS

If a child with autism suffers from a food allergy, sensitivity, or intolerance, it may cause him to have intestinal, respiratory, skin, neurological, behavior, and feeding problems. Gut symptoms, such as reflux, nausea, vomiting, abdominal pain, abdominal distension, gaseousness, loose stools, diarrhea, and chronic constipation, are painful for the child. The child will quickly learn that eating food makes him feel bad. The child may often refuse food, gradually limit the number of foods he is willing to eat, and have tantrums and behavioral

problems at mealtime. Identifying food allergies, sensitivities, and intolerances; and eliminating the problematic foods from the child's diet is a critical component of his comprehensive treatment plan.

### *Food Reactions – Autism – Behavior Connection*

Food reactions do not cause children to have autism, but they do affect children with autism more than typically-developing children. Children with autism tend to have some degree of Sensory Processing Disorder. Children with Sensory Processing Disorder have difficulty responding appropriately to sensory information from their environment. They are more sensitive, become easily overwhelmed, and may over react or under react to auditory, visual, and tactile stimulation. If the child has sensory issues, food reaction symptoms will stress his sensory system further, making it even more difficult for him to function normally. The combination of food reactions and sensory issues can hinder the child's ability to sit still, concentrate, maintain focus, process information, learn, and control his impulses and behavior. Relieving the child of food reaction symptoms will lessen the sensory burden he has to deal with, which will improve his behavior.

Children with autism are unique because they are often unable to verbally express the physical discomfort and pain they feel from food reaction symptoms. If the child is non-verbal or has an expressive language delay, he can not tell you if he feels nausea, abdominal pain, chest pain from reflux, or headaches. Instead, the child has to communicate physical pain through his behavior, such as head banging, tantrums, irritability, and food refusal. These behaviors are mistaken for typical autistic behavioral problems instead of behaviors caused by undiagnosed food reactions.

**What is a Food Allergy?** Food allergy is an adverse immune response to a food protein. The immune system mistakenly identifies a specific protein found in food as a harmful substance and defends against it. Food allergies are classified as either IgE mediated or non-IgE mediated.

Food allergies are becoming a serious concern for children in the U.S. In 2007, approximately 4

percent of children under the age of 18 were reported to have a food allergy; with children under the age of 5 have a higher rate (76). There is evidence that indicates there may be an increased incidence of food allergies among children with autism and related disorders, such as ADHD, compared to the general population of children (77, 78, 79, 80). Children with autism may be more vulnerable to food allergies because of abnormalities in their digestive and/or immune systems (81). Research also supports a link between food allergies and behavioral problems (82, 83).

The following foods are responsible for 90 percent of allergic reactions:

- Milk
- Wheat
- Soy
- Egg
- Peanuts
- Tree nuts (pecans, walnuts, almonds, cashews, hazel, and Brazil nuts)
- Fish
- Shellfish

Milk, wheat, soy, egg, and peanuts are the most common food allergens in children under the age of three. Allergic reactions to fish and shellfish are more common in adults and allergic reactions to fruits and vegetables also tend to occur later in life.

**What is Food Sensitivity?** Food sensitivity is a general term used to describe an abnormal reaction to a food or food additive. Food sensitivity is different from a food allergy because the reaction does not involve the immune system. Food sensitivity symptoms are virtually identical to those of an allergy, but they tend to be much milder. If the child is sensitive to a particular food, he is most likely reacting to the artificial food additives in the food as opposed to the food itself. The most common artificial additives that the child may react to are sulfites, aspartame, MSG, yellow dye No. 5, and the preservatives BHT and BHA.

**What is Food Intolerance?** Food intolerance does not involve the immune system. It occurs when something in a food irritates a person's digestive system or when a person has too few or none of the enzymes that enable him to properly digest a food. For instance, if the child has too few or is missing the enzymes necessary to break down carbohydrates in the small intestines, the carbohydrates pass undigested into the colon where they ferment and produce excess gas, bloating, abdominal cramps, and diarrhea. The three most common carbohydrate food intolerances are lactose, sucrose, and fructose.

#### **Classic Food Reaction Symptoms:**

- Ears: otitis media (ear infections)
- Nose: nasal congestion, sneezing, runny nose
- Eyes: tearing, puffy eyes, dark circles under eyes
- Oral: swelling of lips, tongue, mouth, and throat
- Skin: hives, eczema, red cheeks, itching
- Respiratory: difficulty breathing, cough, wheezing, asthma
- Intestinal: reflux, vomiting, nausea, abdominal pain, diarrhea, constipation
- Neurological: headache, migraine, and behavioral problems such as tantrums, irritability, and hyperactivity

**How to Identify Problematic Foods** – If a food reaction is suspected, a referral to a board-certified allergist for a definitive diagnosis is warranted. The allergist will perform a physical exam, review the child's medical and dietary history, and order diagnostic tests to rule out other medical conditions. An IgE RAST and skin prick test are ordered to help identify an IgE mediated food allergy. If the IgE RAST or skin prick test is positive, the physician should conduct a physician-supervised oral food challenge to confirm positive test results. Since an IgE RAST and skin prick test can not identify non-IgE mediated food allergies, a short-term elimination/challenge diet is required to identify any non-IgE mediated food allergies.

A short-term elimination/challenge diet involves two basic steps: Eliminate the suspected food from the child's diet for at least 2 weeks. This will give the child's allergy symptoms time to subside. If the child has EE, EG, and/or EC, the suspected food allergens need to be eliminated for 8 to 12 weeks to achieve symptom improvement. The first foods eliminated are those that had positive IgE RAST and/or skin prick test results. If both of these tests were negative, eliminate the most common allergenic foods: milk, wheat, soy, egg, peanuts, nuts, fish, and shellfish. The challenge phase involves reintroducing the eliminated food back into the diet and observe for recurrence of allergy symptoms.

An excellent resource of educational materials and more detailed information related to food allergies, including list of foods and ingredients to avoid can be found on the *Food Allergy and Anaphylaxis Network (FAAN)* Web site at [www.foodallergy.org](http://www.foodallergy.org). A referral to a Registered Dietitian is necessary to assist parents in implementing the elimination/challenge diet; parents should not attempt to implement this diet on their own.

Identifying which foods a child may react to is complicated, test results are difficult to interpret,

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current blood lab and skin tests are not always accurate, some allergy tests are controversial, and treatment is challenging. Even so, identifying and treating the child's food reactions has enormous benefits. The child will experience a wide range of physical, gastrointestinal, behavioral, and neurological improvements. Identifying problematic foods is a critical step in nutritional treatment for a child with autism.

## SUMMARY

Integrative nutritional interventions can have a major impact on a child with autism. Use of whole foods, nutritional supplements, natural healing of the gut, and eliminating problematic foods are essential in restoring the child's nutritional health. Although it varies for each individual child, after implementing appropriate nutrition interventions, one may expect to see improvements in the child's behavior, mood, aggression, impulsivity, learning, attention, language, focus, eye contact, sleep difficulties, gastrointestinal problems, growth, and overall health. Registered Dietitians play a key role in incorporating nutrition therapy as a component of the child's comprehensive treatment plan.

Elizabeth is a published author, the title of her book is *"Eating for Autism ... The 10-Step Nutrition Plan to Help Treat Your Child's Autism, Asperger's, or ADHD"*. She is a member of the Dietitians in Integrative and Functional Medicine Dietetic Practice Group of The American Academy of Nutrition and Dietetics.

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## 14

# Integrative Cancer Therapy

## Richard Linchitz, MD



In order for the reader to understand the rationale for our comprehensive anti-cancer regimen, I would first like to share my own personal experience with cancer.

In December, 1988, after a routine exam for an unrelated condition, my doctors found a cancerous tumor the size of a large lemon in my right lung. I had never smoked and was always athletic, so I was understandably shocked by the diagnosis. Gradually, the shock turned into a mission to understand the nature of cancer and help others find their own path to healing. In the early days and weeks after my diagnosis, I realized that my previous responses to my patients who found themselves in similar situations were incomplete. In the past, I would have immediately advised patients to contact an oncologist and put themselves in his or her hands. When it came down to my own condition, however, I began to doubt that advice. When I looked into the available treatments, I realized that for a minimal proven benefit, I would face treatment that would seriously compromise the quality of my life. There did not seem to be any traditional medical resource that could help me

discover the underlying reasons for my cancer. There were also no traditional resources to help improve my strength and resistance to the disease that was threatening to take my life.

I gradually came to realize that truly comprehensive cancer treatment should include a two-pronged approach. One prong would be to find an effective way of killing cancer cells without destroying the immune system and without destroying the overall health and integrity of the body. The second prong would be to actually improve the health and cancer-fighting ability of the body through what I came to call "The Six Pillars of Vibrant Health."

I will first describe the six pillars and how they are integrated into a comprehensive approach to cancer care, and then go into more detail about effective techniques of killing cancer cells.

The first pillar of vibrant health is our diet. In cancer this takes on an even more urgent importance. Cancer cells, like most cells, require glucose to derive energy. However, cancer cells, because of their more primitive and inefficient anaerobic metabolism, require much more sugar than normal cells to survive. If they are to maintain their rapid growth pattern they need that

much more sugar. All our cells take in sugar through a mechanism that can be conceptualized as a “lock and key” system where insulin is the key and an insulin receptor is the lock. It turns out that cancer cells have many more “doors” with these “locks and keys” than normal cells. This is understandable because any cancer cell without a mechanism for concentrating sugar will not survive. Only those cells with high concentrations of these receptors will be able to rapidly divide and develop into cancerous tumors.

Conventional physicians are aware (or should be) of this mechanism and even use it to help diagnose cancer with the PET scan (positron emission tomography). Its theory is very simple: a radioactively labeled sugar is injected into the person's vein. The sugar travels through the body and causes the body to produce insulin. The insulin “keys” then attach to the receptor “locks” on all the body's cells and the “doors” of the cells open. Cancer cells, however, will have many more “open doors” and therefore will concentrate the sugar with the radioactive tracer. The body is then scanned for radioactivity and the cancer “lights up” on the scan.

If we think about this process carefully, does it tell us anything about the way we should eat? Of course we should limit (or preferable eliminate) our sugar intake and our intake of anything else that will cause a significant rise in our blood sugar (especially refined carbohydrates but even sweet fruits and grains can be a problem in some patients). This is essentially the same diet we recommend for our patients with diabetes. In fact, there is an association between diabetes and pre-diabetes with high blood sugar and insulin levels on the one hand and with cancer incidence on the other hand. We also know that rising blood sugar interferes with immune function.

We also need to eat organic food to limit the toxins entering our body. We must be careful to limit our intake of omega 6 fats which are pro-inflammatory and pro-cancerous. We should increase our intake of omega 3 fats which are anti-inflammatory and generally anti-cancer. The proper balance of these fats fights inflammation

and cancer. We must avoid trans fats or partially hydrogenated fats which are pro-inflammatory and interfere with cellular communication and with the transport of nutrients. In short, a whole food diet, focusing on plenty of vegetables (mostly raw) with organic, naturally fed (grass for cows, grass and worms for chickens) animal products (free-range chicken and eggs, wild salmon, grass fed beef, raw milk, kefir and cheese, etc). Recent studies have shown that the right diet can improve survival rates for several cancer types.

The second pillar is supplements. Many supplements have been shown to have anticancer effects in preclinical studies and some even in clinical studies in humans. Some have been shown to be powerful immune stimulants (such as the various mushroom products). Others have been shown to have direct effects on cancer metabolism causing cancer cells to die. It's a good idea to develop a protocol of natural agents that interfere with cancer angiogenesis (cancer blood vessel formation). If cancer cannot make blood vessels, its growth and ability to spread would be severely limited. This is the theory behind conventional agents such as Avastin but the natural agents work through many mechanisms. This protocol could even potentiate the effects of agents like Avastin as well as classic chemotherapy drugs. There are other natural agents that have been shown to potentiate conventional chemotherapy drugs by increasing their penetration into cancer cells and by interfering with the ability of the cancer cells to become resistant to these drugs.

Exercise is another crucial pillar. Recent studies have shown improved survival rates in patients battling cancer as well as improved quality of life. Exercise can be thought of as a continuum between activity and rest, both of which are important. Overtraining can be just as destructive to immune health as inactivity. We have found that the most effective exercise program is the one that patients are willing to follow. It can be walking, swimming, yoga, weight lift training, etc. Ideally, short bursts of intense activity with longer periods of rest or easy activity in between, will

provide optimal immune stimulation and will be manageable for most patients.

Stress can play an important role in interfering with immune health, in causing inflammation, and in disrupting hormonal balance. The fourth pillar, stress management, is a general term under which spirituality and living with meaning or purpose can be included. Patients should be encouraged to meditate, to pray, do yoga, tai chi, or anything else that gives them relaxation, peace and a sense of inner strength. One can also use “quantum biofeedback” and “EFT” (Emotional Freedom Technique) to help reduce stress and improve emotional balance and well-being.

The fifth pillar is detoxification, a subject curiously ignored in conventional medicine. Heavy metals, for example, are known immune disruptors and many of them are frankly carcinogenic. Those patients with body burdens of these substances need chelation to help restore immune competence and cellular energy. Pesticides, plasticizers, and many other environmental toxins are endocrine disruptors and have been implicated in the rising incidence of breast and prostate cancer as well as other types of cancer. In addition to chelation, it is good to offer far-infrared sauna treatments and colon hydrotherapy to aid in the detoxification process. The first pillar, a clean diet, will also limit toxin exposure. Vegetable juicing and eating high-fiber food will speed elimination and detoxification as well.

The final pillar is hormone balancing. One important example of the hormone problem is the growing epidemic of unrecognized hypothyroidism. It has been recently noted in studies that breast cancer is associated with high TSH values (a symptom of hypothyroidism). Hypothyroidism suppresses immune function in general. Many patients have cancers that are sensitive to hormones. In fact, it is sometimes the presence of higher levels of toxic estrogen metabolites (like 4.-OH and 16-OH estrone) that may have predisposed the patient to cancer in the first place. Fortunately, the thyroid gland can sometimes be naturally stimulated (in some cases the removal of toxins from the body can aid in

this process). For other patients, replacement of thyroid hormone is indicated. In the case of toxic estrogen metabolites, diet change, simple supplements, and exercise can lower these levels. There are other hormonal issues that can also play a role. All must be taken into account in order to optimize treatment.

All these six pillars are covered, but what about aggressively killing the cancer cells that have appeared in our body? Insulin Potentiation Therapy Low Dose™ chemotherapy (IPT) is an effective, yet gentle way of killing cancer cells. The theory behind IPT could not be more logical. Cancer cells in general concentrate sugar through their abundance of insulin receptors as described earlier. If a small measured dose of insulin is given, the cancer cells become selectively more permeable, and then the insulin receptor sites are maximally saturated with insulin (the therapeutic moment). Very small doses of chemotherapy agents are then introduced into the body and these doses are effectively concentrated into the cancer cells providing enhanced killing powers with a much lower side effect profile.

How do we choose among different chemotherapy drugs? As with conventional oncology, we can choose an agent that has been shown to be effective in most patients with a specific type of tumor. However, in the interest of a truly individualized approach to treatment, we can send the patient's blood to a laboratory in Europe that will test the blood for circulating tumor cells and then test these for resistance to various chemotherapy drugs. This will allow us to pick out the most effective drugs for each individual patient. These drugs could be very different from the standard protocols in oncology. This laboratory will also test for alternative (natural and nontraditional) agents that can help overcome chemotherapy resistance or even directly kill cancer cells. Natural killer cell function (a measure of immune function) is also assayed (tested) and information is given as to the most effective agents to more effectively attack the cancer.

One can often use high dose vitamin C intravenously as part of the overall regimen. This can be combined with vitamin K3 (which has been shown to potentiate (make stronger) the cancer killing effects of vitamin C). The National Institutes of Health is currently studying high dose vitamin C and has shown it will kill most cancer cells when given in high enough concentrations (these concentrations can be achieved only with intravenous vitamin C).

There are many other potential treatments available, some of them very innovative. All treatments are individualized to each patient with the goal of maximizing benefit. As new research emerges, it is good to constantly update protocols to offer the most effective treatments.

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**Richard Linchitz** has dedicated his life to medical health and patient care. After graduating with honors from Cornell University Medical College, he completed his residency at the famed University of California, San Francisco, Moffit Hospital.

Moved by the personal stories of those living with chronic pain, Dr. Linchitz founded the first and only outpatient nationally accredited multi-specialty pain program in New York. Over the 22 years he managed the Pain Alleviation Center, he developed an integrated program of pain intervention based on lifestyle changes, rather than pharmaceutical-based solutions. Dr. Linchitz has always lived by his own advice. An accomplished athlete, he lived what he thought was a healthy lifestyle until a diagnosis of lung cancer in 1998 (despite never having smoked) forever changed his life, career and overall perspective on medicine. After receiving a bleak prognosis for survival, he sought to understand his disease from the inside out and to design his own path towards balanced Wellness. This path also led him to become a member of the Society for Integrative Oncology.

Determined to share the lessons learned from his own recovery, Dr. Linchitz became an expert in integrating conventional and alternative approaches to treat disease. He became a Board Member of the International College of Integrative Medicine.

Consequently, he has created a unique program of health based on prevention and natural remedies. Dr. Linchitz is board certified by the American Board of Psychiatry and Neurology, the American Board of Pain Medicine, and the American Board of Anti-aging Medicine. He has successfully passed board exams from the American Board of Clinical Metal Toxicology and the International Board of Oxidative Medicine. He is also trained and certified in Medical Acupuncture and Insulin Potentiation Therapy (IPT), an innovative cancer treatment. He is a member of the Medical Advisory Board for the Int'l Organization of IPT Physicians.

Dr. Linchitz's other memberships include Program Co-Chair of the Chelation Examination Committee, Board Member of the American College for Advancement in Medicine and a member of the International Oxidative Medicine Association.

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# 15

## Hyperbaric Medicine : Applications And Evidence : Multiple Sclerosis, Autism, Traumatic Brain Injury

### Jamie Wright, DO, FACOOG

#### INTRODUCTION

The use of oxygen and compressed atmospheres dates back to the 1600's when attempts were made to treat a variety of conditions in crudely built chambers which were able to increase atmospheric pressures. The late 1800's and early 1900's saw a surge of interest in compressed air therapy. When oxygen became more readily available in the 1920's, the use of highly concentrated oxygen environments and compression chambers was expanded to include a wide variety of medical conditions from gas gangrene to organ transplantation and cardiac surgery. (1)

In North America, the first therapeutic hyperbaric chamber was constructed in Canada in 1860.



The US navy discovered the tolerance limits of concentrated oxygen, demonstrating reversible toxic effects on the nervous system at 3 atmospheres of pressure or higher. (3, 4) In the United States, the approved indications for use of hyperbaric oxygen therapy (HBOT) is limited to burns, wounds, decompression sickness, and toxic gas poisoning. These treatments are typically performed in a clinical setting with high pressures and the administration of a pure oxygen environment.

"Mild" hyperbaric oxygen therapy refers to the use of HBOT at lower pressures (1.3 to 1.7 atm) and lower oxygen concentrations (80% to 100%). Mild HBO therapy is often used to treat a wide range of conditions, such as fatigue and fibromyalgia, autoimmune disease, migraine, autism/spectrum disorder, to athletic injury.

As with many non-standard, non-pharmacologic approaches to chronic disease, controversy seems



to follow the use of HBOT in these “non-traditional” conditions. This chapter is not designed to outline the established uses of hyperbaric medicine, which are well published and documented. Rather, the purpose is to review the current literature regarding the use of HBOT for the treatment of three of our most challenging conditions: multiple sclerosis, autism, and traumatic brain injury.

## Multiple Sclerosis

### Clinical Vignette

*RW, a 56 year old married white female, began to have atypical headache approximately 25 years ago. She presented repeatedly to her primary care physician over the course of 10 years with complaint of head and neurological changes. Her husband, an internal medicine specialist, sought expert opinion from a local university with a specialty head pain clinic. She was given a diagnosis of “complex migraine stroke” after having normal brain studies and neurological examinations. She continued to experience atypical migraine headache with subsequent temporary loss of vision and motor function. After approximately 10 years, she was diagnosed by MRI with relapsing-remitting multiple sclerosis, based on typical periventricular white matter changes. Further studies such as spinal fluid analysis for oligoclonal banding was not pursued. She has been treated with a variety of interferon medications and is currently taking interferon-beta (Rebif), muscle relaxors and an antidepressant. Neuropathic pain is managed with a Fentanyl patch every 72 hours. Physical exam findings include obesity and right lower extremity weakness, particularly quadriceps weakness, necessitating the use of a cane for assistance with ambulation. The patient’s husband admits to concerns with her ability to reason and emotional lability. Neuropsychological assessment has not been performed (Beck Depression Inventory, Modified Boston Naming Test, MMSE, Constructional Praxis, and Word List Memory as examples.)*

### Review of the Literature and Discussion

Multiple sclerosis (MS), a disease of unknown etiology, is the “most common autoimmune inflammatory demyelinating disease of the central nervous system.” (5) It is characterized by inflammation of the central nervous system leading to nerve demyelination. Ultimately, axon degeneration leads to clinical manifestations, such as weakness of extremities, numbness, and psychological changes. (6) MS is most commonly known to affect women of childbearing age of Northern European lineage, with Northern Ireland having the highest per capital population of MS patients. (7)

The differential diagnosis of MS is fairly broad and includes genetic and congenital CNS diseases, inflammatory diseases such as polyarteritis nodosa, systemic lupus erythematosus (SLE), Behçet’s disease, Sjögren’s disease, retroviral illness, and syphilis. Many of these conditions can cause similar MRI changes and manifest with peculiar neurological symptoms. (8)

The current standard for diagnosis is the McDonald criteria. The principle of diagnosis rests with establishing a pattern of clinical findings and MRI changes across both space (different areas of the CNS) and time (symptoms and lesions are evolving). Clinical findings suggestive of the disease include age of onset between 15 and 50 years, a relapsing remitting pattern of neurological change, optic nerve involvement, and fatigue.

The diagnosis does not rely upon laboratory evidence of the disease. (9) The pathophysiology of MS revolves around the concept of CNS vascular inflammation causing disruption of the blood brain barrier leading to an autoimmune assault involving the myelin sheaths. This repetitive demyelination ultimately leads to permanent neurologic damage and subsequent clinical symptoms. (10)

The cornerstone treatment of MS involves immune modifying interferon beta-1b (Betaseron) and beta-1a (Avalox), and glatiramer acetate (Copaxone). Other treatments focus on relieving symptoms and improving quality of life through the use of physical therapy, occupational therapy, anti-

depressants, neuroleptics, and pain relievers. Our discussion will focus on the evidence for the use of HBO therapy in the treatment of MS.

Hyperbaric oxygen therapy, detailed in the introduction, is the use of supplemental oxygen therapy under increased atmospheric pressures. There is divergent opinion on the effectiveness of HBO in the treatment of MS, particularly between the United States and the United Kingdom. HBOT was embraced in the UK and freestanding charity clinics were established throughout Europe, making HBOT a standard treatment in MS for over 20 years.

The mechanism of action of HBOT in relationship to MS is thought to include both suppression of the immune response and reduction in partially reduced reactive oxygen species. Partially reduced reactive oxygen species are free radicals which can interact with organic molecules, interfering with enzyme activity and damaging cell membranes.(11) Concern with the use of oxygen and its oxidation promoting potential, as seen in re-perfusion injury, has not been established. For use in MS, Neubauer's protocol involved the use of oxygen at lower pressures than typical hyperbaric treatment, and it is thought that this may limit the oxidative damage. No recent theory on the mechanism of action of HBOT on MS exists.

Case and clinical studies using HBOT to treat MS have been present in the American literature since the 1980's. Fischer et al. published a randomized, placebo-controlled, double-blinded study in the New England Journal of Medicine evaluating 40 patients.

Objective improvement occurred in 12 of 17 HBOT patients and 1 of 20 placebo ( $P<0.0001$ ). Deterioration at one year follow-up was 12% in the HBOT group versus 55% in the placebo group ( $P<0.0008$ ). The article concluded that HBOT in MS could not be recommended, but that further studies were warranted.(12)

This began the HBOT controversy and, according to an account by the late European HBOT pioneer, Neubauer, M.D., this study was only published after one year of debate and analysis. Fischer was subsequently fired and his chamber dismantled. (13)

Fischer's study seemed to fuel a grass roots effort by patients in Dundee, Scotland, who developed a community-based treatment center. This model was then expanded throughout the United Kingdom.

Subsequent studies using a variety of protocols were performed throughout the 1980s. Studies included generally small numbers of patients, measured a range of outcomes, and achieved variable conclusions. Studies showed improvements in bladder control with normal-baric oxygen therapy (14), a possible beneficial effect of HBOT in patients with less severe MS (15), possibly less deterioration in cerebellar function after 20 sessions of HBOT in patients with chronic progressive MS (16), a worsening of Kurtzke functional assessment score in patients with chronic progressive MS (17), and no differing MRI changes among HBOT versus hyperbaric air therapy in chronic progressive MS (18).

In 1989, Gottlieb published an article theorizing that MS was a "wound" of the central nervous system resulting in inflammation, loss of the blood brain barrier, and formation of reactive oxygen species. He concluded that low pressure HBOT, therefore, may function to dampen the immune response and reduce inflammation and edema.(19)

MS patients commonly suffer from neuropsychiatric and urogenital problems and two studies support an HBO therapy benefit. In 1990, Oriani et al. performed a doubleblinded placebo-controlled trial looking at brainstem evoked potentials. He concluded that there was a significant beneficial difference for the HBOT group based on neuropsychologic investigations.(23) Cundall et al. showed that HBOT improved pudendal nerve latency in patients with fecal incontinence. This

effect persisted for one month, but not 6 months.(24) He did not, however, measure for improvements in the frequency or severity of fecal incontinence.

The most compelling recent study, authored by the late D. Perrins in 2005, evaluated 117 patients who received HBOT treatments without interruption for 5 to 15 years in the UK. The authors followed 703 MS patients treated with HBOT 5 or more years previously. Pressure and oxygenation protocols were consistent over the years.

Assessments were made between 2 and 3 years, then again between 6 and 8 years, with a final survey being conducted at 11 to 14 years from the first HBO treatment.

Among this group, 117 people attended clinic regularly and without interruption for 5 to 17 years. Their findings support that 300+ treatments with low pressure HBOT over 10+ years was required to retard progression of disability. Five-hundred treatments were more effective as these patients had even less disability overall.(25)

Despite these positive findings, three separate reviews of HBOT and treatment of MS were performed from 1995 to 2010. All authors concluded that the use of HBOT for the treatment of MS was not recommended based on limited study populations, variable treatment protocols, and a lack of demonstrated benefit.(20, 21, 22)

Expert opinion on the use HBOT for MS is controversial. MS is a condition with wide ranging clinical presentations and outcomes. Studies of HBOT in the treatment of MS have used a variety of different treatment protocols, varying in the amount of pressure and oxygen, the number of treatments, how long the clients were followed and the the end-point measured.

It appears that the use of HBOT is unlikely to significantly affect patients with longstanding disease, such as chronic progressive MS. Those advocating the use of HBOT in MS suggest that it

be used immediately upon diagnosis and chronically thereafter.

The use of HBOT in MS has not been compared to the use of interferon, the most recent FDA approved disease modifying agent. Nor have the two been studied together. At this time, the use of HBOT should be considered an adjunct to FDA approved treatments. Possibly the long term use of HBOT in combination with immune modifying drugs would provide patients with the improved outcomes. Continued study is warranted, focusing on the long term use of low pressure HBO therapy in those newly diagnosed or with more mild disease.

## Autism

### Clinical Vignette

*JS is a 3 1/2 year old boy born to a 27 year old white female who had an uncomplicated pregnancy and normal vaginal delivery. JS experienced normal developmental milestones with appropriate feeding, sitting up, crawling, social interaction and expressiveness. At age 2 1/2 he experienced a flu-like illness with high fever and diarrhea and was treated with hospitalization, IV hydration and antibiotics. Over the coming months JS's parents noted significant regression of his prior verbal development, ultimately experiencing social withdrawal, failure to make eye contact, and difficulty managing sensory stimulation. He was diagnosed with autism spectrum disorder at the age of 3 1/2.*

### Review of the Literature and Discussion

Disorders in the development of socialization, communication, and behavior characterize autism spectrum disorders (ASD).(1) This neurodevelopmental disorder may affect up to one out of 150 individuals in the United States and the prevalence of autism may be increasing.(2, 3)

The use of a multi-disciplinary team with expertise in the diagnosis and treatment of ASD is preferred. This includes a detailed history and

physical examination, assessment of the child's communication skill and cognitive development, and standardized parental interviews.(4)

Diagnosis of ASD is based on clinical findings with a focus on developmental delay or regression of social interaction, social communication, or behavior before the age of 3.

Childhood Disintegrative Disorder (CDD) and Rett disorder must be excluded. Several diagnostic tools exist, such as the Child Autism Rating Scale, but none are specifically recommended or standardized.(5) The gold standard for diagnosis is considered to be the Autism Diagnostic Observation Schedule-Generic, but it requires expertise to administer.(6)

Beside ruling out CDD and Rett disorder, the differential diagnosis of ASD includes developmental disorder and delay, hearing impairment, reactive attachment disorder, OCD, anxiety, and language-based learning disability. Consideration for metabolic and genetic testing is warranted based on clinical suspicions.

Current theories regarding the pathophysiology of ASD revolve around the concept of brain injury, inflammation, and oxidative stress. This injury may result from a number of pathways, such as mitochondrial dysfunction, cerebral hypoperfusion, auto-antibodies toward brain tissue, gut inflammation, autoimmunity, and impaired detoxification systems.(7) Reviewing the different theories regarding the pathophysiology of autism will allow us to understand the potential mechanism of action of HBO therapy for this disorder.

Cerebral hypo-perfusion in autistic patients was first identified by advanced brain scanning in the late 1980s and early 1990s. (8,9) Two studies revealed bilateral hypoperfusion localized to the temporal lobes. A recent review of these studies points out that this particular sulcal area of the temporal lobes connects the frontal lobes, the limbic system, and auditory areas.(10) Hypo-perfusion was confirmed by an Indian study which showed bilateral frontal and temporal lobe

involvement.(11) Dysfunction of the temporal lobe brain region suggests a plausible construct to understanding the wide variety of behavioral and emotional abnormalities displayed by autistic patients (social, emotional, and perceptual respectively). The cause of cerebral hypo-perfusion has not been explored in the scientific literature.

CNS inflammation may play a role in the pathophysiology of autism, and inflammatory markers have been identified in the brains and cerebrospinal fluid of autistic patients.

Cerebrospinal fluid from autistic subjects was found to contain a "unique profile" of inflammatory cytokines; furthermore, biopsy specimens from the cerebral cortex and cerebellum revealed an active inflammatory process.(13) Disruption of the gastrointestinal and brain blood barrier may also be a mechanism for the promotion of CNS inflammation and therefore ASD. This finding is supported by the ten-fold increased rate of ASD in patients who have a rare condition called mast cell activation syndrome.(14, 15)

Gastrointestinal disturbances are common among autistic individuals and intestinal inflammation has also been associated with autism. de Magistris et al. looked at the heritable nature of "barrier function deficit" in 90 children and 146 of their relatives.

Lactulose/mannitol testing for intestinal hyper-permeability was performed and found to be significantly elevated in those with autism (46.7%) as well as their relatives (21.2%) versus controls (4.8%). The authors recommend hyper-permeability testing to identify the subgroup of autistic patients who may benefit from dietary changes to reduce the inflammatory response of the immune system to food products.(16) Intestinal microflora imbalance may also play a role in ASD. (17,18)

The role of oxidative stress in ASD has been explored as well as biological markers indicating upstream metabolic derangements which may play a role in the disorder. (19,20) Free

radical formation can lead to oxidative stress. Biomarkers related to the body's ability to compensate for oxidative stress include carnitine, urinary 8-isoprostane, vitamin D, glutathione, ammonia, lactic acid, transferrin and ceruloplasmin. (21) These biomarkers have been identified as useful in estimating the oxidative burden and guiding the nutrient management of autistic patients. Other biomarkers considered for use in establishing a treatment regimen for patients with ASD include organic acids, intestinal permeability testing, calprotectin levels, stool cultures, methylation and transsulfuration markers. Autistic children in particular may be more vulnerable to oxidative stress in the form of lipid peroxidation and deficient antioxidants. (22,23)

Mitochondrial disease (MD) is likely present in a subset of autistic individuals. Mitochondrial dysfunction can lead to multiple metabolic problems. The incidence of genetic MD in the general population is greater than 1:2000. (24) Statistically, if ASD and MD were unrelated, they would uncommonly occur together as 17 million people would be required to find 76 patients with both disorders. However, studies indicate between 4-8% of autistic patients have MD. (25)

Furthermore, multiple organ dysfunction is common in patients with MD with the most common systems affected being the brain, skeletal muscle, and the gastrointestinal tract creating a wide variety of seemingly divergent symptoms. (26) Gastrointestinal symptoms are very common among ASD patients. One study compared children with ASD to normal controls and those with developmental disability. GI complaints were present in seventy percent of children with ASD versus 28% and 42% in the normal and disability group, respectively. (27) This may only indicate that GI symptoms are more bothersome to ASD patients since other studies have not supported an increased prevalence in ASD. (28) Because every cell in the human body depends on mitochondria, these patients often experience multiple system disorders with the end result involving neuroinflammation and cytokine release.

Autism is characterized as a neurodegenerative disease involving decreased cerebral perfusion, inflammation, and oxidative stress and researchers have explored the use of HBO therapy to address ASD. (33) HBOT has been successfully used in the treatment of neuropathy (29), closed head injury (30), stroke (31) and Crohn's disease (32) all of which involve similar mechanisms of injury. Therefore, it seems reasonable that autistic individuals may benefit from HBO treatment and this has recently been explored.

A prospective open-label pilot study performed in 2007 looked at the potential role of HBOT on oxidative stress in ASD. Eighteen children ages 2-16 underwent multiple HBO treatments following two protocols. Assessment included parental symptoms rating and evaluation of C-reactive protein and glutathione levels before and after the completion of treatments. HBOT was found to not worsen oxidative stress and to significantly reduce the CRP values; parental symptoms ratings were favorable. (34)

These same authors subsequently performed a multicenter, randomized, double-blind, controlled trial to assess the efficacy of HBOT in autistic children. The study randomized sixty-two children ages 2-7 to 40 one-hour treatments of either HBO therapy or pressurized room air. The study concluded that, compared to children treated with slightly pressurized air, the HBOT group had significant improvements in "overall functioning, receptive language, social interaction, eye contact, and sensory/cognitive awareness." (35)

In a similar study, 16 patients with ASD underwent 40 HBOT treatments to evaluate the effect on behavior. No significant effect was observed among the observed behaviors studied. (36) These authors did not look at the effect of HBOT on inflammatory and oxidative stress markers.

Finally, a small Thai study evaluated social, fine and gross motor, language, and self-help domains before and after 10 HBO treatments, reporting that 75% of participants showed

improvements.(37) They concluded that HBOT was a new therapy for the treatment of ASD in Thai children.

Because of its potential regenerative capacity, stem cell therapy has been proposed as a potential treatment for autism spectrum disorder.(38) HBOT has been shown to mobilize stem cells from the bone marrow and therefore may act to stimulate the body's own native healing processes.(39,40) The mechanism of action of stem cell treatments in autism may be the regeneration of damaged nerve tissue and reduction of inflammation or immune modulation. Although many more studies are needed to evaluate the viability of this treatment option, it is interesting to consider the use of HBOT to stimulate the body's native regenerative process.

Autism is considered a multisystem disorder. Hyperbaric oxygen therapy may be beneficial to the treatment of autism because of its general effects on the body, with minor side effects (ear pain, sinus pain, claustrophobia).

ASD is a complex neurodevelopmental disorder demonstrating brain inflammation, cerebral hypoperfusion in the temporal lobes, gut inflammation and dysbiosis. The central mechanism of this disorder may be inflammation and this could explain seemingly divergent symptoms present in this population. HBOT has been demonstrated to have anti-inflammatory effects, to improve cerebral perfusion, upregulate anti-oxidant enzyme systems, and reduce intestinal dysbiosis in scientific studies. It seems well founded that HBOT should continue to be explored in the treatment of ASD since its mechanism of action on the human body may directly counter many of the pathophysiological mechanisms of disease in this population.

## Traumatic Brain Injury

### Clinical Vignette

*CR is a 17 year old male who presented for further physical rehabilitation for gait ataxia due to*

*hemiparesis. Two years ago CR was hospitalized for 6 weeks after he sustained severe traumatic brain injury as an unrestrained motor vehicle passenger. CT scanning revealed multiple areas of brain trauma and hemorrhage involving the right temporal area, left internal capsule, right frontal lobe, and bilateral parietal lobes. CR received 14 months of residential and outpatient rehabilitation. A repeat CT scan at 19 months showed only a small lacunar infarct.*

## Review of the Literature and Discussion

Traumatic brain injury is a common cause for disability in young people. TBI is thought to affect approximately 530 per 100,000 people in the United States with the male to female incidence nearly double. TBI encompasses disorders of varying degrees of severity and disability. Pathologic consequences result from both primary injury (hypoxia, hemorrhage, diffuse axonal injury, etc.) and the subsequent inflammatory and reparative process that follows, often called secondary injury. (1)

The majority of scientific and clinical efforts are being focused on mitigating the pathophysiologic consequences of the secondary injury since this appears to be modifiable. Cerebral ischemia, energy failure, inflammation, oxidative stress and neuronal death is the final outcome of the secondary injury.(2)

Understanding the mechanism of the secondary injury will aid in establishing effective treatment strategies of which HBO therapy may be able to address.HBOT has been used for the treatment of brain injury for over forty years, with a large body of work from the Russian literature which we do not have access to.(3) An early prospective controlled trial of sixty patients evaluated HBOT for the treatment of head injury coma, finding that HBOT can counteract ischemia and edema.(4) In a group of severely brain injured pediatric patients, Brown et al. found that HBOT temporarily reduced intracranial pressure, however did not not demonstrate a clinical improvement in this group.(5)



The use of HBO in the acute closed head injury was studied in 1992 by Rockswold et al. when they randomly selected for HBO treatment from 168 patients who had a Glasgow Coma Score of 9 or less for at least 6 hours. HBOT did not increase the number of patients in the favorable outcome category. (6) It is now believed that there is a therapeutic window of between three and 6 hours for the treatment of TBI with HBOT(7), although delayed multiple HBO treatment may be beneficial.(8)

HBO can protect the nervous system by improving brain metabolism, decreasing intracranial pressures, blunting the inflammatory response, improving the integrity of the blood brain barrier and reducing edema, and mitigating apoptosis.(9) HBOT was found to improve cerebral blood flow, as determined by SPECT scan, in a study of 50 patients with chronic brain injury (10) An improvement in aerobic brain metabolism was seen in 37 severely brain injured patients after they underwent up to seven one-hour treatments with HBOT. These authors demonstrated a reduction in cerebrospinal fluid lactate, a reduction in intracranial pressure, and an increased cerebral metabolic rate.(11) None of these studies looked at clinical outcomes.

Longhi et al. reported later that there was no evidence of a clinical benefit of hyperoxia for head injury, demonstrating that the ratio between lactate and pyruvate, which they deemed a better indicator of brain metabolism, was unchanged after hyperoxia (not HBOT).(12)

In a review of the literature, McDonagh et al. reported in 2004 that the clinical significance of HBOT on functional status was "unclear," but that the evidence did support a small decrease in overall mortality.(13) Shi et al., however, concluded that HBO therapy had "specific curative effects" after studying the use of HBO therapy in 320 patients post-brain injury. They measured the recovery of clinical symptoms, control of epilepsy, and resolution of hydrocephalus. SPECT imaging was performed before and after treatment to assess the therapeutic effects of HBOT. These

authors concluded HBO therapy was superior to medications alone and that SPECT imaging could be used to demonstrate those individuals with neurological dysfunction that may be amenable to HBO treatment.(14)

HBOT has been used as an adjunct to radiation-induced necrosis of the brain which demonstrates its potential neuroprotective role.(15) The use of HBOT for bony injuries and soft tissue radiation injury was recommended by Feldmeier after a review of 74 studies in the literature. He further noted that there was increasing evidence in support of HBOT for radiation-induced brain necrosis.(16)

Treatment frequency of HBOT has been found to be a factor in improving neuropsychiatric effects of chronic brain injury and this may occur via enhanced mitochondrial recovery. This benefit is proposed when HBO treatment is used at lower pressures and greater frequency. Many reports describe the use of "mild" hyperbaric oxygen therapy at pressures of 1.5 atmospheres or less and ongoing treatments.(17)

This was illustrated by a pilot case study of a 54-year-old male who had sustained a TBI one year previous, causing permanent neurological symptoms. Electrophysiological, behavioral, and metabolic measures were obtained to evaluate the impact of HBOT on his neurocognitive function. After the first series of 20 treatments, the authors noted improvements in motor and sensory measures. These were paralleled by electrophysiological measures. The improvements were not sustained at one year. He then received a second series of 60 HBO treatments one year later.(18)

Notable aspects of this case study are the documented measurable clinical improvements coincident with enhanced electrophysiological testing (P300 brainwave amplitude); however, there was no concomitant improvement in SPECT imaging seen.

This may indicate that SPECT imaging is not the appropriate surrogate test to validate functional

improvement and that clinical improvements may precede any measurable SPECT changes. They also note that the patient's second series of 60 treatments not only re-instated the previous gains from one year prior, but yielded greater benefits than those initial 20 treatments. Gains were seen in gait velocity, working memory, language, and the processing speed of information. This supports other author's suggestion that there is neural tissue around the area of damage that may be idle, yet viable, for several years after the initial neurological insult.(19)

Similar results were also found by Golden et al. who studied both children and adults with chronic brain injury who had gone one year without clinical progress despite multimodal treatment. Patients who had previously decided to use HBOT were enrolled into HBO therapy programs, however the report did not indicate the specific HBOT protocols used. Outcome of HBO participants was measured with validated neuropsychological measures assessing a broad range of cognitive, social, and motor function (Vineland assessment). The results suggested that non-responders and responders existed within the treatment groups. Furthermore, the number of total treatments, not the treatment time period, was most suggestive of benefit. SPECT imaging was performed on these subjects as well. SPECT changes did not progress as quickly as cognitive changes progressed. The authors believed their results were "strongly supportive" for HBOT in the treatment of chronic brain injury and that SPECT changes may not be a reliable correlate of clinical improvement.(20)

Even comatose patients may benefit from HBOT. Liu et al. found improvement in cerebral perfusion by SPECT and Glasgow Coma Score in a prospective trial of comatose patients undergoing median nerve stimulation with or without (control group)HBOT. Control patients showed no measurable improvement while 6 of 12 patients in the HBOT group emerged from coma, none of the HBO group needed assisted ventilation, and only one still needed nasogastric tube feeding at one year.(21)

HBOT may have benefits from a neuropsychologic standpoint, as studies suggest beneficial effects on behavior and mood after HBOT. This could change the perspective on future HBOT research, allowing us to understand the role of HBOT in improving more subtle aspects of neurocognitive function. Improvements at this level are clinically measured in terms of enhanced mood and cognitive function. Most previous HBOT work has focused on the measurement of grossly observable changes (motor function,etc.), the measurement of metabolic changes that would validate improvement in ischemia, or objective measures of improved brain function (SPECT, EEG). These modalities of evaluation may not be accurate surrogates to determine an HBOT benefit as cognitive function may not be easily measured by physiologic or electrophysiologic changes.

HBOT may provide clinical benefit in traumatic brain injury in the acute and chronic injury settings. It appears to offer neuroprotective benefits in acute TBI as well as long-term beneficial effects during recovery from a brain insult. The clinical benefits of HBOT in TBI is being actively explored in the literature. HBO therapy may work by improving oxygen delivery to metabolically inactive, yet viable tissue, reducing inflammation, aborting apoptosis, improving cerebral metabolism, and enhancing brain plasticity. HBOT likely has application to specific types of injury at specific times. More studies will be necessary to differentiate responder and non-responder types.

HBOT has a very safe side effect profile and therefore, aside from cost, has little down side. Few good medical treatments exist for TBI; therefore, HBOT should continue to be researched to determine its full application and utility in the treatment of various forms of TBI.

## Summary

Hyperbaric oxygen therapy is approved for the treatment of wounds and burns, decompression illness, and gas poisoning. Based largely on animal studies, its mechanism of action is likely based in its ability to reduce inflammation through its immune dampening effects. HBOT increases the

oxygen saturation of blood plasma and therefore is able to deliver oxygen to tissues independent of hemoglobin.

Improving the delivery of oxygen to hypoxic tissues which have poor vascular supply may be one mechanism of action. Although not completely defined, the pathophysiology of multiple sclerosis, autism, and traumatic brain injury may be similar since all involve some degree of brain inflammation. The literature regarding the pathophysiology of autism suggests a variety of factors that can lead to brain inflammation: gut dysbiosis, intestinal hyperpermeability, mitochondrial disease, poor cerebral perfusion, oxidative stress and free radical damage. Studies on the pathophysiology of MS and TBI did not appear to evaluate these pathophysiological mechanisms, which may be a valuable area of research to explore, particularly with MS since it is an autoimmune disorder. Restoration of mitochondrial function may be a protective mechanism of HBO therapy for both autism and brain injury as suggested by animal studies.(22)

This author suggests that the current multi-modal treatment strategies used for autism, although many of which are “off-label”, could be used as a model for the treatment of MS and TBI since these disorders may share similar physiologic mechanisms of neurologic injury. For instance, the acute secondary injury following TBI is similar in many ways to the more chronic inflammatory issues of autism since both involve perfusion issues, inflammation, and metabolic derangements.

Furthermore, multimodal therapy for brain injury, as is common to the treatment of autism, may be of great benefit for the treatment of MS and TBI. Outcomes from brain injury may be improved using nutrients, such as B-vitamins and folic acid, which alter homocysteine metabolism, omega 3 fatty acids and krill oil to balance inflammatory cytokines and reduce C-reactive protein, and bioavailable forms of choline to enhance brain recovery.(23)

Clearly delineating the role of HBOT in the treatment of neurologic disorders will take careful

study with respect for the multiple factors that may impact treatment outcomes.

Variables for HBO treatment include pressure, percentage of oxygen, length and frequency of treatment. Subpopulations of disease may also benefit differently from HBOT. The disorders discussed here have multiple pathways that lead to neurologic injury and dysfunction, and it is likely that individualized protocols will need to be developed based on the specific needs of the patient. HBO therapy appears to be a promising treatment modality for autism, multiple sclerosis, and traumatic brain injury and should be further explored.

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## 16

## Vitamin D: The Essential Sunshine Nutrient and Its Many Roles

**Jay H. Mead, MD,  
FASCP**



Vitamin D is a fat soluble vitamin and prohormone that exists in several different forms. Ergocalciferol (Vitamin D2) is not produced in the body and comes from plant sources, whereas cholecalciferol (Vitamin D3) is found in cold water fish, such as salmon, mackerel and sardines, is often fortified in milk and is manufactured in the skin with adequate exposure to the sun's UVB rays<sup>i</sup>.

The New England Journal of Medicine estimated that 30–50% of children and adults in the US are at risk for vitamin D deficiency and 32% of healthy adults age 18–29 were measured as Vitamin D deficient at the end of a winter in Boston<sup>ii</sup>. This is likely a consequence of inadequate dietary intake

that may be exacerbated by fat malabsorption coupled with insufficient exposure to UVB sunlight. Note: Synthesis from sunlight requires that the sun

be **greater than 45° above the horizon** and most sunscreens block UVB rays. People with increased melanin (darker skin) require longer exposures to sunlight to produce the same amount of Vitamin D.

### Effects

Bioactive vitamin D binds to specific receptors in the cell (known as VDRs or Vitamin D receptors)<sup>iii</sup> and induces the transcription of more than 50 genes<sup>iv</sup> that have far reaching effects in the body, including the following:

**Osteoporosis / Calcium Balance** – Vitamin D increases intestinal absorption of dietary calcium, increases reabsorption of calcium filtered by kidneys and mobilizes calcium from bone when there is insufficient dietary calcium. We have long known the influence vitamin D had in formation of bone, as evidenced by the incidence of rickets with low Vitamin D levels<sup>v</sup>.

**Anti-Cancer** – Vitamin D inhibits proliferation and stimulates the differentiation of cells when bound to VDR receptors. Vitamin D has also been shown to induce apoptosis (programmed cell death)<sup>vi</sup>.

**Immunity** – There are a significant number of VDR receptors on T cells and macrophages and there is evidence that when bound to these receptors, vitamin D acts as a selective immunosuppressant and can either prevent or significantly affect many autoimmune diseases including rheumatoid arthritis, SLE, type 1 diabetes and IBD<sup>vii</sup>. Vitamin D can also enhance innate immunity and has been shown to be beneficial against tuberculosis and through this mechanism may be useful against additional infectious agents, such as influenza<sup>viii</sup>.

**Diabetes** – The bioactive form of Vitamin D has been shown to stimulate insulin production in the pancreas in type 1 diabetics and may play a role in the pathogenesis of type 2 diabetes through its ability to impair insulin synthesis and secretion<sup>ix</sup>.

**Blood Pressure Regulation** – Vitamin D can decrease the expression of the gene that codes for rennin, and therefore plays a role in controlling hypertension<sup>x</sup>.

### Toxicity

Vitamin D is a fat soluble vitamin that is stored in the liver and fatty tissue and is eliminated more slowly than water-soluble vitamins. Excess levels of Vitamin D can cause hypercalcemia, hypercalciuria, hypertension, constipation, fatigue and more. While adequate levels of Vitamin D are very important, you can get too much of a good thing. Monitoring therapy is important to ensure adequate, but not excessive dosage.

### What to Test

Whether supplemented or manufactured in the skin, cholecalciferol (D3) is hydroxylated in the liver to form 25-hydroxycholecalciferol (25(OH)), and this is the major circulating form of the vitamin. Though it goes through an additional hydroxylation (primary in the kidney) to form 1,25-dihydroxycholecalciferol before it is biologically active, the 25(OH) form is considered the most accurate measure of the amount of Vitamin D in the body, which is why testing 25(OH) is preferred<sup>xi</sup>.

**Jay H. Mead** is the President and Medical Director of Labrix Clinical Services, Inc. and a visionary for innovative testing for discerning practitioners. He is a leading expert in Salivary hormone and Urine iodine testing. Dr. Mead has been practicing as a clinician for over twenty years and understands the need and value of accurate, reliable laboratory testing. Dr. Mead is a board certified pathologist (AP/CP), a retired USAF Flight Surgeon and cofounder of a progressive full-service complementary and alternative medical clinic. He also has board certification in blood banking and has led the Pacific Northwest Region of the American Red Cross as the Chief Medical Officer for over 10 years. Dr. Mead is the co-author of the newly released book: *Slim, Sane and Sexy; Pocket Guide to Natural, Bioidentical Hormone Balancing*.

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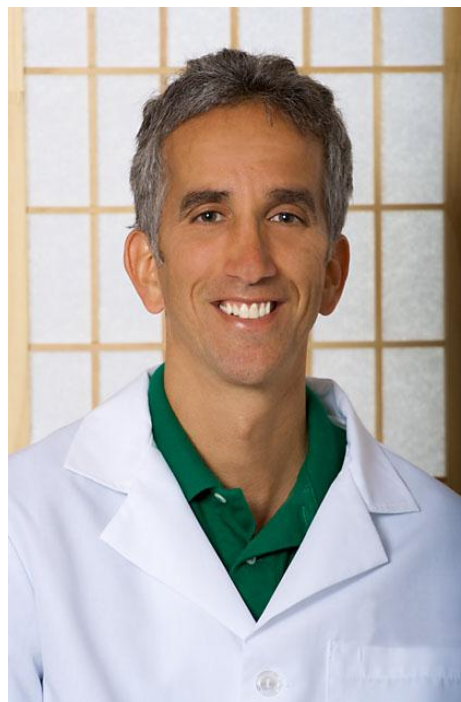
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## 17

# Iodine: Why You Need it, Why You Can't Live Without it

## David Brownstein, MD



I get asked by my patients if I had only one natural item to treat my patients with, which would it be? The answer to this question is not hard. Though there are so many natural items that provide such wonderful effects for the body, one nutrient stands head and shoulders above the rest. Can you guess which one it is? Iodine.

In all my years of practicing medicine, I have yet to see one item provide such miraculous effects on the body as iodine does. This article will illustrate the wonders of iodine and why you need to take a close look at your supplement regimen to ensure you are getting enough iodine in your daily regime. I would like to dedicate this article to my mentor on iodine, Dr. Guy Abraham. So, how come you haven't heard much about iodine? That is because iodine is truly the most misunderstood nutrient. There are so many myths about iodine. This issue will tackle the two most common myths about iodine:

Myth 1: We get enough iodine from salt.

Myth 2: Iodine supplementation will cause/worsen thyroid disorders.

Because of these myths, people have the mistaken idea that iodine is a toxic substance that needs to be avoided. How prevalent are these myths? They are repeated over and over in conventional medicine as well as the media. I guess if you repeat something over and over it must be true—However, that is not the case. Let me provide you with an email that was recently forwarded to me. The email, sent by an endocrinologist in the U.S., was forwarded to me by a nurse who read my iodine book and wanted to begin supplementing her patients with iodine.

*"We only see iodine deficiency in third world countries. We have never seen it here in my past eight years as a physician and the experience of other endocrinologists that I know as well. So, I don't trust books and information that is out there. Our salt is iodine fortified, so just eating a regular diet, we get about 10-20x the amount of iodine in the diet."*

Unfortunately, this is the prevailing opinion of most endocrinologists and mainstream doctors about iodine. The doctor has not seen it in eight years because he has not tested for it. And, of course, he mentions the salt myth. No wonder iodine is the most misunderstood nutrient. Let's see why people are so confused about iodine.

### History of Iodine

Iodine was found to treat goiter (swelling of the thyroid) by Coindet (1774–1834). This was the first time a single item (iodine) was used to treat a specific illness (goiter). This is known as the birth of Western medicine as doctors are still taught today to make a diagnosis and provide the one item--in most cases a pharmaceutical drug--that can treat the illness.

In the early 1900's, there was a high prevalence of goiter in the Great Lakes area of the United States. The soil in this area is known to be very deficient of iodine. Nearly 40% of school-aged children had goiter at this time.<sup>i</sup> David Marine was a physician from Ohio who had been doing research on animals and humans and their problems with iodine deficiency. In fact, Dr. Marine had done research with goitrous (swelling of the thyroid) dogs and found that when he added iodine to their feed, he had seen them change from "wizened and listless" to "active and robust".<sup>ii</sup> <sup>iii</sup> <sup>iv</sup> He did further research on iodine deficiency and thyroid problems in fish, sheep and other farm animals. He found that iodine could rectify thyroid problems and goiter in a wide variety of animals suffering from iodine deficiency. From the results in animals, Dr. Marine estimated the amount of iodine necessary to treat the goiter epidemic that was occurring in vast areas of the U.S. in the early 20th century.

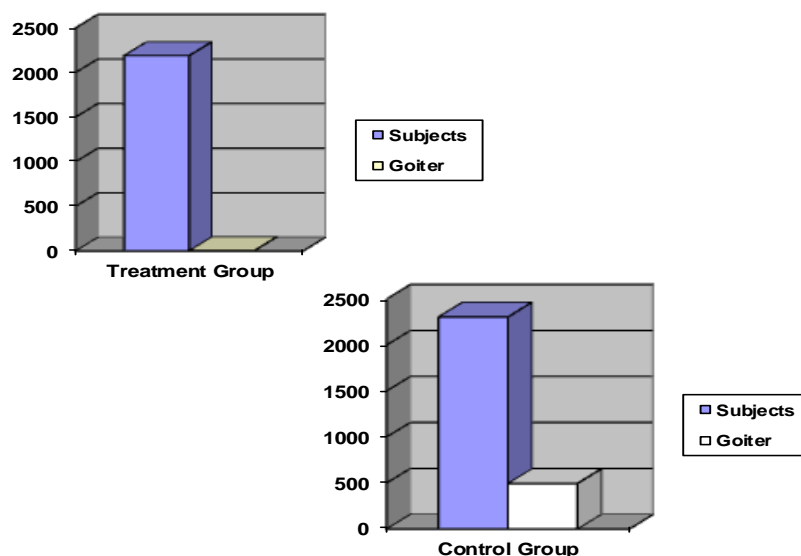
In Akron, Ohio, Dr. Marine conducted the first large-scale study on using iodine as a therapy to reduce goiter in people. Dr. Marine chose Akron due to the high rate of goiter that was occurring in school aged girls. In the early 1900's, approximately 56% of school-aged girls had goiter in Akron.<sup>v</sup> There was a 600% increase in goiter in adolescent girls versus boys.<sup>vi</sup> Why would there

be such a large difference in girls versus boys? The first tissue to grow during puberty is breast tissue. Breast tissue contains the second largest concentration of iodine (next to the thyroid gland). Therefore, at puberty, as a girl begins to grow breast tissue her iodine requirements become larger as compared to a boy.

Marine studied two groups of students:

1. A control group of 2305 students where no iodine was given.
2. A treatment group of 2190 students who were given 9mg/day of sodium iodide (averaged daily) for 2.5 years. This dose of iodine is nearly 100x the RDA for iodine.

The results were stunning (see Figure 1). The control group (no iodine) showed a 22% increase of goiter. The treatment group had a significantly lowered 0.2% incidence of goiter.<sup>vii</sup> Dr. Marine reported these results and the U.S. quickly implemented the iodization of salt in the Great Lakes. The rest of the country adopted the policy of adding iodine to salt shortly thereafter. Today, the World Health Organization actively promotes the use of iodized salt to prevent goiter.



The iodization of salt was hailed as the first public health miracle. However, I will show you that although the iodization of salt can prevent goiter in the vast majority of people, it does not provide



enough iodine for normal thyroid function or provide enough iodine for the rest of the body's needs.

#### Myth 1: WE GET ENOUGH IODINE FROM SALT

Iodine is added to table salt at 100ppm as potassium iodide, which amounts to 77µg iodide/gm of salt. The RDA for iodine is set at 150µg/day for adults in the U.S. and slightly more during pregnancy and lactation. Remember, the RDA was only set to prevent goiter (swelling of the thyroid) in the vast majority of people. The average American takes in 4–10gm/day of refined salt/day. If we do the math (77µg/gm x 4–10gm/day=308–770µg/day)

We can see that we are ingesting more than the RDA. So, isn't myth 1 true? Don't we get enough iodine from salt?

The research is crystal clear that we DON'T get enough iodine from salt. An interesting study completed in 1969 showed that only 10% of iodine in salt is bioavailable.<sup>viii ix</sup> Therefore, if we go back to our original calculations, we can now see that iodized salt provides somewhere between 30–77µg/day—which is markedly **below** the RDA for iodine. Refined salt is a lifeless, devitalized product that is best avoided.

Not only is iodized salt a poor source of iodine, we have been conditioned to avoid salt by the media and mainstream medicine. Presently, less than 50% of U.S. households use salt. What is the consequence of this? Iodine levels have fallen over 50% over the last 30 years according to the National Health and Nutrition Examination Survey.<sup>x</sup> You can see that this is a recipe for making a whole population of people iodine deficient. That is exactly what has happened in the United States.

Myth 2: Iodine supplementation will cause/worsen thyroid disorders.

If Myth 2 were correct, the declining iodine levels would be a good thing for preventing thyroid disease. However, this has not been the case. As iodine levels have been falling over the last 30 years, thyroid disorders, including hypothyroidism, Hashimoto's disease, Graves' disease and thyroid cancer have been increasing at near epidemic rates.

We would expect the opposite to occur—thyroid illnesses declining-- if iodine were the cause of these disorders. In fact, I find it impossible to treat any thyroid illness if there is an inadequate iodine level in the body.

#### OTHER REASONS FOR IODINE DEFICIENCY

The largest amounts of iodine occur in the oceans. Sea vegetables and ocean fish can contain larger amounts of iodine and are the foods that provide the most utilizable iodine for the body. Diets lacking in sea food can predispose to iodine deficiency. Also, diets high in refined bakery products, such as breads, pastas, and cereals can cause/worsen an iodine deficiency problem.

#### WHAT HAPPENED TO BAKERY PRODUCTS? BROMINE

I believe one of the reasons I am seeing such a huge percentage of iodine deficient patients is due to mismanagement of our food industry. The food industry has given us refined, devitalized food that has left us, as a population, nutrient deficient, obese and fatigued. Although there are many problems with the food industry, I will concentrate on the food industry's biggest mistake: not putting iodine in our bakery products.

Up until the early 1970's, iodine was added to bakery products as a dough conditioner. In the early 1970's, the food industry changed its practice and began substituting bromine for iodine. Why did this substitution occur? It is not clear from the literature. Bromine is in the chemical family of halides, of which iodine is a member. Bromine and iodine are very close to the same size and structure. All halides compete with one another for binding and absorption. The body has receptors and uses for iodine, such as making thyroid hormone. There is no known use of bromine in the body. Bromine interferes with iodine utilization in the thyroid as well as wherever iodine concentrates in the body. <sup>xi</sup>

Bromine is a known goitrogen—it promotes the formation of goiter in the thyroid. Bromine can bind to iodine receptors in the breast and is a known carcinogen to the breast. On the other hand, iodine has anti-carcinogenic properties. Remember, iodine will concentrate in the glandular tissue of the body—the thyroid, breasts, ovaries, uterus, and probably

the prostate gland—and has anti-cancer effects in these tissues.

Is it any wonder that thyroid, breast, ovarian, uterine, and probably prostate problems are occurring at epidemic rates when we are so toxic in bromine and deficient in iodine? Remember, iodine and bromine compete with one another. If we have too much bromine, iodine will be released from the body. The receptors that are supposed to bind iodine will now bind bromine. The hormones that are supposed to contain iodine will now contain bromine. For example, the thyroid gland produces thyroxine, or T4. The '4' refers to the number of iodine molecules on the thyroxine molecule. In the case of T4, there are four iodine molecules attached to it. If we ingest too much bromine and too little iodine, there is a good chance that our thyroid hormone will not contain iodine, but instead be brominated with bromine. Regular thyroid blood tests cannot distinguish between the two.

What are the consequences of bromine toxicity?

Bromine has been shown to cause delirium, psychomotor retardation, schizophrenia and hallucination. Bromine can make subjects feel dull and apathetic and have difficulty concentrating. Bromine can also cause depression, headaches and irritability. There are multiple sources of bromine exposure in our toxic environment: hot tubs and pools, as a fumigant for agriculture, fire retardant in carpets, clothing, curtains, etc., brominated vegetable oil (in many sodas), and a constituent of most computer and electronic equipment. The U.S. produces the most bromine in the world.

My experience has clearly shown bromine toxicity to be a huge problem. In fact, every one of the 150 patients that I have tested for bromine has shown high levels. Those with chronic illness, especially cancer of the breast have higher levels as compared to healthy people.

**WHAT CAN YOU DO?** It is important to ensure that you have adequate iodine levels in your body. Urinary testing is the easiest way to do this. I recommend three labs for iodine testing:

FFP Labs  
Hakala Research Labs  
Doctor's Data

To get the best results, I suggest working with a health care provider knowledgeable about iodine deficiency. Two organizations that train doctors about the use of natural items that have lists of doctors include the following:

Broda O. Barnes, M.D. Research Foundation: [www.Brodabarnes.org](http://www.Brodabarnes.org) or 203.261.2101

American College for the Advancement in Medicine: [www.acam.org](http://www.acam.org) or 949.309.3520

When supplementing with iodine, I recommend using iodine supplements that contain both forms of iodine—iodide and iodine. Lugol's iodine and its tableted form Iodoral® have proven effective. Lugol's iodine contains 6.25mg of iodine/iodide per drop. Iodoral® contains 12.5mg of iodine/iodide (or 2 drops of Lugol's) per capsule. My clinical experience has shown that the most effective doses of iodine vary between 6.25 and 50mg/day. Generally, sicker patients including those with cancer of the breast, prostate, uterus, ovaries and thyroid require larger amounts of iodine.

**David Brownstein** is a family physician who utilizes the best of conventional and alternative therapies. He is the Medical Director for the Center for Holistic Medicine in West Bloomfield, MI. Dr. Brownstein is a graduate of the University of Michigan and Wayne State University School of Medicine. He is Board-Certified by The American Academy of Family Practice. Dr. Brownstein is a member of the American Academy of Family Physicians and the American College for the Advancement in Medicine. He is the father of two wonderful girls, Hailey and Jessica.

Dr. Brownstein has lectured internationally about his success using natural items. Dr. Brownstein has authored ten books: *Drugs that Don't Work and Natural Therapies That Do*, 2<sup>nd</sup> Edition, *The Miracle of Natural Hormones* 3<sup>rd</sup> Edition, *Overcoming Thyroid Disorders* 2<sup>nd</sup> Edition, *Overcoming Arthritis*, *Iodine: Why You Need It, Why You Can't Live Without It* 4<sup>th</sup> Edition, *The Guide to Healthy Eating* 2<sup>nd</sup> Edition, *Salt Your Way to Health* 2<sup>nd</sup> Edition, *The Guide to a Gluten-Free Diet*, *The Guide to a Dairy-Free Diet*, and *The Soy Deception*.

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# 18

## Bioidentical Breakdown: Emerging Field of Hormone Replacement

### Jay H. Mead MD, FASCP



There has been a lot of press in recent years about the pros and cons of hormone replacement as it relates to breast health and cardiovascular disease. Most of the media reports are referring to artificial, chemically produced hormones that look nothing like the molecules that are produced by the human body. These synthetic molecules must be differentiated from hormones that are molecularly identical to endogenous hormones, or bioidentical hormones. Though there can be risks to all hormone imbalances, the side effects and risks associated with supplementation using bioidentical hormones in a balanced fashion are significantly less than the effects of conventional HRT<sup>i</sup>. The key to safe and effective use of these hormones requires individual analysis of native hormone levels and supplementation of only the needed hormones in balanced formulas.

#### Women:

It's no secret that as a woman ages, her hormone levels fluctuate and change significantly.

Estrogen levels drop by approximately 40% and progesterone levels plummet by close to 90% as a woman goes through menopause<sup>ii</sup>. Beyond the primary decline in ovarian function, there is very little extragonadal production of progesterone.

Estrogen levels on the other hand, often remain adequate and even robust due to conversion of testosterone to estradiol by the aromatase enzyme. This enzyme is particularly active in adipose tissue, and therefore, women who have a higher body fat percentage are more likely to have elevated estrogen levels. Because of this variability, it is important to test a woman's hormones prior to initiating hormone replacement treatment as the formula will vary significantly depending on the woman's endogenous hormone levels. Low range estrogen levels are often associated with "typical" menopausal symptoms including night sweats, hot flashes and vaginal<sup>iii</sup> dryness. Replacing estrogen in deficient women can provide significant relief to these symptoms; however, estrogen replacement should never be

given without concomitant progesterone supplementation regardless of whether or not the patient has had a hysterectomy. Balancing with adequate progesterone is not only important to prevent endometrial cancer, but will also protect the brain, the heart and the breasts<sup>iv</sup>. Estrogen doesn't refer to a single hormone, but is rather a group of hormones that differ distinctly in molecular structure as well as in physiologic role. The human body produces three primary estrogens: estrone, estradiol and estriol. Estradiol is the most biologically active of the three, and therefore, one of the most commonly prescribed; however, it is best when given in combination with estriol<sup>v</sup>. Estriol (E3) is the weakest of the estrogens; though it binds to the same estrogen receptors, its action is significantly weaker. Because of this property, the presence of estriol can work to govern the proliferative effects of estradiol by competing for receptors<sup>vi</sup>. A combination of estradiol (E2) and estriol (E3) is often referred to as biest or two estrogens. The third estrogen, estrone, is not recommended for hormone replacement, as many of its metabolites are carcinogenic.

Though there is much individual variability in estrogen levels, progesterone levels are almost always low in the peri and post menopausal population<sup>vii</sup>. It is the relative loss of progesterone compared to the decline in estrogen that causes a number of symptoms including breast tenderness, menstrual irregularities, mood changes, depression, tearfulness, foggy brain and more. The disproportionate loss of progesterone (termed "estrogen dominance") begins in the latter stages of a woman's reproductive cycle, when the luteal phase of the menstrual cycle begins to malfunction<sup>viii</sup>. Because the corpus luteum is the primary source of progesterone, when there is no ovulation, there is very little progesterone produced.

The term "estrogen dominance" can be confusing at times because it is less related to the amount of circulating estrogen and more related to the ratio of estrogen to progesterone in the body. Symptoms of Estrogen Dominance include:

- Mood Swings

- Irritability
- Depression
- Irregular Periods
- Heavy Menstrual Bleeding
- Hot Flashes
- Vaginal Dryness
- Water Retention
- Uterine Fibroids
- Decreased Libido
- Headaches
- Fatigue
- Weight Gain: Hips, Thighs and Abdomen
- Sleep Disturbance (Insomnia, less REM sleep)
- Breast Tenderness/Fibrocystic Breasts
- Bone Mineral Loss (Osteoporosis)
- Short-term Memory Loss
- Lack of Concentration
- Dry, Thin, Wrinkly Skin
- Thinning of Scalp Hair
- Increased Facial Hair
- Diffuse Aches and Pain

Hormone imbalance, and particularly estrogen dominance, is not a condition that is limited to the menopausal population. In a cycling woman, progesterone is the hormone that should be dominant during the second half of the menstrual cycle<sup>ix</sup>. There are many factors that can affect the ability of the corpus luteum to produce adequate progesterone including stress, diet and the use of exogenous hormones, such as birth control pills. The hormones found in birth control pills are not the same as progesterone produced by the body. Synthetic progestins differ significantly in molecular structure as well as in action<sup>x</sup>. While natural progesterone decreases a woman's risk of breast cancer and cardiovascular disease, synthetic progestins increase it. The most famous study illustrating this fact is the Women's Health Initiative, a large multi-armed research project that followed over 16,000 women for an average of 5.2 years and concluded that the participants who had been taking the progestin medroxyprogesterone acetate had a statistically significant increase in rate of breast cancer,



coronary artery disease, stroke and pulmonary embolism<sup>xi</sup>.

One of the most common endocrine disorders that leads to anovulation and subsequent estrogen dominance is polycystic ovarian syndrome (PCOS), a metabolic disorder where the ovaries and adrenal glands produce excessive androgens due to stimulation from insulin<sup>xii</sup>. Though there can be a genetic predisposition to this condition, it is often exacerbated by a diet that is high in simple carbohydrates and low in fiber that leads to increased insulin resistance. The insulin stimulates testosterone production in the ovaries and DHEA production from the adrenal glands. The androgens are converted into estrogens, primarily estrone, in the periphery and feed back to the hypothalamus and pituitary, which interferes with LH and FHS levels that stimulate ovulation. With no ovulation, there is no corpus luteum produced and therefore little progesterone, leading to estrogen dominance. While the crux of treating this condition often requires significant diet and lifestyle changes, supporting the body with progesterone to balance excess estrogen can help significantly.

Regardless of a woman's age, proper analysis of endogenous hormone levels and correction of any imbalance will reduce risk of proliferative diseases, such as breast and endometrial cancer as well as treat a myriad of common symptoms. When creating a treatment plan, the dosage as well as route of administration of hormones is important. Progesterone has a large first pass effect, meaning that a significant majority of the hormone is metabolized by the liver immediately after being absorbed through the gastrointestinal tract<sup>xiii</sup>. Because of this, the preferred method of delivery is in a transdermal (topical) cream or gel applied to an area of the body with very little subcutaneous fat. In this medium, the hormone is absorbed directly into the capillary beds and delivered to tissues and bypasses the immediate first pass through the liver<sup>xiv</sup>. Estrogen supplementation is also best when done in a topical cream, due to the fact that oral estrogens reduce the liver's production of growth hormone<sup>xv</sup>.

Though there is much variability in the dosages recommended to patients, a general rule of thumb is to use the lowest amount needed for therapeutic effect<sup>xvi</sup>. The following guidelines are provided based upon 35 years of clinical experience in balancing women's hormones. The dosages, intervals and applications listed below have been determined to be excellent starting points once a need for supplementation has been established clinically and through laboratory validation. Please note that these are starting dosages, which need to be monitored through laboratory and clinical follow up. Routinely check saliva for baseline hormone levels prior to initiating supplementation with repeat laboratory testing and clinical follow up at 2 month intervals until hormones are balanced; then yearly thereafter.

#### Progesterone:

Pre-menopause interested in conception: USP Progesterone 20–30mg in a transdermal base applied day 15 through 28 of the menstrual cycle. Rotate application daily to the “thin” region of the body: inner wrist, behind knees, upper inner arm or upper chest. Dose may be given qd or split into bid application as preferred by provider and patient. An example script: P4 25mg/ml, #14, Sig: ½ml bid or 1ml qd (day 15 through 28). You may want to give 2 refills, which will take the patient up to the 2 month retest interval.

Pre-menopause NOT interested in conception: USP Progesterone 20–30mg in a transdermal base (applied day 7 through 28 of the menstrual cycle. In other words, apply on days not menstruating. Rotate application daily to a “thin” region of the body: inner wrist, behind knees, upper inner arm or upper chest. An example script: P4 25mg/ml, #21, Sig: ½ml bid or 1ml qd (day 7 through 28). You may want to give 2 refills, which will take the patient up to the 2 month retest interval.

Post-menopause: USP Progesterone 20–30mg in a transdermal base applied daily. Some providers prefer to cycle dosage, e.g., 3 weeks on and 1 week off. Rotate application daily to a “thin” region of the body: inner wrist, behind knees, upper inner arm or upper chest. Example



scripts: P4 25mg/ml, #30, Sig: ½ ml bid or qd or alternatively: Sig: ½ ml bid or 1ml qd (3 wks on, 1wk off). You may want to give 2 refills, which will take the patient up to the 2 month retest interval

### Bi-Estrogen (Biest)

Pre-menopause interested in conception: USP Estriol(E3) and estradiol(E2) combination: 1mg (E3:E2;4:1) in a transdermal base applied day 1 through 12 of the menstrual cycle. Rotate application daily to the "thin" region of the body: inner wrist, behind knees, upper inner arm or upper chest. Dose may be given qd or split into bid application as preferred by provider and patient. An example script: Biest 1mg (E3:E2;4:1)/ml, #13, Sig: ½ml bid or 1ml qd (day 1 through 12). You may want to give 2 refills, which will take the patient up to the 2 month retest interval.

Pre-menopause NOT interested in conception: USP Estriol(E3) and estradiol(E2) combination: 1mg (E3:E2;4:1) in a transdermal base applied day 1 through 25 of the menstrual cycle. Rotate application daily to the "thin" region of the body: inner wrist, behind knees, upper inner arm or upper chest. Dose may be given qd or split into bid application as preferred by provider and patient. An example script: Biest 1mg (E3:E2;4:1)/ml, #26, Sig: ½ml bid or 1ml qd (day 1 through 25). You may want to give 2 refills, which will take the patient up to the 2 month retest interval.

Post-menopause: USP Estriol(E3) and estradiol(E2) combination: 1mg (E3:E2;4:1) in a transdermal base applied daily. Some providers prefer to cycle dosage, e.g., 3 weeks on and 1 week off. Rotate application daily to a "thin" region of the body: inner wrist, behind knees, upper inner arm or upper chest. Example scripts: Biest 1mg (E3:E2;4:1), #30, Sig: ½ml bid or 1ml qd or alternatively: Sig: ½ml bid or 1ml qd (3 wks on, 1wk off). You may want to give 2 refills, which will take the patient up to the 2 month retest interval.

Men:

Hormone balancing isn't just important for women. Men experience a significant shift in their hormones as they age and these changes can have some very profound effects on their health. Declining testosterone levels are commonly seen in men beginning in the fourth decade of life.<sup>xvii</sup> Suboptimal or low testosterone levels in males are often associated with symptoms of aging and are referred to as andropause or male menopause. This is the equivalent of menopause in women when ovarian production of estrogens and progesterone begins to decline.

Testosterone is an important anabolic hormone in men, meaning it plays important roles in maintaining both physical and mental health. It increases energy, prevents fatigue, helps maintain normal sex drive, increases strength of all structural tissues such as skin/bone/muscles, including the heart, and prevents depression and mental fatigue.

Testosterone deficiency is often associated with symptoms, such as night sweats, insulin resistance, erectile dysfunction, low sex drive, decreased mental and physical ability, lower ambition, loss of muscle mass and weight gain in the waist<sup>xviii</sup>. The primary cause of this increase in girth is visceral fat, not excessive subcutaneous fat (fat under the skin).

The visceral fat cells are the most insulin resistant cells in the human body<sup>xix</sup>. They have excess hormone binding receptors for cortisol and androgens and decreased receptors for insulin (resistance to insulin). As a person ages, hormone levels change in favor of insulin resistance. The cortisol and insulin levels rise, while progesterone, growth hormone and testosterone decline. The visceral fat cell with its increased receptors, blood supply and innervation begins to collect more fat in the form of triglycerides. A vicious cycle is initiated, which if not interrupted with natural hormone balancing, will lead to abdominal obesity, diabetes and high cholesterol levels. This phenomenon is known as metabolic syndrome.

Stress management, exercise, proper nutrition, dietary supplements (particularly adequate zinc and selenium), and androgen replacement therapy

(controversial in prostate cancer) have all been shown to raise androgen levels in men and help counter andropause symptoms<sup>xx</sup>. The “trick” is to know how much testosterone is required for each individual male. This is where knowing the salivary testosterone levels come into play. Initial salivary testing and following salivary monitoring are crucial for determining the most optimal prescription<sup>xxi</sup>. Free testosterone can also be calculated in serum using total testosterone and SHBG. With these levels one can calculate the Free Testosterone Index (FTI) – Total Testosterone/SHBG X 0.0347. The normal FTI range is 0.7–1.0. If one's FTI is below 0.7, testosterone therapy should be initiated. The final dosage will be the amount required to correct the FTI ratio.

Prior to initiation of testosterone therapy the PSA level needs to be within the expected range. There is no evidence that testosterone increases the risk of prostate gland cancer; however, if cancer has already developed, testosterone may accelerate its growth<sup>xxii</sup>. The PSA test is a good guide as to presence or absence of cancer and is a good indicator of inflammation within the prostate gland.

In addition to declining testosterone levels, many men also experience rising estrogen levels as they age. The mechanism behind this is similar to what we often see in women, the aromatase enzyme converts testosterone into estradiol. This process often creates a state of relative estrogen dominance in men and this state is particularly important as it relates to prostate health<sup>xxiii</sup>. Prostate cells are very susceptible to fluctuating hormone levels and respond to estrogen in a similar way to endometrial cells in the woman. In both cases, estrogen causes growth and proliferation, particularly when not governed by adequate progesterone levels. While progesterone is a hormone that is primarily associated with women, its role in men's health should not be overlooked. In addition to protecting the prostate, progesterone is protective to the cardiovascular system by governing cell adhesion molecules and preventing plaque formation and is neuroprotective<sup>xxiv</sup>.

A complete hormonal analysis of male patients is recommended to evaluate and identify important deficiencies, such as inadequate testosterone production and lack of sufficient progesterone to balance estrogen. Just as with female patients, treatment should be limited to replacement with physiologic doses of bioidentical hormones.

#### Testosterone:

Men: USP testosterone: 10 mg in a transdermal base (e.g. Vanpen) applied daily. Rotate application daily to a “thin” region of the body: inner wrist, behind knees, upper inner arm or upper chest. Example scripts: Testosterone 10mg/ml, #30, Sig: ½ml bid or 1ml qd. You may want to give 2 refills, which will take the patient up to the 2 month retest interval. Note: It is important to monitor PSA and CBC levels during the treatment interval.

#### Progesterone:

Andropause (Men): USP Progesterone 5 to 10 mg in a transdermal base (e.g. Vanpen) applied daily. Rotate application daily to a “thin” region of the body: inner wrist, behind knees, upper inner arm or upper chest. Example script: P4 10mg/ml, #30, Sig: ½ml qd. You may want to give 2 refills, which will take the patient up to the 2 month retest interval.

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**Jay H. Mead** is the President and Medical Director of Labrix Clinical Services, Inc. and a visionary for innovative testing for discerning practitioners. He is a leading expert in Salivary hormone and Urine iodine testing. Dr. Mead has been practicing as a clinician for over twenty years and understands the need and value of accurate, reliable laboratory testing. Dr. Mead is a board certified pathologist (AP/CP), a retired USAF Flight Surgeon and cofounder of a progressive full-service complementary and alternative medical clinic. He also has board certification in blood banking and led the Pacific Northwest Region of the American Red Cross as the Chief Medical Officer for over 10 years. Dr.

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Dr. Mead speaks at national and international conferences on topics including: Best Practices for State-of-the-Art Hormone Testing; Best Practices for Men's Hormone Health; Beyond Testosterone...Progesterone for men, Youth's Best Kept Secret; Vitamin D The Forgotten Hormone; Neurodegenerative Disease and Endocrine Balancing; an Integrative Approach; Thyroid Health and Prostate Health.

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