AAPI'S NUTRITION GUIDE TO

OPTIMAL HEALTH:
USING PRINCIPLES OF

FUNCTIONAL MEDICINE & NUTRITIONAL GENOMICS

PART III - 2017

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

CONTRIBUTING AUTHORS

Lise Alschuler, ND FABNO
Daniel Amen, MD
Scott J. Banks DC, IFMCP
Susan Blum MD MPH
David M Brady, ND DC CCN DACBN
Dale Bredesen, MD
Marlisa Brown, MS RD CDE CDN
Garry D›Brant DC, CTN, LCSW, DACBN, CDN, DIPLAC
Ruth DeBusk, PhD RDN
Lisa Dorfman MS RD CSSD LMHC FAND
Regina Druz, MD FACC FASNC AFMCP
Karla Dumas, RDN, LDN
Corie Edwards, ND
Joel M Evans, MD
Felice L Gersh, MD
Alexandria L Gesing, BA
Trupti Gokani MD
Angela Grassi, MS RDN LDN
Stephanie Harris, PhD, RDN, LD
Shashank Joshi, MD, DM, FRCP, FACE, FACP, FICP
Shilpa Joshi, MS, RD
Ellen Kamhi, PhD RN AHG AHN-BC
Annie B Kay, MS RDN E-RYT500
Kiran Krishnan, Microbiologist
Maria E Levada MD, FACOG FACS
Susan Linke, MBA MS RD LD CGP CLT
Loren Marks DC DACBN
Zahra Mehdizadeh Kashi, PhD
Deanna Minich, PhD FACN CNS IFMCP
Kelly Morrow, MS, RDN, CD
Jonathan Seyppel Orban
Akil Palanisamy, MD
Gita Patel, MS, RDN, CDE, LDN, CLT
Mark C Pettus, MD, FACP
Lauren Pitts, MA, RD, LD
Michael Posner, DC
Rammohan V Rao, PhD
Emily Rydbom, BA, CNC, CNP, CHN
Michael J. Schneider, DC PhD
Corey Schuler, RN MS LN CNS DC DBM FAAIM
Cathy Snapp, PhD
Leslie P. Stone MD IFMCP
Michael Stone MD, MS, IFMCP
Frederick Tinari DC, MS, DACBN, DCBCN
Brigid Titgemeier, RDN,
Terry L Wahls, MD MBA, IFMCP
Izabella Wentz, PharmD, FASCP
Eugene Zampieron, ND, AHG

American Association of Physicians of Indian Origin
600 Enterprise Drive, Suite 108, Oakbrook, Illinois, 60523 USA
630-990-2277 • info@aapiusa.org
www.aapiusa.org

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Acknowledgements

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Lise Alschuler

Amen Publishing

Daniel Amen

Dawn Anatra

Jacqueline Arellano

Ashland Comprehensive Family Medicine – Stone Medical

Asian Indians in Nutrition and Dietetics Member Interest Group Academy of Nutrition and Dietetics (AINDMIG)

Jennifer Assael

Scott J Banks

Aarti Batavia

Kashi Batheja

Shaena Behbahany

Blum Center for Health

Susan Blum

David M Brady

Dale Bredesen

Marlisa Brown

Constance Brown Riggs

Francesca M Caputo

Zamher Chalisa

Garry D'Brant

Ruth DeBusk

Diabetes and Care Education Dietetic Practice Group Academy of Nutrition and Dietetics (DCE DPG)

Dietitians in Integrative and Functional Medicine

Dietetic Practice Group Academy of Nutrition and Dietetics (DIFM DPG)

Lisa Dorfman

Nicole Dotman

Regina Druz

Karla Dumas

Christine Eberhard

Corie Edwards

Joel M Evans

Functional Formularies

Felice L Gersh

Alexandria L Gesing

Angela Grassi

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Stephanie Harris

Katherine Halbeck

Michael F Hoffman

Integrative Cardiology Center of Long Island

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Shashank Joshi

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Ellen Kamhi

Zehra Mehizadeh Kashi

Annie B Kay

Kiran Krishnan

Sarah Harding Laidlaw

Donna Lalwani

Brian Lamphier

Maria E Levada

Susan Linke

Long Island Chiropractic PC

Alex Lubarsky

Loren Marks

Peter Matz

Robin Gentry McGee

Deanna Minich

Kelly Morrow

Jonathan Seyppel Orban

Oxford Biomedical Technologies, Inc.

Akil Palanisamy

Gita Patel

Mark C Pettus

Lauren Pitts

Lois Posner

Michael Posner

Andrea Przybyla

Amen Publishing

Sudha Raj

Rammohan V Rao

RSDigital Productions

Emily Rydbom

Kim Schneider

Michael J Schneider

Corey Schuler

Paul Sherman

Cathy Snapp

Rich Stern

Leslie P Stone

P. Michael Stone

Kathie Madonna Swift

The Institute for Functional Medicine

Debbie Thoensen

Thyroid Pharmacist

Frederick Tinari

Brigid Titgemeier

Bob Tygenhof

University of Bridgeport

University of Iowa

University of Pittsburgh

Wahls Institution

Terry L Wahls

Kate Wells

Izabella Wentz

Eugene Zampieron

Zira Mind and Body Center

SARAH HARDING LAIDLAW
MS, RDN, CDE

Editor's Note

Welcome to the AAPI eBook, third edition. As with previous editions, this is a compilation of manuscripts from leading integrative and functional medical practitioners throughout the world, new and updated, with the latest information for your practice. With 37 chapters and 48 authors, this book is the go-to reference for understanding and applying the principles of functional medicine and nutritional genomics for optimal health.

Today's health professionals have observed devastating turns in the health of patients, much of it related to poor nutrition, stressful environments, and unhealthy behaviors. As a result these behaviors are contributing to the obesity epidemic, an increase in type 2 diabetes and its comorbidities as well has changes in the human genome and health problems of immense proportion. This e book provides the experience and knowledge of the authors surrounding the successful treatment of and outcomes for a wide range of chronic conditions.

Functional medicine centers on the interactions between behaviors, the environment and the impact on the immune system, GI tract (microbiome), mental health, and endocrine system. Functional approaches to treatment of a variety of conditions frequently seen as well as recommendations for maintaining the health of body systems are offered. Nutrition, as an integral part of integrative and functional medicine, is woven into most chapters while many are predominantly nutrition focused.

This book is written by health professionals for health professionals and consumers alike, however it is not intended to be specific recommendations for treatment, but is an interpretation of evidence and experience of the authors who are integrative and functional medical professionals. The authors provide evidence based approach as well as anecdotal information that is helpful to anyone practicing or interested in integrative and functional medicine.

Sarah Harding Laidlaw, MS, RDN, CDE

Peaknut70@gmail.com

Editor, *TheIntegrativeRDN*

Dietitians in Integrative and Function Medicine, Dietetic Practice Group

Academy of Nutrition and Dietetics

RITA KASHI BATHEJA
MS, RDN, CDN, FAND, AFMCP

Introduction

Rita Kashi Batheja, MS, RDN, CDN, FAND, AFMCP

"OM SHANTI "

Shanti means peace in the Indian Language.

"Our lives have changed in many ways from the foods we eat, to the way we are born, the way we spend our days, the medications we consume and the environmental stressors we are exposed to." Tieraona Low Dog, MD

"Give me the Book" said Ellis Island Medal of Honor recipient Ajay K Lodha, MD in the beginning of his term in June 2016, as AAPI National President. I said "Which book?" and he said "Dietitians book". I am so glad that he believes in RDNs and has trust and faith in our services. He was visualizing all along and whenever we met at social events, Dr. Lodha reminded me of his inquiry, and I laughed it off. Belief is potent medicine.

In my mind I have the finest physician, P. Michael Stone, MD, Medical Director of Ashland Clinic from Oregon and a faculty member of the Institute for Functional Medicine who could not make it in AAPI's eBook I and II. Dr. Stone did an excellent job on his chapter on the ABCD Functional Nutrition Evaluation for the clinician. Another great board Certified OB / GYN and international physician educator Joel M Evans who also was unable to contribute his chapter in earlier eBooks I and II. Michael Stone does an excellent job on Nutrition focused physical exam. Joel serves as United Nations Representative and Chief Medical Advisor for OMAEP – World Organization of Prenatal Education Association and is a member of the senior faculty of two of the most prestigious teaching institutions-Institute of Functional Medicine and Center for Mind Body Medicine. Thank you, Alexandra Gesing, Research Assistant for helping Dr. Evans with The power of food to change the damaging gene expression caused by unhealthy relationships. Health does not come from medicine most of the time; it comes from the peace of mind, heart and soul. It comes from laughter and love.

On March 3 2017 at 2:00 am I decided to compile eBook III with nationally and internationally renowned physicians, RDNs, and allied healthcare professionals. I began writing down their names, invited them to contribute their chapters, and two and half months later we are with the finished product. My sincere congratulations to these authors who without even blinking their eyes made this AAPI's eBook III available in such a short period of time as a service to the Global Community and thanks to Zamher for formatting in spite of a time crunch. There is no price attached to this invaluable eBook III. A big thank you to Dr. Lodha who made it possible to get it posted on AAPI's website so that everyone worldwide can download the information at no cost. I am sure every breathing person in many continents will benefit from these author's chapters and may be able to access their services in their offices!

Each chapter is different and author's information is included at the end of the chapter. I am amazed with the wealth of knowledge they have contributed. Attitude is the mind's paint brush, it can color any situation.

Annie B Kay, RDN is author of the award winning book Every Bite is Divine and a co-author of the American Diabetes Association's Yoga and Diabetes: Your Guide to a Safe and Effective Practice. She is an integrative dietitian, yoga therapist, plant alchemist, and Director of Nutrition at Kripalu Center for Yoga and Health, a premier destination for individuals and organizations seeking joyful, inclusive, and compassionate environment for wellness and learning. Kripalu , www.kripalu.org, is located on a breath taking Campus in the Berkshire of Western Massachusetts and is the largest yoga-based retreat center in North America. Annie says "Yoga, a system of practice originating in ancient India, may provide the modern practitioner accessible tool to facilitate behavior change for those who desire to follow healthy lifestyles yet struggle to sustain change within todays toxic and obesogenic food environment."

I am speechless about Dr. Mark Pettus, MD, FACP a triple board certified internist, Nephrologist and Integrative Medicine physician. He did his Post-Doctoral training at Harvard Medical School. He is Associate Dean of Medical Education of the University Of Massachusetts Medical School and Medical Director for Functional Formularies, and past Medical Director of Kripalu Institute for Integrative Healing. He also serves the teaching faculty at the

Center for Mind Body Medicine in Washington, DC www.cmbm.org and the Meditation Institute in Averill Park, N.Y. I inspire everybody to consider taking the highly acclaimed Food as Medicine professional training program. Out of this World! I was invited to take this course twice in 2008 and 2009. It is a life changing experience and same with Institute of Functional Medicine's AFMCP course (Applying Functional Medicine in Clinical Practice) www.ifm.org. Dr. Mark Pettus says for the first time in human history, chronic "non-communicable disease" e.g. Cardiovascular disease, cancer, diabetes, Alzheimer and autoimmunity pose a greater health burden than infectious disease (source: CDC).

The Washington Post called Dr. Daniel Amen the most popular psychiatrist in America. He is Visionary, 10 times New York Times Bestselling author and International speaker. He is the Founder of Amen Clinics; they have built the World's largest database on Functional brain scans, 135,000 scans from 111 countries by opening up many practitioners' eyes. Dr. Amen is giving us hope that a person may not be bipolar or schizophrenic. Every person working with brain health should look into the root cause.

Izabella Wentz, PharmD, FASCP an internationally acclaimed thyroid specialist is licensed pharmacist. She is author of the New York Times bestselling patient guide, Hashimoto's Protocol: A 90 Day Plan for Reversing Thyroid Symptoms and Getting Back Your Life. She is committed to raise awareness on how to overcome autoimmune thyroid disease through the Thyroid Secret Documentary Series. She inspired me when I listened to her Thyroid Summit. Her message is TSH is just not the only test to consider; one should check thyroid antibodies, Free T3, Free T4 and reverse T3. Do you want to be on Synthroid all your life? No way! How about eating Brazil nuts which are high in selenium, pumpkin seeds high in zinc, and consider iodine which supports thyroid function.

Angela Grassi, MS, RDN, LDN chapter on PCOS is brilliantly written describing how so many teenagers are facing weight issue and are undiagnosed with the condition! Gluten Guru, Marlisa Brown, MS, RD, CDE, CDN educates the reader on gluten sensitivity and Celiac disease which are some of the reasons weight is so stubborn to take off!

I do not know what to tell you about Dale E Bredesen, MD and Rammohan (Ram) Rao, CAS, RYT, PhD and their ability to teach clinicians worldwide, how to work with Alzheimer's disease using an integrative approach. Ram holds doctorate degree in Biochemistry and neurosciences and works as a Research Associate Professor of Neuroscience at the Buck Institute for Research on Aging, Novato, California. www.buckinstitute.org . His research focus is in the area of chronic stress, neuronal cell death and mechanisms of age associated neurodegenerative diseases with special emphasis on Alzheimer's disease. Ram is Clinical Ayurvedic Specialist. He serves as a faculty at the California College of Ayurveda. He is also dedicated Hatha Yoga practitioner and Registered Yoga Teacher (RYT) from Yoga Alliance USA. He is a member of National Ayurvedic Medical Association (NAMA), member of the Research Board of the Association of Ayurvedic Professionals of North America (AAPNA) and Science Editor of Ayurveda Journal of Health. Dr. Bredesen, is internationally recognized as an expert in the mechanisms of neurodegenerative disease such as Alzheimer's disease. His research focuses on the mechanisms of cell death in the nervous system and has led to a new approach to Alzheimer's disease therapeutics. He was a National Institute of Health fellow in the laboratory of Nobel Laureate Stanley Prusiner. He is the Founding President and CEO of the Buck Institute for research on Aging. His group has developed a new approach to the treatment of Alzheimer's disease, and this approach has led to the first description of reversal of Symptoms in patients with MCI and early Alzheimer's disease, with the ReCode protocol.

Dr. Akil Palanisamy, MD is an integrative medicine physician and author of The Paleovedic Diet: A complete Program to Burn Fat, Increased Energy, and Reverse Disease. He blends his Western medical training with functional medicine and Ayurveda, the traditional medicine of India. Dr. Akil studied biochemistry at Harvard University. He completed a fellowship in integrative medicine with Dr. Andrew Weil at the University of Arizona, and is certified by the center for Mind-Body Medicine at Georgetown University. He studied Ayurveda in Southern India. Dr Akil sees patients at a Sutter Health Institute for health and healing in San Francisco. He has been consultant with the Medical Board of California for many years. Akil has spoken at numerous conferences worldwide. His online course on Integrative medicine through www.theayurvedaexperience.com , are viewed by people all over the world.

Trupti Gokani, MD is an award winning board certified neurologist. She has dedicated her life to developing a unique blend of modern medicine and ancient philosophy. She is best known by those on Chicago's North Shore for her revolutionary integrative approach to treating headache pain. The Zira Mind & Body Clinic's pa-

tients swear by her unique methodology focused on healing the head by identifying the disconnect between the mind and the body. Dr. Gokani is credentialed in Ayuverdic medicine, clinical psychopharmacology and transcendental meditation. She has also pursued training in Functional Medicine. She is certified by the American Board od Neurology and Psychiatry. Dr. Gokani recently published her first book, The Mysterious Mind: How to Use Ancient Wisdom and Modern Science to Heal Your Headaches and Reclaim Your Life and is currently contributing to a health documentary on Ayurveda. Dr. Gokani who has appeared many times on Dr. OZ's reporting on resolving the Migraine Epidemic, by blending Ayurveda, Functional and Western Medicine to achieve freedom. Migraine, which was once strictly considered a neurologic condition, can now be traced to any number of conditions, such as digestive imbalances, food allergies or thyroid dysfunction.

In my earlier days I never heard about fibromyalgia however, David Brady, ND, DC, CCN, DACBN and Michael Schneider, DC, PhD has given us invaluable information on the condition and proposed a simple solution. Proper diagnosis is half the cure. How many people do you know who have no energy after a good night sleep? David M. Brady is a licensed naturopathic medical physician in Connecticut and Vermont and board certified clinical nutritionist. He has an experience as an integrative practitioner and academician. He is a prolific author of medical papers and research articles on fibromyalgia and has dedicated large part of his professional career to helping people recover from this mysterious disorder. He is Vice President for Health Sciences, Director of the Human Nutrition Institute, and Associate Professor of Clinical Sciences at the University of Bridgeport in Connecticut. He maintains a private practice, whole body medicine in Fairfield, Connecticut and also the Chief Medical Officer for Designs for Health, Inc. and Diagnostic Solutions Labs, LLC. He is an internationally sought after presenter on nutritional, functional and Integrative medicine and has appeared on the speaking panel of the largest and most prestigious conferences in the field. Dr. Brady dedicated champion and advocate for patients suffering with a fibromyalgia diagnosis. He is the author of the book the Fibro-Fix and hosted an extremely popular and informative online Fibro-Fix Summit. You can learn more from www.Fibrofix_summit.com

Michael Schneider, has maintained a private chiropractic practice that focuses on myofascial and muscular disorders. He has PhD in rehabilitation science from University of Pittsburgh and has graduated from Palmer College of Chiropractic. He is Associate Professor in the school of Health and Rehabilitation sciences, as well as the clinical and translational Science Institute at the University of Pittsburgh. He has a unique understanding of fibromyalgia from his dual experiences as a clinician treating patients with fibromyalgia and as a researcher reviewing the scientific literature about fibromyalgia.

New York Times bestselling author Susan Blum, MD, MPH stressed, in her chapter, that the gut needs to heal in order to repair the immune system. Dr. Blum is an assistant clinical professor in the Department of Preventive Medicine at the Icahn School of Medicine at Mount Sinai, New York. She is the Founder and Director of Blum Center for Health in Rye Brook, New York

Kiran Krishnan, is a Research Microbiologist who comes from a strict research background having spent several years with hands on R& D in the field of molecular medicine and microbiology at the University of Iowa. Kiran established a clinical Research organization when he designed and conducted dozens of human clinical trials in human nutrition. Kiran is acting Chief Scientific Officer of Physician's Exclusive, LLC and Microbiome Labs. He is frequent lecturer on the Human Microbiome at Medical and Nutrition Conferences.

Deanna Minich, PhD, FACN CNS, IFMCP explains why whole detox? Dr. Minich teaches for the Institute for Functional Medicine, the graduate program in Functional Medicine at the University of Western States, and the Doctoral program at the Maryland University of Integrative Health. Her passion is to bridge the gaps between science, soul and art in medicine.

Nationally respected Corey Schuler, RN, MS, LN, CNS, DC, DBM, FAAIM educates on Small Intestinal Bacterial Overgrowth (SIBO) with an integrative approach. SIBO can contribute to or be a causal factor in conditions such as malnutrition, diarrhea, nausea, bloating, vomiting, weight loss, joint pain, fatigue, skin conditions, and depression as reported by patients. The elemental diet is both an evidence based as well as nonpharmacological approach. One must rule out SIBO, if any weight issues. We need to be proactive. SIBO can be trigger for thyroid disease.

Susan Linke, RDN Certified LEAP Therapist (CLT) and Certified Gluten Practitioner reviewed irritable bowel syndrome and other inflammatory diseases that can be a hidden cause of overweight or obesity. Susan is giving

hope to the public with Irritable Bowel Syndrome.

Terry Wahls, MD, MBA, IFMCP says improving the quality of diet may have a significant impact on the development of Multiple Sclerosis (MS) related fatigue. Dr. Wahls also states that Dr. Ray Swank was one of the first to use a dietary plan in treating MS, and did so based on his observation that high levels of saturated fat in the diet were associated with the risk for MS in Norway. This led to his development of the theory that a diet high in saturated fat causes more rapid disease progression.

Regina Druz, MD, FACC, FASNA, AFMCP integrative and functional medicine cardiologist is a blessing to Long Islanders in New York. She is a board certified cardiologist, nationally recognized for her expertise in heart health, cardiac imaging, and clinical research. She Graduated from Cornell University Medical College, her residency in Internal Medicine and Cardiovascular fellowship at the Weil Cornell Medical Center. New York Presbyterian Hospital, a preeminent national institute recognized for its long standing tradition of excellence, seeking to prevent and reverse heart disease and not just merely treat the end stages of it. Dr. Druz immersed herself in the practice of integrative and functional medicine. She has developed Fit in your GENE™ functional medicine program that uses personalized genomics to reverse cardiac disease risk factors, such as inflammation and oxidative stress, and half progression of endovascular damage through targeted lifestyle interventions. Dr. Druz is also a healthcare innovator developing digital and mobile health solutions. She is currently combining her interests in functional medicine and technology by creating a telemedicine platform for holistic heart health. She is a board member of the American Society of Nuclear Cardiology and is an inaugural Chairwoman of the American College of Cardiology innovation section. She is a clinical professor of medicine at SUNY Downstate School of Medicine. A nationally recognized speaker who frequently lectures at the American College of Cardiology, Integrative Health Symposium and American Academy of Restorative Medicine. She is often interviewed as a medical expert by media channels. Dr. Druz maintains a private practice in Integrative Cardiology in Mineola, Long Island, New York. Fit in your Genes™ is a personalized lifestyle intervention plan based on functional medicine.

Ellen Kamhi, RN and Eugene Zampieron, ND did a fabulous job on their chapter about osteoporosis, a disease that can strike anyone at any age. There are several risk factors including soft drink consumption and decreased estrogen levels.

India is considered diabetes capital of the World. American Overseas Dietetic Association (AODA) country representative for India, Shilpa Joshi, MS, RD is doing a marvelous job devoting her time going all over the country on weekends bringing awareness about type 1. She has covered the Medical Nutrition Therapy (MNT) in type 1 Diabetes: Indian Perspective. Approach to dietary management in diabetes, as "carbohydrate counting" along with her husband Shashank Joshi, MD, DM, FRCP, FACE, FACP, FICP. I want you to be aware of Academy of Nutrition and Dietetics Diabetes practice group www.dce.org. Dr. Joshi is the President of Indian Academy of Diabetes, President of Hypertension Society of India, and immediate Past President of Endocrine Society of India. He is Immediate Past President, Association of Physicians of India (API 2014 – 15) and Past President of the Research Society for Study of Diabetes in India (RSSDI). Dr. Joshi is a Consultant Endocrinologist at Lilavati and Bhatia Hospitals and Joshi Clinic. He has more than 600 research publications to his credit. He is the Hon. Emeritus Editor of JAPI (Journal of the Association of Physicians of India), Past Editor of Indian Journal of Obesity, Indian Journal of Endocrinology and Metabolism and Indian Journal of Clinical Pharmacology and Therapeutics and several other leading medical Journals. Dr. Joshi is past president of All Indian Association of Advancement for Research in Obesity, IASO Affiliate, Chapter Chair (India), American Association of Clinical Endocrinology (AACE). He is visiting faculty to several Indian and International Universities. He is actively involved with evidence based work in Endocrinology including Diabetes, Obesity, Thyroid, Osteoporosis and Growth. He was awarded "International Clinician of the year 2012" by the American College of Endocrinology. Dr. Joshi has been conferred "Padma Shri" in 2014 by the Government of India, Unbelievable! I do not know when does he sleep?

Systems medicine is a revolutionary approach to viewing chronic disease through lenses distinct from acute disease, a lens that recognizes interconnectivity of the human organism and its health and disease ramifications. This approach called systems medicine or functional medicine always asks "Why?" Why does this individual have these symptoms? What do symptoms tell us about clinical imbalances that exist? What are the root causes of these symptoms and key underlying mechanisms that are in play? Read well known geneticist and clinical nutritionist Ruth Debusk, PhD, RDN and Cathy Snapp, PhD is an assistant Professor of Family Medicine at the Florida State College of Medicine and a co-developer/ Director of The Mindfulness Based Therapeutic Lifestyle Change program (MBTLC) Michael Stone, MD's chapter. Disease to prevent chronic disease. Over the past 20 years

Cathy and Ruth have been awarded eight million dollars to develop epigenetic, multigenerational behavior and therapeutic lifestyle change programs and resident training curriculum in functional medicine and systems approaches to health and wellbeing.

"By applying a functional medicine approach to pregnancy there are less small and large for gestational age newborns and pregnancy induced hypertension and gestational diabetes in the mothers associated with reduced incidence of hypertension, diabetes, obesity and heart disease in the newborns by the time they are adults." states Emily Rydbom, BA CNC CNP CHN owner of Grow Baby, Leslie Stone, MD, IFMCP Board certified in Family practice with a fellowship in surgical Obstetrics. She is a primary consultant for GrowBabyhealth.com and Michael Stone, MD abstract is really an eye opener. Menopuase is not an optional event for women and they need the advice of Felice Gersh, MD International Speaker, accomplished writer, Board certified OB/GYN, and who has been awarded Physician of Excellence for Orange County, CA for 13 years in a row, named Super Doctor of Southern California for the past few years and recognized as a Top Doc. What an honor!

"Diet has considerable potential to optimize tolerance to conventional cancer therapies. There is evidence to suggest that patient who underwent conventional treatments without receiving nutritional support have higher complication rates." stated Lise Alschuler, Executive Director of Teach Advocate and Practice (TAP) Integrative, a nonprofit educational resource for integrative practitioners who practices Naturopathic Oncology in Scottsdale, Arizona.

Garry D'Brant, DC, CTN, LCSW, DACBN, CDN, DIPLAC has written a brilliant article on natural ways to nourish and support the prostate. He is an award winning alternative healthcare provider who provides compassionate and knowledgeable care, at his D'Brant Infinite Wellness in Glen Cove, Long Island, New York. "While light from the sun has been used over the centuries for healing," per Michael Posner, DC modern science has progressed in leaps and bounds with their remarkable inventions of devices that use light as a healing modality. It is his heartfelt desire to make people more conscious about the benefits of laser for pain, inflammation and cellular healing."

Chronic health conditions are those that last a long time and are difficult to shake. Fortunately, this is the area of medicine where Functional Medicine tends to shine. Functional Medicine board certified Scott Banks, DC, IFMCP concentrates on the whole person not just an isolated set of symptoms. His Natural Cure for Dummies ranks highly on Amazon and was awarded winner of USA Best Book Awards.

Kinesiology is the study of motion and biomechanics. I encourage you to read the short chapter of Fred Tinari, DC, MS, DACBN, DCBCN. Prescription medication for life is not healing patients. Lifestyle and diet changes are! Authors of this eBook are changing lives by making invaluable contributions. Patients are the CEO of their healthcare.

Loren Marks, DC, DACBN has had a keen interest in adrenal physiology for many years. In his chapter he discusses the role of methylation and specific mineral imbalances as they relate to mood, behavior and mental health, and as a driver of chronic adrenal exhaustion. He also mentions that heavy metal accumulation primarily occurs from environmental exposure over time, whether its source in water, food or inhalation. I tell my patients to pay attention to the dirty dozen. www.foodnews.org. I would like you to know about James Maskell, Co-founder Evomed.com, who stresses the importance of bring our planet back in balance.

Maria E Levada, MD and Jonathan Seyppel Orban have written a marvelous chapter on Genetic Adaptation Response and its Relationship to Body Chemistry, Exercise and Nutrition. Dr. Levada is Board Certified OB/GYN, she is past president of Nassau County OB/GYN Society in Long Island, New York and former Director of Gynecology at Franklin Hospital Medical Center. A gifted surgeon who combines the art of medicine with the most advanced technologies to achieve the finest outcomes. She is voted into America's Top Gynecologists and World's leading Physician. Dr. Levada specializes in Natural Bioidentical Hormone Therapy. Dr. Levada is on Medical Advisory Board and Consultant for Integrative Genetic Solutions (IGS). A software company designed to help doctors personalize and optimize their patient's health care by measuring a patient's comprehensive blood chemistry and DNA, then with an unmatched level of precision, prescribe a custom tailored program. Dr. Levada helps both men and women. Jonathan Seyppel Orban is the CEO of Integrative Genetic Solutions (IGS). IGS is the world's leading software for precision healthcare in the medical body chemistry space providing healthcare providers with a specific numerical diagnostic tool. He graduated second in his class at Special Operations Medical School at Ft. Sam Houston and did his clinical rotations at Reynolds Hospital.

Corie Edwards, ND is adjunct faculty of the National University of Natural Medicine where she teaches genetics in their undergraduate program. Zahra Mehdizadeh Kashi, PhD Is a Board Certified molecular immunohematologist. Dr. Kashi is a highly sought clinical laboratory consultant. She is inspector for the college of American Pathologists and an expert witness on genetic identity. Both Corie and Zahra have written a chapter on targeted use of Genetic knowledge for patient outcomes. Genetic testing is on the rise as research identifies significant connections between certain allelic variations in the genetic code and disease states. Medicine is at the cusp of a new way to meet and treat people as individuals. Understanding this advancing technology is the first step. Combining concepts of genetics, biochemistry, physiology and emerging scientific research is a new approach for many practitioners.

As the Running Nutritionist, Lisa Dorfman, MS, RD, CSSD, LMHC, FAND leader to Industry the Academy, the public, and press consults with Olympians. She served as the US sailing Olympic and para-Olympic team nutritionist for the 2008 Beijing Olympics and nutrition expert for Zumba ®Plate program, is a consultant to Sony Entertainment, and works with award winning actors. In 2014 Lisa and Miami organic restauranteurs launched Miami's first farm to Table Performance Nutrition Delivery Service. Lisa serves as US Representative for the American Overseas Dietetic Association (AODA), representing more than 70 countries and over 1000 Nutritionists / Dietitians worldwide. www.americanoverseasdieteticassociation.org. I would like you to be familiar with www.internationaldietetics.org . Lisa's Integrative Sports and Performance nutrition chapter will provide physicians with an integrative sports dietitian's approach to working with athletes including formulas used for assessing nutrition needs, training and competition fuel options, sports supplement considerations, tools, and resources.

A major shift towards a plant based diet is afoot because many people, including medical professional, recognize our dietary scales are currently imbalanced. There's strong scientific support for the many health benefits of a plant based diets. Karla Dumas, RDN, LDN and Lauren Pitts, MA, RDN's have done marvelous job on Plant Based Diets in a Nutshell: Understanding the Latest Research and Recommendations. They are serving on Vegetarian Nutrition practice group's executive committee www.vndpg.org. www.vegetariannutrition.net and both work for The Humane Society of USA.

Vegetarian Diabetes Educator, Gita Patel, MS, RDN, CDE, LDN, CLT shares superb information on her chapter Blending Science with Spices for Feeding Health. It is the position of the Academy of Nutrition and Dietetics to recognize that although all foods provide some level of physiological function, the term functional foods is defined as whole foods along with fortified, enriched or enhanced foods that have a potentially beneficial effect on health when consumed as a part of a varied diet on a regular basis at effective levels based on significant standards of evidence.

The chapter on Dietary Supplementation: Regulations and Recommendations written by Cleveland Clinic's Functional Medicine Director of Nutrition, Brigid Titgemeier, RDN, Assistant Professor in the Department of Nutrition at Case Western Reserve University's School of Medicine Stephanie Harris, PhD, RDN, LD, and Kelly Morrow, MS, RDN CD Associate Professor in the Department of Nutrition and Exercise Science at Bastyr University and Nutrition Clinic Coordinator at the Bastyr Center for Natural Health in Seattle, Washington should be read thoroughly. Kelly leads teams of nutrition graduate students in an integrative medicine teaching clinic where they collaborate with naturopathic doctors, medical doctors and practitioners of East Asian Medicine and Acupuncture. Dietary supplements are products ingested by mouth that are designed to supplement the diet but are not meant to treat or cure disease.

Thank you to Sarah Harding Laidlaw, MS, RDN, CDE, editor of AAPI's eBook III and Dietitians in Integrative and Functional Medicine practice group's newsletter, The Integrative RDN. She is an accomplished triathlete with numerous age group awards under her belt.

"The natural healing force within each one of us is the greatest force in getting well. Let food be thy medicine and medicine thy food"—Hippocrates.

My wish is for all allied health professionals to work together.

My Sincere Thank You to Dr. Lodha for his unconditional support through making AAPI's eBook III available globally, at no cost.

Thank you. Thank you. Thank you to my mentors and friends for Life Pete and Barbara Matz for their constant guidance.

This eBook would not have been possible if it was not for my Dearest husband Kashi, who worked tirelessly to complete AAPI's eBook III.

"Be the change you want to see in the world". -- Mahatma Gandhi.

Nutritionally and Healthfully Yours,

Rita

Rita Shah Batheja, MS RDN CDN FAND AFMCP
New York, USA
krbatheja@gmail.com

Diversity Chair 2016-2017
Dietitians in Integrative and Functional Medicine Dietetic Practice Group

Policy and Advocacy Leader and Reimbursement Representative
Asian Indians in Nutrition and Dietetics Member Interest Group
Academy of Nutrition and Dietetics
www.eatright.org

AJAY K. LODHA
MD

Foreword

"He that takes medicine and neglects diet, wastes the skill of the physician."

- Chinese Proverb

The American Association of Physicians of Indian Origin (AAPI) has taken the approach that those who give advice on healthy living should live the life they recommend. When taking office as President of AAPI in 2016 I enquired of Rita Batheja, MS, RDN, CDN, FAND, AFMCP, about a Dietitian's book; a book on nutrition, health, and functional medicine that would enable practitioners and patients alike, to achieve their goal of healthy living. With this in mind, Rita pursued the task of compiling AAPI's Nutrition Guide to Optimal Health: Using Principles of Functional Medicine and Nutritional Genomics Part III.

This edition is an extension of e-versions I and II, published in 2012. Although those versions continue to be excellent resources for practitioners and patients, version III is much more. With 48 of the most prestigious experts in Integrative and Functional Medicine (IFM) sharing their knowledge about their fields and areas of interest, this book will no doubt become the authoritative reference for those wanting to learn more. The chapters span the field of IFM from nutritional approaches that arrest damaging gene expression to mind-body therapies. It focuses on the whole person rather than just the disease using evidence-based information from researchers, journals, not to mention the experience of the authors.

I would like to personally thank each author for their contribution to this outstanding resource. However, this e-book would not have been possible without the enthusiasm and dedication of Rita who sought out the best and most qualified authors and was persistent in getting this ready for publication by AAPI's annual convention. I also appreciate the work of Sarah Harding Laidlaw, MS, RDN,CDE - Editor.

Through this book, the authors are striving to focus on complex prevention and management of chronic disease to improve patient health in a holistic manner. I am certain that you as a practitioner, patient or person interested in a healthier body, mind and life will find this book to be as an invaluable resource as I have.

"If you don't take care of your body, where are you going to live?" ~Unknown

Ajay K. Lodha, MD

President, AAPI 2017

ANNIE B. KAY

MS, RDN, E-RYT500 C-IAYT

Yoga for Diabetes and Chronic Disease

State of the Literature, Psychophysiologic and Epigenetic Mechanisms, and Opportunities for Practitioners

The part can never be well unless the whole is well.

-Plato

ABSTRACT

Yoga, a system of practice originating in ancient India, (Side Bar 1) may provide the modern practitioner accessible tools to facilitate behavior change for those who desire to follow healthy lifestyles yet struggle to sustain change within today's toxic and obesogenic food environment. New understanding of neurobiology and the emotional nervous system, and advances in ge-nomics provide insight into likely mechanisms underlying observed benefits in early trials of yo-ga for nutrition-related chronic disease including type 2 diabetes and cardiovascular disease.

INTRODUCTION

Seven of the top ten causes of death are chronic disease, much of which is preventable. The eti-ology of type 2 diabetes (T2DM) and other chronic diseases are complex and multifactoral. However, lifestyle factors including lack of physical activity, poor nutrition, and excess use of substances (tobacco and alcohol), are preventable risk factors for much of the illness, suffering and early death related to chronic diseases and conditions. A variety of strategies are needed to help individuals interested in improving lifestyle in order to prevent or address and sustain im-provements in modifiable risk factors for T2DM and other preventable chronic disease.

LITERATURE REVIEW

Nutrition-related Chronic Disease

Practitioners are well aware of the epidemic of obesity and nutrition-related chronic diseases such as type 2 diabetes affecting adults and more recently children. According to national data, during 2009–2010, more than one-third of adults, or about 78 million people were obese (defined as body mass index (BMI) ≥30 kg/m2). In that timeframe, nearly one of five youths aged 2–19 years were obese (BMI ≥95th percentile).

Prevalence of the lifestyle behaviors that prevent or address metabolic syndrome, including weight management and physical activity, is low. In 2011, more than half (52%) of adults aged 18 years or older did not meet recommendations for aerobic exercise or physical activity. In ad-dition, 76% did not meet recommendations for muscle-strengthening physical activity.

Like the obesity epidemic, the chronic disease landscape is increasingly complex and the number of individuals managing more than one chronic condition is rising. One in 4 Americans has mul-tiple chronic conditions. Eighty-four percent of all health care spending in 2006 was for the 50% of the population who have one or more chronic medical conditions.

Two of these chronic diseases - cardiovascular disease (CVD) and cancer - together account for nearly 48% of all deaths. T2DM is the strongest risk factor for CVD, associated with a 2 to 4.5 fold increase in risk. CVD is a major complication of T2DM and over half the individuals with T2DM die from heart disease and stroke. TwDM is also linked to some cancers through eleva-tion in insulin levels and the lifestyle pathways leading to metabolic syndrome.

Yoga Research

Typical of early evolving science, clinical trials investigating yoga in past decades tended to be small, uncontrolled and nonrandomized. Interest in this early work and the continued growth in popularity of yoga in the West are concomitant with growing research interest. Trials conducted in India dominated early clinical investigations. Recent studies are also conducted in the West and include major US research institutions and NIH funding, and a growing number of random-ized clinical trials.

Research investigating yoga for management of chronic conditions and their risk factors is pro-liferating. Studies

have explored yoga as an adjunct therapy for the management of arthritis , lower back pain , high blood pressure , CVD , respiratory disease , and stroke.

Yoga and Diabetes

The majority of randomized controlled trials (RCT)s on yoga for T2DM in peer-reviewed jour-nals suggest improvements in outcomes or risk indices with yoga practice. Results included significant improvements in blood glucose,, , lipid profiles, , blood pressure, body weight or BMI ,, and oxidative stress markers.22

Investigations of mindfulness, a type of meditation similar to the mental practices of yoga, are also of interest. Mindfulness practice focuses attention on the moment-by-moment present with nonjudgmental awareness, that is, no relative preference is attached to any observation (ie, it's not good, it's not bad, it just is). Several RCTs suggest that for individuals with T2DM, mindful eating may be as effective as diabetes self-management education in improving blood glucose management.

The burgeoning field of epigenetics has established that there are distinct changes in genetic ex-pression induced by the in vivo environment and influenced by nutritional, physical, psychologi-cal, social, and cultural aspects of lifestyle. Early studies on yoga and meditation practices are consistent with current epigenetic models and suggest that these practices positively affect gene expression. Specific mechanisms of action are yet to be elucidated.

Possible Mechanisms

Yoga supports positive behavior change by a variety of complex, multifactoral, interacting and dynamic pathways. The emotional nervous system's management of stress and cognitive pro-cessing likely interplay with in vivo biochemistry secondary to the highly refined, highly palata-ble Standard American Diet (SAD). Americans are living with high perceived stress yet are not managing it in healthful ways. Stress negatively impacts eating behaviors. Stress also induces a biochemistry that favors poor food choices and obesity by triggering secretion of glucocorti-coids which increase motivation for food, and insulin, which promotes food intake and obesity. Eating refined food may serve as a feedback signal that reduces perceived stress and thus rein-forces eating in response to stress. Yoga appears to alleviate activation and reactivity of the hy-pothalamic pituitary adrenal axis and sympathoadrenal system, fostering recovery from stress and downstream effects, perhaps including modulation of stress-related eating.

Stress also biases cognition toward lessened executive function and increased emotional activity in the amygdala of the brain. , Thus stress may trigger emotional or habitual food choices ra-ther than reasoned cognitive decision making. , Meditation, yoga and mindfulness have been suggested to increase activity of the prefrontal cortex of the brain and therefore, with practice, support the adoption of lifestyle choices likely to prevent or address chronic disease. ,

The vagus nerve runs from the cerebellum and brain stem to the viscera of the lower abdomen. Stimulating the vagus nerve with deep diaphragmatic breathing (Side bar 1) that includes a lengthened exhale is thought to improve vagal tone, slightly elevating heart rate on an inhale, and decrease heart rate on an exhale, thus increasing heart rate variability (HRV), a marker of cardi-ovascular health. Yoga practice stimulates the vagus nerve and HRV which shifts the autonomic nervous system from sympathetic (fight or flight) toward parasympathetic (rest and recovery) activation directly, providing a mind-body feedback loop for recovery from physiologic stress.

Functional physical fitness may affect metabolism, gastrointestinal and brain function leading to improved resilience to stress. Each of these domains are likely to lead, over time, to epigenetic modulation in yoga practitioners.

CLINICAL APPLICATION

Standard protocols and effective dosage of different aspects of yoga practice for various bi-omarkers have yet to be elucidated. Clinical trials and coordinated research efforts are needed to further understanding of the potential benefits, the mechanisms of those benefits and effective uses of yoga in the prevention and treatment of chronic disease. However, a threshold of benefit for those interested in yoga for adjunctive support to improve lifestyle behaviors for the preven-tion and management of nutrition-related chronic diseases appears to have been achieved.

Yoga and other mind-body modalities are experiential. Practitioners therefore may choose to explore these modalities through adoption of a personal daily mind-body practice. From there, skill building through ongoing study in accredited programs will prepare dietitians to include yo-ga, yoga breathing, meditation and/or mind-fulness practices in their scope of practice. Profes-sional organizations for yoga teachers and therapists include Yoga Alliance (YA, www.YA.org) a national registering body, and the International Association of Yoga Therapists (IAYT, www.IAYT.org). Standards for yoga education and credentialing of yoga therapists are being established by these organizations.

SUMMARY

Most health practitioners work with individuals who wish to change but struggle to eat well and be adequately active on a regular basis within the toxic nutrition environment. Yoga is a safe and inexpensive practice that can be adapted for individuals of all ages and physical abilities and may be an effective adjunctive therapy for the adoption and maintenance of healthful lifestyles. New evidence investigating potential benefits of this ancient practice holds promise in the manage-ment of complex lifestyle-derived chronic diseases including T2DM and CVD. Psychophysiolo-gy and genetics - two areas of rapidly emerging science – are providing new insight into how yo-ga practice may work. Dietitians may find yoga and related mind-body practices accessible and useful tools for supporting and maintaining behavior change in those they serve.

SB1: **Overview: The Practice and Philosophy of Yoga**

The Yoga Sutra, written by the sage Patanjali in approximately 250 CE, codified yoga philoso-phy and practice in 196 sutras or phrase-threads.

Patanjali's Eight-Limbed Path of Yoga Includes:

1. Yama: controls or restraints of attitude or behavior, primarily in community or relationship. These include:

    A. Ahimsa: non-violence, compassion.

    B. Satya: truthfulness.

    C. Asteya: non-stealing.

    D. Brahmacharya: chastity or control of the life force.

    E. Aparigraha: greedlessness or charity.

2. Niyama: observances and attitudes primarily concerned with the individual. These include:

    A. Saucha: purity, cleanliness.

    B. Santosa: contentment.

    C. Tapas: asceticism, simplicity, passion.

    D. Svadhyaya: self-study, self-inquiry, philosophical study.

    E. Isvara Pranidhana: devotion.

3. Asana: literally means "seat" and describes the physical practice of yoga postures.

4. Pranayama: controlling energy and breath.

5. Pratyahara: inward focusing and withdrawal of the senses.

6. Dharana: focused concentration.

7. Dhyhana: meditation.

8. Samadhi: absorption into bliss consciousness.

SB2: **Diaphragmatic breathing**

The diaphragm is a thin skeletal muscle that separates the thoracic cavity containing the heart and lungs from the abdominal cavity. An inhale of the breath occurs when contraction the dia-phragm increases the volume of the thoracic cavity, drawing air into the lungs. Practice this breathing technique regularly to improve vagal tone and HRV.

1. Find a comfortable seated position with a straight spine. Sitting on the edge of a cushion or blanket can be helpful, or sit in a chair.

2. Place your hand on each side of the ribcage. Feel your ribcage expand out as you inhale, thinking about the downward engagement of the diaphragm that fills your lungs.

3. Exhale slowly, feeling the ribcage coming back together as the diaphragm slowly relaxes and the lungs empty.

4. Take several breaths feeling the ribcage, and let your exhale lengthen as you practice. You might count the number of heartbeats it takes you to exhale.

5. Next, place your left hand on the chest, and right hand on the belly. Continue this breath, and notice that the chest stays quiet and the left hand doesn't move very much with the breath. Notice how the right hand on the abdomen may softly rise and fall, but let the ab-dominal muscles stay relaxed. This way, you focus on engaging your diaphragm.

6. Begin practicing for 2 minutes and work your way up to 10 minutes or longer. Notice how you feel after this breathing practice.

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Annie B. Kay MS, RDN, E-RYT500 C-IAYT is an integrative dietitian, yoga therapist and plant alchemist.

She is author of the award-winning book Every Bite Is Divine: the balanced approach to enjoying eating, feeling happy and healthy, any getting to a weight that's natural for you, and co-author of the American Diabetes Association's Yoga and Diabetes: Your Guide to a Safe and Effective Practice. Annie is the Lead Nutritionist at the Kripalu Center for Yoga & Health in Stockbridge, MA, is in private telehealth practice in Alford, MA and speaks on topics of mind-body science, women's health, healthful aging and integrative wellness internationally.

annie@anniebkay.com, www.anniebkay.com.

P. MICHAEL STONE

MD, MS, IFM-CP

The ABCD Functional Nutrition Evaluation for the clinician:
Review of the 10 minute functional nutrition oriented physical exam
With application to a post-bariatric surgery case.
"Every Body Reveals Its Story"

P. Michael Stone, MD, MS, IFM-CP
Ashland Comprehensive Family Medicine-Stone Medical, Ashland Oregon
Faculty Institute for Functional Medicine

Abstract:

Everyone has a story and every body phenotypically reveals the unique story when examined by the clinician with a trained eye to see. Each person deserves a routine, reproducible a nutrition evaluation. A functional medicine nutrition evaluation includes four distinct parts: **A**nthropometrics, **B**iomarkers, **C**linical Physical Exam, and **D**iet, Nutrition and Lifestyle Evaluation. Using this approach allows a routinizing of the nutrition evaluation which can applied to every age group with age appropriate modification. The clinical physical exam portion can be completed in 10 minutes in the clinic setting. The findings in each area of the ABCD's provides a constellation of information directs appropriate interventions to remedy identified deficiencies, insufficiencies and toxicities. Applying this nutrition evaluation helps identify "hidden hunger"- The ABCD's of nutrition evaluation is presented using a post-bariatric surgery case.

Background: The nutrition oriented physical exam has been used to identify nutrition insufficiency and deficiency by aide organizations involved in care for the severely malnourished in humanitarian crisis (1). With the increasing chronic disease in clinical practice the encouraged predictive, preventative, participatory and personalized approach requires each clinician to address underlying nutritional status to better leverage lifestyle changes to help slow chronic disease and restore health and function.

There is a wide disparity in nutrition education in the clinicians practicing today. Nutrition education during undergraduate medical school training is earmarked for a 25 hour but only ¼ of medical school participants reach this this benchmark (2). Nurse practitioners, Chiropractic

Physicians, Naturopathic physicians, acupuncturists and physicians assistants have more nutrition than the average physician by the time they complete their degree. But all of the clinicians no matter what their academic heuristic need to be able to complete a routinized nutrition evaluation.

Today in primary care there are many health circumstances where adequate nutrition status is difficult to maintain. There are socioeconomic conditions and hidden hunger, genetics influencing requirements (single nucleotide polymorphisms), over the counter and prescription drug nutrient interactions, and challenges with food choice and habits. Bariatric surgery induces nutrient malabsorption or induced insufficiency which requires more frequent evaluation. Over 30 percent of the adult population in the United States had Cardiometabolic syndrome and the therapeutic interventions for the hypertension, hyperlipidemia, hyperglycemia and obesity offer significant opportunity for pharmaceutical/nutrient interactions which alter absorption, requirement or speed excretion of nutrients. This combination of realities today necessitates the clinician to have additional tools in our toolkit.

Primary care providers more often than surgeons or endocrinologists are seeing the patients on a chronic ongoing basis. Everyone has their unique story and every body phenotypically reveals their story when examined by the clinician with a trained eye to see. Each person deserves a routine, reproducible a nutrition evaluation.

The functional medicine nutrition evaluation includes four distinct parts: **A**nthropometrics, **B**iomarkers, **C**linical Physical Exam, and **D**iet, Nutrition and Lifestyle Evaluation (3,4). The ABCD Functional Nutrition Evaluation has been developed by the Institute for Functional Medicine for application by clinicians, nutritionists and health coaches. It provides a routinized way to uncover nutrition insufficiency, deficiency, imbalance or be more assured of adequacy. A review of the ABCD of the Functional Nutrition Evaluation is followed by the nutrition evaluation of a post bariatric surgery patient to help each clinician to see more on the other side of the stethoscope.

Anthropometrics and Vitals:

The clinicians exam begins with the anthropometrics which are frequently collected by the associated clinical staff (nurse or medical assistant) and offers the clinician the initial clinical clues of the nutrition evaluation. The anthropometrics and vitals help develop the initial clinical patterns defining nutrition adequacy, imbalance, insufficiency, or deficiency (Table 1).The first step is to identify abnormal findings. All of the anthropometric measurements frequently are collected and presented to the clinician for evaluation by the medical assistant, nurse, or designated office personnel.

Table 1: Anthropometrics and Vitals (5)

Anthropometric measure	Abnormal Finding
Height	Loss of Height for age trajectory, height gain child and adolescence: Inadequacy of protein, calorie adequacy or mal-absorptive conditions. height loss >40 years: protein, vitamin D, Magnesium, Calcium-osteoporosis
Weight	Adequate weight gain, modulating weight loss, BMI changes <18.5, >25, >30, part of body composition evaluation
Waist circumference	>32-36 inches (cm) >15 years of age Female, >38-40 inches >15 yo male increased visceral or subcutaneous adiposity with underlying nutritional and environmental causes. Part of body composition evaluation
Hip circumference	Measured and ratio of hip/waist used to help sort android, gynoid obesity. Part of body composition evaluation
Waist to Hip Ratio	>0.80 female, >0.9 male association with inflammatory processes
Bioelectrical Impedance Analysis (BIA)	Elevated Fat Mass, Low Fat Free Mass, Total Body Water Distribution-Low intracellular water, High extracellular water. Part of body composition evaluation
Temperature	<96>100 (centigrade) nutritional associations with thyroid function, underlying infection or other causes of hypermetabolic states
Respiratory Rate	>20 or <10 adult nutrition associated factors in pulmonary and cardiovascular function
Pulse	<50 or >100 nutrition and environmental factors involved in dysrhythmias
Blood Pressure	<90 or >130 systolic, <60>90 diastolic- factors in endothelial dysfunction
Oxygen Saturation	<94% cardiopulmonary and peripheral vasculature function primarily
Peak expiratory flow rate	<90 % of age and height determined, associated with factors in pulmonary, cardiovascular function and inflammatory balance

Patterns in Body Composition.

The patterns in body composition have inspired artists and sculptors, imaginations and self-doubt over the centuries. There are many body forms. Only since the early 1950's in the United States has Body

Mass Index been. Determining body composition has far advanced since the insurance actuarial tables and the prediction of health risk. The Body mass index helps to classify body composition into underweight, healthy weight, overweight and obese. The use of only BMI mis-identifies body composition when used as a single calculation from height and weight (6). There are age appropriate BMI classifications with infants, and children not using BMI as a marker (7). The addition of waist circumference, waist to hip ratio, and determination of body fat free mass and fat mass as determined by bioelectrical impedance analysis is helpful in directing the clinician to underlying drivers of the body composition (5,8,9). The table below is specifically for body composition evaluation in the healthy, overweight or obese mid adolescent through adult age groups. The waist circumference helps risk stratify the patient. There are ethnic, gender, and waist circumference considerations when assessing risk (Table 2). There are many different body types and composition. The further evaluation and workup of each individual can be informed by the anthropometrics. Whether the patient is cachectic or morbidly obese further evaluation often is merited and some of the considerations are outlined in table 3.

Table 2: Ethnic, Gender and Waist Circumference measurements associated with increased cardiometabolic risk (10,11)

Country/Ethnic Group	Gender	Waist Circumference-Increased Risk	
Ethnic South/Central American	Male	>90 cm	>35.5 inches
	Female	>80 cm	>31.5 inches
Chinese, Japanese	Male	>90 cm	>35.5 inches
	Female	>80 cm	>31.5 inches
Europids, Sub-Saharan African, Eastern mediteranean, Middle East (Arab) populations	Male	>94 cm	>37 inches
	Female	>80 cm	>31.5 inches
USA	Male	>102 cm	>40 inches
	Female	>88 cm	>35 inches

Table 3: Body Composition Patterns, Characteristics and Evaluation Considerations (5,8)

Category	BMI	Waist Circumference	Waist/Hip ratio	Fat(percent)	Fat Free Mass (Percent)	Further Evaluation or Work up
Cachectic	<15	low	<0.8 F <0.9M	Very Low	Very low	Hypermetabolic, malabsorption, underlying disease driven process, or other catabolic driver
Underweight	<18	Low normal variable	normal	Low	Low	Evaluate disordered eating, malabsorption, immune triggers
Normal-ideal Lean	18-24.9	normal	normal	Normal	Normal	Health monitoring
Skinny Fat	18-24.9	variable	Elevated	High(VAT)	Low	Metabolically Obese = Inflammatory Workup, work up for causes of sarcopenia, metabolic syndrome
Android	>25, >30	Elevated	Elevated	High(VAT)	Low	Evaluation of drivers of inflammation and adiposopathy, metabolic syndrome
Small Gynoid	18-24.9	variable	Normal	High (SAT)	Low/ Normal	Gastrointestinal/ Biotransformation/ HPATGG[1] Dysfunction/ Toxicity, Endocrine Evaluations
Gynoid	>25, 30	Elevated	Normal	High(SAT)	Low/Normal	Gastrointestinal/ Biotransformation/ HPATGG Dysfunction/ Toxicity, Endocrine Evaluations
Andro-gynoid	>25,>30	Elevated	Mixed	Over VAT/SAT	Low/Normal	Gastrointestinal/ Biotransformation/ HPATGG Dysfunction/ Toxicity, Endocrine Evaluations and evaluation of drivers of inflammation and adiposopathy, metabolic syndrome
Large Muscled	>25,>30	Elevated	Normal	Low	High	Normal health = monitoring

[1]HPATGG-Hypothalamic-Pituitary-Adrenal-Thyroid-Gonadal-Gastrointestinal axis.

Biomakers:

The use of biomarkers for nutrition evaluation is wide ranging. Common laboratory, chemistry panel, complete blood count with differential, thyroid function, vitamin D3, iron, ferritin and transferrin are frequently ordered. A more thorough clinical prompt has been developed which helps the clinician evaluate the macronutrients (Protein, Fats, and Carbohydrate) and the micronutrients (Minerals, Vitamins and Phytonutrients) through a functional nutrition lens (Figure 1). The common laboratory (tier 1), the less common but ordered when a more focused evaluation of status is desired (tier 2) and the least commonly ordered in very specified situations are (tier 3) are listed in order (5,12).

Figure 1: Nutritional Lab Biomarkers Ordered in the Macronutrient and Micronutrient Groupings[1]

BIOMARKERS: Laboratory Tests Requested

Circle appropriate tests

Protein

Albumin, Globulin, Total Protein ■ Carnitine, Plasma Amino Acids, Prealbumin-Transthyretin ■ Methylhistadine, Fibronectin, Serum Proteins Electrophoresis, Somatomedin C, Transferrin, Urinary Amino Acids

Fats

ApoA1, ApoB, ApoB/A1 Ratio ■ Lipid Panel and Ratios (TC, LDL, HDL, TG), Lipid Particle Number, Size, Subfractions, TG/HDL Ratio ■ Omega 3 Index, Oxidized LDL, Plasma EFA panel, RBC EFA Panel

Carbohydrates

Fasting Blood Glucose, Fasting Insulin, GGT, HgA1c, HOMA-IR Score, Uric Acid ■ Adiponectin, Fructosamine ■ ½ hr gtt for glucose and insulin, 1 and 2 hr gtt for glucose and insulin

Minerals

Calcium: Ionized Ca^{2+}, Serum Ca^{2+} ■ 1,25 OH_2 D_3, 25 OH_2 D_3, Bone Resorption Markers (24 Hour Urine Ca^{2+} 24 Hour Urine Protein, N-Telopeptide, Pyridinium Crosslinks, Deoxypyridinoline, ...), PTH, Urinary Ca^{2+}

Copper: Ceruloplasmin, Serum Copper ■ RBC Copper

Iodine: Spot First Morning Urine Iodine, 24 Hour Urine Iodine

Iron: CBC (Hgb, Hct, MCV, MCH), Ferritin, HFE Gene Panel, Serum Iron, TIBC, Transferrin

Magnesium: RBC Mg^{2+}, Serum Mg^{2+} ■ 24 hour Urinary Mg^{2+} Buccal Cell Mg^{2+} Ionized Mg^{2+} by NMR ■ Mg^{2+} Load

Phosphorus: Serum Phosphorus

Selenium: Serum Selenium ■ RBC Selenium ■ Glutathione Peroxidase

Zinc: Plasma Zn^{2+} ■ 24 Hour Urinary Zn^{2+}, RBC Zn^{2+} ■ Serum Metallothionein

Vitamins

Vitamin A: Serum Beta Carotene, Serum Retinol ■ Retinol Binding Protein

Vitamin D: 25 OH_2 D_3 ■ 1,25 OH_2 D_3 ■ Ionized Ca^{2+} PTH, VDR Gene Panel (Bsm1, Fok1, Taq1)

Vitamin E: Alpha Tocopherol, Gamma Tocopherol, Serum Vitamin E

Vitamin K: PT, PTT ■ Serum Phylloquinone (K1), Under-carboxylated Osteocalcin

Vitamin B1 (Thiamine): Plasma Thiamine ■ RBC Transketolase Index ■ Plasma Isoleucine, Urine Isocaproate, Urine Isovalerate, Urine Methylvalerate

Vitamin B2 (Riboflavin): Plasma Riboflavin ■ Urine Ethylmalonate, Urine Methylsuccinate

Vitamin B3 (Niacin): N-Methylnicotinamide, Urine Lactate, Urine Pyruvate

Vitamin B6 (Pyridoxine): Homocysteine, Plasma P5P ■ Urine Kynurenate, Urine Xanthurenate ■ CBS SNPs, Methionine Load Test, Tryptophan Load Test

Vitamin B7 (Biotin): Urine Alpha and Beta Hydroxyisovalerate

Vitamin B9 (Folate): Homocysteine, MCV, Serum Folate ■ RBC Folate, Urine FIGLU ■ COMT SNPs, MTHFR (677, 1298,...) SNPs, Unmetabolized Folic Acid

Vitamin B12 (Cobalamin): Homocysteine, MCH, MCV, MMA, Serum B12 ■ MTR SNPs, MTRR SNPs

Vitamin C (Ascorbic Acid): Serum Vitamin C, WBC Vitamin C

Phytonutrients

8-OHdG, Lipid Peroxides, Oxidized LDL, Total Antioxidant Capacity ■ RBC Glutathione, Serum CoQ10

Foundational Testing

CBC w/diff, CMP

Other Functional Testing

Autoimmune Panel, Celiac Genetic Testing, Celiac Serology, Heavy Metal Assessment, IgE Food/Environment, IgG/IgG4 Food Sensitivity, Intestinal Permeability, Organic Acid Testing, Sex Hormone Testing, Stool Testing for Infection and Absorption, Hydrogen Breath Test, Thyroid Panel with Auto-antibodies, Urinary Dysbiosis Markers

Other _____

_____

_____

■ *Designates seperation of first, second, and third tier testing.*

Version 2

[1]©Institute for Functional Medicine 2015 (12)

Clinical Exam: The Head to Toe Functional Nutrition Oriented Physical Exam in Primary Care

To perform the 10 minute nutrition physical exam the patient needs to be able to take off their shoes and socks, you will need a stethoscope (to listen to the jaw and chest), a headlamp (outdoor supply store) which allows your hands to be free, a magnifier (to look at skin and nails), a camera with macro (or cell phone), tongue depressor, gauze, long handle q tip and oxygen saturation monitor. A salted rice

cracker and some water allows the practitioner to view chewing and swallowing. A bitter taste strip and smell card for evaluating taste and smell are used.

When starting the physical exam any finding needs to be put in the context of the finding to the history, the patients timeline, the company that the physical exam finding keeps (other signs or symptoms, laboratory), and the quality and quantity of the patients modifiable lifestyle habits (sleep, exercise, nutrition and diet food habits, relationships, and stress and resilience). Understanding the context, company the finding keeps, the quality and quantity of modifiable lifestyle factors can increase the sensitivity and specificity of the findings. The 10 minute nutrition physical exam is outlined in Box 1.

Box 1: 10 Minute Nutrition Physical Exam Highlights

Hair: Thinning, areas of hair loss, color or hair distribution inconsistent with age. Magnify the end of the hair, have the patient put traction on their hair at the nap of the neck and count how many hairs come off in between thumb and first finger pinch. Note the color and luster change.
Scalp: alopecia, seborrhea or dandruff.
Ears: Note the earlobe creases
Nose: Cover one nostril and have the patient breath through the nares. Is it clear air flow- swollen turbinate's, altered septum, test for smell will be altered. Are there allergies? Skin around the nose: look for seborrhea or rosacea
8 Step Mouth exam (Stone IFM): 1. place hands on the TMJ open and close. 4cm + vertical space between teeth of the lower jaw and teeth of the upper jaw. 2. Lips: Evaluate cracking, angles of the mouth. Have the patient pull the bottom and top lip and show you the inner lip mucosa. 3. Soft palate: have the patient show you the soft palate, tonsils size and uvula. Hard palate: have the patient tip their head back 4. Tongue: have the client stick out their tongue look for color, coating (grade 1,2 or 3), symmetry, movement, taste bud distribution and atrophy, piercings, frenulum, vasculature of the under tongue 5. Gums: have the patient pull on their lower and upper lip and show you their gums. Run the q tip along the inner and outer teeth looking for inflammation, pain, bleeding. Signs of gingivitis or periodontal disease. 6. Buccal mucosa: Have the patient open their mouth and to look for lesions, note hypertrophy of stensen's duct orifice. 7. Teeth: Count the teeth. Look for amalgams/dissimilar metals. Note Restorations. Signs of chronic dental plaque. Tooth fractures, enamel attrition. Fluorosis. 8. Chew and swallow. Oxygen saturation and swallowing. Evaluate taste of salt (rice cracker and bitter using a phenylthiocarbamide- bitter strip)
Neck: view the skin, watch the swallow evaluate the movement, Pemburton Maneuver for retrosternal thyroid, palpate the thyroid with each lobe being equal or smaller than size of the patients distal thumb.
Chest: watch the respirations, chest movement. Listen for wheezing, ralls
COR: Feel for lateralized PMI and tachycardia. Use the oxygen saturation monitor for pulse.

Skin: look at the skin of the face, neck, arms, legs, feet, skinfold the thickness on the back of the hand overlying the 4th metacarpal- greater than 2 mm thick is normal.
Nails: have the patient show you the nails of the hands and feet.
Musculoskeletal: look at symmetry, temporal wasting, thenar and hypothenar wasting, tenderness over the growth plates, tenderness over the anterior tibial spine, peripheral edema lower extremity
Neuro: Get up and Go: an evaluatory step for Sarcopenia, CNS, Peripheral NS activation. Romberg, also stand up/sit down 5 times for strength and sarcopenia. Monofilament testing of the first and fifth finger and toe, right and left foot distal most digit. 128 hz tuning fork vibration sense evaluation of speed of extinction of the thumb and 5th finger, great toe and fifth toe distal phalange proximal to the nail.

Hair and Eyebrows (5,13,14,15,16,17)

The Hair exam will often show changes in luster, a transition from silky to course with inadequacy of protein. In diabetics there is a greater change in the sulfur content of hair and nails which results in a change in character. Periodic severe protein inadequacy can lead to the flag sign. Increased antioxidant with the inadequacy of antioxidants or cofactors for superoxide dismutase can result in premature graying. Alopecia, easy pluckability at the nap of the neck is associated with protein, zinc and other nutrients. Loss of hair or thinning of hair seen in copper deficiency, conditions promoting hypothyroidism (iodine, zinc, and selenium deficiencies) or thyroid autoantibody promoting conditions (celiac disease, hashimotos thyroiditis) often have hair changes. The eyebrows lateral hair loss, Queen Annes sign, is associated with hypothyroidism but is poorly sensitive and specific with many other non nutritional associated causes. Many conditions of the hair can have a nutrition deficiency component and should be considered in the differential (Table 4).

Table 4: Hair Findings associated with nutrient deficiency or insufficiency[1]

Finding	Nutrient Deficiency or Insufficiency	Other Conditions Associated With This Finding (partial listing)
Alopecia areata	Protein, iron, zinc, copper, biotin	Autoantibodies (thyroid), gluten, hypothyroid, syphilis, traction alopecia, monilethrix, androgenic alopecia, lupus, discoid lupus, dermatomyositis, tinea capitis, smoking, anemia, heavy metal poisoning, hypopituitarism
Androgenic alopecia	Iron, zinc, vitamin A, vitamin D, vitamin C, biotin, folic acid	Hypothyroid, alopecia areata, syphilis, traction alopecia, monilethrix, lupus, discoid lupus, dermatomyositis, tinea capitis
Hair thinning	Protein, zinc, selenium	Hypothyroidism, anemia
Premature graying	Copper, B12	Genetic, oxidative stress, smoking, UV light
Dry hair	EFA	Hypothyroidism

Dandruff	EFA, zinc	Seborrheic dermatitis, psoriasis, atopic dermatitis, tinea capitis, rosacea, xerosis, chemical drying, vitamin A toxicity
Dull hair, lusterless	Protein, iron, EFA	Chemical effects
Hair depigmentation	Protein, copper, zinc, biotin, B12	Chemical or hair treatment effects, sun or environmental exposure
Corkscrew hair	Vitamin C	Steroids, tinea capitis, rare autosomal disorders, ectodermal dysplasia, scurvy
Swan-neck hairs	Vitamin C	Scurvy

[1]Stone, PM, Dotson N, Institute for Functional Medicine: Applied Functional Medicine in Clinical Practice, ABCD of Functional Nutrition Evaluation Companion Guide. Institute of Functional Medicine, Federal Way, Washington. 2017

Eyes (18,19)

Turning the attention to the eyes, first simply retracting the lower lids often reveals pallor. The subconjunctival pallor of the lower lid is very predictive of all cause anemia (20), with the likelihood ratio of 16. The underlying causes nutritionally include: protein, iron, folate, B12, and vitamin C most commonly, but other nutrients involved as cofactors in hematopoiesis have been associated with anemia. The lateral corner of the eye dryness or inflammation is associated with riboflavin insufficiency and the conjunctiva can reveal dryness (vitamin A), hyperkeratotic bitot's spots (vitamin A), and corneal xerosis responds well to vitamin A drops. Dark vision adaptation is not commonly completed in the primary care clinic, but night vision loss not improved by vitamin A supplementation can be improved with the addition of zinc.

8 step mouth exam

Oral health problems are preventable, common and painful. Access to dental and mouth care is becoming more difficult. A recent study in the United States documents that 65 percent of the adults over the age of 65 and half the Medicaid population has no dental insurance (21). Primary care clinicians need to feel comfortable with the 8 step mouth exam which reveals findings linked to nutrition insufficiency (22). The 8 step mouth exam is summarized in Box 2

Box 2: 8 Step Mouth Exam

8 Step Mouth Exam[1]
1) Jaw Movement: symmetry, crepitus, pain, mouth opening >4 cm
2) Lips: Dry cracking, angular stomatitis/cheilitis, ulcerations, fissures, perioral rash, loss of lip borders, lesions, edema, piercings, developmental deficits
3) Hard and Soft palate: cleft or oropharyngeal deficits, boney lesions- torus palatinus or mandibularis, assymetric movement, uvula swelling of absence, lesions- stomatitis or ulcerations
4) Tongue: abnormal movement, enlarged, scalloping, color (red, pale, black, white), coating (brown black, white, yellow), glossitis with pain, taste bud distribution and prominence, fissuring: central, transverse, lambda. Ankyloglossia, lesions: ulcerations, cysts, plaques, Tongue varicosities, Wharton duct blocked.
5) Gums: Bleeding, friability, bruising, lesions, macules, tenderness, burtons lines, gingivitis, periodontal disease, hyperplasia
6) Buccal Mucosa: Abrasions, lesions-macules, papules, plaques, ulcerations, linea alba, amalgam tattoos, stenson's duct papilla, xerostomia
7) Teeth: Missing teeth, tooth attrition or abrasions, dissimilar metals, periodontal ligament pain, enamel dysplasia, enamel discoloration (fluorosis), plaque (tartar)
8) Chew and Swallow: chew without pain, swallow without choking, oxygen saturation drop of >2% if difficulty swallowing. Tastes: Salty, sweet, bitter, sour

[1]Stone, PM, Institute for Functional Medicine: Functional Nutrition Exam: The Mouth Companion Guide. Institute of Functional Medicine, Federal Way, Washington. 2015

The 8 step mouth exam starts with opening the mouth. Can the patient open their jaw (step 1). Decreased movement of the jaw, pain in the temporomandibular joint, increased pain and decreased upper and lower tooth distant opening <4 cm is associated with increased malnutrition (22). The lips (step 2) can be dry and cracked from increased environmental dehydration, radiation damage, but can also show mild to severe vertical cracks (cheilitis). The corners of the mouth with inflamed sores can be angular stomatitis associated with a number of mineral and vitamin insufficiencies. The oral mucosa findings associated with micronutrient deficiencies are summarized in table 5.

Table 5: Oral mucosal findings with associated micronutrient deficiencies (23)

Oral mucosal FIndings	**Associated Micronutrient Deficiency**
Angular Cheilitis (corner of the mouth), Cheilisis (dry cracking) of the lips	Riboflavin, Nicotinic acid, Folic Acid, Biotin Cobalamin, Vit C, Fe, Zn. /Riboflavin, Niacin, Pyridoxine
Burning Mouth Syndrome	Pyridoxine
Candidiasis	Folic acid , Cobalamin, Iron
Glossitis	Riboflavin, nicotinic acid, pyridoxine, folic acid, Cobalamin, iron, protein energy malnutrition
Lip fissures	Pyridoxine

Oral Sensitivity	Thiamine, pyridoxine
Recurrent apthae	Riboflavin, Folic acid, Cobalamin, Ascorbic Acid
Stomatitis	Nicotinic acid, Folic acid, Cobalamin.
Periodontal disease	Vitamin A, D, E, B-Carotene, Thiamin, Folate B12, E, C, Ca, Se
Poor mucocutaneous border	Riboflavin, Niacin, pyridoxine, Zinc

The soft palate movement or lack there of provides clues to the ease of airway protection. The hard palate body defects and oromaxillary clefts are associated with methylation factor inadequacy during early organogenesis (24,25,26, 27). These can be genetic or environmentally nutrition impacted. The degree of swelling of the tonsils gives the clinician hints of chronic, recurrent infection history or tissue redundancy might lead to consideration of sleep apnea. With the patient saying Ahhh, or breathing in the normal movement of the soft palate an uvula provides reassurance of probable airway protection. When breathing out, the clinician may sense the odor of the breath. Intraoral conditions cause the majority of halitosis. Associated breath odors are listed in table 6.

Table 6: Breath Odor and associated pathology or conditions (5, 28)

Compounds	**Odor Description[1,2,3]**	**Systemic Pathology[4]**	**Other Conditions**
Ketones	Sweet, decomposing apples	DM, Ketoacidosis	Low fat, low CHO diet/Fasting
Dimethylamine, trimethylamine	Fishy, rancid butter, boiled cabbage	Uremia, Renal Failure, Trimethylaminuria, haemophilus influenza or Strep pneumonia lung infections	Menstruation, Preterm infants fed choline food supplement, Alzheimer's disease
Diamines- cadaverine, putricine	Putrid	Scurvy, Periodontal abscess, herpetic gingivitis, oral ulscers	Chronic tonsillitis, tonsilloliths, foreign bodies in the nose
Dimethyl sulfide, mercaptins, dimethyldisulfide (volatile sulfur compound)	Fetor Hepaticus	Liver Diseases, hepatocellular failure	Sulfur Drugs-disulphiram
Limonene	Citrus	Hepatic encephalopathy	
Hydrogen Sulfide	Rotten eggs, feces	Periodontal disease, abscess, oropharyngeal infections-anaerobes	Endogenous oral malodour (Tongue biofilm)
Volatile organic compounds including the Volatile sulfur compounds.	Sewage Breath	Bronchiectasis, gastroparesis, intestinal obstruction, pulmonary abcess	Periodontal disease, dental abscess, tonsillar infection.

C2-C8 normal and BCAA	Uremic	Uremia or Oropharyngeal cancers	Oversupplementation of branch chain aminoacids.
Acetone	Solvent smell	Lung carcinoma	Rapid fat loss in calorie restricted diets[5]

[1] Kapoor U, Sharma G, Juneja M, Nagpal A : Halitosis: Current concepts on etiology, diagnosis and management. Eur J Dent. 2016 Apr-Jun; 10(2): 292–300. doi: 10.4103/1305-7456.178294 [2]Hayden GF: Olfactory diagnosis in medicine. Postgrad Med 1980:67:110-118. [3]O'Hara ME, Fernández Del Río R, Holt A, Pemberton P, Shah T, Whitehouse T, Mayhew CA. Limonene in exhaled breath is elevated in hepatic encephalopathy. J Breath Res. 2016 Nov 21;10(4):046010.[4]Das S, Pal S, Mitra M: Significance of exhaled breath test in clinical diagnosis: a special focus on the detection of Diabetes Mellitus. J Med Biol Eng 2016;36:605-624.[5] Ajibola OA, Smith D, Spanel P, Ferns GAA: Effects of dietary nutrients on volatile breath metabolitesJournal of Nutritional Science 2013: 2, e34, 1-15,doi:10.1017/jns2013.26

The tongue (step 4) might be sore (glossitis- niacin), have altered color (red-iron, magenta riboflavin, pale iron, B12, or folate anemia, or coating of black, brown, white (5,29,30) with different levels of anaerobic bacteria suggesting dysbiosis of the upper gastrointestinal tract (31). The median glossitis seen in the posterior middle of the tongue is most associated with candida overgrowth. (31). The tastebud atrophy without glossitis has different initiators than the shorter list of nutrients associated with painful glossitis (Tables 5,8). Checking the taste sensitivity with phenylthiocyanate taste strips or simple a salted rice cracker (salt), a chocolate chip (sweet), kale or a taste of coffee (bitter), or lemon juice (sour) can inform taste sensitivity and preferences which are altered by many medications (32,33). Taste loss is seen in severely, zinc, vitamin A, copper patients in gastric bypass (34,35). The tongues thickness will diminish in protein under-nutrition and weight loss which can lead to increased difficulty eating, and positioning food to swallow leading to increased chocking (36).

The gums (step 5) looking inflamed, bruising or bleeding with touch, flossing, or brushing can be indicative of vitamin C deficiency, infection, or coagulopathies not with nutrition undertones. Periodontal disease can have systemic effects (37,38) Darkened lines on the gums just above the gum line (Burton lines) can be due to lead, barium, other heavy metal, or cisplantin staining. (39,40,41).

The Buccal mucosa, holds stentens duct, or parotid duct allows saliva from the parotid to bath the mouth. It is near the second upper molar exiting through the buccal mucosa. The stensens duct papillae can be hypertrophic in thiamine deficiency, and the parotids are also enlarged in patients who have alcohol induced thiamine deficiency. Psoriatic plaques or celiac associated lesions of the buccal mucosa (step 6) are seen suggesting up-regulated immune response often visible in the oral mucosa long before or in isolation of other skin lesions (psoriatic plaques or dermatitis herpetiformis)(42,43,44). Many of the nutrient deficiencies affecting the gums and buccal mucosa are found in Tables 7 and 8.

The teeth (step 7) can be acutely decalcified in prolonged malabsorption of calcium (45,46). The caries associated with chronic oral dysbiosis can be seen. The oral bacteria changes with many conditions associated with under-nutrition (bulimia, celiac, autoimmune conditions, diabetes,) and with the diminishment of salivary quantity and pH and medications the teeth are susceptible as the pH drops below 5.8. Cracked or broken teeth and tooth loss are associated with greater under-nutrition. Having less than 20 teeth in the mouth is a harbinger or predictor of osteoporosis a latency disease of hypovitaminosis D, calcium, magnesium, and protein undernutrition.(47). A mouth with many amalgums or restorations suggest a history most commonly of prolonged dysbiosis of the oral cavity. Tooth enamel dysplasia is also 20 X more common in celiac patients, though hypovitaminosis A and D in the womb are also associated with marked enamel dysplasia (48). The challenges of restorations and the effects on certain people sensitive to the metal alloys has led to studies on the metallic ions released from the orthodontic allowys their toxicity and DNA effects (49). Chronic fluoride toxicity, dental fluorosis is increasing and may play a role in subclinical hypothyroidism in children (50,51)

Having the patient chew a rice cracker and swallow (Step 8) water successfully without choking, delay, hesitancy suggests that they can protect their airway and if their oxygen saturation does not drop 2% while chewing and swallowing they are at decreased risk of aspiration or pneumonia (52,53,54). The smooth muscle of the esophagus and its normal function magnesium sufficiency, and adequate melatonin for control of gastric reflux (55,56). A more in depth and specific nutrition evaluation of the mouth and dental exam have been recently available through the N-sight.org nutrition physical exam functional medicine teaching sight (22, 57).

Single nutrient deficiencies can cause pleomorphic signs and symptoms depending on the individual requirements altered by their individual genetic single nucleotide polymorphisms. By considering the diet, nutrition and lifestyle influences and the physical exam findings the clinician can be clued to clinical patterns. The mucosa of the mouth rapidly turns over making it vulnerable to nutritional inadequacy. The individual nutrient deficiencies associated with oral findings and linked to other signs and symptoms are listed in Tables 7 and 8.

Table 7: Mineral deficiency and toxicity signs in the mouth (58)

Mineral	Condition
Iron	Glossitis, angular Cheilitis, mucosal atrophy (increased susceptibility to carcinoma), candidosis
Copper	May prevent acid production in dental plaque, High copper Chewing habits (areca nut) promotes oral submucous fibrosis.
Zinc	Delayed wound healing, supplementation postpones radiation induced mucousitis, oral candidiasis, increased incidence taste disturbance. Associated with loss of smell, first with the sensation of salt taste. Toxicity associated with metallic taste (>1000mg).
Selenium	Deficiency impairs wound healing, toxicity associated with garlic odor (dimethylselenide)

Table 8: Vitamin deficiency signs in the mouth (59,60)

Deficiency	Manifestation
Vitamin A	Hyperkeratinization of oral mucosa, impaired healing, impaired bone and tooth formation, blockage of salivary duct/reduced saliva flow, mucocutaneous candidiasis, potentiates existing inflammation
Vitamin D	Delayed tooth eruption/development, enamel hypoplasia, rickets, osteoporosis and low alveolar bone density, increased gingival bleeding, increased susceptibility to dental caries
Vitamin E	Rare-anemia
Vitamin K	Impaired blood clotting, gingival bleeding
Vitamin C	Gingival bleeding, impaired wound healing, impaired mucosal membrane integrity, salivary gland hypofunction
Folic Acid/folate	Anemia, Glossitis, chelitis, increased carriage of candida, cleft palate, orofacial clefts*.
Thiamin	Stomatitis, burning mouth syndrome
Riboflavin	Angular cheilitis, burning oral mucosa, ulceration
Niacin	Angular stomatitis, papillary atrophy of tongue, fissuring, painful glossitis, halitosis
Pyridoxine	Glossitis, angular stomatitis, cheilitis
B12	Pernicious anemia, redness and burning of the tongue, tongue fissuring, nuclear enlargement of mucosal cells, epithelial dysplasia

Smell and Taste

Many conditions change the sense of smell and taste. The loss of smell or the altered sense of taste changes what our patients choose to eat, how they recall memories around meals and relationships in their past and impacts their health because of the altered variety of foods that are chosen in the course of their day.

To test the sense of smell, each nostril should be tested individually for patency first and then the smell offered to the patient. Simple cinnamon, coffee or clove oil can be used, however recently more precise cards or smellent pens are available to the clinician. Determining anosmia, hyposmia is important

because it leads the clinician to look further into underlying conditions which affect the patients health, food choices, and potentially nutrition adequacy (Table 9)(5).

Table 9: Smell evaluation using a 4 odor smell card [1]

Finding	Nutrient Deficiency or Insufficiency	Other Conditions Associated With This Finding (partial listing)
Smell identification with 4 odors[2]		
Normal: 6-8/8	None associated	
Hyposmia: 1-5/8 Anosmia: 0/8	Zinc, copper, iron, iodine, vitamins A, E, B complex: B2, B3, pantothenic acid, biotin, folate, B12	Medications (partial list): ○ Calcium channel blockers: nifedipine, amlodipine, diltiazem ○ Lipid lowering: cholestyramine, clofibrate, pravastatin ○ Antibiotic/antifungal: streptomycin, terbinafine, doxycycline, ciprofloxacin ○ Antithyroid: carbimazole ○ Opiate: codeine, morphine ○ Antidepressant: amitriptyline ○ Antiepileptic: phenytoin ○ Nasal decongestant: phenylephrine, pseudoephedrine, oxymetazoline - Inhalants or topicals: smoking, agyria (topical silver nitrate), cadmium fumes, pesticides, intranasal cocaine - Other etiologies: 15-25% post URI, head and dental trauma, neurologic disease (Alzheimer, Parkinson, multiple sclerosis).

[1]Stone, PM, Dotson N: Applied Functional Medicine in Clinical Practice, ABCD of Functional Nutrition Evaluation Companion Guide. Institute of Functional Medicine, Federal Way, Washington. 2017. [2]Upsit 4 odor identification screen. Sensonics international. Sensonics.com.

People who are super bitter tasters consume up to 200 less servings of vegetables a year (62, 63). Using a simple bitter taste strip allows the easy evaluation of the super bitter taster patient. This allows the clinician, nutritionist or health coach to steer the patient to different food choices in the therapeutic plan. To offer a bitter taster a morning vegetable smoothie with large amounts of kale, arugula, or other high calcium (bitter) vegetables would not be successful. But knowing the patient is a super bitter taster would encourage the addition of coconut oil, a bit of sweet (dates, honey for example) or sour (lemon or citrus) and adding ice which would make the high calcium, magnesium, potassium, vitamin A, beta carotene rich smoothie more palatable. The associations of bitter taste, taste loss and food choice are outlined in table 10.

Table 10: Bitter Taste, Taste Loss, Nutrient insufficiency and Food Choice Associations[1]

Finding	Nutrient Deficiency or Insufficiency	Associations
No bitter taste	Genetically determined	Increased intake of greens improves the intake of plant-based antioxidants, minerals, and essential fats compared to super bitter tasters
Some bitter taste	Genetically determined	Intermediate vegetable eaters
Super bitter taster (often prominent anterior tongue taste buds)	Genetically determined	Less intake of vegetables/year; less intake of calcium-rich vegetables
No taste or loss of taste (one or more individual tastes: sweet, salty, bitter, sour, umami)	Protein malnutrition, copper, iodine, iron, zinc, vitamins A, D, E, niacin, riboflavin, pyridoxine, pantothenic acid, folic acid, B12	Causes of taste change or loss: - Infection/abscess: oral candida, periodontal disease, gingivitis, URI - Oral appliances: dentures, prosthetics - Postsurgical: middle-ear surgery affecting chorda tympani; oral or dental surgery, especially third molar extraction - Radiation: HEENT irradiation with oral mucositis, xerostomia - Medications: intranasal zinc, chlorhexidine, chemotherapy, ACE inhibitors, ARBs, calcium channel blockers, diuretics, macrolides, terbinafine, fluoroquinolones, protease inhibitors, griseofulvin, PCN, tetracyclines, metronidazole, antiarrhythmics, antidepressants, anticonvulsants, lipid-lowering agents - Toxins: pepper gas, weed killer, ammonia, benzene, cadmium, iron, lead - Head trauma: concussions, closed head injury

[1]Stone, PM, Dotson N, Institute for Functional Medicine: Applied Functional Medicine in Clinical Practice, ABCD of Functional Nutrition Evaluation Companion Guide. Institute of Functional Medicine, Federal Way, Washington. 2017

Neck

The skin of the neck might reveal acanthosis nigricans or increased skin tags common with insulin resistance so underlying causes for that resistance should be considered including adequacy of vitamin D and chromium. The increased epidermal growth factor involved in the mechanism of increasing skin tags with insulin resistance is also influenced by larger doses of niacin. Thyroid enlargement is associated with endemic goiter (iodine), but also with conditions which diminish zinc, selenium, or protein inadequacy with tyrosine. Competing cations (Bromine, fluoride, chloride, or radioisotopes of iodine) can also influence the thyroid function. The other associated signs and symptoms of

hypothyroidism are well documented and can be scored by the Billawicz score (Table 11). The addition of the Billawicz score here is to emphasize that none of the nutrition deficiency signs or symptoms occur in isolation. The clinician always needs to consider the plethora of intricate roles each of the nutrients play in our normal physiologic balance. The case of the hypothyroid patient who presents with a constellation of signs and symptoms the deficiency of zinc or selenium, iodine or tyrosine is not always considered when writing for thyroid replacement. But by considering the nutritional influences or environmental nutrient interactions (bromine, fluoride, chlorine) and correcting any deficiencies the restoration of normal thyroid axis function is more likely.

Table 11 : **Billawicz Score for Hypothyroidism (20)**

Finding	**Present**	**Absent**
Symptoms		
Diminished sweating	+6	-2
Dry skin	+3	-6
Cold intolerance	+4	-5
Weight Increase	+1	-1
Constipation	+2	-1
Hoarseness	+5	-6
Parasthesias	+5	-4
Deafness	+2	0
Physical Signs		
Slow Movement	+11	-3
Course Skin	+7	-7
Cold Skin	+3	-2
Periorbital Puffiness	+4	-6
Pulse rate <75	+4	-4
Slow ankle jerks	+15	-6

Score of >+30 has A likelihood ratio of 18.8 or approximately 60% chance (without Laboratory)(20)

Chest:

The Respiratory rate and chest movement with or without the presence of wheezing can be indicative of bronchoconstriction (magnesium and other nutrients of mitochondrial function and diminished oxidative stress), increased pulmonary inflammation (vitamin C, essential fatty acids, vitamin A, vitamin D) or secretions (phytonutrients- quercetin) which can each have nutritional insufficiency associated causes. Ralls can be heard in many conditions associated with congestive heart failure. High output failure is seen in thiamin deficiency. Though beriberi is considered rare in developing countries, with the increased use of bariatric surgery there have been more cases of "bariatric beriberi" documented (Table 10) (63). Coenzyme Q10 has been successfully used to improve patients from New York heart association class 4 to 3 and those in class 3 to class 2 (64, 65).

The cardiac exam might reveal high output failure of thiamine deficiency, arrhythmias associated with hypo-magnesemia, hypokalemia, or essential fatty acid inadequacy (63, 66) Orthostatic changes associated with sympathetic dysfunction are seen with malnutrition, anorexia, chronic vomiting.

The **Abdominal exam** might reveal fluid accumulation of inadequate intake or absorption of protein with a markedly decreased oncotic pressure there is increased change of extravascular fluid accumulation. Insulin resistance associated with visceral adiposity is also associated with increased abdominal waist to hip ration (see anthropometrics). Previous surgical sites or slowly or poorly healing wounds are seen in protein, arginine, essential fatty acids- EPA and DHA to aid in the inflammatory axis, zinc, vitamin A, D, C under nutrition and have improved wound healing when these nutrients are optimized (67). But when considering the optimization of healing, all of the macronutrients and micronutrients play a significant role (67). Diet, nutrition and lifestyle evaluation should be considered in all those with chronic wounds. Chronic wounds are often seen on the lower extremities, sacral or ischial pressure points in the chronically ill. Chronic wounds require 5 main areas controlled: adequate oxygen, adequate nutrition, minimal edema, minimal shear stress, and no infection. These are the 5 fingers in the glove of wound healing

Skin (17)

The examination of the skin starts on the back of the hand. Overlying the back of the hand, the 4th metacarpal pinch the skin. If the skinfold is greater than 2 mm then there is a decreased incidence of osteoporosis. Look at the skin on the hands and forearms for bruising (vitamin C and K) capillary instability). Looking for skin changes on the hands and forearms could include signs of xerosis (essential fatty acid insufficiency), sunlight associated changes darkening and flakiness (niacin), or on the back of the arms hyperkeratosis pilari (vitamin A, essential fatty acids, the B vitamins associated with the desaturases and elongases of essential fatty acid deficiency). Though hyperkeratosis pilari and the associated toad skin of phrynoderma, which often overlies elbows is associated with vitamin A, B complex, or essential fatty acid deficiency, it is also associated with the deficiency of the cofactors involved with elongase and desaturase functions of essential fatty acid metabolism.

The skin of the face might reveal seborrhea of the eyebrows, about the nose whose nutrient insufficiency associations are biotin, essential fatty acids, occasionally zinc, and vitamin A insufficiency or toxicity. The irritations of angular blepharitis and angular stomatitis have been discussed above.

While examining the skin and skin of the feet, increased warts (zinc insufficiency) have increased incidence in zinc deficiency agricultural regions. Zinc is necessary for adequacy of the T cell function associated with virus surveillance.

The skin color changes associated with iron deficiency, or the bronzing with hemochromatosis and iron toxicity are generalized and noted. Malassma can be associated with B12 inadequacy (B12 trap) in the setting of folate supplementation. Darkening of the skin overlying the extensor surfaces of the joints of the toes and fingers is also seen in severe B12 deficiency as B12 is needed for normal tyrosine metabolism and if it not present there is shunting toward melanin formation. This is the same mechanism suggested for melisma and is more prominent in the sun exposed areas.

The scalp often reveals increased dandruff of seborrhea and the considerations of essential fatty acid adequacy, zinc undernutriture, vitamin A and D balance should be considered. The cradle cap in infants can be correlated to fatty acid balance (>omega 6 with inadequacy of omega 3 levels). The skin around the mouth, entroitus, urethra, and anus are areas where severe zinc deficiency and associated periorificial rash of genetic or acquired acrodermatitis enterohepatica is revealed.

Thickened calluses out of perportion to lifestyle, occupation, or exercise is associated with essential fatty acid (omega 6) inadequacy. As with many of the physical exam findings. They do not appear singularly, meaning that rarely do you see only thickened calluses and not one of the other essential fatty acid insufficiency signs.

Table 12: Macro and Micro Nutrient Insufficiency skin signs with other constellation signs of deficiency

Nutrient	Symptoms or Findings (Partial list)
Macronutrients	
Protein energy malnutrition	Skin: dry, thin, loose, wrinkled Hair: fine brittle hair, alopecia Nails: fissuring and impaired growth Mouth: angular cheilitis, loss of buccal fat GI: abdominal distension and occasional rectal prolapse, diarrhea, constipation Musculoskeletal: loss of subcutaneous fat and muscle mass General: failure to thrive
Protein energy malnutrition with edema	Skin: generalized dermatitis, "flaking enamel paint" or "cracked pavement" dermatitis, edema, increased pigmentation on arms and legs Hair: dark brown hair becomes a rusty red, light colored hair becomes blonde (flag sign) GI: distention of abdomen Neurologic: irritability, lethargy, apathy General: failure to thrive

Essential fatty acid deficiency	Skin: xerosis, scaly, diffuse erythema, poor wound healing, traumatic purpura, alopecia, thickened calluses, Nails: brittle nails Neurologic: associated with attention deficit disorder
Micronutrients	
Copper deficiency (genetic—Menke's disease)	Skin: hypopigmentation, follicular hyperkeratosis, inelastic depigmented skin at nape of neck, axillae, trunk Hair: kinky or steel-wool hair: short, sparse, lusterless, tangled, depigmented Mouth: arched palate, delayed tooth eruption Musculoskeletal: hypotonia Neurologic: ptosis, reduced facial movements, multifocal degenerative disease of grey matter, demyelinating disease, ataxia, hypotonia, seizures General: failure to thrive, developmental delay Genetic: Menkes gene on chromosome X q13; P-type ATPase
Copper deficiency (acquired)	Skin: poor wound healing Hair: hair loss, alopecia Musculoskeletal: muscle and joint pain Hematologic: anemia and neutropenia Neurologic: optic neuropathy, myelopathy, paresthesia's, carpel tunnel syndrome General: fatigue
Iron deficiency	Skin: generalized pruritus Hair: lusterless, dry, focally narrow and split hair shafts, heterochromia of black hair, hair loss (alopecia) or thinning Nails: fragile, longitudinally ridged, lamellated brittle nails with thinning, flattening of nail plates, koilonychias Ocular: blue sclera Mouth: aphthous stomatitis, angular stomatitis, glossodynia, atrophied tongue papillae
Zinc deficiency (genetic—acrodermatitis enteropathica)	Skin: eczematous and erosive dermatitis, preferentially localized to periorificial and acral areas, alopecia, superinfection with Candida albicans and Staphylococcus aureus GI: diarrhea Neurologic: irritability, whining and crying General: lethargy Genetic: defect in the intestinal zinc transporter (ZIP4)
Vitamins	
Vitamin A deficiency	Skin: xerosis, skin fissuring (dermatomalacia), phrynoderma, perifollicular hyperkeratosis Ocular: impaired dark adaptation, exopthalmia, corneal xerosis, ulceration, keratomalacia, corneal perforation, blindness Mouth: xerostomia Musculoskeletal: hypotonia Neurologic: hypogeusia
Vitamin D Deficiency	Skin: pale, increased inflammation, thicker increased basal cell, squamous cell and thicker melanoma compared to normal vitamin D level patients. Hyperaesthetic pain response to skin lesions, increased pain sensitivity Musculoskeletal: hypotonia, increased pain. Metaphaseal, periosteial pain Cardiovascular: increased hypertension Neurologic: increased hyperesthesia, pain.

Thiamine, Vitamin B1 deficiency (beriberi)	Skin: edema of face, sacrum; decreased sweating or hyperhidrosis; atrophy of the skin with distal extremity hair loss Cardiovascular: tachycardia, CHF, cyanosis. Respiratory: occasional pulmonary hypertension GI: anorexia, vomiting, diarrhea Neurologic: irritability, apathy, restlessness; Wernicke's encephalopathy; ophthalmoplegia, ataxia, nystagmus, laryngeal nerve paralysis (aphonia—especially in infant beriberi) Adult: Dry form: symmetric distal peripheral neuropathy, sensory and motor Wet beriberi: neuropathy with cardiac involvement General: irritability, apathy, restlessness
Riboflavin, Vitamin B2 deficiency	Acute: Skin: erythema, epidermal necrolysis, mucositis Chronic: Skin: seborrheic dermatitis of nasolabial folds, nostrils, nasal bridge, forehead, cheeks, posterior auricular areas, flexural areas of limbs and genitalia Mouth: angular stomatitis, cheilosis with erythema, xerosis, fissuring, glossitis, magenta tongue Neurologic: photophobia
Niacin, Vitamin B3 deficiency (pellagra)	Skin: painful pruritic dermatitis of sun-exposed skin—scaly, dry, atrophic, in intertriginous areas, dorsum of the hands (gauntlet); dorsum of feet (gaiter) macerations and abrasions may occur; Casal's necklace in the neckline exposed to sun leads to dermatitis with erythema and hyperpigmentation; malar suborbital pigmentation (butterfly distribution), scrotal dermatitis, erythema, and hyperpigmentation Mouth: angular stomatitis, cheilitis, glossitis GI: diarrhea, nausea, vomiting, abdominal pain, anorexia Neurologic: nervousness, apathy, impaired memory, depression, psychosis, dementia General: insomnia, fatigue
Folate, Vitamin B9 deficiency	Skin: perirectal ulcerations, perineal seborrheic dermatitis, diffuse brown hyperpigmentation concentrated in the palmer creases and flexures Mouth: glossitis with atrophy of the filiform papillae, angular cheilitis, mucosal ulceration GI: diarrhea Hematologic: macrocytosis, neutropenia Neurologic: (cerebral folate deficiency): seizures, neurologic delay, depression, anxiety; MTHFR SNPs associated with functional folate deficiency
Vitamin B12 deficiency	Skin: cutaneous hyperpigmentation—diffuse, symmetric or scattered macules with greatest concentration on hands, nails, face, palmar creases, flexural regions, and pressure points; vitiligo or hypopigmentation Hair: hair depigmentation—localized or diffuse Mouth: glossitis—atrophic red painful with atrophy of the filiform papillae in early states may be linear glossitis, angular cheilitis Hematologic: macrocytic anemia Neurologic: generalized weakness with paresthesias progressing to ataxia, symmetric loss of vibration, proprioception worse in the lower extremities and progressing to spasticity, paraplegia and incontinence; associated apathy, somnolence, irritability, memory loss, dementia, psychosis

Nails:

Most nutrient deficiencies will present on the nail before they show up in any other clinical or laboratory findings and in autoimmune disease and systemic diseases, onset will often show up first with nail changes

The finger and toenails gradually grow and replace themselves over a course of 6 months to 18 months. Nails grow at an average rate of 3 millimeters (1/8 inch) a month. Fingernails require 3 to 6 months to regrow completely, and toenails require 12 to 18 months. (68). . If you have a postmenopausal woman with brittle nails that should alert you to check bone mineral density and when you actually treat the bone mineral density issue, the nails also should show up strong (69).

The diet and disease process plays a role in the content, strength, shape, and surface of the nail (69,70)) The hard, strong and flexible nail plate is influenced in growth by adequacy of keratins and cysteine rich high sulfur proteins. Flexibility is influenced and improves with increasing the water content (71). Most of the water content is in the middle nail with water making up 18% weight in the healthy nail, if the water content drops below 18% the nail is brittle or above 30% the nail is soft (72).

The common signs of brittle nails (Biotin, Protein insufficiency)(**73**), or brittle weak ragged cuticles (Protein, Zinc, Iron, Boron, Silica deficiencies) (73), thin brittle soft nails (iron, vitamin A, C, B6 sulfur)(68, 72, 74, 75), or Weak, thin, easily bendable, with frequent cracks or chips (calcium zinc, and essential fatty acids) are somewhat difficult to distinguish (73,74, 75) because of the definition of "weakness" so if you remove the adjective weak then you can begin to distinguish and sort strength. Ridging of the nail longitudinally or verticle (Protein, iron, folate, b complex)((76-79) or onychorrhexis- the longitudinal ridging and fissuring of the nail plate with brittleness (protein malabsorption via hypochlorhydria) might be predicted by diet intake and medical treatment with proton pump inhibitors.

Central ridging can be seen with peripheral artery disease but also with severe malnutrition (80). The surface of the nail can have beading (B vitamin Deficiencies)(81), or transverse ridging (protein). Beau's lines- deeper transverse ridging of multiple fingernails is seen with protein or zinc deficiency but also pellagra (niacin)(82,83 ,84).

The alteration of shape with beaking (protein or in osteoporosis), clubbing (protein malnutrition) or spooning of the nail (iron, copper, chromium and zinc, protein, cysteine or methionine)(70, 73,85,86)

Spots and lines on nails mainly involve protein or mineral insufficiency with a few exceptions (87). Muehrcke lines (banded nails, paired narrow white transverse bands) is seen with protein malnutrition

(86,88). Terrys nails (opaque white plate obscuring the lunula) can be caused by general malnutrition but also copper deficiency (89) while Lindsay half and half nails (20-60% of nail) can be seen in zinc deficiency (90). Nails with white opaque spots (leukonychia punctate) can be seen with anemia, hypoalbuminemia, zinc or niacin deficiencies (86). The toxicities of antimony, arsenic, fluoride, lead and thallium can also cause lesions which look very similar (91).. The leukonychia striae (white lines) can develop with hypoalbuminemia, selenium toxicity and deficiency (92). Brown nail- melanonychia have been identified in those suffering from B12 deficiency or malnutrition (7). The Summary follows in Table 13.

Table 13: Selected Nail Findings, Nutrient Associations and Other considerations [1]

Nail Findings	Nutrition-Associated Deficiency/Insufficiency (exceptions noted)	Other Considerations (partial listing)
Shape		
Clubbing (hypertrophy of soft tissue components of the digital pulp, hyperplasia of fibrovascular tissue at base of the nail, with local cyanosis) - Lovibond angle >180 (normal 160-165) - Schamroth's window test (diamond-shaped window between forefingers when nails are placed together is absent)	Protein (Kwashiorkor) Iodine (associated with cretinism) Vitamin A toxicity	Acquired clubbing - **General:** Kwashiorkor - **Cardiovascular:** congenital heart disease, endocarditis, arteriovenous malformation, aortic aneurysm - **Bronchopulmonary:** neoplasm, cystic fibrosis, chronic obstructive pulmonary disease (COPD), malignancy, asbestosis - **Gastrointestinal**: celiac, cirrhosis, crohns irritable bowel syndrome (IBD) (5%), bacillary or amoebic dysentery, liver disease, tropical sprue Thyrotoxicosis. - **Metabolic-** citrullinuria - **Poisoning**: phosphorus, arsenic, alcohol, mercury, beryllium, vitamin A
Koilonychia (spoon nails)- (more often local rather than systemic issues)	Protein, cystine or methionine. Iron, copper, chromium, selenium, zinc Riboflavin, niacin (pellagra), vitamin C	Wide differential: Physiologic - child Idiopathic (congenital) Acquired **Metabolic/endocrine:** Insulin resistance (IR), diabetes mellitus (DM), acromegaly, hemochromatosis, porphyria, dialysis, thyroid disease

		Dermatological: alopecia, areata, Darier's disease, lichen planus, psoriasis, Raynaud's syndrome, autoimmune (systemic lupus erythematus[SLE]), **Lifestyle:** walking barefoot or crawling can lead to only lower extremity koilonychias (benign) **Occupational:** Exposure to petroleum-based solvents, contact with oils, engineering industry **Infections:** syphilis, onychomychosis **Traumatic:** Toes of crawling children or rickshaw boys, carpel tunnel syndrome (hands) **Cardiovascular**: aortic stenosis, hemodialysis in chronic renal failure. **Transplacental**: PCB, PCDF exposure **Hereditary:** Plummer-Vinson syndrome (S/Sx: iron deficiency anemia, dysphagia, glossitis), Turners syndrome
Parrot-Beaked Nails	Protein	Cocaine-Nails triad, Hereditary
Color Changes or Pattern of Color (lines/spots)		
Terry nails **transverse leukonychia** (opaque white plate obscuring lunula extending within 0.5-3 mm from distal edge, all nails involved)	Malnutrition, Copper (genetic), Zinc (acrodermatitis enteropatica) Niacin (Pellagra)	- **Hepatic disorders:** failure, cirrhosis - DM, CHF, Psoriasis hyperthyroidism, Menke's syndrome, Renal failure (brown band at the junction of erythema and free edge)
Lindsay half and half nails: (proximal nail dull white obscuring lunula (20-60% of nail), distal nail pink-reddish)	Zinc, niacin (pellagra)	Chronic renal disease, Kawasaki disease, cirrhosis, Crohn's disease
Muehrcke lines (banded nails: paired narrow white transverse bands, parallel to lunula, transverse depigmentation), do not move with nail growth, fade with nail pressure	Protein, zinc	Hypoalbuminemia (many causes), cancer chemotherapies, unilateral changes following trauma, hemodialysis for renal failure, acrodermatitis enteropathica
Mees lines Transverse white lines that move with nail growth and do not fade with nail compression	Zinc, niacin	Sickle cell, heavy metal toxicity, arsenic, chemotherapy, thallium, nephrotic syndrome, Hodgkin's, CHF, leprosy, malaria, carbon monoxide poisoning
Leukonychia punctate (white opaque spots)	Protein (resultant hypoalbuminemia) zinc, niacin (pellagra) Anemia (all causes)	**Multiple Associations** **Toxicity:** antimony, arsenic, fluoride, lead, thallium, iron (hemochromatosis)

		Dermatologic: alopecia areata, exfoliative dermatitis, erythema multiforme, psoriasis **Infection or immune:** leprosy, ulcerative colitis **Metabolic:** gout, hemochromatosis, hypocalcemia **Occupational:** trauma
Leukonychia striata (transverse leukonychia)	Protein (hypoalbuminemia), Zinc, Selenium deficiency, Selenium toxicity, Severe hypocalcemia (all nails affected) Niacin (pellagra)	**Toxicity** selenium, arsenic Genetic: Zinc Finger Protein Deficiency- acrodermatitis enteropathica Darier's disease
Melanonychia, melanonychia striata, or longtitudinal melanonychia (brown lines)	Brown: Malnutrition, folate, B12, vitamin D	Black: - Normal variant in darker-skinned people - Splinter hemorrhages, nevi, malignant melanoma - Drugs: Adriamycin, cyclophosphamide Brown: - Drugs and dyes (i.e., potassium permanganate, dithranol, sulfonamides, cytoxins, acyclovir) - Endogenous: nevi, lentigines, Peutz-Jeghers, - Associated with genetically determined darker skin tones - Endocrinologic: Addison's, hemochromatosis, thyroid disease. - Low glutathione levels inhibiting tyrosinase. - Breast cancer, trauma Life cycle: pregnancy
Splinter hemorrhages [6](hemorrhage of the distal capillary loops)	Vitamin C	If the splinter hemorrhages are close to the lunula there is an association with systemic disease Subacute bacterial endocarditis, SLE, trichinosis, Pityriasis rubra pilaris, psoriasis, renal failure, peptic ulcer disease, malignancies, oral contraceptive use, pregnancy, trauma
Blue	Copper Excess	Cyanotic, Wilson's disease, tetracycling, 5 FU, Argyria

Red or Pink discoloration	malnutrition	Systemic Lupus, carbon monoxide poisoning (cherry red), Lichen Planus Polycythemia (Dark Red)40[2]
Brown-Gray Nails	B12	CVD, DM, Breast Cancer, Malignant melanoma, lichen planus, syphilis, hair dyes, varnish, formaldehyd[2]
Yellow Nails Nails stop growing, hard excessively curved side to side; diffuse pale yellow to dark yellow or green, affecting all 20 nails	Carotonemia Vitamin D	Amyloid, DM, Lymphedema, tetracycline (fluorescent), lung disease, bronchiectasis, COPD, cancers, RA, internal malignancies, thermal burns, Juandice (multiple causes)[82]
Absent Lunula Color	Malnutrition	Anemia, multiple myeloma, Raynauds, AIDS, hereditary, hypothyroid
Beau's lines: transverse ridging of multiple fingernails	Protein, malnutrition, vitamin A, C, niacin (pellagra), calcium (with associated hypocalcemia),iron, zinc	- **Systemic disease**: febrile illness - **Infection:** i.e.,typhus, rheumatic fever, diphtheria syphilis, malaria, gonorrhea, scarlet fever - **Autoimmune:** psoriasis - **Cardiovascular:** i.e., myocardial infarction (MI), peripheral vascular disease, Raynaud's, pulmonary embolism - **Endocrine**: DM, hypothyroidism, hypocalcemia, hypoparathyroidism - **Gastrointestinal:** diarrhea, cholitis, pancreatitis with malabsorption, sprue, severe gastritis, acrodermatitis enteropathica (zinc) - **Drugs reactions and toxicity:** i.e chemotherapeutics (cisplatin), retinoids, chronic alcoholism, arsenic toxicity - **Gynecological:** pregnancy, dysmenorrhea - **Local:** chronic skin disease-paronychia, eczema, psoriasis, pemphigus - **Renal:** Hemodialysis and renal failure **Structural:** Carpel tunnel syndrome

[1]© Institute for Functional Medicine. (93)

Muscle weakness due to sarcopenia as a result of protein under nutrition, absorption, or excessive loss can affect the ability to stand from a chair, walk 3 meters, turn around and walk back within 10 seconds. The get up and go test is strongly correlated to under nutrition and sarcopenia. The balance required to do this maneuver is influenced by the nutrients that affect peripheral sensation. The weakness and tibial tenderness associated with vitamin D inadequacy is well documented. Sarcopenia is associated with decreased protein intake, lack of anaerobic exercise or increased protein requirement with each passing decade beyond 50 years of age.

Peripheral Nerve Exam

The nutrition associated **peripheral nerve exam** has been well documented (63,94). Checking Reflexes, Balance, Vibration Sense, Monofilament Testing are all useful physical exam evaluations which can point to large fiber, small fiber, or mixed peripheral nerve associated nutritional impacts.

The large fibers which control the large flexors and extensors of the hips, knees, and lower leg are susceptible to thiamine, riboflavin, niacin, folate, vitamin B12 (63). The minerals copper, magnesium, calcium, potassium are necessary as cofactors in function. Undernutrition or malabsorption in any of these important nutrients affects nerve and muscle function. Proton pump inhibitor use is associated with malabsorption in many of the acid sensitive nutrients (protein, amino acids, magnesium, calcium, iron, manganese, folate B12)(63,95). The myelin sheath produced by the Schwann cell is susceptible to inflammation from many infectious, inflammatory, autoimmune, and nutritional causes. The myelin sheath requires adequacy of phospholipids, choline, vitamin D, antioxidants lipoic acid (63). Large fiber neuropathies are common in the setting of alcoholism and the toxicities of arsenic, mercury, lead, certain chemotherapeutics (cisplatin). Diminished vibratory sense as determined by a shorter latency to extinction is documented as a sensitive screen for large nerve neuropathy (63). It would lead the examiner to pursue further neurologic workup. The more rapid extinction of the symmetrical lower extremity and upper extremity vibration sense can be influenced by autoimmune disease (rheumatoid arthritis), degenerative arthritis (osteoarthritis) or most conditions of increased inflammation or toxicity. A diminished vibratory sense should trigger further nutritional and other root cause determinations (63).

Small nerve, minimally myelinated of unmyelinated nerves are susceptible to undernutrition of methyl folate, methyl cobalamin and pyridoxine 5 phosphate because of their essential antioxidant, mitochondrial and microvascular roles especially in the setting the hyperglycemia of type two diabetes. The monofilament testing is a standard of care clinical test which if the abnormal exam is neglected

predicts the severity of neuropathy 4 years later (96). In the mixed and small nerve neuropathy there has been recent success in stimulating new nerve growth in type 2 diabetics with focused medical nutrition therapy and instigating a metabolic correction promoting healthier nerve function (97, 98, 99)..

Hyporeflexia is seen when the large fiber associated nutrients (thiamine, cyanocobalamin, niacin, B6 are insufficient) although many other pathologies can cause hyporeflexia discussed in excellent reviews elsewhere (63).

Often nutrition insufficiency, deficiency or toxicity signs are seen in a pattern of phenotypic expression. It is the constellation of signs and symptoms that helps the clinician diagnose the root cause especially when an adequate timeline of the signs and symptoms and the diet, nutrition and lifestyle journal is provided by the patient. The nutrient insufficiencies associated with neurologic symptoms are found in Table 14. Once the constellation of signs, symptoms, and diet, nutrition and lifestyle patterns are identified the nutrients can be evaluated and treatment initiated as suggested in table 15.

Table 14: Nutrient insufficiency associated with neurologic symptoms

Nutrient	Neurologic Symptoms
Thiamin	Beriberi (dry, wet, infantile, gastrointestinal, bariatric), Wernicke encephalopathy or Korsakoff syndrome, encephalopathy, sensorimotor distal axonal peripheral neuropathy, calf cramping, muscle tenderness, burning feet, irritability.
Niacin	Peripheral neuropathy, encephalopathy
Pyridoxine	Peripheral neuropathy, pure sensory neuropathy in toxicity
Folate	Similar to cobalamin deficiency, peripheral neuropathy
Cobalamin	Myelopathy, peripheral neuropathy, neuropsychiatric, optic neuropathy, autonomic dysfunction
Vitamin D	Cutaneous hyperalgesia, bone pain of osteomalacia
Vitamin E	Spinocerebellar syndrome, peripheral neuropathy, opthalmoplegia
Copper	Myelopathy/myeloneuropathy
Protein	Muscle wasting, weakness, hypotonia, hyporeflexia

Adapted from: Kumar, N: Neurologic Presentations of Nutritional Deficiencies. Neurol Clin 28:107-170. 2010 (63).

Table 15: Nutrient Associated laboratory evaluation and interventions.

Nutrient	Laboratory	Intervention

Thiamin	Serum Thiamin, RBC transketolase, RBC thiamin diphosphate, Urinary Thiamin	Thiamin IV, IM, Oral
Niacin	Urinary excretion of methylated niacin metabolites	Nicotinic acid oral, IM
Pyridoxine	Plasma pyridoxal phosphate, P5P	Pyridoxine oral (P5P over Pyridoxine HCL if using higher doses)
Folate	Serum, RBC Folate, Plasma Hcy,…SNP- MTHFR, Urine Formiminoglutamic Acid	Methyl folate, folate
Cobalamin	Serum Cbl, MMA, plasma Hcy, CBC, MCV…	IM B12, Methyl cobalamin, Hydroxy cobalamin
Vitamin D	25 OH vitamin D, 1,25 DHCC, PTH, Ionized Ca	Appropriate Vitamin D dosing
Vitamin E	Serum Vitamin E ratio (a-tocopherol to sum serum cholesterol+TG)	Vitamin E oral or IM
Copper	Serum, RBC, Urinary Copper, serum ceruloplasmin, CBC (anemia, neutropenia, vacuolated myeloid precursors)	Oral elemental copper

As with all physical exam signs there are many similar pathological processes that can cause similar changes to the nutritional causes so it is important to not neglect the other possible considerations while focusing on the nutrition associated deficiency consideration.

The 10 minute functional nutrition oriented physical exam can be completed with accuracy and reproducibility. The ABCD of the functional nutrition evaluation takes more time with the collection of the anthropometrics most often by office staff, the biomarkers collected from the medical record or ordered by the clinician following the exam, and the diet, nutrition and lifestyle assessment recorded by the patient with the use of a 1 or 3 day diet record, 1 day diet recall, and the documentation of sleep, exercise, and stress evaluations. All of the modifiable lifestyle factors can influence nutrient needs and impact chronic health conditions.

The case below applies the ABCD of the functional nutrition evaluation in the clinic setting.

Case Presentation:

A 24 year old female with a 5 year history of weight loss following a biliopancreatic diversion with duodenal switch surgery for a weight of 450 lb prior to surgery. She had lost nearly 250 lb in the previous 5 years. She presents for the first time to clinic with intermittent vomiting, loose stools, weight gain of nearly 30 lb over the 4 weeks prior to being seen. For months she

was treating abdominal discomfort and pain for months with increasing amounts of acetaminophen and hydrocodone (10mg/325 mg). She had had 3 months of nutrition follow up after surgery was minimal because of provider and patient relocation. She was seeing different providers to assess her pain. She was a pediatric clinic medical assistant and was having more days off work due to the fatigue, difficulty with mentation. She was in generalized pain, complained of not being able to smell or taste. Her family complained of her hallucinations and mental status changes. She complained of swelling all over (gained 20 lb. in 2.5 weeks). A head to toe physical exam revealed many nutrient insufficiency signs which led to further history, laboratory and aggressive therapeutic nutrition interventions as an inpatient in the 12 hours following the initial clinic visit. The case is presented in the ABCD nutrition evaluation format.

Anthropometrics: Oximetry 94%, RR 16, HR: 110, BP 96/40, Weight 249, Height 5'7" BMI: 39 (73) Waist > Hip (44"> 43") W/H: 1.02 Android Obese, appeared sarcopenic. Orthostatic hypotension with HR increasing to 140 and blood pressure dropping to 74/-- with standing.

Biomarkers: The laboratory was collected after the physical exam, assessment of need for hospitalization and was resulted within 12 hours of admission (Box 3). It is re-organized in the functional nutrition Protein, Fat, Carbohydrate, Mineral, Vitamin, Phytonutrient format to better see the macronutrient and micronutrient abnormalities (Box 4)

Box 3: Admission Laboratory – Abnormal Blood Chemistries and Complete Blood Count

Glucose	101	mg/dL	70-99	mg/dL
Sodium	124	mEq/L	136-145	mEq/L
Potassium	3.3	mmol/L	3.5-5.0	mEq/L
Calcium	7.5	mg/dL	8.2-10.5	mg/kL
Calcium-ionized	0.92	mmol/L	1.05-1.3	mmol/L
Magnesium	1.6	mg/dL	1.6-2.2	mg/dL
Cholesterol	58	mg/dL	<200	mg/dL
LDL cholesterol	9	mg/dL	<100	mg/dL
HDL cholesterol	32	mg/dL	>50	mg/dL
Triglycerides	49	mg/dL	<150	mg/dL
Protein (total)	4.2	g/dL	6-8.5	g/dL
Albumin	2.0	g/dL	3.5-5	g/dL
Globulin	2.2	g/dL	2.0-3.5	g/dL
Prealbumin	7.0	mg/dL	20-40	mg/dL
Bilirubin	3.2	mg/dL	0.3-1.5	mg/dL
Alanine aminotransferase	45	U/L	10-35	U/L
Amylase	<5	U/L	30-70	U/L
Iron[1]	85	mcg/dl	30-165	mcg/dL
Transferrin	60	mg/dL	220-430	mg/dL
Total Iron Binding	84	ug/dL	250-370	ug/dL
CBC				
WBC ($X10^3$)	3.8	cells/mm^3	4.3-10.8	cells/mm^3
RBC ($X10^6$)	2.34	cells/mm^3	4.2-5.9	cells/uL
Hemoglobin	8.6	g/dL	12-16	g/dL
Hematocrit	28.9	%	37-48	%
Mean Corpuscular Volume	110.6	um^3	80-100	um^3
Red cell Distribution Width	14.1	%	11.6-14.5	%
Platelet ($X10^3$	63	/mm^3	150-450	/mm^3
Neutrophils	76.4	%	54-65	%
Lymphocytes	13.4	%	25-40	%
Macrocytosis	2+		0	
Reticulocyte Count	2.0	%	0.5-1.5	%
Vitamin D3 (25 OH)	7	ng/ml	>30	ng/ml
Parathyroid Hormone	139	pg/mL	10-55	pg/mL
Zinc	0.3	mg/dL	60-130	mg/dL
Thiamine	40	nmol/L	74-222	nmol/L
Riboflavin	<2	mcg/L	2-19	mcg/L
Vitamin K	<0.03	ng/mL	0.2-3.2	ng/mL
Ammonia	146	mcg/dL	15-45	mcg/dL
Thyroid Stimulating Hormone	7.22	mIU/L	0.4-4.0	mIU/L

[1]Serum Iron levels though normal, were included since the other markers of iron status were abnormal.

Box 4: Abnormal Blood Chemistries Reorganized in the [1]Functional Medicine Macronutrient (Protein, Fats, Carbohydrate) and Micronutrient (Minerals, Vitamins, Phytonutrient) Order.

Protein					
	Protein (total)	4.2	g/dL	6-8.5	g/dL
	Albumin	2.0	g/dL	3.5-5	g/dL
	Globulin	2.2	g/dL	2.0-3.5	g/dL
	Prealbumin	7.0	mg/dL	20-40	mg/dL
	Alanine aminotransferase	45	U/L	10-35	U/L
	Ammonia	146	mcg/dL	15-45	mcg/dL
Fat					
	Cholesterol	58	mg/dL	<200	mg/dL
	LDL cholesterol	9	mg/dL	<100	mg/dL
	HDL cholesterol	32	mg/dL	>50	mg/dL
	Triglycerides	49	mg/dL	<150	mg/dL
Carbohydrate					
	Glucose	101	mg/dL	70-99	mg/dL
Minerals					
	Sodium	124	mEq/L	136-145	mEq/L
	Potassium	3.3	mmol/L	3.5-5.0	mEq/L
	Calcium	7.5	mg/dL	8.2-10.5	mg/kL
	Calcium-ionized	0.92	mmol/L	1.05-1.3	mmol/L
	Magnesium	1.6	mg/dL	1.6-2.2	mg/dL
	Iron[1]	85	mcg/dl	30-165	mcg/dL
	Transferrin	60	mg/dL	220-430	mg/dL
	Total Iron Binding	84	ug/dL	250-370	ug/dL
	Zinc	0.3	mg/dL	60-130	mg/d
	Amylase	<5	U/L	30-70	U/L
	WBC ($X10^3$)	3.8	cells/mm^3	4.3-10.8	cells/mm^3
	RBC ($X10^6$)	2.34	cells/mm^3	4.2-5.9	cells/uL
	Red cell Distribution Width	14.1	%	11.6-14.5	%
	Neutrophils	76.4	%	54-65	%
	Lymphocytes	13.4	%	25-40	%
Vitamins					
	Hemoglobin	8.6	g/dL	12-16	g/dL
	Hematocrit	28.9	%	37-48	%
	Mean Corpuscular Volume	110.6	um^3	80-100	um^3
	Macrocytosis	2+		0	
	Platelet ($X10^3$	63	/mm^3	150-450	/mm^3
	Reticulocyte Count[1]	2.0	%	0.5-1.5	%
	Vitamin D3 (25 OH)	7	ng/ml	>30	ng/ml
	Parathyroid Hormone	139	pg/mL	10-55	pg/mL
	Thiamine	40	nmol/L	74-222	nmol/L
	Riboflavin	<2	mcg/L	2-19	mcg/L
	B12	98	pg/mL	160-900	pg/mL
	Vitamin K	<0.03	ng/mL	0.2-3.2	ng/mL
Phytonutrients			None Evaluated		

[1]Institute for Functional Medicine ABCD Functional Nutrition Evaluation 2011 fxmed.org.[2] Note the CBC with Differential is dispersed into the different areas taking into account history.

The physical exam was completed before the laboratory were drawn. But in this order of the ABCD you might predict, seeing the laboratory what you might see on physical exam. So often in clinical practice, depending on the setting, the most recent laboratory are presented to the most current clinician seeing the patient. The laboratory are part of the history. The nutrition oriented physical exam predicts the laboratory and the diet, nutrition and lifestyle. Much the same way the diet, nutrition and lifestyle can forecast what the clinician will see on the laboratory and physical exam.

The abnormalities are across all macronutrients and micronutrient categories measured. Bariatric surgery has one of three results. The techniques either increase malabsorption (by bypassing or shortening nutrient absorptive surface area), limit volume (removing, sleaving, ballooning, cuffing or artificially introducing a space filling "bezoar"), or a combination of the two.

Clinical Exam: She looked ill. She was vomiting with slurred speech. She was mildly photophobic and accompanied by her very attentive Mother. She was pale, her skin was sallow (Figure 1).

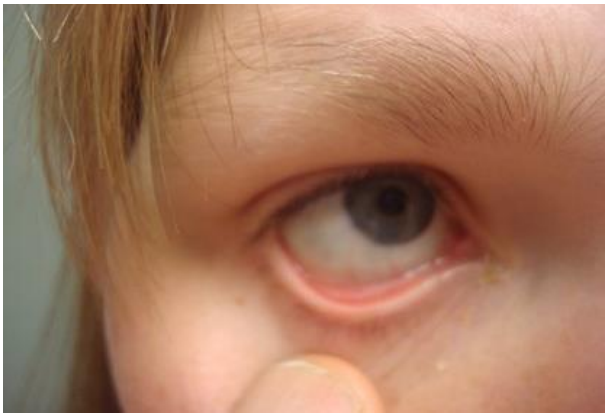


Figure 2: Pallor, Subconjunctival Pallor, Lateral Eyebrow Loss

Her speech was slow. Starting from the top of her head- hair was thinning on the scalp and was very fine. Her eyebrows were missing the lateral 1/3rd. (Figure 2) The lateral corner of her eyes were irritated. Her conjunctiva showed subconjunctival pallor. Her conjunctiva were dry. She

had rhinorrhea her turbinate's were swollen. The angles of her mouth showed angular stomatitis, her lips had cheilitis. (Picture 3a, 3b) Her lips were pale, the tongue was burning with mild glossitis, and showed atrophic taste buds. (Figure 4a and 4b) The gums were inflamed and the teeth were in poor repair with demineralized enamel, periodontal disease and untreated teeth fractures and infection (Figures 5a and 5b). She had significant hepatic/infected fetor.

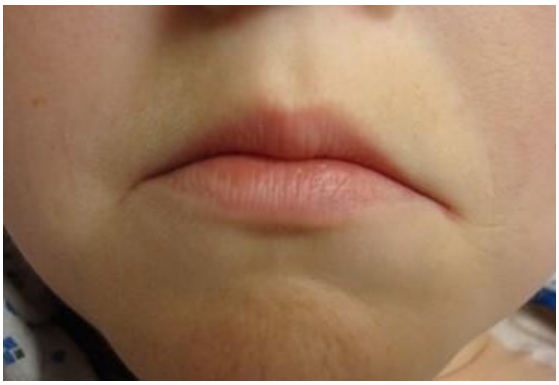


Figure 3 a Angular Stomatitis hinted

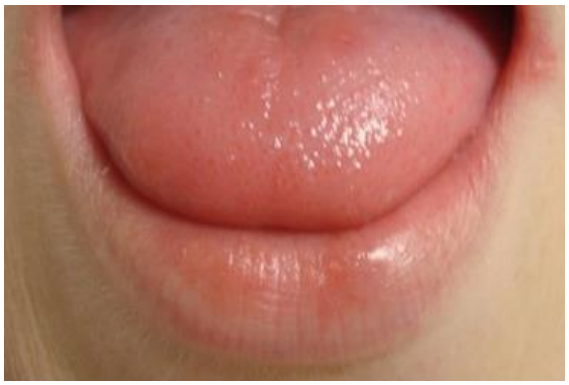


Figure 3b Mild cracking of lips-Cheilitis

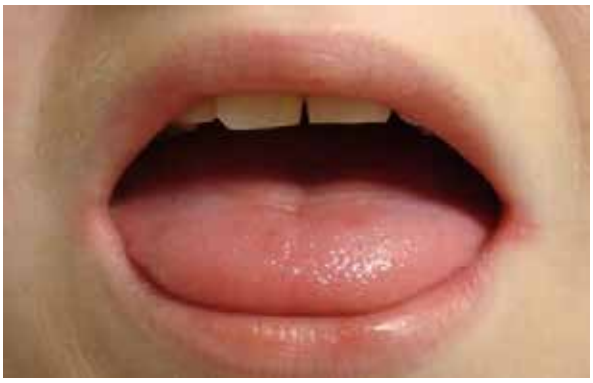


Figure 4a: Note Pale lips, smoothness of tongue

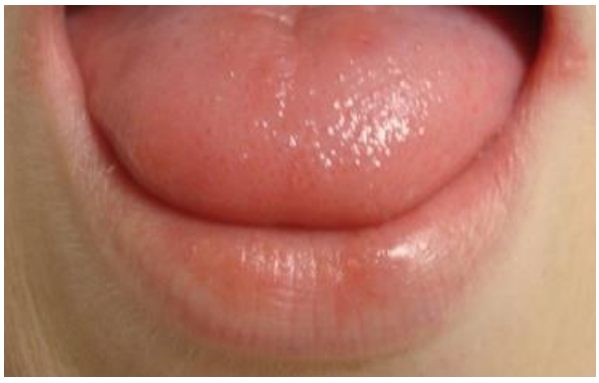


Figure 4b: Taste bud atrophy, mild glossitis

With some contribution from the amount of oral dysbiosis and acidity suggested by the tooth plaque buildup at her tooth gum borders. She had gingivitis (Figure 6) Dental hygeine had been difficult for her. There were no mucosal erosions on the side of her mouth. Her parotid glands were not enlarged.

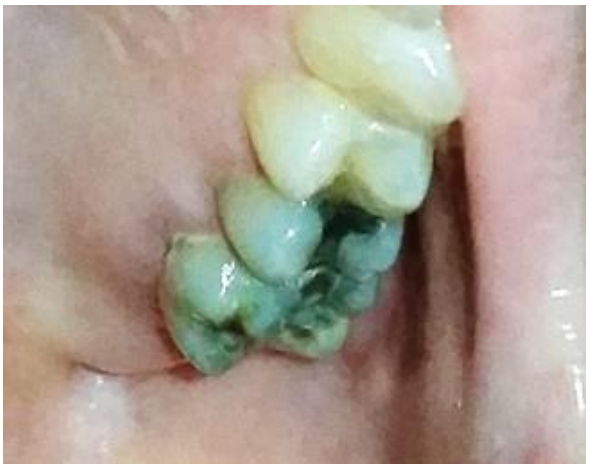


Figure 5a: Demineralized teeth, poor restorations Silver amalgum, Infection.

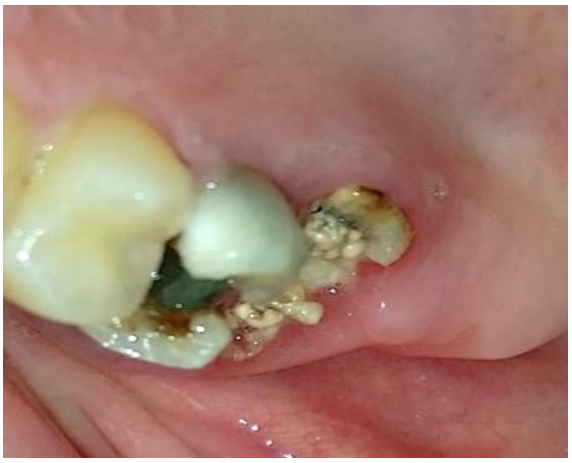


Figure 5b: fractured teeth, periodontal disease Fractured resoration

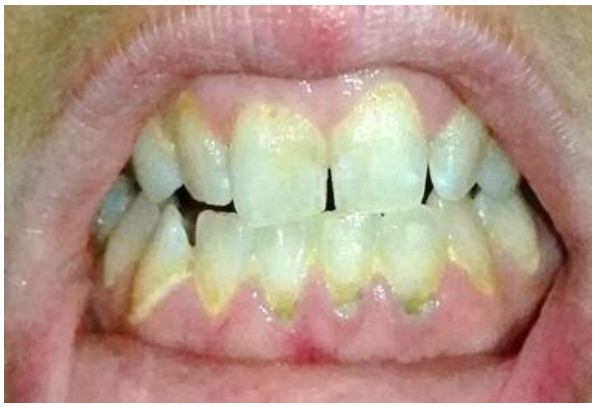


Figure 6: Gingivitis, Plaquing, Enamel Erosion

Cardiac exam revealed tachycardia with orthostasis, a slightly lateralized point of maximal impact (PMI). Basilar rales bilaterally. The abdomens midline scar from her abdominal surgery has some superficial breakdown (Picture 7), a wound that had been present for a number of months. Her muscular skeletal exam offered muscle weakness, hip flexor weakness.

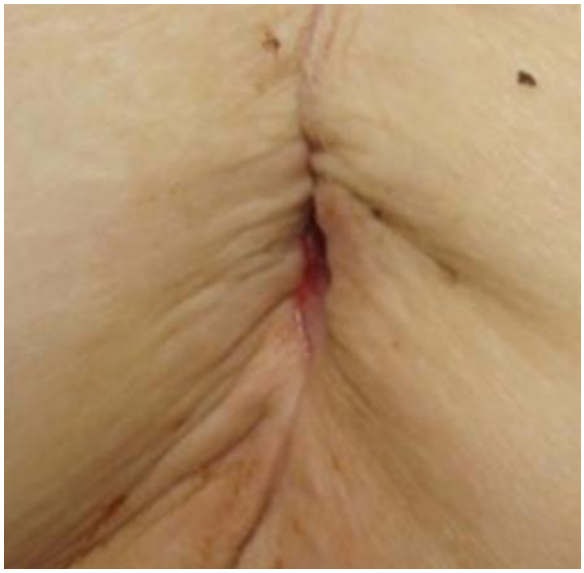


Figure 7: Chronic Wound at Midline Abdominal incision 2 X 1 X 1 cm

Musculoskeletal exam: 16/18 fibromyalgia trigger points positive, anterio tibial spine tenderness with mild pressure, weak hip flexors uncertain gait, walked with steadying support of a family member. She could not walk without an assist.

Neurologic exam revealed decreased smell, slowed reflexes, ocular horizontal bilateral nystagmus and hippus. Positive Romberg. Could not balance without holding on with a wide base. She had 3 beat asterixis, variable monofilament testing, proprioception was okay bilaterally big toes but she had decreased 128 hz tuning fork vibratory sense symmetric feet first and fifth digits > than hands (first and 5^{th} digits).

The nails of the hands and feet had leukonychia (Figure 8). The nails were thin and pliable. There was no paronychia or pealing of the skin at the finger ends suggestive of essential fatty acid insufficiency. There was no koilonychia.

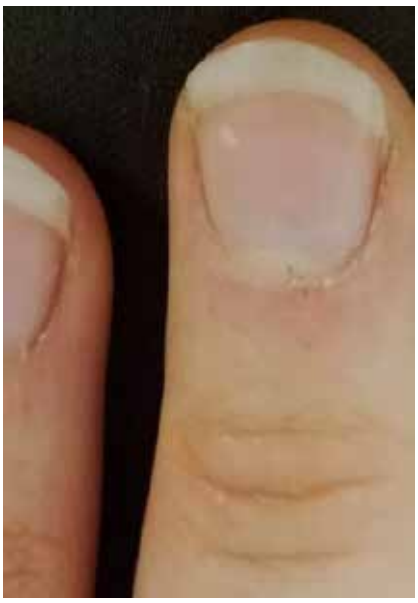
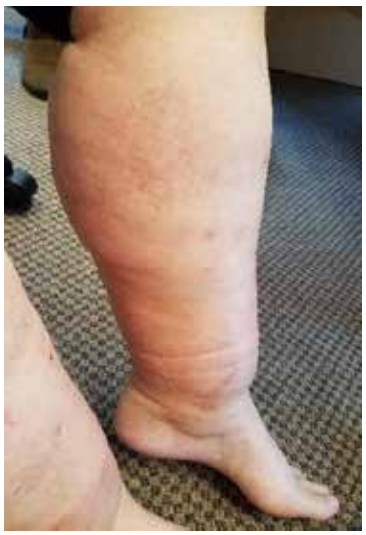
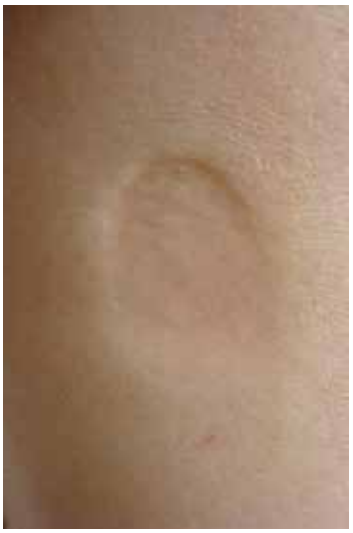


Figure 8: Leukonychia punctate

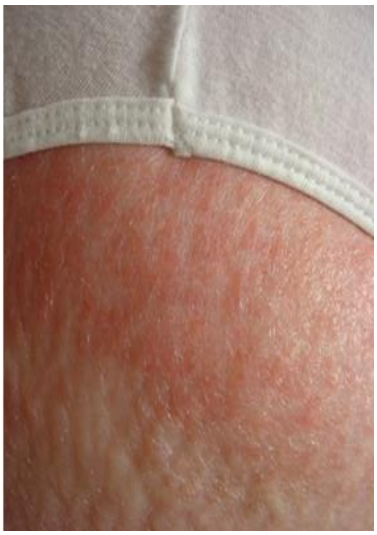
The skin had mild hyperkeratosis pilari on the back of the arms, skin was xerotic. She had edema of her soft tissue of her ankles and inflamed pitting edema of her legs and panniculitis at the patty line of the lateral thighs (Picture 9a, 9b, 9c).



9a: Lower extremity edema



9b: Edema Lateral Thigh



9c: Inflammed Adipose Thigh

Other: Stool and emesis: guaiac negative. UA: >1.030 and dip negative except ketones. No glucose or protein.

<u>Diet, Nutrition and Lifestyle</u>:

Her sleep is 14-18 hours a day and often disoriented. Movement: Walking less than a ½ mile a day. No routine exercise. The 24 hour diet recall is from her mother and notes the following.

Breakfast: white rice (1/2 cu), two eggs, apple juice 1 cup. Vomited 30 minutes later
Lunch: Mashed potato (1/4 cup) and two table spoons of butter
Ice tea (one quart in the afternoon)
Dinner: ¼ cups of peas, 1 egg, ice tea and sugar. 1 hour later vomited.
"She has eaten poorly for the last month"

Integrating Laboratory and Physical Exam, seeing the connections:

In the nutrition evaluation, seeing the connections between the symptoms and the biomarkers and clinical exam is the next step in assessment and pattern recognition. Figures 10 a, 10b, and 10c help link the symptoms and findings to some of the laboratory. These are functional points of connection between the history, signs and symptoms, biomarkers and the clinical exam.

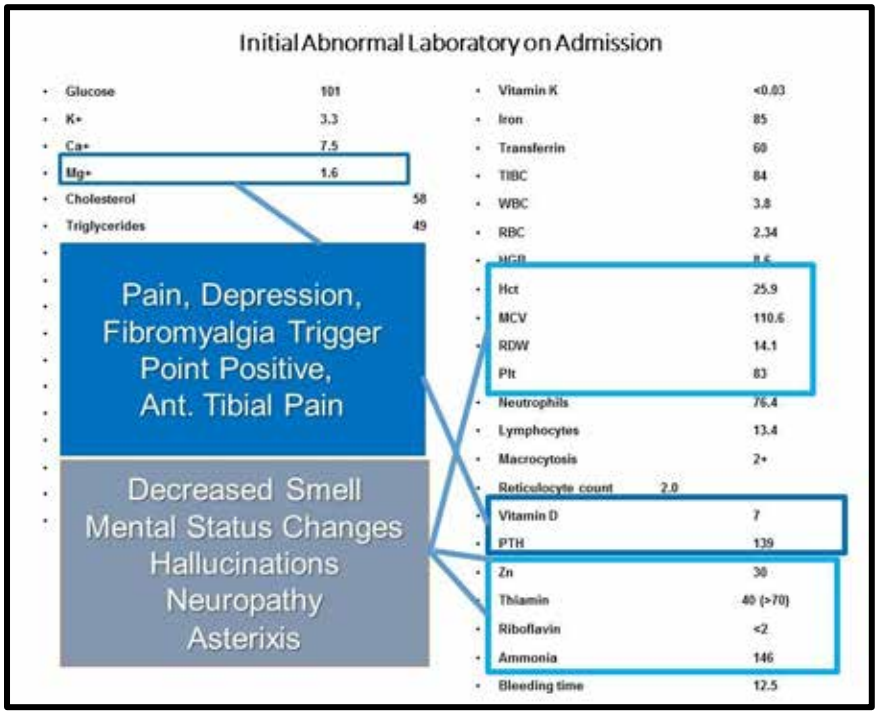


Figure 10a: Functional Connections Between Symptoms, Signs, and Biomarkers

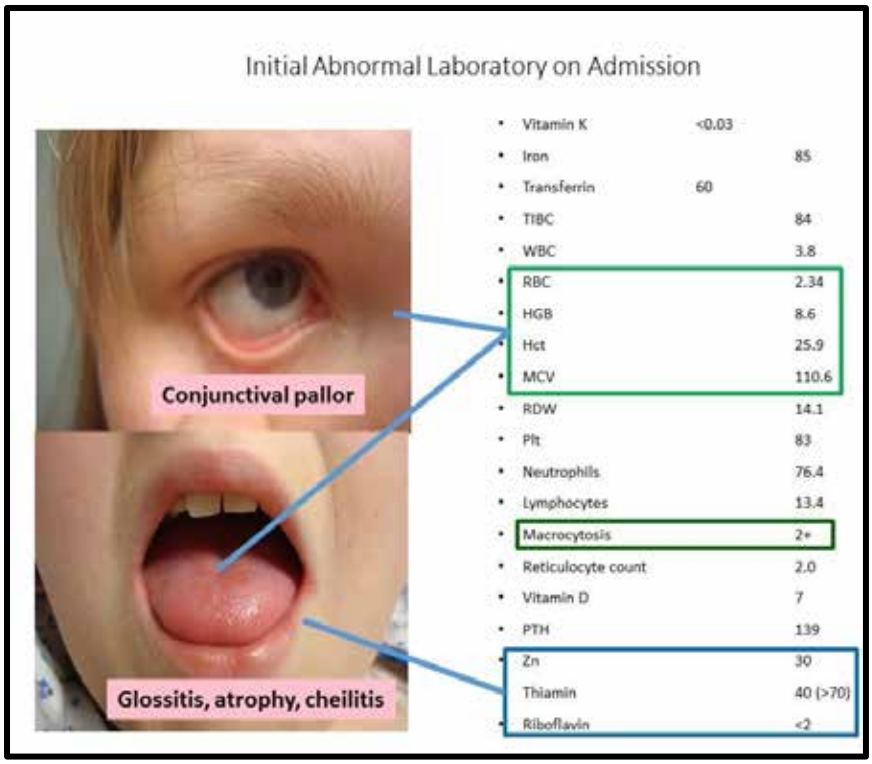


Figure 10b: Functional Connections between Biomarkers and Clinical Exam

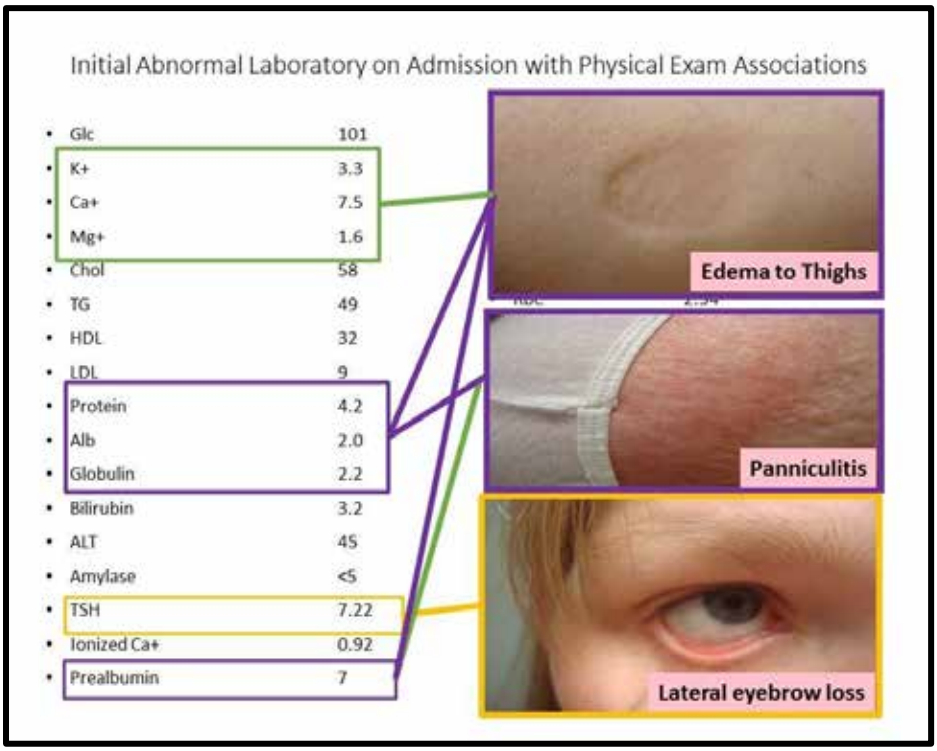


Figure 10c: Functional Connections between Biomarkers and Clinical Exam

Admitting Diagnosis:

1. Toxic Encephalopathy with Chronic malnutrition following aggressive bariatric surgery with probable liver failure worsened by her malnutrition and inadequate liver biotransformation pathways in the setting of acetaminophen and codeine overuse. Acetaminophen levels when drawn were not elevated on admission..
2. Volume depletion with possible post bariatric high output failure due to her thiamin deficiency. Macrocytic anemia secondary to B12 deficiency.
3. Multifactorial peripheral neuropathy, sarcopenia and cerebellar dysfunction (Romberg) secondary to the above.
4. Sarcopenia
5. Hypothyroid with secondary effects of low zinc, low tyrosine, probable low iodine
6. Thrombocytopenia- nutritional
7. Insulin resistance

Upon Admission to the Hospital: Further documentation was presented that indicated that the bariatric surgery had left between a 50-90 cm section of small intestine functionally intact. The effect was short bowel syndrome, and marked malnutrition and liver failure in the setting of the acetaminophen opiate pain medication and inadequacy of her imbalanced biotransformation pathways. She also was diagnosed with blind loop syndrome. Note the ammonia level which accounted for her hallucinations. She was initially placed on the liver transplant list but needed to be "tuned up" for transfer. It had been over 5 years since her initial bariatric surgery and unfortunately she was not followed closely.

Nutritionally Monitoring Bariatric Surgery Patients

As a primary care clinician the ABCD of functional nutrition evaluation should be considered at least twice a year for the bariatric surgery patient. The concern of developing nutrition insufficiency is greater depending on the procedures completed (100,101). Table 16 summarizes the type of bariatric surgery and the necessary nutrition monitoring following the procedure. Consistant follow up is a necessity. The nutrition intervention often is more than just a multivitamin and it has to be individualized and precise (102). The simple screening for neuropathy that is outlined here helps the clinician uncover the neuropathy. Neuropathy occurs

commonly in the post bariatric patient with different nutrient etiologies depending on where the bypassing or altering of normal anatomy was preformed (103-108). The Metabolic and nutritional complications of bariatric surgery are wide ranging and the astute eye and ear of the clinician will help address and likely reverse morbidity. The patterns of neuropathy or other nutriional deficiencies constellations can be mixed. And with the increased frequency of the surgeries occuring we will likely need to become more familiar with beriberi, copper and zinc deficiency and acquired actrodermatitis enterohepatica and wernickes encephalopathy in the young.(109-114).

Table:16 Nutrient and Biomarker associated with Primary Signs and Symptoms of deficiency following the listed bariatric surgical procedures.

Nutrient	Biomarker[1]	Primary Symptoms/signs	[2]Procedures
Protein	Serum Albumin, plasma amino acids,	Edema, excessive alopecia, poor wound healing, sarcopenia, neurotransmitter inadequacy	AGB,VSG,RYGB, BPD, BPD-DS
Fat	Serum Lipids, Oxidized LDL, Lipid Subfractions, RBC EFA or Omega 6/Omega 3/Arachadonic acid ratio	Xerosis, Hyperkeratosis pilari, slow to poor wound healing, Finish	RYGB BPD BPD-DS
Carbohydrate	Glucose, insulin, hemoglobin A1c	Acanthosis nigricans, increased skin tags, peripheral neuropathy with decreased peripheral monofilament sensitivity	AGB,VSG,RYGB, BPD, BPD-DS
Minerals			
Iron	Serum ferritin, TIBC, CBC	Microcytic anemia, fatigue, pallor, koilonychia, glossitis	VSG, RYGB, BDP-DS
Magnesium	Serum Mg, RBC Mg (if symptomatic)	Muscle cramping, increased premature ventricular contractions, atrial fibrillation	AGB,VSG,RYGB, BPD, BPD-DS
Calcium	PTH, Ionized calcium, 24 hour urine calcium	Fatigue, bone pain,	AGB RYGB, BPD-DS
Zinc	Serum zinc	Increased night vision issues, decreased smell, glossitis, periorificial rash, seborrhea, leukonychea	RYGB, BPD, BPD-DS
Copper	Serum Copper	Anemia, peripheral neuropathy	RYGB, BPD, BPD-DS
Selenium	Serum Selenium	Leukonychia striae, edema	RYGB, BPD, BPD-DS
Vitamins			
Thiamin- B1	Whole blood Thiamin	Ophthalmoplegia, nystagmus, ataxia, rapid vision loss, Wernicke encephalopathy, Peripheral neuropathy, edema	AGB,VSG,RYGB, BPD, BPD-DS

Niacin- B3	Plasma niacin	Dermatitis, diarrhea, memory issues, edema	AGB,VSG,RYGB, BPD, BPD-DS
Folate	Red Blood Cell Folate Methyl Folate, Homocysteine	Megaloblastic Anemia, glossitis, anxiety or depression, peripheral neuropathy	AGB,VSG,RYGB, BPD, BPD-DS
B12	Serum B12, methyl malonic acid, MCV, transcobalamin	Anemia, Neuropathy, memory loss, visual loss, Darkening of the skin over joint surfaces,	RYGB, BPD-DS
Vitamin D	25 OH vitamin D, calcium, phosphorus, parathyroid hormone	Decreased bone density, secondary hyperparathyroidism, tender anterior tibia, increased inflammation, affective disorder, increased hypertension, insulin resistance	BPD, BPD-DS
Vitamin A	Plasma Retinol	Reduced night vision, visual impairment, hyperkeratosis pilari, poor immune function	BPD, BPD-DS
Vitamin E	Plasma alpha tocopherol	Neuropathy, ataxia, visual changes	BPD, BPD-DS
Vitamin K	Prothrombin Time, serum uncarboxylated osteocalcin,	Bleeding, easy bruising,	BPD, BPD-DS

[1] Some of the biomarkers (lipids) are more elaborately completed in our clinic as we are assessing the inflammatory lipoprotein characteristics. [2]Procedure type: AGB- adjustable gastric band, VSG-vertical sleeve gastrectomy, RYGB- Roux-en-Y Gastric Bypass, BPD-Biliopancreatic Diversion, BPD-DSBiliopancreatic Diversion-Duodenal Switch

Hospital Course

Appreciating the multiple issues led to a combination of TPN with augmented medical nutrition therapy orally once her vomiting was controlled. Identification of IgE reactions to casein and eggs changed diet options to a modified elimination diet.

The illustration of her surgery brought to the hospital by her father notes the surgical technique. The effect was short bowel syndrome, and marked malnutrition and liver failure in the setting of the pain medication and her altered biotransformation pathways. Note the ammonia level which accounted for her hallucinations.

1) Acute Treatment of encephalopathy, nutrition deficiencies using IV supplementation 3 weeks. Antibiotic (neomycin, lactulose was initiated)
2) Address acetaminophen exposure with presumed inadequacy of n-acetyl cysteine and glutathione (nebulized n-acetyl-cysteine and glutathione)
3) Rapid addition of enteral feeding using aggressive addressing of Phase 1, Phase 2 biotransformation requirements and antioxidants (water, fat soluble) food/nutrient.
4) Utilize smoothies of medical foods, and vegetables, berries. After 1.5 weeks when vomiting stopped, and became less encephalopathic.
5) Remove Foods driving gut permeability issues, Gel Coombs reactions type 1 (IgE) and 3 (IgG) immunity reaction (casein, egg).
6) Address insulin resistance, inflammatory, membrane permeability and biotransformation issues

7) Combination Elimination (Casein, Egg) and Low Glycemic Diet
8) Promote Membrane Integrity by addressing vitamin D, A, and EFA insufficiencies. Nutritional Deficiencies
9) Address Insulin Resistance issues with Diet
10) Increased EFA, Pancreatic enzymes, Fiber, Fluid Intake
11) Gastroenterology, Neurology, Physical Therapy, Surgery Consults

After 5 weeks as an inpatient the patient was transferred for further revision of her previous procedure which changed the anastomosis of her bypass and blind loop to gain additional surface area for nutrient absorption. A sketch of the revision of her original surgery adding an additional intestinal absorptive lumen extending it to 140 cm (Figure 11). Recognizing the normal areas of nutrient absorption (Table 17). An understanding of her initial surgery, the resultant short bowel syndrome, blind loop syndrome with gradual multimineral, multivitamin, and macronutrient malabsorption the findings on her admission laboratory and clinical exam could almost be predicted. Location, location, location as in real estate it is in bowel revision surgery, what normal absorptive surfaces are being taken "off-line".

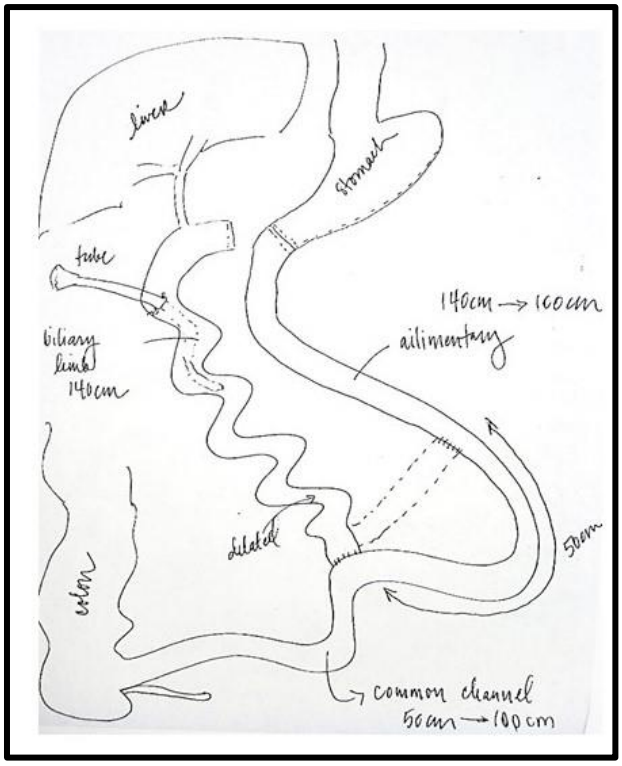


Figure 11: Post revision. Dilation of the blind loop to improve Drainage of the biliary limb, Increasing the length of the common channel

Table 17: Location of Normal Nutrient Absorption

Location	Nutrient Absorption
Stomach	Alcohol
Duodenum	Chloride, SO_4^-, Iron, Calcium, Magnesium, Zinc, glucose, galactose, fructose
Jejunum	Amino acids, dipeptides, tripeptides, vitamin C,, Thiamin, Riboflavin, Pyridoxine, Biotin, Pantothenic acid, Folic Acid, Vitamin A,D,E,K, Fat, Cholesterol
Ileum	Bile Salts, Vitamin B12
Colon	Sodium, Potassium, Vitamin K from bacterial action, Water

As a result of her aggressive enteral and intravenous nutritional resuscitation and her surgical revision with additional close evaluation she improved. Her thyroid was supplemented with levoxyl initially, and her requirement continued to drop as she became more replete of zinc, selenium, and iodine. She has had enough improvement in her condition and resolution of her liver failure. She had enough improvement in her nutritional status that she returned home with ongoing monitoring of her nutritional status, counseling, nutritional supplementation orally, sublingually and with monthly intravenous multi-minerals and vitamins. She has been followed for over 5 years.

Conclusion:

This review of the ABCD of the Functional Nutrition Evaluation and used the example of a post bariatric surgery patient to highlight clinical signs and symptoms of nutrition inadequacy. The functional nutrition evaluation can be applied precisely and with reproducibility in the primary care clinic using a team approach to capture and document the nutritional status of every patient with chronic disease. By using this method the appreciation of nutritional insufficiency and deficiency affecting the long term health of each patient can be uncovered and treated with more proficiency.

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Rogue Valley Institutional Review Board approved the use of the deidentified patient history and clinical course. Approved December 2014.

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.P. Michael Stone MD, MS, IFM-CP started as a WIC nutrition counselor, has completed nutrition assessment of children at the headwaters of the river Kwai, and helped start nutrition services in American Hospitals. He

teaches workshops and lectures internationally on the nutrition oriented physical exam to help clinicians see more.

He received his MD at University of Washington Seattle and His Graduate Degree in Nutrition at Washington State University. He completed Residency and Fellowship at UCLA Ventura in Family Medicine. Additional Certification in Functional Medicine.

He is the director of Ashland Comprehensive Family Medicine –Stone Medical. He continues as faculty for the Institute for Functional Medicine and is involved in their nutrition education curriculum and N-sight projects.

mstone@ashlandmd.com

AKIL PALANISAMY
MD

INTEGRATING AYURVEDA, FUNCTIONAL MEDICINE, & MODERN SCIENCE – THE PALEOVEDIC APPROACH

We know that "one size fits all" doesn't work in nutrition, but figuring out the diet that is best for your patients is much harder. To help individualize diets for people I rely on Ayurveda, the five-thousand-year-old traditional medical system from India. In this chapter, I integrate the core principles of Paleo with the science of Ayurveda to help you determine the optimal, individualized diet for your patients—the Paleovedic Diet.

As a Harvard-trained M.D., I integrate a strong scientific background in biochemistry and Western medicine with training in Ayurveda and study of ancestral societies around the globe. This unique background enables me to seamlessly blend Paleo and Ayurvedic principles with the latest research in nutrition, food science, and medicine. I provide definitive, practical health information based on cutting-edge research and clinical experience.

In my practice, I incorporate an integrative medicine modality known as functional medicine, which uses specialized lab testing to diagnose and treat imbalances in the function of different organ systems. My approach has benefited thousands of patients who have utilized this approach to improve energy, lose weight, and reverse disease. The Paleovedic Diet provides practical guidelines on how to integrate the seemingly opposed worlds of ancient wisdom and modern science to create a customized nutrition plan for optimal health.

The Paleovedic Approach

I have seen how people following a Paleo diet can inadvertently hurt themselves by not tailoring it to their Ayurvedic body type. Many people do not know that they need to customize Paleo for optimal results. Using Ayurveda to inform and customize a diet that is right for your constitution is the essence of the Paleovedic approach. Here are three examples that illustrate this.

Case—Excess Vata

Jessica was a thirty-eight-year-old mother of two who came to see me for chronic constipation, fatigue, and anxiety. She was having small, hard bowel movements every three to four days, and disabling anxiety that made it hard for her to function at work. She had switched to a Paleo-type diet a year before seeing me, and initially felt more energy, but then did not notice any improvement in symptoms. Her diet consisted of large salads daily for lunch and cold cuts or smoked salmon with vegetables for dinner. Her doctors had told her that drinking more water would help with her bowel movements, so she was drinking large quantities of ice water every day. She did not know why she was not feeling better despite avoiding all grains, eliminating gluten, and following a Paleo diet.

After getting her history and examining her, I determined that she had an excess of vata and a very weak Agni or digestive fire. Her daily salads and cold foods were in fact further increasing her vata and exacerbating her condition. A common symptom of elevated vata is anxiety, which was her most bothersome symptom. Her two water bottles per day filled with iced water were in fact depressing her Agni and further reducing her capacity to digest food effectively.

I had her change her diet to eliminate all raw foods such as salads and all cold foods. She began eating cooked vegetables, soups, and warm meat dishes instead of cold cuts. I told her to drink only warm water or room temperature water and avoid ice. I instructed her to incorporate more spices into her cooking such as turmeric, cumin, coriander, and ginger to help stimulate her digestive fire and boost her metabolism. I encouraged her to

use sesame oil, which is considered in Ayurveda to have medicinal properties for balancing vata dosha, in her everyday cooking.

Within two months, she reported that her chronic constipation had resolved. She was surprised to report that her anxiety had improved dramatically. Her energy, while not yet optimal, had increased to about 70 percent of normal. I reassured her that as she continued to balance her vata and strengthen her Agni, thereby improving her digestive capacity, her energy levels would return to normal.

Case—Excess Pitta

Russell was a thirty-two-year-old male with severe ulcerative colitis, an autoimmune disease in which the body attacked the colon, leading to inflammation and loose stools. Despite being on the anti-inflammatory drug mesalamine, he still had elevated levels of C-reactive protein (CRP), a blood marker that indicated persistent inflammation. He was having eight to ten bowel movements per day with blood and mucus in his stools. He had been on a strict Paleo diet for six months, and his diet consisted of eggs, red meat, fermented dairy products, sauerkraut, and a limited number of vegetables.

After talking to him I realized that he had excess pitta, which was manifesting as inflammation in his colon, bloody diarrhea, and a frequent sour taste in his mouth. I realized that the foods that he was eating were all very hot in terms of their qualities and properties. While meat, eggs, and dairy products are wonderful nutrient-dense foods, in his case they were actually not beneficial because of their heating properties.

I had him start a modified Paleovedic Diet without meat, eggs, or dairy products. For three weeks he consumed bitter greens such as arugula, spinach, and kale, which have very cooling energetic properties. I also encouraged him to eat kitcheri once a day, which he was open to doing even though it contained rice (which is not strictly Paleo by some definitions), because of its soothing effect on the gut. I encouraged him to liberally incorporate turmeric into his cooking. I suggested that he temporarily reduce consumption of sour foods such as sauerkraut because they can potentially aggravate pitta. Lastly, I suggested that he take a supplement containing Boswellia serrata, an herb that balances pitta and is often used to reduce inflammation.

At a three month follow-up visit, he reported that his symptoms had improved by 80 percent. He was having two to three bowel movements per day and there was no blood or mucus present in his stool. He was no longer experiencing the sour taste in his mouth. After continuing to work with me over the next year, we were able to wean him off the mesalamine and control his symptoms using diet and select supplements.

Case—Excess Kapha

Rhonda was a fifty-four-year-old female who was struggling with obesity, fatigue, and a sluggish thyroid. Her TSH (thyroid stimulating hormone) had been hovering just outside the optimal range for many years. She had a strong aversion to taking medications and was opposed even to taking a natural form of thyroid hormone. She felt like she was too fatigued even to exercise, although she had been very active for most of her life. She was following a gluten-free Paleo diet with a lot of fruits and vegetables and loved dairy products of all kinds including milk, cheese, and yogurt. She explained that she was from Wisconsin, where dairy farming is common, and that's why she loved drinking milk every day.

After talking with her I determined that she had excess kapha as well as very low Agni. I had her follow a ka-

pha-pacifying diet. Traditionally, Ayurveda recommends eliminating dairy products during such a diet. Even though it was very difficult for her, Rhonda stopped eating dairy products and started following the kapha meal plan. I also encouraged her to incorporate warming spices into her diet, such as ginger, turmeric, black pepper, and chili. Lastly, I suggested that she begin taking an herbal supplement called Guggulu, which is effective at reducing excess kapha and is also traditionally used to support healthy thyroid function.

After three months, she was excited to report that she had lost fifteen pounds just from changing her diet. Her energy had improved to the point where she was able to start a regular exercise program. As she began exercising, her energy improved further and she lost another ten pounds. After six months, we repeated her thyroid function tests and found that they had normalized.

Why Paleo?

Now, why even follow a Paleo diet in the first place? The premise is simple. Our human genetic code was basically shaped by the 2.5 million years our ancestors lived as hunter-gatherers, before the advent of agriculture approximately ten thousand years ago. This period of time is known as the Paleolithic era, and comprises the vast majority of human history. It's estimated that human beings have lived approximately one hundred thousand generations as hunter-gatherers, compared to about six hundred subsequent generations as farmers. Therefore, for the vast majority of human history, our genes were shaped by the lives our ancestors lived as hunters and gatherers. The agricultural era has had limited effects on our genetic makeup.

British epidemiologist Geoffrey Rose, an expert in public health, explained these ideas in a lucid manner. He wrote that in order to prevent chronic disease, public health officials should recommend removing "unnatural factors" and restoring "'biological normality'—that is, the conditions to which presumably we are genetically adapted." While Rose was referring to factors such as cigarette smoking and physical inactivity, other "unnatural factors" are the industrial processed foods that have appeared in our modern era. The conditions to which we are genetically still adapted are diet and lifestyle patterns that mimic those of our Paleolithic ancestors.

What the Caveman Really Ate

To determine what exactly human beings ate during the Paleolithic era, scientists have examined the fossil record and also studied modern hunter-gatherer societies. Although the popular perception is that ancestral eating centers on meat consumption, anthropological analysis reveals that some of these populations consume very little meat. For example, the Kitava people from the island of Papua New Guinea consume tubers (sweet potato, yam, and taro), vegetables, fruit, coconut, and fish. They typically consume 70 to 80 percent of calories from carbohydrates. Contrast this with the Inuit Eskimos from Greenland, who consume 70 to 80 percent of calories from fat, mostly saturated fat. Their diet consists of seal, walrus, whale, caribou, fish, and occasionally seaweed.

Researchers analyzed 229 hunter-gatherer populations that had survived long enough to be studied by anthropologists to determine what type of diet they followed. It was found that these populations consumed animal products whenever possible, and had higher intake of fat and protein and relatively lower intake of carbohydrates (averaging 22 to 40 percent of calories) compared to modern diets. They also preferred fatty animal foods, including organ meats, over the lean muscle meats that we typically find at the grocery store. The wild plant foods they consumed differed from modern carbohydrates in that they were much higher in fiber, higher in nutrients, and lower in simple sugars—they would be very slow to raise blood sugar, causing a correspondingly

slow insulin response.

Healthy Starches Were Part of the Paleolithic Diet

Scientists have performed sophisticated analyses (using isotope signatures from fossilized bones) and determined that our ancestors also ate roots, tubers, rhizomes, and other underground plant storage organs; it is likely that the consumption of starchy plants goes back at least two hundred and fifty thousand years, well before the advent of agriculture. Therefore, the perception that Paleo is a low-carb, all-meat diet fails to appreciate the fundamental role that healthy starches played in the dietary patterns of our ancestors. To me Paleo should be a plant-based diet with fruits and vegetables as the foundation and starting point.

The Science of Life

Next, let me tell you more about Ayurveda, which is named from the Sanskrit words "Ayu" meaning "life" and "Veda" meaning "science"—i.e., "The Science of Life." Ayurveda is a holistic system of medicine that has a comprehensive approach to understanding the body. It can be traced back at least three thousand years, and is probably the oldest system of medicine in the world.

The Ayurvedic approach to science is different, although no less rigorous, than the allopathic paradigm. When I began studying Ayurveda in the late 1990s, I found Ayurvedic theory logical enough to satisfy my Western training. Ayurveda offers an explanation of why different people require different diets, even if they are part of a population with very similar genetic makeup. It also provides detailed insights into how to individualize a dietary program for each person. Each of us has a different Ayurvedic body type, and a simple questionnaire can help determine your body type and understand the optimal foods for each type. You may want to understand how this applies to yourself first before making recommendations to patients.

Understanding the Doshas

The foundation of Ayurveda is the concept of doshas, or physiological principles. You can think of the doshas as forces within the body that are responsible for all the physiological and psychological processes in your body and mind. There are three main doshas—vata (which you can think of as wind), pitta (equivalent to fire), and kapha (earth). The doshas are shifting constantly, due to diet, lifestyle, and environment. As long as they are balanced and working harmoniously together, good health is possible. When the doshas are imbalanced, disease results. Let us look at each of the doshas in more detail:

Vata

- Vata is the subtle energy that governs all movement in the body, including respiration, heartbeat, nerve impulses, blood flow, etc.
- Like "wind," vata's qualities are light, cold, dry, and mobile
- Associated with creativity and rapid thinking, but also fear, anxiety, and restlessness

Pitta

- The bodily heat-energy of metabolism, manifesting in digestion, absorption, temperature regulation
- Like "fire," pitta is hot, sharp, penetrating, and intense
- Linked with Agni, digestive capacity
- Associated with intelligence and insight, but also anger, irritability, and frustration

Kapha

- The force that forms body structure and provides biological "strength," associated with bones, joints and ligaments, skin moisture, and joint lubrication
- Like "mud," it is heavy, cool, slow, and damp
- Associated with love and calmness, but also attachment, depression, and inertia

The 7 Dhatus or Tissues

In addition to the three doshas, there are seven dhatus or tissues that constitute the structure of the body. These include rasa (plasma and lymph), rakta (blood), mamsa (muscle), medas (fat), asthi (bone), majja (bone marrow and nerve tissue), and shukra (reproductive tissue). These tissues are also in a state of constant transformation and interplay, just like the doshas, and optimal dhatu status is essential for good health.

Every Person Is Unique

Every person is born with a distinct combination of doshas that comprises their constitution, which is as unique as a fingerprint. Nobody has exactly the same ratio of vata, pitta, and kapha. Also, each person manifests the qualities of their doshas in a slightly different way as a result of their personality and other factors. The goal in Ayurveda is to maintain your unique balance of doshas, which was determined at conception.

For example, let's say that you are 50 percent vata, 30 percent pitta, and 20 percent kapha (every person has at least a little bit of all three of doshas). Consequently, the optimal dosha balance that you want to strive for is 50 percent vata, 30 percent pitta, and 20 percent kapha, which is identical to your constitution. You are not trying to get equal amounts of all three doshas, which is a common misconception.

Using the same example, your primary dosha would be vata and your secondary dosha is pitta. As a rule of thumb, the primary dosha has the greatest tendency to increase and become imbalanced. Therefore, a vata person is more likely to experience a vata excess and thereby suffer vata-related disease. That is why the diet for each dosha has qualities and characteristics opposite to the dosha. For example, the qualities of the vata dosha are light, cold, and dry; the foods that are recommended as part of the vata diet are heavy, warm, and moist—both in terms of physical characteristics and subtle qualities.

In general, "like attracts like," and this may or may not be beneficial depending on the dosha. For example, pitta body types tend to love hot, spicy food, although that is potentially aggravating for their pitta dosha in excess.

They might do better with spices that are considered cooling, such as cumin, coriander, fennel, and cilantro. The typical recommended diet for pitta people contains foods that would be considered to have cooling properties.

Interestingly, this appears to extend beyond dietary preferences. In my practice, I see many kapha patients who love to relax and enjoy sitting quietly, whereas intense, vigorous, and stimulating activities would be beneficial for them. Many of my vata patients take on too much activity and tend to crave fast action and new experiences, and I remind them to slow down and incorporate more downtime and relaxation. Pittas are attracted to competitive sports that reward intensity and aggression, whereas more restorative exercise would be balancing for them. Of course these are generalizations, but I find it striking how often they are relevant to patients in my practice.

Ayurveda is able to take the science of prevention to the next level, by telling you what types of imbalances and diseases you are most prone to as a result of your specific body type. This enables you to anticipate potential illness and take corrective steps before it manifests. This is one reason why I find Ayurveda to be so powerful.

Eat Right for Your Body Type

Ayurveda recommends a different diet for each constitution, and so you would follow the diet recommended for your body type. Ayurveda also believes that the diet should be individualized based on season, environment, activity level, and overall goals. For example, each season is associated with a certain dosha; winter is a time when the excess cold can provoke vata, and the heat of summer can increase pitta. To learn about your body type and its recommended diet, please complete the questionnaire either at www.doctorakil.com or in my book "The Paleovedic Diet: A Complete Program to Burn Fat, Increase Energy and Reverse Disease".

Strengthen Your Agni or Digestive Fire

The concept of Agni, or digestive fire, which determines our ability to digest, absorb, and assimilate our food, it is fundamental to Ayurveda. Agni, which means "fire" in Sanskrit, refers broadly to your capacity to digest and process all experiences. Now we will focus on the physical Agni, which is a measure of your capacity to digest food. A healthy and strong Agni is indispensable for good health. If your Agni is weak, you will not be able to optimally extract nutrients and energy from the food you taken, even if the food is of very high quality. Agni is correlated to some extent with stomach acid, digestive enzymes such as pancreatic enzymes, and bile from the gallbladder.

Signs of a healthy Agni include a healthy appetite, normal elimination, the absence of excessive gas or bloating, and normal energy levels. The strength of your Agni is a direct determinant of your capacity to effectively process raw foods, which are difficult to digest. This explains why certain people thrive on a raw-food diet (strong Agni) while other people actually may feel worse if they only eat raw foods.

If your Agni is weak, you will not break down your food properly, and that will lead to the production of ama, or toxins. Ama is a by-product of improperly digested food that in Ayurveda can accumulate in any part of the body, leading to inflammation and disease. It is believed that all disease begins with some imbalance in the gut that affects Agni, subsequently leading to the production of toxic ama, which is only later followed by the development of symptoms.

Complexities of Ayurvedic Medicine

The science of Ayurveda is extremely complex, and for the purposes of this chapter I have oversimplified it. You can imagine that three thousand years of practice has led to the development of a vast ocean of knowledge.

Completing the questionnaire will give you an initial idea about your body type. However, an Ayurvedic practitioner will be able to come to a more accurate conclusion, based on history and physical examination including a detailed qualitative pulse exam (different from measuring heart rate) and tongue diagnosis. In addition, since doshas are always changing, your current state may be different from your original body type. It is also possible for more than one dosha to be imbalanced, in which case you would need to determine which one is the priority for treatment. As you can see, Ayurveda can become complex very quickly, so if you have any questions please consult with your local Ayurvedic practitioner.

Ayurvedic Therapeutics

There is an advanced understanding of various diseases and their therapies in Ayurveda. In order of potency, recommendations usually start with dietary change, followed by use of spices, and finally herbs and supplements. Mind-body techniques including meditation, breathing techniques, and yoga are commonly recommended as part of a treatment plan.

There is also an intensive form of detoxification therapy known as panchakarma; typically panchakarma is done in the inpatient setting in Ayurvedic hospitals or treatment centers. Patients, usually with more serious illnesses, may stay between two weeks to two months to receive the treatment, and I have seen some remarkable results with it.

Ayurvedic Pathogenesis

There is a six-stage model in Ayurveda that explains how disease develops. Symptoms only appear at later stages, and the goal of Ayurveda is actually to detect imbalances and prevent disease before overt symptoms develop. In this way, Ayurveda is very focused on the root cause of disease and strongly emphasizes prevention. Therefore, Ayurveda is the original functional medicine, a modern specialty that assesses the function of different organ systems and attempts to uncover the root cause of illness. Ayurveda believes that all disease starts in the gut, at least to some degree, usually with weakening of the Agni.

1. Stage I—dosha imbalance and/or weakened Agni, leading to production of toxins (ama)
2. Stage II—imbalanced doshas build up in their respective organs
3. Stage III—doshas spread from their organs
4. Stage IV—imbalanced doshas and ama move to and localize at weak body tissues (dhatus), causing nonspecific symptoms
5. Stage V—early tissue damage occurs, major symptoms occur, leading to the development of a diagnosable disease
6. Stage VI—progressive disease, potentially with complications

Diseases at all stages are treatable, but the later the stage when treatment is begun, the more involved and time-consuming the therapy will be. The earlier that treatment is begun, the more likely the disease process can be fully reversed. If you are under the care of an Ayurvedic physician, the true measure of success would be catching imbalances at stage III or earlier, before symptoms have manifested, and addressing them before they progress any further.

Eat All Six Tastes

In Ayurveda, food is described as having six different tastes. Most foods are a combination of two or more tastes; e.g., coffee is considered both bitter and pungent. Some tastes are obvious—e.g., honey is considered sweet—but others are less intuitive, as ghee is also considered sweet.

It is ideal to consume foods from all six tastes in some form every day. If not possible, at least having as many different tastes as possible every day will help your diet to be more satiating and balanced.

The reason for this is that "taste" in Ayurveda has a sophisticated meaning that extends beyond the perceptions in your mouth. The six tastes each have different energetic and subtle effects on the doshas, with some increasing vata and others decreasing it, some having warming properties (thereby increasing pitta) and others cooling, etc. Therefore, ensuring that your diet has foods from all six different tastes is another strategy that helps promote the dosha balance, which in Ayurveda is indispensable for health.

Here is more information about foods in each taste category and the energetic properties and physiological effects of each taste:

Table—The Six Different Tastes

Taste	Examples of Foods	Effects in the body
Sweet	Rice, whole grains, sweet potato, pumpkin, ghee; honey, molasses, and all natural sweeteners	Nourishing, rejuvenating, tonifying, strengthening
Sour	Lemon, tomato, citrus fruits, alcohol, yogurt, vinegar (apple cider vinegar is especially good), and all fermented foods	Stimulates saliva production, digestion, and appetite, aids in elimination
Salty	Salt of any type (Himalayan salt or sea salt recommended), seaweed, anchovies	Moisturizing, lubricating, clears obstructions, helps with fluid balance
Bitter	Leafy green vegetables, chocolate, coffee, turmeric, rhubarb, bitter melon, bitter gourd	Detoxifying, reducing inflammation, cooling, drying, balancing all other tastes
Pungent	Garlic, onion, ginger, chili, mustard, clove, black pepper, and most spices	Keeping the digestive fire strong, improving circulation, clearing mucus
Astringent	Brussels sprouts, asparagus, okra, cranberry, plantain, pomegranate, tea, chickpeas, lentils, sprouts of any type (e.g., alfalfa or clover)	Cleansing, purifying, removes excess moisture

You can see from the table above how the different tastes have complementary properties and function like a system of checks and balances. Our modern diet typically has too much of the sweet and salty tastes. The tastes that are routinely underemphasized or missing in Western diets are the bitter and astringent tastes. Interestingly, these are the tastes which are most cooling in terms of energetic properties and would be especially helpful for reducing inflammation, which is considered a condition of excess heat or pitta in Ayurveda. Incorporating more of the pungent taste through spices can have a whole host of health benefits.

The concept of six tastes is another unique lens that Ayurveda can offer to help ensure more balance in your diet. Again, it's important not to incorporate too much of any one taste, because excess use of a particular taste can also cause imbalances in the doshas. The key as in all things is moderation.

Conclusion

As you can see, Ayurveda can be used to help customize a Paleo diet that is right for your body type. Incorporating foods from all six different Ayurvedic tastes is a helpful strategy to improve satiety and ensure a balance of different qualities and energies in your diet.

Ayurveda also has particular expertise in the realm of spices, which it considers to be an entire category of medicine because of their tremendous health benefits. Spices can help reduce inflammation, combat oxidative stress, optimize the digestion, maintain healthy blood sugar, prevent insulin resistance, and maintain a healthy microbiome by preventing microbial overgrowth. In addition, I recommend other Ayurvedic strategies such as intermittent fasting, daily cleansing practices, mind-body techniques, and detoxification strategies. While fairly simple, these approaches all have a powerful effect on health.

Ayurveda is the original personalized medicine, and when combined with modern functional medicine and Paleo principles through the Paleovedic approach, offers a powerful and comprehensive strategy to help your patients achieve optimal health and wellness.

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Dr. Akil Palanisamy, MD, is an integrative medicine physician and author of "The Paleovedic Diet: A Complete Program to Burn Fat, Increase Energy, and Reverse Disease". He blends his Western medical training with functional medicine and Ayurveda, the traditional medicine of India.

"Dr. Akil" studied biochemistry at Harvard University, received his medical degree from the University of California, San Francisco, and completed his residency at Stanford University. He also completed a fellowship in integrative medicine with Dr. Andrew Weil at the University of Arizona, and is certified by the Center for Mind-Body Medicine at Georgetown University.

Dr. Akil studied Ayurveda in Southern India, and found a powerful synergy in combining Ayurveda with the paleo diet in his clinical practice. This led him to coin the term "Paleovedic Diet ", which refers to a nutrient-dense customized Paleo diet that incorporates spices, specific fruits and vegetables, intermittent fasting, and an Ayurvedic lifestyle.

He sees patients at the Sutter Health Institute for Health and Healing in San Francisco, where he also serves as Physician Director for Community Education. Dr. Akil has been a consultant with The Medical Board of California for many years.

He is a dynamic and highly sought after speaker who has spoken at numerous conferences and venues worldwide. His online courses on integrative medicine through theayurvedaexperience.com are viewed by people all over the world. He maintains a popular blog at doctorakil.com.

DEANNA MINICH

PhD, FACN, CNS, IFMCP

Introduction: Why Whole Detox?

My patient Sandy was frustrated.

"Dr. Minich," she said, "I'm really hoping you can help me. I feel like I've tried every detox under the sun, and they all work—but only for a little while. I've heard that your detox does some really great things, and that it will change my life, and I really hope that's true. Because honestly, I'm starting to lose hope."

I could well understand Sandy's frustration. Like many of my patients, she was looking for a way to lose weight, feel great, and boost her energy. Sandy was also struggling with brain fog and some mild anxiety. Some of my other patients suffer from aching joints, sleep problems, depression, listlessness, or fatigue. For many, I'm not the first stop on the health-care trail—they've tried conventional medicine, a number of supposedly healthy diets, a wide range of fitness programs, and at least one or two cleanses. Many even improve—for a while. Then, like Sandy, they start to drift back to the same set of problems that sent them searching for help in the first place.

Does that sound like you? Are you also frustrated that those five or ten or twenty pounds keep coming back after you've worked so hard to lose them? Do you also wish there was a way to regain your lost energy and sharpen up your brain? Are you struggling with sleep problems, anxiety, or depression that you'd prefer to treat naturally? Do you feel as though you keep running into the same brick wall?

If so, I hear you. I've spent enough of my own life seeking answers for my health problems to know just how frustrating and sometimes scary that can be. When I began as a functional medicine nutritionist, I was thrilled that I'd have the chance to translate my years of science and research into practical ways of giving people access to the vibrant health that is our birthright. At that point, I had a lot of faith in good nutrition as the royal road to health—the key to living well and feeling great.

Over the years, though, I, like Sandy, became frustrated. I began to see that for many patients, the wonderful nutritional suggestions that I was making simply didn't "take."

Maybe they would for a while. They would be incredibly excited as they finished the consultation, thrilled with their jumpstart to a healthy life. They had shed pounds and lost inches. Their brain fog had cleared. Their anxiety had calmed. Their depression had lifted. Detox had given them a glimpse of just how great life could be when they felt this good, all the time.

And then, a month, two months, half a year later, many of those same patients would return, discouraged, maybe even defeated. They had started to re-gain the weight. Their aches and pains were back. They no longer felt the energy, the hope, the vibrant health they had once enjoyed.

What had gone wrong? Why would an approach that works so well stop working?

I struggled with this problem for several years—and then finally I got it.

The reason most detoxes have so little staying power is that they treat only a part—but not the whole.

They deal with part of your body—not your whole body.

They tell you what to take out—but they don't focus on what to put in.

They deal only with your physical body—not with your whole self.

And as a result, they often fail.

Why Most Detoxes Don't Last

They don't deal with your whole body

Most detoxes pick one single aspect of your body—your liver, perhaps, or your gut. But very few programs look comprehensively and systematically at your entire body and make sure that every aspect of your physical self—from your feet through your belly through your heart to your brain—has every bit of support it needs to expel all your toxins.

This whole body approach is essential, especially given that the latest developments in medicine focus on the activity and interrelationships of your body's networks: not just your gut, but your digestive system; not just your digestive system but the interaction between it and every other organ and system in your body. Your liver doesn't work separately from your gut: They work together. (The scientific terms for this type of thinking are "network medicine" and "systems biology.")

They focus on what to take out—not what to put in

Most detoxes zero in on reactive foods, industrial chemicals, and other environmental toxins. They tell you how to protect yourself from these toxins, and maybe they even offer you a few weeks' worth of meal plans. Or they focus on a few potentially toxic foods—caffeine, sugar, and gluten, perhaps, or maybe soy, peanuts, and artificial sweeteners. Some detoxes are more restrictive, with an even longer list of things to cut out. But none of these approaches gives enough attention to your whole body, comprehensively, systematically, making sure that every one of your vital systems is getting the full spectrum of nutrients that it needs.

They focus on the body—not the whole self

Most detoxes tell us how to avoid reactive foods and industrial chemicals, which is great. But do they help us shed toxic thoughts, let go of limiting beliefs, or cope with the stressful situations that frequently make us ill? Not that I've seen.

Every time you encounter an upsetting relationship, a frustrating personal situation, or a depressing day at work, your body is flooded with powerful biochemicals that have the power to sabotage your health. I'm talking about stress hormones like cortisol, which cues your body to put on the pounds, disrupt your sleep, and drive up your blood pressure, potentially sending you down the road to obesity, diabetes, autoimmune conditions, and cancer. I'm talking about the shattering experience of heartbreaking grief, which research has shown can literally disrupt the workings of your heart. I'm talking about lives which seem plagued by loneliness and boredom, which numerous studies have shown are plagued with more chronic health problems and also end sooner than lives full of passion, meaning, and community.

We now have volumes full of research showing that stress, boredom, frustration, and heartbreak aren't simply psychological states. Rather, they are physical conditions that profoundly affect your health: through your hormones, your blood pressure, your neurotransmitters, and, ultimately, your entire biochemistry. A happy, contented person is biochemically different from an angry, sad, or fearful one. Our bodies affect our thoughts and feelings…and our thoughts and feelings affect our bodies. This interaction is straight out of Human Biochemistry 101. It can be a significant disrupter of our health—or a profound tool for healing.

Yet most detoxes ignore this "life" component and stick strictly to nutritional advice. Even when they pay lip service to "stress relief" or "taking time for yourself," they fail to offer any concrete, workable program to actually get rid of your "life toxins." As a result, most detoxes are sadly incomplete, because if you don't heal the whole person, you'll just see the same problems coming back again and again and again.

Detox's New Frontier

I didn't want my patients to keep suffering. I didn't want them to follow up their brilliant initial success with detox with a disappointing fizzle a few weeks later. I didn't want a detox that worked only briefly, randomly, or occasionally; and I didn't want a detox that addressed the body alone.

So I began searching for a program that would allow us to remove every single toxic barrier that kept us from total health and vital, fulfilling lives. I drew on my years doing academic and professional research into the biochemical and nutritional properties of food, and on my experience as a clinician who worked with hundreds of patients. I wanted a comprehensive, systematic detox that spoke to every aspect of our bodies and our lives—a clear, actionable program that even the busiest and most stressed of my patients could follow.

The culmination of this process was Whole Detox: the first comprehensive, systematic approach to breaking through all the toxins that hold you back. But first, I had to rethink what I meant by "toxin."

Redefining "Toxin"

Okay, we all know that "detoxification" means, literally, to get rid of toxins. But what exactly are toxins? We're used to speaking of them in purely physical terms. My research and my clinical practice has taught me that they are much, much more.

Toxins are better understood less as poisons than as barriers—obstacles to the life and health we truly want.

On a physical level, this is pretty clear. If you look at the thyroid signaling system, for example—the complex network of glands and hormones that regulate our thyroid function—you will see that poor thyroid function makes the whole body more vulnerable to environmental toxins, interfering with our ability to detoxify. At the same time, the increasing toxic burden disrupts the thyroid signaling system, making it more difficult for different parts of the system to communicate with one another. These toxic barriers to communication further depress thyroid function, creating a vicious cycle that can sabotage a patient's entire quality of life. Depression, weight gain, brain fog, exhaustion, memory problems, and, potentially, heart disease are only some of the chronic conditions that can result.

And yet, when you remove the toxic barriers, communication resumes. Thyroid function improves, and the patient suddenly has a new lease on life.

Slowly I came to see that the very same principle applies to "life toxins." If mental, emotional, or spiritual challenges are standing in our way, they can block our progress—and undermine our health. I began to see that by helping my patients release their "life toxins," their health improved as well.

For example, my patient Marqueta had struggled for years with a limiting belief: she couldn't be a successful, empowered woman and also retain her femininity. Marqueta's mother had grown up in a very traditional religious household, and she had tried to instill those same values in her daughter, including the notion that women were supposed to be quiet, timid, and sexually passive.

This limiting belief was keeping Marqueta from pursuing relationships with men who really interested her. Any time she found a man she liked, she worried that she was being "too sexual" and "too forward." She also worried that the man would be put off by her success as the administrator of a local hospital.

When Marqueta came to me, she was suffering from crippling menstrual cramps. She also described herself as

"dried up—my brain just won't work." Once a creative, vital person, Marqueta was clearly struggling with many toxic barriers. Her physical symptoms expressed her life issues; her life issues were shaped by her physical problems. Enter Whole Detox: a comprehensive way to surmount barriers in both health and life.

I addressed Marqueta's hormonal issues in a variety of nutritional ways: healthy fats, better hydration, some herbal supplements. I also worked with her to identify the limiting belief that functioned as such a powerful obstacle. I encouraged her to foster her own creativity, even in such little ways as how she dressed or how she decorated her office. I asked her to write in her journal about the women she admired and wanted to emulate, and to identify the qualities in herself that resembled those women. Through a wide variety of modalities—diet, supplements, lifestyle, self-exploration, journaling, and creative activities—I helped Marqueta get rid of the toxic barriers that were holding her back.

Once Marqueta understood how to identify and overcome all the toxins in her life—from reactive foods to limiting thoughts to frustrating relationships—she was able to reclaim her health. Because she wasn't following an abstract system but rather identifying her own personal toxins, she was empowered far beyond what partial detoxes could achieve. Thanks to the tools she had learned through Whole Detox, Marqueta would be able to target and defeat her personal toxins for the rest of her life.

Even after a few weeks, the results were astonishing. Soon after we began working together, Marqueta transformed her wardrobe from dull greys and beiges to brilliant oranges and yellows that suited her much better. She began to feel creative and "flowing" again, no longer "dried up" and "stuck." She started a new relationship, slowly and tentatively, but with more passion and excitement than she had previously allowed herself. Her menstrual cramps disappeared. Her hormones were in balance. The culmination came on her last appointment, when she showed up with a haircut so dramatic and different from her previous style that I almost literally didn't recognize her.

This, to me, is the essence of Whole Detox. Marqueta had broken through the toxic barriers that were limiting her life so that she could finally savor the full spectrum of her whole self.

Discovering Whole Detox

When I developed Whole Detox, I had been working for nearly a decade as a nutritionist. I had done graduate research into the nutritional properties of the carotenoids that give foods their color, as well as into the biochemical properties of fats.

I had also explored other ancient healing arts, including Traditional Chinese Medicine, Ayurveda, and many others. A single yoga class that I took more than twenty years ago first turned on the light bulb in my head, illuminating the many healing truths that are available to us, even if they are often neglected by conventional practitioners.

So in my quest for detox's new frontier, I went back and searched my library for every discipline I had ever studied: nutrition, neuroscience, epigenetics, physiology, and psychology, as well as yoga, Ayurveda, Chinese Medicine, and traditional healing. Odd as it might sound, I also explored color and drew on my background in the visual arts. After all, color has long been associated with emotion and mood, as well as to the phytonutrients that make fruits, vegetables, herbs, and other plant foods such a crucial part of our diet. Color also plays a key role in East Indian healing.

Working with this rich array of influences, I came up with a new systematic, comprehensive approach to detox. Its power was astounding. As I introduced this approach to my patients, I saw how deeply mind, body, spirit, and emotions all affect one another. Remove a toxic food from your diet and you might also free yourself from depression, anxiety, or helplessness. Eliminate a toxic thought and you might also rev up your metabolism and lose some unwanted weight. Tear down the barriers to your sense of purpose and connectedness, and you might also revitalize your immune system and restore your optimism.

The opposite was also true. Hold onto a toxic belief and the healthiest diet in the world might not free you from troublesome symptoms. Remain mired in a stressful life, and even without caffeine, sugar, and refined flour, you might still feel wired, anxious, or depressed. A raging hunger for meaning or community might keep you dissatisfied and edge even when your body is fully nourished.

Every one of us is a complex biochemical structure in which every factor affects every other factor in an endless synergistic loop. Sometimes this synergy works against us: Negative thoughts can impair our health; poor health can breed negative thoughts. As your health gets worse, your thoughts get bleaker; as your thoughts get bleaker, you move less, crave more sugar, send more stress hormones coursing through your veins. You feel even sicker… and your thoughts spiral further down into depression. Talk about a vicious cycle!
But with Whole Detox, you can transform the downward spiral of disease into an upward spiral of vibrant health. By addressing nutrition, exercise, thought patterns, and many other factors at the same time, you can break through toxic barriers and create a vibrant, healthy life.

What Whole Detox Will Do For You

Whole Detox integrates Western science and Eastern medicine. It is a systematic way of overcoming every barrier that keeps you from health, energy, and fulfillment. So welcome to Whole Detox, because it can change your life:

- You begin to heal the parts of your body that are struggling under their toxic burden, including your endocrine system, digestion, heart, bones, and brain.
- You shed pounds, boost energy, heal aches and pains, and recover from debilitating symptoms, feeling calmer, more vital, and more energized than you have in years.
- You detoxify your relationship to your community, your family, and yourself.
- You detox through food—and also through movement, new thought patterns, and emotional expression.
- You break through conflicts, sexual frustration, and creative blocks, freeing you to pursue long-deferred dreams for work, love, and personal satisfaction.
- You'll feel nourished, not deprived—because sometimes the best detox is not cutting something out but rather bringing in more of what you need!

Most important, Whole Detox is a personalized approach. You zero in on the parts of your body—and your life—that most need cleansing, healing, and revitalization. You also acquire the lifelong ability to target your own personal barriers by using the Whole Detox Questionnaire. As a result, Whole Detox is the fastest and most effective way to become your healthiest, most energized, and most fully realized self.

The Power of Whole Detox

To illustrate the power of Whole Detox, let me share with you the story of George, who came to me frustrated and helpless about six months after completing his last detox with another practitioner. George's problem was that he couldn't sleep—an aching frustration that had been with him ever since his sophomore year in college. Now in his mid-forties, George was paying a heavy price for his insomnia. He often found himself short-tempered with his children as well as his wife. Since George's own father had been a short-tempered, angry man, George hated the feeling that he was repeating his father's version of family life.

At work, too, George struggled to remain calm and centered. The owner of a small tech company, George frequently had to travel on business, working with clients in various parts of the country. He knew that a sleepless night before an important meeting could jeopardize an important relationship—yet he hated to depend on sleep aids.

Sleep problems were ruining George's life, as he told me frankly the first time we met. His despair was all the greater because he had recently completed a detox that, for a few sweet weeks, had finally seemed to heal the problem. George cut out caffeine, sugar, white flour, and unhealthy fats. He drank water with lemon juice to flush the toxins out through his urine, and he took yarrow pills to support his liver's detox function. He got a water filter, an air purifier, and blackout curtains to keep "light pollution" out of his bedroom. Anything that could interfere with his sleep, George got rid of.
And, for a time, it worked. George's sleep quality continued to improve until finally, after less than two weeks, he was sleeping deeply throughout the night. For the next few months, George felt as though he had witnessed a miracle.

Then, slowly but surely, the old sleep problems began creeping back. When a loud noise in the hotel corridor woke up him one night, George tossed and turned for hours. When a difficult client meeting loomed the next day, George couldn't fall asleep till nearly 5 a.m. When George's 10-year-old daughter came down with a high fever one night, George lay rigid beside his sleeping wife, imagining all the terrible ways her illness might play out.
"What's the problem?" George asked me, about two months after he had completed the unsuccessful detox. "Once I started sleeping again, why couldn't I keep sleeping?"
"I think three things might be going on," I suggested. "First, there may be some toxins that are personal and specific to you—some reactive foods or problematic chemicals that are disrupting your body. Most detoxes are cookie-cutter—one size fits all. They can be a great first step, but they don't necessarily identify the toxins that are disrupting your system."

George nodded, beginning to look more hopeful.
"Second, although your last detox focused on what to cut out, you didn't really find out what to put in. Healthy fats are really important for sleeping. So are complex carbs. There may be some other imbalances we discover, as we work through your entire body—systems in your body that are not getting all the nourishment they need."
George nodded a second time, seeming even more hopeful.
"Finally—and maybe most important—we can't just look at your body. We have to look at your whole self."
Now George was startled. "You mean there's something wrong with me—with my personality?" he asked.
"Not at all," I said quickly. "But your body and your mind aren't really separate. They're both part of the same

system. Your thoughts and feelings are biochemical events that have a profound effect on the rest of your physiology. We can work only on the 'body' level, as your last detox did. But this is Whole Detox, and I think it would help you to work on the 'life' level as well."

George and I had many long talks about what might be keeping him awake. As he thought about his bad-tempered father, he recalled many late-night arguments that his parents used to have. George's father had worked until midnight at the restaurant he owned, and when he came home, he expected George's mother to offer a sympathetic listening ear and a plate of hot food. George's mother, for her part, was exhausted after a long day of working at an office downtown and then making dinner for her children. George's father frequently woke her up, and the two fought, waking George. The sense that night was the time to be alert, on edge, ready to protect the people he loved yet helpless to do so, had never really left George.

George had also held on to the sense that to be a truly successful businessman, like his father, you had to stay up late, worrying about your business. Without realizing it, he had adopted that same worry, as though, by falling into a deep sleep, he was neglecting his business and letting down his clients. Of course, the exact opposite was true. George's sleep problems were actually interfering with his ability to be a good family man and an effective businessman.

Certainly, George had found it helpful to cut out the foods and beverages that had disrupted his sleep, and he had also benefited from adding in the supportive foods I had suggested. But George was a whole person, and he needed a whole detox, one that included both health and life issues. To solve his sleep problem, he had to identify all the toxic barriers that kept him up at night—not just the nutritional ones.
Your 21-Day Program

So here's what we're going to do.

In Chapter 1, I'm going to give you an overview of the cornerstone of Whole Detox: the 7 Systems of Full-Spectrum Health. These are 7 clusters of physical and life issues that can be supported, healed, and detoxed in similar ways.

Once you've learned about each separate System, Chapter 2 will help you see how all work together. It's called The Power of Synergy because synergy—the extra benefits you get from many systems all working in harmony—is truly the power behind Whole Detox.

Then, in Chapters 3-9, I'm going to zero in on each system, one by one. You'll get a real in-depth look into every system so that by the time you begin your own Whole Detox, you'll be able to see your body, your life issues, and your goals in those terms.

This approach offers you two striking advantages that make Whole Detox more effective and longer-lasting than any other detox I've seen. First, these 7 Systems target every aspect of your body and your life: every anatomical system and also every life issue (work, love, community, spirituality, etc.). When you target each of the 7 Systems, you guarantee yourself a truly Whole detox, identifying every single barrier that stands between you and optimal health, between you and a wholly inspired and fulfilling life.

Working with the 7 Systems also enables you to create a truly personal detox—one that zeroes in on the specific barriers that are most troublesome to you. The Whole Detox Questionnaire (see page 000) helps you work

through every one of the 7 Systems, identifying each specific physical, mental, or emotional issue that stands in your way. What most people discover is that one or two Systems are more out of balance than the others, while one or two Systems are key areas of strength and power. When you identify your strengths and weaknesses, you can find ways to immediately support your strengths and improve your weaknesses, so that you are taking immediate steps to improve your physical, mental, and emotional well-being.

THE 7 SYSTEMS OF FULL-SPECTRUM HEALTH

(comp, please set each bf term in color: The Root, red; The Flow, orange; The Fire, yellow; The Love, green; The Truth, blue-green; The Insight, purple; The Spirit, white)

* The ROOT: adrenal glands, immune system, DNA, bones, skin, survival, communities

* The FLOW: ovaries/testes, reproduction, fertility, kidneys, colon, relationships, creativity

* The FIRE: pancreas, digestive system, blood sugar, work-life balance, energy production

* The LOVE: thymus, heart, blood vessels, lungs, compassion, expansiveness, service

* The TRUTH: thyroid gland, throat, ears, nose, speaking, choice, authenticity

* The INSIGHT: pituitary gland, brain, neurons/neurotransmitters, sleep, mood, thoughts, intuition

* The SPIRIT: pineal gland, electromagnetic fields, circadian rhythms, connection, purpose, meaning

These 7 Systems might seem a bit counter-intuitive at first—why should adrenals, the immune system, family issues, and the color red all be part of the 1st system, while kidneys, ovaries, creativity, fertility, and the color orange fit together in the 2nd? But I promise, by the time you've finished reading Chapters 1-9, these 7 Systems are going to seem intuitive and even a little obvious. And by the time you've finished your 21-day program, you won't remember thinking any other way.

As a clinician, I found that these 7 Systems of Health were my keys to the kingdom: Through them, I could see that seemingly disparate issues—usually separated into nutritional, anatomical, psychological, and spiritual—did actually benefit from being treated together.

For example, the 1st System of Health includes, among other things, immune function, bone health, identity, rootedness, and security: all the things that ground us and define us in a physical way. I could address immune function by giving my clients an immune-healthy diet—but I could also help them to create a strong sense of personal boundaries. They could enhance their bone health through supplements—but also through yoga exercises that helped them feel grounded. Meanwhile, a healthy immune system and strong bones could help them create a feeling of rootedness, safety, and security. In other words, treating one "red"/ROOT issue could open the door to a whole new world of improvement.

Then you'll be ready to start your 21-day program. Every 3 days, you'll detox another System of Health, starting at the ROOT and working your way up to the SPIRIT. By the end of your 3-week program, you will have addressed every toxic barrier in your life.

I'll take you by the hand and be with you every step of the way. I'll tell you exactly what to eat each day (the

recipes are simple, colorful, and delicious!). And I'll guide you through each day's activities: affirmations, journaling, explorations of limiting thoughts, recommendations for healthy movement, and many other ways of breaking through your own personal toxic barriers. The instructions are clear and unambiguous—all you have to do is follow directions.

I've provided every single thing you need to complete this program successfully, including mouth-watering recipes that can each be prepared in 30 minutes or less. I've also shared shopping lists and some suggestions for how to prepare the week before you start.
Whole Detox may be one of the most exciting journeys you'll ever take—and it doesn't end after 21 days. I've also included a section on how to maintain Whole Detox for life—so that you can be sure to keep removing barriers and creating fabulous results.

Detox for the 21st Century
I'm thrilled to share Whole Detox with you, because I think it's high time that we found a new definition for detox. We need a detox that employs the whole spectrum of ancient and modern knowledge, and one that treats the whole spectrum of who we are. As a functional-medicine nutritionist, I believe that "food is medicine," but I've come to believe that this approach is not enough. Most people cannot heal on food alone. Yes, health requires a foundation of good eating—but good eating will not necessarily solve our emotional woes, limiting beliefs, and toxic self-talk.

The 7 Systems of Full-Spectrum Health have been recognized by ancient healing traditions for thousands of years. They still hold true in the present day. Our physiologies are so intricate and complex—and so are the ways that these bodies interact with every other aspect of our being. No two of us are alike—yet each of us contains these 7 Systems, this spectrum of color that helps define our bodies and our lives.

Whole Detox empowers us to remove not just physical toxins but all the barriers that impede our growth. Whole Detox is a 21-day program, yes—but it's also the beginning of a whole new way of life.

DR. DEANNA MINICH is a health educator and author with more than twenty years of experience in nutrition, mind-body health, and functional medicine.

Dr. Minich holds Master's and Doctorate degrees in nutrition and has lectured extensively throughout the world on health topics, teaching patients and health professionals about health. She is a Fellow of the American College of Nutrition, a Certified Nutrition Specialist, and a Certified Functional Medicine Practitioner.

Currently, Dr. Minich teaches for the Institute for Functional Medicine and for the graduate program in functional medicine at the University of Western States and doctoral program at the Maryland University of Integrative Health. Her passion is bringing forth a colorful whole-self approach to nourishment called Whole Detox and bridging the gaps between science, soul, and art in medicine.

Her new book is called Whole Detox: A 21-Day Personalized Program to Break Through Barriers in Every Area of Your Life (HarperOne, 2016).

Visit her at: www.drdeannaminich.com.

BRIGID TITGEMEIER
MS, RDN, LD

STEPHANIE R. HARRIS
PhD, RDN, LD

KELLY MORROW
MS, RDN

Dietary Supplementation: Regulations and Recommendations

Definition and Regulation of Dietary Supplements in the U.S.

Dietary Supplements Defined

In 1994, Congress passed the Dietary Supplement Health and Education Act (DSHEA) of 1994, in order to define and provide a regulatory framework for DS in the United States. Under DSHEA, a DS is defined as a product other than tobacco that is designed to supplement the diet and contains one or more of the following ingredients: "a vitamin, a mineral, an herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total dietary intake, or a concentrate, metabolite, constituent, or extract" (1). This definition includes DS that can be ingested in various forms by mouth, such as tablets, capsules, softgels, powders, or liquids (1, 2). DS are not meant to be and therefore cannot be represented as a conventional food item or a sole item of a meal or diet. They are also not intended to "treat, diagnose, prevent, or cure disease" and must be identified as a DS on the label (1, 2).

DS are often categorized by the type of nutrient they provide and/or the purpose they serve. These categories may include vitamins (e.g. vitamin A and folic acid), minerals (e.g. calcium and magnesium), herbs or other botanicals (e.g. St. John's wort and ginseng), amino acids (e.g. glutamine and arginine), fatty acids (e.g. omega-3 and fish oil), meal replacements (e.g. Ensure® and SlimFast®), weight loss or weight management supplements (e.g. green coffee and garcinia cambogia), and sports or performance enhancing supplements (e.g. whey protein and creatine) (10). While the latter represent some of the commonly used categories for DS, it is important to note that various sources will categorize supplements differently.

Regulation of Dietary Supplements in the U.S.

Under DSHEA, there are two main bodies that govern the regulation of DS: the U.S. Food and Drug Administration (FDA) and the Federal Trade Commission (FTC). The FDA is responsible for regulating the manufacturing and labeling of DS (according to DSHEA), overseeing the market for any unsafe or adulterated supplements or false claims, and ensuring the accuracy of labels, claims, and product literature surrounding supplements (1). The FTC, working with the FDA, regulates the supplement claims that appear in television, Internet, and print advertisements (11). In accordance with FDA regulations, DS can only include ingredients that are deemed safe by the FDA. These include ingredients used in DS prior to the passage of DSHEA in 1994 (as those ingredients are assumed to be safe based on their history of use), as well as new dietary ingredients (or NDI's, which are ingredients in DS that were not marketed in the U.S. prior to the passage of DSHEA). A manufacturer must notify and provide the FDA with reasonable evidence that an NDI is safe under the conditions recommended for use on the label before a supplement containing that ingredient can be manufactured/sold (12). However, this does not guarantee safety of the NDI by the FDA (13).

The manufacturing practices of DS companies are also regulated by the FDA. Current good manufacturing practices (cGMPs) are a set of mandatory, minimum requirements that all supplement manufacturers must follow to help ensure the quality and composition of DS and the production of properly labeled supplements. These requirements aim to prevent contamination of DS, prevent inclusion of harmful substances, and prevent addition of too much or too little of intended ingredients (i.e. to ensure the identity, purity, strength and composition of supplements). This is done by requiring certain activities in the manufacturing, packaging, labeling, and holding

steps of production, as well as requiring testing of ingredients/final products and recordkeeping of those test results (12, 14, 15).

The FTC regulates the advertisement of DS in the media (including magazines, television and radio ads, catalogs, and other marketing materials). DS claims in the media must not be misleading or untruthful, and the claims must be substantiated. The FTC generally relies on the FDA to determine whether a claim is adequately supported (11). The FDA also plays a role in the regulation of DS advertising, including labeling, point of sales materials, package inserts, product literature, and Internet promotion.

Under DSHEA, every DS must bear a Supplement Facts Panel, which details the contents of the supplement, including ingredients and nutritional contents. Additionally, under DSHEA, supplements are not meant to treat, prevent or cure disease and therefore cannot make claims to do so. However, there are three main types of claims that supplements can make: structure and function claims (e.g. "fiber maintains bowel regularity"), health claims (e.g. "adequate calcium may reduce osteoporosis risk"), and nutrient content claims (e.g. "30% omega-3 fatty acids") (16). Like the contents of DS, most label claims are not pre-approved by the FDA and must have a disclaimer stating so (health claims are an exception as they are subject to premarket FDA approval) (16). But, the FDA requires that there is adequate scientific evidence supporting the claims and the claim must be truthful and not misleading. If the manufacturer does not comply with the labeling or advertising standards, the FDA has the right to remove the product from the market (12).

Although the FDA and FTC both play significant roles in the regulation of DS, it is important to note that this regulation is mostly post-market. DSHEA does not require the federal government to approve DS (for quality, safety, or efficacy) before they are sold on the market (12). Instead, the federal government is responsible for monitoring the marketplace for unsafe DS and products making misleading claims. The FDA monitors the serious adverse event reporting that is required by DS manufacturers and the voluntary adverse event reporting done by consumers or healthcare professionals (17). Under DSHEA, the FDA can take action against supplements and supplement manufacturers (such as restrict use of a product or remove it from the marketplace) once they have identified and demonstrated "significant or unreasonable risk of illness or injury, or that a product is otherwise adulterated or misbranded" (17). However, this is after the DS is already being sold in the marketplace. Thus, manufactures are primarily responsible for ensuring safety, proper labeling and truthful claims, and compliance with DSHEA law prior to marketing a product.

Dietary Supplement Use in the U.S.

Prevalence of Use

The use of dietary supplements among the total adult population in the U.S. has stayed fairly consistent between 1999-2012, with approximately half of adults using dietary supplements (3-5). According to NHANES 2007-2010, 45% of the 12,000 adults surveyed reported taking dietary supplements to improve their health and 33% took supplements to maintain their health (4). Women were more likely to report taking supplements for bone health (36%), while 18% of men reported taking supplements for heart health (4). Those over the age of 60 years old reported taking supplements for systems-specific use such as heart, bone and joint, and eye health while younger adults were more incentivized by short-term effects such as energy or immunity (4).

Interestingly, studies show that DS users are more likely to report better health and participate in healthy

behaviors such as regular physical activity, eating a balanced diet and abstaining from smoking, a concept known as the inverse supplement hypothesis (4-6, 8, 18-20). Those that take supplements are generally healthy individuals that take an active role in their health and may not be the population that is most in need of the nutritional support. For example, data on adults' age 51 and older from the Continuing Survey of Food Intakes by Individuals and Diet and Health Knowledge Survey showed that DS users are more likely to meet their vitamin and mineral needs through food alone compared to non-users(19). Although regular DS users may not always be those who need or would benefit from DS the most, it is still essential to assess each individual and whether they would benefit from a supplement.

Healthcare practitioners need to develop a more centralized role in recommending and discussing supplement use with patients. Many adults decide to take DS on their own instead of being advised by a healthcare practitioner. According to NHANES 2007-2010, only 23% of adult supplement users take supplements that were recommended by their healthcare practitioner (4). A 2015 survey from the Council for Responsible Nutrition reported that 85% of adults inform their doctor about their use of dietary supplements while only 55% consider their medical doctor to be a trusted or reliable source of information on supplements (7). In a 2014 survey from the Council for Responsible Nutrition, 52% of those surveyed stated that their doctor or physician was a trusted source of reliable information on supplements while 28% and 28% identified their respective pharmacist and nutritionist as a reliable source of information. The remaining 20% identified their friends or family as a reputable source of supplement information (8). Providers can have a more active role in patient's use of dietary supplements by discussing the use of dietary supplement use with their patients and educating them on the importance of making individualized dietary supplement recommendations.

When it comes to the most common supplements being used by the adult population, various surveys have shown that the top two are multivitamin/multiminerals (MVMM) and calcium (4, 5, 21). According to NHANES 2007-2010, 32% of dietary supplement users reported taking a MVMM, making it the most common among supplement users. Calcium is the second most common supplement used in the general population as 12% reported taking the mineral. Calcium is particularly common among older adults. NHANES 2011-2012 found that 27% of supplement users 60 years and older are taking calcium for bone health (an increase of 6% from NHANES 1999-2000) (4, 5).

The third most common DS, according to NHANES 2007-2010, is omega 3 fats or fish oil. Approximately 10% 10% of adult supplement users reported taking omega 3s (4). According to the 2015 National Health Statistics Report, which analyzes trends in complementary medicine for 89,000 individuals, the use of fish oil is very common in the adult population (9). The survey reported that the most popular complementary health approach was nonvitamin, nonmineral dietary supplements with fish oil supplementation and glucosamine, chondroitin being the two most commonly used between 2007-2012 (9). Additional supplements that are more commonly used among adults include botanicals (8%), vitamin C (7%), multivitamins (6%), vitamin D (5%), vitamin E (4%), joint formulas 4%), vitamin B12 (3%), folic acid (2%), protein/sports formulas (2%), and fiber (1%) (4).

Evaluating Quality, Safety, and Efficacy of Dietary Supplements

Quality

Clinicians have a responsibility to be aware of how to evaluate the quality, safety and efficacy of dietary supplements before making recommendations to their patients. The FDA does not approve DS for quality, safety, or

efficacy before they are sold on the market which makes it difficult to identify supplements that provide quality, safety and efficacy. The current good manufacturing practices (cGMPs) that are outlined by the FDA are aimed at preventing adulteration and ensuring the quality of DS. However, manufacturer adherence to cGMPs is sometimes questionable. In order to determine compliance, the FDA is only required to conduct random audits (12, 23). For example, testing of various DS have shown that their contents do not always match what is listed on the label(23, 24). Independent lab test results from ConsumerLab.com in 2016 revealed that 22% of protein powders, 18% of MVMM's, and 4% of probiotic supplements did not meet label claims(25). The Natural Products Insider reported that over a three-year period (2010-2012), 444 out of 626 inspections by the FDA resulted in cGMP non-compliance violations(26). Poor compliance with cGMPs is also linked to undeclared allergens and lack of standardization between supplements (each pill in each bottle of a specific supplement may not have the same contents) - all of which can be avoided with proper quality control and compliance with the FDA's cGMPs(23, 24).

Aside from cGMP compliance, quality control can continue with independent third party quality verification programs, which can provide quality testing and communicate which DS meet quality standards. Some companies that provide this additional step in quality assessment include ConsumerLab.com, NSF International, Informed-Choice, and US Pharmacopeial Convention (USP). The verification programs can be paid by supplement manufacturers test the supplement for identity, ingredient quality, strength, purity/contaminants, consistency on the product label, and freshness and disintegration, as they apply to each supplement(25, 27-30). Some companies even perform on-site testing for cGMP compliance. With any of these verification companies, if the supplement meets quality standards, supplement manufacturers may use that company's seal of approval on packaging and advertising materials(27). This seal marked on a supplement package is a good indicator of a quality supplement and can provide consumers with more confidence in the supplements they purchase (12). However, the cost of the third party verification seals can be limiting and may not always be displayed as manufacturers cannot always afford both the testing and the seal. It's also possible for the manufacturer to feel that their quality standards are already high enough(27). ConsumerLab.com is a leading provider of independent lab testing of DS. For a nominal subscription, members can access reports about whether DS meet label claims for potency and purity of products that have been pulled off of store shelves(25).

Other elements of DS packaging can also be used to help determine the quality. Supplement labels that do not comply with DSHEA guidelines, such as the absence of a supplement facts panel, serving size, or %DV (when available), may indicate poor quality control. Supplements that advertise their patent or products with unrealistic "too good to be true" claims are often red flags for poor quality(31).

According to the FDA, DS that are sold on the Internet or from obscure retailers may pose an increased risk of having poor quality or containing adulterants. Additionally, the supplements with the greatest risk of contamination and poor quality include those promoted for weight management, bodybuilding and sexual enhancement (32). The FDA has a number of resources for identifying tainted or recalled supplements. Consumers and healthcare providers can report tainted supplements using the following websites:

MedWatch Safety Alerts (http://www.fda.gov/Safety/MedWatch/SafetyInformation/default.htm)

Medication Health Fraud DS subsection (http://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/MedicationHealthFraud/default.htm)

The Warning Letters Database (http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm) and Consumer Updates on DS (http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm153239.htm).

Safety

Supplement companies are responsible for ensuring the safety of each supplement as well as reporting any serious adverse events to the FDA but healthcare practitioners can also play an active role in reporting adverse events. A serious adverse event is defined as something that "results in death, a life-threatening experience, inpatient hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect, or requires ... a medical or surgical intervention to prevent" one of the stated outcomes. While manufacturers are required to report serious adverse events to the FDA, healthcare practitioners and consumers should also submit adverse event reports to the FDA via the online MedWatch program or by calling 1-800-FDA-1088(15, 33).

There is a risk of supplement contamination without proper compliance to cGMPs. Heavy metals, fungus/microbes, or pesticide contaminants along with the presence of controlled or banned ingredients found in supplements pose a health risk to consumers, and without testing, it is not clear whether a supplement is contaminated or not(34, 35). Additional concerns involve the use of ingredients that are not approved in the U.S. or ingredients that have not been studied in humans(15, 34). A further concern is that FDA recalled supplements are not effectively removed from the market. In a sample of supplements recalled for presence of banned ingredients, almost 67% were still available for purchase six months after the recall with 63% of them containing the same adulterant identified by the FDA. This adds to the safety risk of DS, showing that FDA action has not been 100% effective in removing potentially harmful products from the market (36).

Additional safety concerns include recommendations made by providers that pertain to the dose, the route of administration and medical contraindications. When making recommendations for the dose, the practitioner should ensure that they make safe and cautious recommendations that are specific to an individual's need. Different routes of administration such as oral capsules, liquid, nasal sprays, topical, suppositories, or IV affect the safety of the supplement too and the safest, most effective route should be determined by the healthcare practitioner. Medical contraindications to be aware of are kidney disease, liver disease, prescription medication users and the immunocompromised. Vulnerable groups that may be more sensitive to supplements include infants, children, adolescents, pregnant and lactating women, and the elderly. (need to add citation)

Efficacy

The FDA is only responsible for post-market quality and safety but does not assess the efficacy of DS since they are regulated more like foods than drugs. Those recommending DS need to be aware of the clinical efficacy based on published research. Efficacy is determined by potency, dose, active ingredients, and overall quality of the DS(34, 37). In order to stay current with the DS literature, practitioners can access evidence-based databases such as ConsumerLab.com, which is targeted to consumers but may still be valuable and the Natural Medicines Database, which targets healthcare practitioners specifically (22, 25). The Natural Medicines Database provides in depth information such as safety and efficacy ratings for DS and detailed information about drug-nutrient interactions(22).

Health care practitioners should identify the strength of evidence that exists for supplement use and discuss benefits and risks with patients. The Evidence vs. Harm Grading Strength of the Recommendation Taxonomy (SORT) system was designed as a tool to help practitioners make informed decisions about DS use and recommendations(38).

The following grades help assess the evidence of efficacy that exists on various supplements:

Grade A: Based on consistent, good-quality, patient-oriented evidence (systematic review or meta-analysis showing benefit)

Grade B: Based on inconsistent or limited-quality patient-oriented evidence

Grade C: Based on consensus, usual practice, opinion, and disease-oriented evidence

The following grades assess harm of various supplements:

Grade 3: Most Harm. Therapy may result in death or permanent disability.

Grade 2: Moderate Harm. Therapy has the potential to cause reversible side effects or negatively interact with other therapies.

Grade 1: Least Harm. Therapy poses little, if any, risk of harm.

For example, as discussed previously, glucosamine sulfate has inconsistent evidence for its use with osteoarthritis, but also has very little evidence of harm. Therefore, it could be classified as a Grade B1. Utilizing the SORT system can allow the practitioner and patient to be more informed on the research that exists to support DS use, in addition to any potential risk.

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Brigid Titgemeier, MS, RDN, LD
Registered Dietitian
Cleveland Clinic Center for Functional Medicine

Brigid Titgemeier is a Registered Dietitian Nutritionist at the Cleveland Clinic Center for Functional Medicine and an Adjunct Instructor at Case Western Reserve University. In 2014 Brigid co-developed the Center for Functional Medicine's nutrition department and has since trained their team of dietitians and developed shared nutrition appointments. Brigid has worked with over 2,000 functional medicine patients using a whole foods approach to optimizing health. She is completing her functional medicine training through the Institute for Functional Medicine and has trained with the Integrative and Functional Nutrition Academy.

Prior to working in functional medicine, Brigid worked at the Cleveland Clinic Wellness Institute and contributed to research initiatives in the Center for Lifestyle Medicine and nutrition strategies for corporate wellness clients. She is a published author of dozens of articles for U.S. News and World Report, the Huffington Post, and Cleveland Clinic Health Essentials. Brigid holds a Bachelor's of Science in Dietetics from Miami University and a Master's of Science in Public Health Nutrition from Case Western Reserve University. She completed her dietetic internship at Case Western Reserve University where she received the Charlotte Smith Award in Public Health Nutrition for outstanding academic performance and possessing potential for professional success.

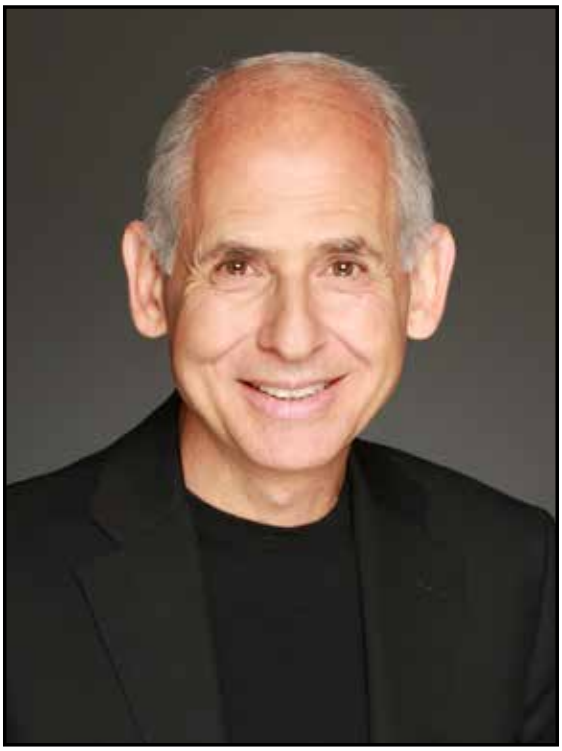
Stephanie R. Harris PhD, RDN, LD
Assistant Professor
Director, Combined Dietetic Internship/Master's Degree Program
Department of Nutrition
School of Medicine
Case Western Reserve University

Stephanie Harris is a Registered Dietitian Nutritionist and an Assistant Professor in the Department of Nutrition at Case Western Reserve University's School of Medicine in Cleveland Ohio. She is also the Director of the Combined Dietetic Internship/Master's Degree Program in the Department of Nutrition at CWRU. Stephanie teaches classes for undergraduate and graduate level nutrition majors, as well as medical students. She is also involved in the development of dietary supplement, wellness, and food as medicine/culinary medicine curriculum for medical students studying in the JJM Mandel Wellness and Preventative Care Pathway at CWRU. Her research interests have centered on the use of metabolomics and stable isotope techniques for the discovery of new metabolites in various disease states, and more recently expanded to (i) dietary supplement use and motivations for use, (ii) education, knowledge, and attitudes of integrative medicine among dietetics practitioners and educators, and (iii) nutrition education for health care professionals. Stephanie has served on the Executive Committee of the Academy of Nutrition and Dietetics Dietitians in Integrative and Functional Medicine (DIFM) Dietetics Practice Group since 2013. She received Ohio's 2015 Outstanding Dietetic Educator Award. Stephanie obtained her PhD in Nutritional Biochemistry & Human Metabolism and her MS in Nutrition from CWRU. She completed her dietetic internship at University Hospitals Cleveland Medical Center and received her BS in Nutrition, Food and Agriculture from Cornell University.

Kelly Morrow, MS, RDN is an Associate Professor in the department of Nutrition and Exercise Science at Bastyr University and Nutrition Clinic Coordinator at the Bastyr Center for Natural Health in Seattle, Washington. At the Bastyr Center, Kelly leads teams of nutrition graduate students in an integrative medicine teaching clinic where they collaborate with Naturopathic Doctors, Medical Doctors and practitioners of East Asian Medicine and Acupuncture.

Since 2002, she has been teaching faculty at Bastyr University delivering lectures in both the undergraduate and master's programs in Nutrition as well as the Naturopathic Medicine, Midwifery and Acupuncture programs. She regularly speaks to lay populations and at professional conferences, is a media representative for Bastyr University and a past Media Representative for the Washington State Academy of Nutrition and Dietetics. Kelly has delivered talks for the Academy of Nutrition, Northwest Renal Dietitians, The Washington Association of Naturopathic Physicians, The Greater Seattle Dietetic Association among others.

Kelly is an author for the Inflammation Module of the Integrative and Functional Nutrition Certificate of Training through the Academy of Nutrition and the author of the Integrative Nutrition and Dietary Supplements chapter for the 14th Ed. of Krause's Food and the Nutrition Care Process.
Kelly has served on the Professional Advancement and Communications committee and also served as Chair for Dietitians in Integrative and Functional Medicine (DIFM).



DANIEL G. AMEN
MD

The Brain Warrior's Way

A warrior is someone who is committed to master oneself at all levels, who develops the courage to do the right thing for yourself, others, and community.
—THE WAY OF THE SEAL BY MARK DIVINE

THE WAR FOR YOUR HEALTH is won or lost between your ears, in the moment-by-moment decisions your brain makes every day. When your brain works right your decisions are much more likely to be effective and add laser-like focus, energy, and health to your life. When your brain is troubled, for whatever reason, you are much more likely to make bad decisions that steal your energy, focus, moods, memory, and health and lead to your early destruction and trouble in future generations.

Bushido (Japanese: "way of the warrior") is the code of ethics for the samurai. It is a way of living that is required to be a warrior. Samurais ascribe to a culture focused on constant, never-ending self-improvement in an effort to protect themselves and those they love. The Brain Warrior's Way is also a way of living, a clear path we have developed over three decades of helping tens of thousands of patients at Amen Clinics have better brains and better lives. In addition, we have used this path to help people in the military, businesses, churches, schools, and drug rehabilitation centers. Living the Brain Warrior's Way will improve your decision-making ability and sense of personal power and help your

Energy	Weight
Focus	Relationships
Moods	Work
Memory	Overall health

The Brain Warrior's Way is a unique and powerful program and the only one of its kind to improve the health of your brain and body. It is grounded in scientific research and designed to help you live with vitality, a clear mind and excellent health—even if you are struggling or are in pain right now—even if you've made unhealthy choices for many years. This program will help you turn your health around. Don't you want to wake up feeling good inside and out every day?

By following the Brain Warrior's Way, you will transform the health of not just your brain and body, but the brains and bodies of those you love and care for. The new science of epigenetics has taught us that your habits turn on or off certain genes that make illnesses and early death more or less likely in you, and also in your children and grandchildren. The war for the health of your brain and body is not just about you. It is about generations of you.

Step by step, this book will show you how to develop a Brain Warrior's MASTERY over your physical and mental health. It will teach you:

Mind-set of a Brain Warrior—knowing your motivation to be healthy and focusing on abundance, never deprivation

Assessment of a Brain Warrior—having a clear strategy, brain health assessment, knowing and optimizing your important numbers, fighting the war on multiple fronts, and always being on the lookout to prevent future trouble

Sustenance of a Brain Warrior—knowing the food and supplements that fuel success and give you a competitive edge

Training of a Brain Warrior—engaging in the daily habits and routines that protect your health

Essence of a Brain Warrior—transforming your pain into passion and knowing why the world is a better place because you are here

Responsibilities of a Brain Warrior—taking the critical step of sharing information and creating your own tribe of Brain Warriors

Yearlong Basic Training of a Brain Warrior—making lasting changes with tools that will last a lifetime

RULES OF ENGAGEMENT: BRAIN WARRIORS ARE

Serious
Purposeful
Informed
Aware
Prepared
Nourished
Highly trained
Deeply honest
Passionate
Protective
Relentless

Along the way you will meet dozens of triumphant Brain Warriors who were once prisoners of the war for their health. Their stories will inspire and encourage you into a new way of living.

BRAIN WARRIOR BILL

Here is a note from the leader of an East Coast Young Presidents' Organization (YPO) Pod whose group spent three days with us at Amen Clinics learning the principles of the Brain Warrior's Way.

"The program dramatically changed my life, allowing me to lose weight, and to focus unlike I could ever remember. My depression faded away and my focus and productivity improved. As a group, we universally agreed that the visit to Amen Clinics had the greatest impact on our lives in over a decade of being together."

Most people don't want to think about wars and warriors, and we would prefer not to either, but if you open your eyes and tell yourself the truth about what is happening in our society it is painfully obvious: we are in a war for the health of our brains and bodies. Americans die younger and experience more illness than people in other wealthy nations, despite spending nearly twice as much on health care per person.1 Close to 75 percent of our health-care dollars are spent on chronic preventable illnesses, including Alzheimer's disease, depression, ADD/ADHD, diabetes and prediabetes, and obesity.

WHY WE ARE IN A WAR FOR OUR HEALTH

And this is not just an adult war. Huge corporations are targeting your children and grandchildren. When a clown or a king with a billion-dollar bankroll can come into your living room and bribe your children with toys to get them to eat low-quality, nonnutritious foods that promote illness and early death it's time to fight back. According to a recent study, the toys fast-food companies use to entice children are highly effective weapons in hooking their developing brains to want more of what will hurt their health.2 In addition, well-meaning organizations, such as the Girl Scouts, enlist young girls to sell unhealthful cookies as a way to fund their activities, and few people think twice about the sugar, vegetable oil, partially hydrogenated fats, and artificial preservatives that promote disease.

You are in a war for your health. Nearly everywhere you go (schools, work, shopping malls, movie theaters, airports, ball parks, and so on), someone is trying to sell you food that will kill you early. The standard American diet (SAD) is filled with pro-inflammatory foods that increase your risk for diabetes, hypertension, heart disease, cancer, ADHD, depression, and dementia.3 It is also associated with a smaller hippocampus, one of the major memory structures in the brain.4

The real weapons of mass destruction in our society are foods that are

Highly processed
Pesticide sprayed
Artificially colored and sweetened
High glycemic
Low fiber
Foodlike substances
Laden with hormones
Tainted with antibiotics

Plus the companies that produce these unhealthful foods not only use toys to hook tiny human brains but also use neuroscience tricks to hijack adult brains. They purposefully associate gorgeous, scantily clad women with poor-quality food to hook your pleasure centers, somehow getting you to make the illogical connection that if you eat those foods, either these women will want you or you will look like them. You must know there's no way these beautiful women would look the way they do if their diet regularly consisted of cheeseburgers that dripped mayonnaise, mustard, and ketchup down their blouses.

In addition, many corporations brag about the addictive nature of their foods, "Bet you can't eat just one." They hire food scientists to combine fat, sugar, and salt with the perfect texture, crunchiness, meltiness, and aroma to overwhelm the brain with flavor to trigger the "bliss point" in your brain, which is akin to taking a hit of cocaine, making you literally fall in love with low-quality foods. This is one of the reasons people say they love candy, doughnuts, pastries, french fries, and bread and can't ever conceive of giving them up. They are not eating to live; they are eating to feed addictions that were artificially created for a profit motive. We had one woman tell us she would rather get cancer than give up sugar. We wondered aloud if she dated the bad boys in high school. Being in love with something that hurts you is a position that needs some serious reexamination.

No food of any kind belongs in the same emotional place in your brain as the love you have for your spouse, children, or grandchildren. Many ancient warriors considered dependence on anything, especially food, a weakness, and totally unacceptable. They ate to win; their survival depended on it. We want you to do the same thing if you truly love yourself, your health, your loved ones, and future generations.

The war for your health is not just about our modern-day adulterated food. News outlets repeatedly pour toxic thoughts into our brains, making us see terror or disaster around every corner to boost their ratings. The constant frightening images activate our brains' primitive fear circuits (amygdala) that once ensured our survival but are now obsolete. The news always highlights the sensational, evil, and most awful stories to keep you hooked to their channels or websites. Unless you purposefully monitor your news intake, these companies succeed in raising your stress hormones, which over time shrink the major memory centers in your brain and put excessive fat around your waist—and belly fat is particularly toxic, because it converts healthy testosterone into unhealthy, cancer-promoting forms of estrogen. Do you reach for your phone first thing in the morning to see what awful things have happened in the world overnight? You might not have known that this habit is adversely affecting your health, but now you do.

You are in a war for your health. It is further fueled by technology companies that are constantly creating addictive gadgets that hook our attention and distract us from meaningful relationships.5 Many people are on their phones at mealtimes, rather than interacting with family members. A 2015 study found that teens actually spend more time on social media (average 9 hours) than they do asleep. Tweens are online 6 hours a day.6 Technology has hijacked developing brains with potentially serious consequences for many.

At Amen Clinics we have treated many teens and adults with video game or pornography addictions. One teenager became violent whenever his parents limited his play. We scanned his brain while he played video games and then later after he had abstained from playing any games for a month. It was like we were looking at the brains of two different people. The video games caused abnormal firing in his left temporal lobe, an area of the brain often associated with violence. When he was off video games, he was one of the sweetest, most polite young men we had met; but when on them, it was a completely different story.

Daniel did a Tinder experiment for the Dr. Oz Show using brain scans to see the effect of the dating site on mood and focus. He demonstrated that, in some individuals, the dating site can make people more vulnerable to anxiety and depression.

As video game and technology usage goes up, so do obesity and depression. 7 Ian Bogost, famous video game designer (Cow Clicker and Cruel 2 B Kind) and chair of media studies and professor of interactive computing at the Georgia Institute of Technology, calls the wave of new habit-forming technologies "the cigarettes of this century" and warns of their equally addictive and potentially destructive side effects.8

As part of the gadget revolution, disturbing new research from Microsoft reported that humans lose concentration after about 8 seconds, while the lowly goldfish loses its focus after about 9 seconds.9 It seems like evolution may be going in the wrong direction. In 2000, the human attention span average was estimated at 12 seconds,

which is not great; but losing a third of our attention span in fifteen years is alarming!

According to an article in Harvard Business Review, "Beware of the Busy Manager," our unhealthful lifestyles are diminishing our capacity at work.10 Only 10 percent of managers score high in both focus and energy, two of the main ingredients for success. The authors found that 20 percent of managers were disengaged, 30 percent scored high in procrastination, and 40 percent were easily distracted. This means that 90 percent of managers, and likely the rest of us, lack focus and/or energy.

These and other assaults on our brains and bodies have potentially devastating long-term consequences.

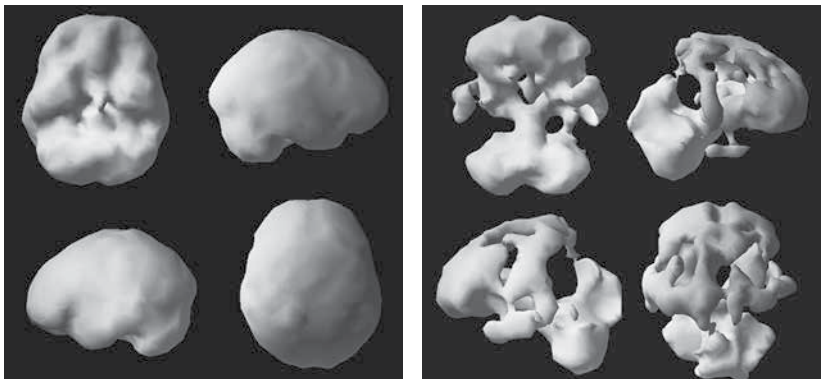
THE CONSEQUENCES OF THE WAR FOR OUR HEALTH

Genes play a more minor role than you might think, and many diseases are born out of unhealthful choices and behaviors, regardless of whether there is a genetic predisposition. Sadly, all around us we can see the devastating consequences of preventable illness.

Alzheimer's disease is expected to triple by 2050, and there is no cure on the horizon. Alzheimer's disease affects 50 percent of people age eightyfive and older. If you are fortunate to live until you are eighty-five or beyond you have a one-in-two chance of losing your mind along the way. To make matters worse, recent brain-imaging research has demonstrated that Alzheimer's disease and other forms of dementia actually start in the brain decades before you have any symptoms. Below is a brain SPECT scan, which measures blood flow and activity, of a fifty-nine-year-old woman diagnosed with Alzheimer's disease compared to someone with a healthy brain. You can see the back half of her brain is deteriorating. She likely had trouble in her brain in her thirties or forties.

Premature cognitive impairment leads to diminished work performance, which can lead to hardships among a workforce that grows older every year. With people working longer than ever before, even minor drops in brain function can jeopardize your productivity and job security. Since the 2008 recession, the average retirement age has risen from age fifty-seven to age sixty-two and by 2020 it is estimated that 25 percent of American workers will be fifty-five or older. The exciting news is that new research suggests that you can decrease your risk of Alzheimer's disease and other forms of dementia by 60 percent or more, and those same strategies will help your mood, focus, and memory. The Brain Warrior's Way will clearly lay out those strategies for you.

HEALTHY VERSUS ALZHEIMER'S DISEASE



Healthy
Full, even, symmetrical activity

Alzheimer's
Decreased activity in back of brain

Depression is one of the greatest killers of our time. It affects 50 million Americans at some point in their lives and has increased 400 percent since 1987. Depression is associated with suicide, divorce, job failure, heart disease, obesity, and dementia. Depression doubles the risk of Alzheimer's disease in women and quadruples it in men. A staggering 23 percent of women between the ages of twenty and sixty are taking antidepressant medications. The risk of depression also significantly increases after the age of sixty-five.11

Attention deficit disorder (ADD), also called attention deficit hyperactivity disorder (ADHD), is now being diagnosed more frequently than ever. Statistics from the Centers for Disease Control and Prevention (CDC) report that

nearly one in five high-school-age boys and 11 percent of school-age children overall have received a diagnosis of ADD, including an estimated 6.4 million children between the ages of six and seventeen. This is a 16 percent increase since 2007 and a 41 percent increase in the past decade.12 This rapid rise of ADD is due to many factors, including low-fat, low-fiber, high-glycemic diets; increased use of electronics; decreased exercise; and diminished sleep. Many people underestimate the devastating consequences of ADD. Yet, when left untreated, it is associated with school underachievement and failure (35 percent never finish high school), drug and alcohol abuse (according to one study from Harvard, 52 percent of untreated ADD adults have a substance abuse problem), job failure, divorce, incarceration, obesity, depression, and dementia.

Diabetes or prediabetes now affects 50 percent of the U.S. population, according to a 2015 study published in the *Journal of the American Medical Alzheimer's Association.13* Blood sugar problems have dramatically escalated in the last thirty years. In 1960, one out of a hundred people in America had type 2 diabetes; today that ratio has changed to one out of ten people, a tenfold increase. Since the 1980s, the rate of type 2 diabetes has gone up 700 percent. 14 The standard American diet is likely to blame and the sad news is that a majority of these cases are preventable. Most people don't fully understand the devastating consequences of diabetes and even prediabetes, in which blood sugar levels are higher than normal but not yet high enough to qualify for a diagnosis of diabetes. High blood sugar levels damage blood vessels, inhibit healing, and damage every organ in the body. We have both lost loved ones with diabetes who had limbs amputated and suffered from depression, dementia, heart disease, and blindness.

Obesity is a serious national crisis with two-thirds of Americans overweight and one-third obese. Obesity increases inflammation, which is a low-level fire in the body that destroys our organs and is a risk factor for more than thirty medical illnesses, including cancer, diabetes, depression, and dementia. There are many published studies, including two by the research team at Amen Clinics, that report as your weight goes up, the size and function of your brain go down. This is the biggest brain drain in U.S. history and is now a national security crisis. Around 75 percent of young applicants for the military are rejected. The Department of Defense stated, "Being overweight or obese turns out to be the leading medical reason why applicants fail to qualify for military service. Today, otherwise excellent recruit prospects, some of them with generations of sterling military service in their family history, are being turned away because they are just too overweight."

Our national weight problem is not just an adult issue. Childhood obesity has increased from 4 percent in 1982 to 18.5 percent in 2015, a 350 percent increase. And it is very clear that the food scientists and fast-food companies are going after your kids. If you are not a warrior for the health of your brain and the brains of those who depend on you, ADD, depression, dementia, premature aging, diabetes, obesity, and premature death are the consequences for your loved ones and yourself.

When we first came to understand the interrelatedness of these illnesses and implemented integrated treatment strategies, we were so excited with the outcome for our patients: better energy, focus, mood, memory, weight, and even pain relief. Initially, when we started to talk about the Brain Warrior's Way, some people pushed back, saying, "But I don't want to fight—being a Brain

The answer to these epidemic problems is not to see them as separate disorders with their own unique treatments, but rather as different expressions of the same unhealthy lifestyle that have exactly the same cure. In other words, there are many ways to become sick, but there is one clear path to wellness, and it's simpler than you think: It is the Brain Warrior's Way.

Warrior sounds hard." Our response was and still is, "Being sick is hard. Being a Brain Warrior is easy once you understand and implement the principles." Having your health, with better energy, memory, mood, and focus, is priceless. More than anything, being a Brain Warrior is an incredible mind shift with lifelong benefits—and you will

never want to go back to bad habits and poor choices for your health.

We recently gave a presentation to the eighteen-member executive team of a multibillion-dollar technology company. At the end of the first morning, the CEO pulled Daniel aside and said he had to plant brain health in his company. "It could be our competitive advantage," he said, "especially when we are competing for talent with the likes of Google, IBM, and Microsoft." Just as it is for them, brain health is your competitive advantage in life. It will help you thrive in every aspect of your personal life, health, work, finances, and relationships.

There is a proverb in martial arts,
"Master, why do you teach me to fight, but
speak of peace?"
The master replies,
"It is better to be a warrior in a garden,
than a gardener in a war."

If you are a lover or a healer and not a fighter, like Daniel, then harness the healing power by becoming a peaceful Brain Warrior. The most effective warriors in human history never picked up a physical weapon. Think of Jesus, Gandhi, Nelson Mandela, and Martin Luther King Jr., all of whom inspired massive numbers of people to work for just causes and changed history forever. Their fights were personal and principle centered and were won with their brains, not their brawn, which is exactly what we will show you how to do.

If you are a fighter like Tana, who has black belts in both Tae Kwon Do and Kenpo, this book will make perfect sense to you, too. Tana has been through a war with her health and never wants to go through it again. As her sensei Bob White says, "If you are prepared for the worst, you can expect the best." For her, martial arts is symbolic of overcoming barriers and never giving up.

DANIEL AND TANA'S BRAIN WARRIOR PATHS

The Brain Warrior's Way is deeply personal for both of us. We love our mission of creating and leading the Brain Warrior community of people who are serious about the health of their bodies and brains. Here is a brief summary of our individual journeys, so you can understand why this movement is important to us.

DANIEL'S BRAIN WARRIOR PATH

The warrior mind-set has been with me since 1972 when I enlisted in the U.S. Army at the age of eighteen to become an infantry medic. Working with wounded soldiers was where my love of medicine was born. As a medic, I was a warrior servant and loved supporting the health of our fighting men and women. After about a year, I realized that as much as I loved the medical aspects of being a medic I really hated sleeping in the mud and being shot at, so I got myself retrained as an X-ray technician and developed a passion for medical imaging. As our professors used to say, "How do you know unless you look?"

In 1979, when I was a second-year medical student, someone I cared about deeply tried to kill herself, and I took her to see a wonderful psychiatrist. I came to realize that if he helped her, which he did, it would not only save her life, but it could also help her children, and even her future grandchildren, as they would be shaped by someone who was happier and more stable. I fell in love with psychiatry because I realized it has the potential to change generations of people.

Since deciding to become a psychiatrist, I have been at war nearly every day fighting for the mental health and brain health of my patients. I fight with them for their sanity, marriages, children, grandchildren, and jobs as well as their will to survive and thrive. In my work, I have been at war taking care of children, teenagers, and adults who have been suicidal, homicidal, scarred by trauma, psychotic, depressed, manic, panicked, addicted, and demented.

The journey to becoming a dedicated Brain Warrior began in earnest in 1991 when I attended my first lecture on brain SPECT imaging. SPECT stands for single photon emission computed tomography, a nuclear medicine study that looks at blood flow and activity in three-dimensional maps. SPECT was presented as a tool that could give psychiatrists more information to help their patients. In that one lecture, my two professional loves, medical im-

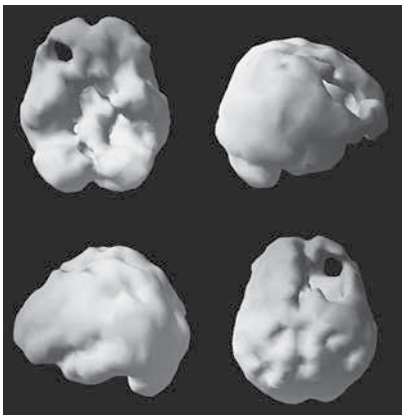
aging and psychiatry, came together and, quite honestly, revolutionized my life. Over the next twenty- five years my colleagues and I at Amen Clinics would build the world's largest database of brain scans related to behavior, totaling more than 125,000 scans of patients from 111 countries.

SPECT basically tells us three things about brain function: good activity, too little activity, and too much activity. Below are scans of people with traumatic brain injury and drug abuse. The images taught us many important lessons we will share with you in this book, such as how playing football, drinking too much alcohol, and using illicit drugs damage your brain and your life.

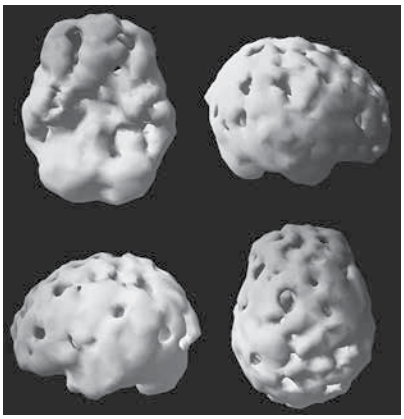
You've heard it said that a picture is worth a thousand words, but a map is worth a thousand pictures. A map tells you where you are and gives you directions on how to get to where you want to go. That is what SPECT imaging does for us at Amen Clinics. It gives us a map to help us better diagnose and treat our patients.

One of the first lessons the scans taught me was that "brain envy" is the real secret to happiness and longevity. When I first started to order scans I was so excited about the technology, I scanned many people I

TRAUMATIC BRAIN INJURY AND DRUG ABUSE

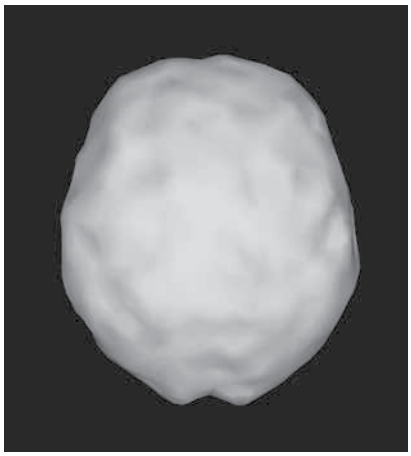


Low activity in the right frontal lobe from a traumatic brain injury



Holes indicate overall low activity, consistent with toxic effects of addiction

MY MOTHER'S BEAUTIFUL SPECT SCAN AT AGE SIXTY



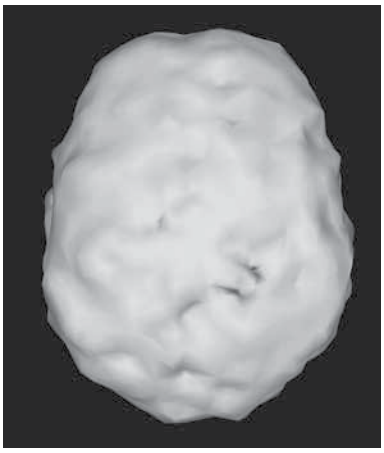
Full, even, symmetrical, healthy appearance

knew, from a friend who had bad temper problems, to a cousin with apanic disorder, to my sixty-year-old mother, who happened to have a stunningly beautiful brain, which reflected her loving, amazing life.

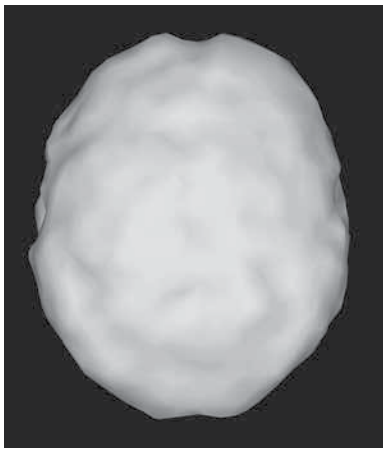
I was thirty-seven the first time I was scanned, and my brain was not healthy. I played football in high school, contracted meningitis as a young soldier, and had many bad brain habits. I didn't sleep much, was chronically stressed, and carried an extra thirty pounds. Seeing my brain caused me to develop brain envy and really care about it. Besides, how could my sixty-year-old mother have a younger-looking brain than I did? That was really irritating. The Brain Warrior's Way program we are going to give you in this book is the same one I initially developed for myself and for our patients. Now, twenty-five years later, my brain looks younger and healthier, which is not usually what happens as we get older. Typically, brains become less and less active over time, but now we know it doesn't have to be that way. We've discovered that with the right strategies brain aging is optional.

The health of your brain is much more about
your actions than your age.

DANIEL BEFORE AND DANIEL TWENTY-FIVE YEARS LATER



Bumpy, toxic appearance



Much healthier

TANA'S BRAIN WARRIOR PATH: YOUR HISTORY IS NOT YOUR DESTINY

The word victim conjures different emotions for everyone. I find it repulsive. It's personal. People who know me often describe me as an "ass kicker." It's true. I'm an ass kicker, a loving ass kicker, but an ass kicker nonetheless. My ass-kicking abilities were born of necessity. It would be fair to say I did not grow up in the All-American-Dream situation. In fact, reality television had nothing on my family. I was a little girl who grew up with a lot of trauma and drama. I still remember the day when I was four years old and saw my mother and grandmother falling to the floor sobbing in grief when they discovered that my uncle had been murdered in a drug deal gone wrong.

We were poor, so as a latch-key kid I soothed my anxiety with my best friends: the leprechaun (Lucky Charms), the captain (Cap'n Crunch), and the tiger (Frosted Flakes). The chronic stress in my house paired with the poor-quality food attacked my immune system. I was sick a lot and became a frequent flyer at the hospital. I earned my miles the hard way, but being in the hospital so frequently gave me the desire to help others who were sick.

When I was seven years old, my grandmother came to live with us because her diabetes had become unmanageable. It wasn't so that she could take care of me, but rather so I could help take care of her. By the time I was eleven, I had to inject her with insulin, because she had gone legally blind from the diabetes. My mother wasn't home to do it because she was working several jobs to make ends meet. I was terrified when the teaching nurse gave me an orange to practice on, telling me that if I gave my grandmother the wrong dose I could kill her.

The decision to learn how to fight, really fight, stems from a very personal traumatic experience. One day while walking to school at age fifteen, I was attacked by a large man. He clawed and grabbed very personal parts of my body as he overpowered me, pushing me toward the bushes in the nearby alley. Oddly, it didn't occur to me to be scared at the time, which ultimately may have saved my life. This psychopath in a suit was planning on raping me. Righteous indignation and fury were the only emotions coursing through my veins and gave me the fuel to scream, rip his shirt, slam my knee into his groin, and run . . . fast! Being overpowered is not a feeling you ever forget. Following the shock of that event, I felt terrified that any man could overpower me, simply because

he was larger or stronger. Outrage quickly triumphed over terror. It took about a week before I resolved never to be a victim, or at least never act and feel like one. I taped a picture of Ms. Olympia to my mirror and began training to be strong, muscular, and agile. I wanted nothing to do with the image society was shoving down the throats of young women to be impossibly thin. I wanted to be a warrior!

What I never anticipated was the attack that came quietly eight years later, with no fanfare. Without warning a different kind of perpetrator knocked me flat on my back. It was a sucker punch I never saw coming. In fact it came from inside my own cells. I felt totally betrayed by my body when I was diagnosed with thyroid cancer in my early twenties. It had metastasized into my lymph nodes and recurred multiple times. For the next eleven years, while my friends were graduating from college and getting married, I was undergoing surgeries and radiation treatments and was dealing with a multitude of other health issues that followed as a result. For the second time I knew what it felt like to be a victim and I despised it. I became so depressed I literally prayed that I would die. I thought, "If there is a God, He has given up on me."

At one point I was so sick I was on nine prescriptions and taking medications just to handle the side effects of some of the drugs. When I complained, the doctor told me it was genetic, that I was in denial, and said maybe I should see a psychiatrist! Let me be clear: that is not how I met Daniel! I was never a patient at the clinics, even though Daniel often says I'm a psychiatrist's dream.

When I was sick, I was fighting an invisible phantom, and I realized I was in for the fight of my life. It was so much harder to fight for my own health. I was never given explanations about how I would respond physically and emotionally to the medical treatments I was undergoing. No one explained that when my thyroid gland was removed and I was taken off of thyroid medication for two months to go through treatments, I would feel so horrible that I would wish I were dead. The depression enveloped me like a dark cloud, and I couldn't see the sun to save my life. All I knew was that I couldn't get out of bed, and I would rather be dead than go on wasting oxygen and being a burden to my family. That's when I became certain that God had abandoned me.

But God hadn't given up on me. Somehow, over time, I managed to summon every ounce of power in my being and, with God's help, I transformed my anger and fear into a positive energy that fueled a phoenix-like rise from the ashes of poor health. I went on to become a different kind of warrior. That's when I became my own best health advocate.

What does growing up in poverty, having chronic stress, and being assaulted have to do with being attacked by cancer? A lot; chronic stress attacked my immune system and made me vulnerable to illness. I had to fight back, which is how I found my Brain Warrior path and decided to help myself and others transform their brains and bodies. I became a trauma/neurosurgical ICU nurse, and I took care of the sickest patients in the hospital. I also became a martial artist because it made me feel empowered and gave me the mind-set of a warrior.

The wisdom I gleaned from martial arts was more than fighting, more than a sport, more than an art. Being a warrior is a mind-set. Being a Brain Warrior is putting these concepts into a brain health model. Anyone can have a Brain Warrior mind-set with a little training and a lot of focus. I want to be an example of strength, health, and fitness for my daughter and my patients. I quickly realized that my martial arts training and my warrior mind-set combined to form the perfect metaphor to help empower patients who have felt weak, depressed, sick, and victimized.

My goal is to teach you the way of the Brain Warrior so you can get a black belt in health.

FAST-TRACK VERSUS INCREMENTAL APPROACH

In our experience, there are two major types of people seeking help:

1. Some are like Tana and have a natural warrior mind-set. They want to jump in with both feet to feel better as quickly as possible. They are the kind of people who say, "Just tell me what to do and I'll do it all." They are often sick or they have experienced a major health crisis. They are tired of feeling sick and tired.

2. Other people will take an incremental approach. They will do one thing at a time, then another, then another, and over time plant as many good habits into their life that seem to make sense and are easily doable. This is more consistent with Daniel's path over the years.

Whichever path you choose, this program can help you. One of our most inspiring Brain Warriors, Nancy (whom you'll meet in Part 4), took the incremental approach and within a year lost 70 pounds and completely transformed her life. Daniel's father (you'll meet him in Part 7), on the other hand, was very sick, and when he jumped in to become a Brain Warrior he did everything we told him to, including changing his diet, exercising regularly, managing his stress, and taking his vitamins and supplements, and he powerfully transformed his health in a much shorter period of time. It is up to you to choose the path that is best for you; either one can lead you to great success.

BRAIN WARRIORS ADVANCE IN STAGES: PRIMITIVE, MECHANICAL, SPONTANEOUS

Every martial artist, athlete, or musician remembers how awkward she felt when she first started learning complex moves. Most felt like their bodies would never cooperate. However, over time the moves became smoother, until they eventually felt like second nature. The brain and body needed time to grow, make new connections, and adapt to new ways of working and thinking.

When someone is first starting the Brain Warrior's Way program she often feels a bit overwhelmed and confused.

> Hey, where's the sugar?!
> Everything in moderation!
> What happened to the bread and pasta? When are they coming back?
> But I love french fries and sodas!
> I don't know where to shop or what to buy!
> I don't want to get 8 hours of sleep!
> I don't want to exercise!
> I'm too busy, too stressed, too used to my old ways.

We tell our Brain Warriors in training not to worry, because they are in the **primitive phase,** when things feel impossible and hard, and they think they'll never be able to do it. It just takes trust, a bit of knowledge, success in feeling better quickly, and persistence to get to the next stage. Pretty soon, often within thirty days if you are on the fast track or thirty to ninety days if you are taking a more incremental approach, your taste buds regenerate themselves, the brain makes new connections and begins to grow, and soon enough, everything becomes easier.

Then you will transition to the **mechanical phase,** when you develop a healthy rhythm. You find the foods you love, exercises you can do, and brain healthy habits come easier to you. Clarity and energy replace brain fog. You start associating certain foods with feeling happier and more energized or with feeling sadder and more lethargic. It starts to become much easier to make healthy choices. You become better at noticing your negative thought patterns and begin questioning the negative thoughts running through your head. In this phase you still have to closely follow the Brain Warrior's Way program, because it is not yet second nature to you. This phase may last for one to three months for the fast-track folks and three to six months for the incrementalists.

Our goal is for you to reach the **spontaneous phase,** when your habits and responses become automatic and second nature. This usually occurs between four and six months for the fast-track folks and six and twelve months for the people who are taking things step by step. And if you persist through your challenges and setbacks, such as job or work challenges, divorce and deaths (which we all experience), the Brain Warrior's Way will last a lifetime.

In the spontaneous phase, the responses and habits become automatic.

> Do you want dessert? Yes, but I want something that serves my health, rather than steals from it.
> Do you want bread before dinner? No.
> Would you like a second glass of wine? No.
> You schedule your workouts and rarely miss them, as you would rarely miss your child's sporting event or a doctor's appointment. They are important to you.
> You don't have to think about your responses because they are spontaneous and habitual in a good way.

Get your black belt in brain health. Being a black belt doesn't mean you are tougher or stronger or that you don't

get scared. Being a black belt means you never give up, you face your fears, you persevere, and you always get up one more time!

A black belt is just a white belt who never quit.

This gives you permission to fall without failing, as long as you get up and try again. It is a process. Most important, you pass on the information by becoming a mentor to someone who is struggling. To get your black belt you are expected to be a mentor, to teach others your art. By teaching others, you powerfully reinforce in yourself what you've learned. It truly is in the giving that we receive.

PRIMITIVE—MECHANICAL — SPONTANEOUS

Based on our experience, the most successful Brain Warriors go through the following three phases over the course of a year.

Months One to Three: The Primitive Phase

In the primitive phase, just follow the steps and do what we ask you to do; it won't feel natural, so it is important to follow the map or you will get lost.

Recognize the war for your health and make a decision to change (Mind-Set, Part 1)

Assess your brain to know your type and get your important health numbers (Assess, Part 2)

Clean out your pantry, stock your kitchen with great food, start some simple supplements (Sustenance, Part 3)

Start developing brain healthy routines around exercise and sleep (Training, Part 4)

Begin to identify your essence, and ask yourself why you really want to be healthy and clarify your purpose (Essence, Part 5)

Think about who needs you to be healthy and who you are responsible for now and in the future, and look for friends who can do the program with you (Responsibility, Part 6)

Don't think of this as a quick fix; complete the 14-Day Brain Boost (Yearlong, Part 7)

Plan on making many mistakes; expect it, but don't think of falling as failing. To move to the mechanical phase, it is essential to pay attention to mistakes and start learning from them. Months Two to Six: The Mechanical Phase The mechanical phase is when your confidence begins to grow. You have the sense you can do it, but you still need a mentor and help.

Become more committed to being a Brain Warrior sheepdog for yourself and loved ones, after becoming aware of the toxicity and illness around you. You are focused on the abundance of health rather than being deprived of treats. Increased success leads to increased determination. You are better at ignoring or deflecting the criticism of others; it is bound to come from your unhealthy friends. (Mind-Set, Part 1)

Know the lab values of your important health numbers and work to optimize them. You attack vulnerability to disease on multiple fronts (inflammation, blood sugar control, antioxidant support, nutrient loading). You know your risk factors of depression, accelerated aging, and Alzheimer's and are actively taking steps to prevent them. (Assess, Part 2)

Find multiple foods you love that also love you back. Your supplements are more targeted to your brain type. (Sustenance, Part 3)

Expand your brain healthy routines to include simple meditation, deep relaxation, and learning to question the negative thoughts that try to steal your happiness. You feel a continual need to keep

learning. Your routine becomes easier and more defined. (Training, Part 4)

Start to discuss your past failures and painful moments with friends and family and see the meaning in prior suffering. (Essence, Part 5)

Start to share this message with friends, coworkers, and loved ones. Your Brain Warrior tribe becomes a critical part of your life. (Responsibility, Part 6)

Feel all in, not for a few months, but for the rest of your life. (Yearlong, Part 7)

Begin to make fewer mistakes. There will still be bad days, but you are better at learning from them and quickly turning them around.

Months Six to Twelve: The Spontaneous Phase

Habits become routine in the spontaneous phase. You say to yourself, "I got this; it is not hard." You naturally respond by doing the right things.

Never think of giving up, even when you fall. You jump back into the game and start doing the right things again. You develop a sheepdog attitude and identify with being healthy. **(Mind-Set, Part 1)**

Retest your important numbers to see your improvement. You're more focused on long-term prevention strategies. (Assess, Part 2)

Find new foods and recipes, as if on a treasure hunt. Your nutrition and supplement routine is consistent. You feel joyful in your food choices and realize eating poorly is depriving yourself of your health. (Sustenance, Part 3)

Feel uncomfortable or irritated when you are out of your Brain Warrior routine—it feels better to do the right thing than to do the wrong thing. New learning excites you as you feel more focused and cognitively sharper. (Training, Part 4)

Be excited to help others; being healthy and sharing the Brain Warrior message becomes part of who you are because you have a secret that can change the world. (Essence, Part 5)

Become motivated to mentor others, to share your success. (Responsibility, Part 6)

Celebrate the process of becoming a Brain Warrior and feeling better and stronger for a lifetime. (Yearlong, Part 7)

IS THIS PROGRAM FOR YOU?

This program is for those who want to be serious about their health, either out of desire or necessity. It is for people who want to look and feel their best for as long as possible and for those who want to excel at work and school and in their relationships. It is also for people who struggle with problems such as:

Depression
ADHD
Anxiety disorders
Post-traumatic stress disorder
Addictions
Bipolar disorder
Traumatic brain injuries
Memory problems
Early dementia
Alzheimer's disease or other forms of dementia in their families
Obesity
Diabetes or prediabetes

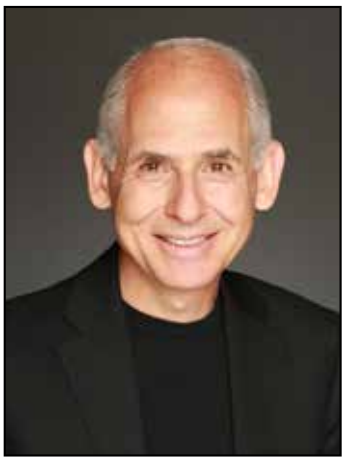
Heart disease
Cancer
Cognitive effects of chemotherapy

The Brain Warrior's Way is also for the parents of children with disabilitiesand those taking care of elderly or impaired parents. It is for those who want to build a legacy of health, rather than leave a legacy of illness; it's for those who want to be empowered; and it's for those who feel as if they were in a war for their health.

The Brain Warrior's Way is not for everyone. It is for people who want to change their brains and bodies for the rest of their lives. It is not for those looking for a quick fix, or cheat days, or wanting to take the month of December off. It is not for those who say "everything in moderation." Arsenic, cocaine, or having affairs in moderation can be very problematic. We are also not looking for people who have to be perfect. That is often an excuse to fail. We expect you will make mistakes and you will fall, just like toddlers fall when learning to walk, but Brain Warriorslearn from their mistakes and make fewer and fewer of them over time.

We are recruiting and training Brain Warriors—people who are serious about the health of their brains and bodies, and the brains and bodies of those they love. Once you develop brain envy, a deep abiding love for the most precious organ in your body, you have the opportunity to become a Brain Warrior and everything changes for the good. The Brain Warrior's Way is a war cry to rally our families, businesses, schools, communities, and tribes to finally get and stay healthy. Join us.

Daniel Amen believes that brain health is central to all health and success. "When your brain works right," he says, "you work right; and when your brain is troubled you are much more likely to have trouble in your life." His work is dedicated to helping people have better brains and better lives.



The Washington Post called Dr. Amen the most popular psychiatrist in America and Sharecare named him the web's #1 most influential expert and advocate on mental health.

Dr. Amen is a physician, double board-certified psychiatrist, 10 time New York Times bestselling author and international speaker. He is the founder of Amen Clinics in Costa Mesa and San Francisco, California; Bellevue, Washington; Reston, Virginia; Atlanta, Georgia; New York, New York and Chicago, Illinois. Amen Clinics have one of the highest published success rates treating complex psychiatric issues, and they have built the world's largest database of functional brain scans, totaling more than 135,000 scans on patients from 111 countries.

Through his research using the Amen Clinics database Dr. Amen has published over 70 scientific articles on a wide range of topics including autism, resistant depression, suicide, attention deficit hyperactivity disorder, post-traumatic stress disorder, traumatic brain injury, and others that have appeared in many prestigious journals, including Molecular Psychiatry, PLOS One, Nature's Translational Psychiatry, Nature's Obesity, Military Medicine, and Journal of Neuropsychiatry and Clinical Neuroscience.

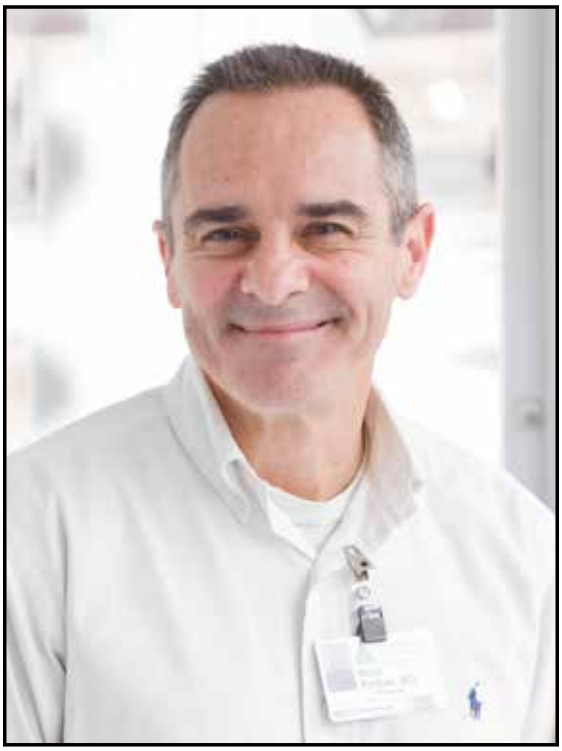
Dr. Amen is the lead researcher on the world's largest brain imaging and rehabilitation study on professional football players. His research has not only demonstrated high levels of brain damage in players, it also showed the possibility of significant recovery for many with the principles that underlie his work. His research on posttraumatic stress disorder and traumatic brain injury was recognized by Discover Magazine in its Year in Science issue as one of the "100 Top 100 Stories of 2015."

Together with Pastor Rick Warren and Dr. Mark Hyman, Dr. Amen is also one of the chief architects on Saddleback Church's "Daniel Plan," a program to get the world healthy through religious organizations, which has been taught in thousands of churches around the world.

Dr. Amen is the author of over 30 books, including the #1 New York Times bestseller, Change Your Brain, Change Your Life, The Daniel Plan, Unleash the Power of the Female Brain and Healing ADD. In November 2016 Penguin published Dr. Amen and Mrs. Amen's two newest books The Brain Warrior's Way and The Brain Warrior's Way Cookbook.

Dr. Amen has written, produced and hosted 12 popular shows about the brain on public television. He has appeared in movies, including After the Last Round and The Crash Reel, and in Emmy-winning television shows, such as The Truth About Drinking and the Dr. Oz Show. He was a consultant on the movie Concussion, starring Will Smith. He has also spoken for the National Security Agency (NSA), the National Science Foundation (NSF), Harvard's Learning and the Brain Conference, the Department of the Interior, the National Council of Juvenile and Family Court Judges and the Supreme Courts of Delaware, Ohio and Wyoming. Dr. Amen's work has been featured in Newsweek, Time Magazine, Huffington Post, BBC, The Guardian, Parade Magazine, New York Times, New York Times Magazine, Washington Post, LA Times, Men's Health, and Cosmopolitan.

Dr. Amen is married to Tana, the father of four children and grandfather to Elias, Emmy, Liam and Louie. He is an avid table tennis player.



MARK PETTUS

M.D. FACP

Creating Health

Sugar, Fructose and Carbohydrate Density: The Unsweetened Truth

It is almost impossible for anyone in health care to look around and not be struck by how unhealthy Americans have become. We care for people who are more complex, older, and sicker than ever! Equally stunning is how quickly this epidemic of chronic complex disease has evolved. Over the last two generations we have seen greater longevity - the good news - and an enormous decline in health and functional capacity, the not so good news. Fifty percent of Americans have at least one chronic disease diagnosis and 1 in 4 have two or more as well as some decline in their capacity to function as they once did. And if that was not concerning enough, we are witness to an unprecedented impact on the health of young children and adolescents. Mothers are giving birth to larger babies, obesity effects 1 in 6 children, asthma, ADD, autism spectrum, metabolic syndrome, and anxiety-depression are more prevalent than ever in our precious young children and adults (source: CDC).

For the first time in human history, chronic "non-communicable diseases" e.g. cardiovascular disease, cancer, diabetes, Alzheimer's, and autoimmunity pose a greater health burden than infectious diseases. Any society that has adopted a western diet, characterized by low cost, decreased nutrient density that is highly processed has seen a dramatic rise in obesity and prevalence of chronic complex disease. Remarkably, 30% more people are obese than who are undernourished and as many as 40% of non-obese individuals have evidence of chronic disease including metabolic syndrome. An important consideration is that obesity is not the cause of diabetes or chronic disease but rather a "phenotype" that is a marker for metabolic dysfunction that is even more prevalent. In this context, obesity is more a consequence than a cause.

The current trajectory of health in America is not very good. Some estimate that by 2030, 165 million Americans will be obese. One hundred million Americans may have diabetes by 2050. The current and long-term economic costs are staggering with an estimated 65 billion in lost productivity and 245 billion in health care services annually for morbidities associated with metabolic syndrome. This represents a 41% rise over the last 5 years. There have been many reasons for this e.g. changes in our environment i.e., food supply, diminished need for movement, disrupted circadian rhythm or loss of entrainment, environmental toxic burden, stress, etc. A cogent case can be made that leading the way, above and beyond all environmental changes over the last three generations, is the amount of sugar, fructose (from sugar and high fructose corn syrup) and refined grain flour consumption which tripled over the last 50 years.

In 1980, James Fries MD, Professor Emeritus at Stanford published a landmark article in the New England Journal of Medicine entitled "Aging, Natural Death and the Compression of Morbidity". In his prescient synthesis Dr. Fries reviewed the concerning growth trajectory of chronic complex disease and introduced the radical notion that we have the potential to "compress" morbidity over our lifetime with greater attention to the translation and application of healthier lifestyle principles. He suggested that instead of a more predictable decline in quality of life and functional capacity over time (the current "norm"), we could "rectangularize" the relationship between aging and quality of life. In other words, we have the capacity to live well up until something takes our life. The ideal would be to help individuals live in a way that would compress, over a longer lifespan, morbidity that would diminish quality of life. In this context, creating health is about optimizing organ reserve i.e., getting the most out of our capacity for resilience, restoration, and regeneration. Health should not be left to chance. Health requires conscious effort i.e. choosing wisely, on the part of the organism. In 2015 we need to be more aware of how compatible our environment is with what we need to live long and well.

So what is going on here? Why is it so hard to be well and to stay well? If the natural state of any human is to heal his-herself, then what is interfering with that innate capacity? How have we come to assume that getting larger, slowing down, having more health concerns, and experiencing a diminished capacity for thriving are normal and inevitable consequences of aging? If I feel terrible (and some days I do) is it because I am getting old? While this is not about immortality, I no longer drink the Kool-Aid that suggests getting older inevitably means falling apart.

I am going to examine the evidence that our modern environment has become less compatible with our fine-tuned evolutionary biologic design. The proposition is as follows:

1. Creating health requires more conscious attention to the alignment of one's environment with that which we have evolved to be in relationship with.

2. Our DNA or "Book of Life" continues to have a stone-age imperative.

3. Our "environmental inputs" i.e., how we eat, sleep, connect, move, manage toxic burden, tend to our microbiome, and interpret and response to events in our lives, etc. require wiser choices in order to prevent a dysfunctional metabolic landscape from emerging. I will suggest that our current epidemic of chronic complex disease has become the new norm as a default response to complex gene-environment interactions gone awry.

When it comes to creating health, the last place one wants to be is at the American norm. I am going to challenge some conventional wisdom that shapes perceptions that lead to behaviors that create formidable obstacles to creating health. In doing so, I will use best available evidence to support this synthesis:

1. Your DNA is not your destiny. We'll explore this on a future review of epigenetics. If your parents and grandparents had a particular disease, you are not necessarily destined for that disease. In addition to inheriting protein-coding genes that put us at increased risk, we inherit the environmental and social conditions within which our recent generations lived! Growing evidence suggests our environment plays a central role in influencing how our gene expression patterns emerge.

2. Fat does not make you fat. At least it is less a contributor than conventionally thought. Fructose, sugar and refined grain-flour foods with high glycemic effect are much more likely to make you fat.

3. The first law of thermodynamics i.e., you gain weight because you consume too many calories and burn to few, is not totally accurate when applied to dynamic biological systems.

4. Food is much more than calories, energy, macronutrients, vitamins, minerals and essential fatty and amino acids. Food is information that influences (for better…or more commonly for worse) that influences gene expression (epigenomics-genomics); protein function (proteomics); metabolism (metabolomics) and our microbiome, which influences many aspects of human health.

In Part 1 of this series I am going to examine the evidence that changes in our modern dietary patterns compared to that of our ancestors, have propelled this current plight of poor health. While there are many other modern environmental contributors for future consideration e.g. changes in our microbiome, environmental toxin burden, loss of entrainment, etc. I will focus on the dietary bad boys of sugar, fructose and refined grain flours, most of which are from modern wheat. First I wish to briefly examine some important shifts in the understanding of human biology that will place these food-health interactions into a more systems-based context. In this context, what is on the end of our forks interacts with our gene expression patterns via epigenetic influence; alters the balance of our microbiome; disrupts cell-signaling e.g. insulin resistance; hinders mitochondrial function; disrupts immune vigilance; disrupts our neuro-endocrine-immune network; alters post-translational protein structure-function, and wreaks havoc with our cellular membrane structure-function. The molecular translation of the molecules we consume will migrate toward health when those molecules are familiar to the systems doing the translation.

Epigenetics: the future ain't what it used to be.

An important place to start is with the findings of the genome project, completed now almost 10 years ago (A Life Decoded: My Genome My Life by Craig Ventor. Penguin Books 2008). Conventional wisdom was that elucidation of the human genome would reveal specific disease genes that would advance our understanding of what drives disease and lead to novel biotechnological interventions. For the most part there are no disease-specific genes. Yes there are exceptions e.g. Huntington's chorea and Cystic fibrosis but most chronic complex diseases do not demonstrate a singular, dominant mutation. One unexpected surprise was to find that humans have fewer genes than expected, approximately 23,000 protein-coding genes. The pinot noir grape has approximately 30,000 genes.

What we have instead is a Book of Life with many, many typos called single nuclear polymorphisms aka SNPs. These SNPs (we have millions) are present throughout our Book of Life and current thinking is that the constellation of these SNP patterns that may actually create our disease risk. As interesting and unexpected as many of the findings of the genome project were, the current construct of human biology was shifted even further by the emergence of epigenetics. The rapidly growing field of epigenetics would suggest that in addition to inheriting the protein-coding genes from our parents, we perhaps just as importantly inherit the social and environmental conditions within which they lived. In this context, if your grandfather smoked at the age of fifteen in 1900, your health in 2014 could be under the influence of the epigenetic "tags" from that time.

What is now emerging is a complex regulatory function of our genome at the level of histones and throughout our DNA that can determine whether or not our genes are turned on i.e. translated or not. All aspects of our lifestyle and environment, as it now appears, influence our gene expression patterns. Randy Jirtle PhD while at Duke, demonstrated the capacity to silence dominant expressive genes in the agouti mouse (a mouse model for obesity and metabolic syndrome) by exposing a pregnant Agouti mouse to "methylating agents" e.g. B12, folate, choline. Methylation acts as a "stop sign" preventing genes from being expressed. While all Agouti mice ever known were large, yellow, sick, and short-lived, the offspring in Jirtle's experiments were dark, lean, healthy and lived much longer! (Figure 1) This was a different organism! When examined, the offspring had the dominant Agouti gene passed along; it was surrounded by methyl groups and ultimately never expressed. Even more astounding, the offspring of the leaner, healthier mouse had the same phenotype. These epigenetic effects were trans-generational.

igure 1: Jirtle and Waterland, J Nutr 2002; 132:2392S

There is now a rapidly growing fund of knowledge to suggest epigenetic influences on health in animals and humans from various environmental inputs in our lives. For example:

- Nutrients e.g. high-glycemic foods up regulate inflammatory pathways
- Movement alters gene expression to reduce inflammation, enhance insulin signaling and increase mitochondrial biogenesis
- Early childhood bonding alters cortisol receptor function later in life
- Prenatal environmental conditions e.g. food deprivation alter the health of offspring well into adulthood via altered methylation patterns.
- Meditation and many mindfulness-based stress reduction strategies down-regulate NFkappa-B expression i.e., lowers inflammation and improved biogenesis i.e., mitochondrial function and ATP generation

While we inherit our DNA hardware and it indeed has many individualized glitches that impact operation throughout life, our software that RUNS the hardware is influenced by our lifestyle and is more dynamic and malleable than ever imagined. From a self-care perspective, we are all software engineers of our lives. Creating health requires thoughtful software engineering. This is truly a game-changer. Epigenetics has catapulted us into the era of personalized medicine. Let's now examine more specifically how sugar, fructose and carbohydrate-dense grain-based flour are biologically translated.

The Epidemiology of Sugar (fructose) and Obesity-Insulin Resistance.

So common have problems of obesity, pre-diabetes, diabetes, metabolic syndrome, and CVD become that it is easy to forget how uncommon they were just 2-3 generations ago. If one looks at the Mexican Pima Indians who have migrated north of the border to Arizona, one sees a 5x increase in the prevalence of type 2 DM that has emerged just over the last 1-2 generations. This is an incredible shift in prevalence that cannot be explained by new genetic mutations or a classic Mendelian model. This is an example of epigenetic drift on a large-scale population that has emerged over the last two generations and the impact a Standard American Diet (among other factors) can have on the phenotype of humans.

If one examines gene expression patterns in humans in relationship to changes in the glycemic-effect (i.e., insulinogenic effect) over 12-weeks, one sees significant up regulation of inflammatory cytokine pathways, oxidative stress and insulin cell signaling in over 62 genes that are completely reversed when switching back to carbs with a lower glycemic effect independent of changing calories or macronutrient balance.13

There have been many interesting factors leading to the increased consumption of sugar, fructose and refined grain-based, carbohydrate-dense foods. As the prevalence of heart disease was rising in the 60s there was growing concern about the relationship of fat (saturated fat more specifically) and coronary artery disease risk. It seemed intuitive and plausible that a lesion formed of cholesterol plaques was driven largely by the fats we consume in our diets. The diet-heart hypothesis promoted by Ancel Keys PhD emphasized the connection between fat consumption (saturated fat emphasized) and cardiovascular mortality as published in his 7 Country Study. Keys looked at 22 countries though chose to include data only for the seven that supported his hypothesis. His findings based on skewed epidemiologic data, led to an interpretation of clear cause-effect that was never ultimately substantiated in good clinical trials. This soon became the policy that defined what would become the roadmap for what constitutes a healthy human diet.

The USDA, under George McGovern, developed policies that led to rapid emergence of inexpensive grain-based processed foods that were "low-fat", tasted great, and fit nicely into the food pyramid where cereal grains, bread, and carbs became the healthy, low-fat foundation. Low fat became equated with healthy. Low fat (i.e. fewer calories) became equated with weight-loss advantage. And while low-fat can indeed be healthy, most Americans replaced fatty foods with high-glycemic, tasty and affordable carbohydrate-dense foods. The quickest way to undermine the capacity to create health is to consume commonly processed low fat foods. John Yudkin, a British physiologist and Professor in the Department of Nutrition at Queen Elizabeth College in London published Pure White and Deadly in 1972 . It was a scientific perspective, albeit counter to the prevailing view that had fat in its crosshairs, of the health hazards of sugar, and refined flour-carbohydrates. Yudkin also raised concerns regarding the risks of limiting healthy fat sources in the human diet. Yudkin was a voice in the wilderness and marginalized by the diet-heart establishment.

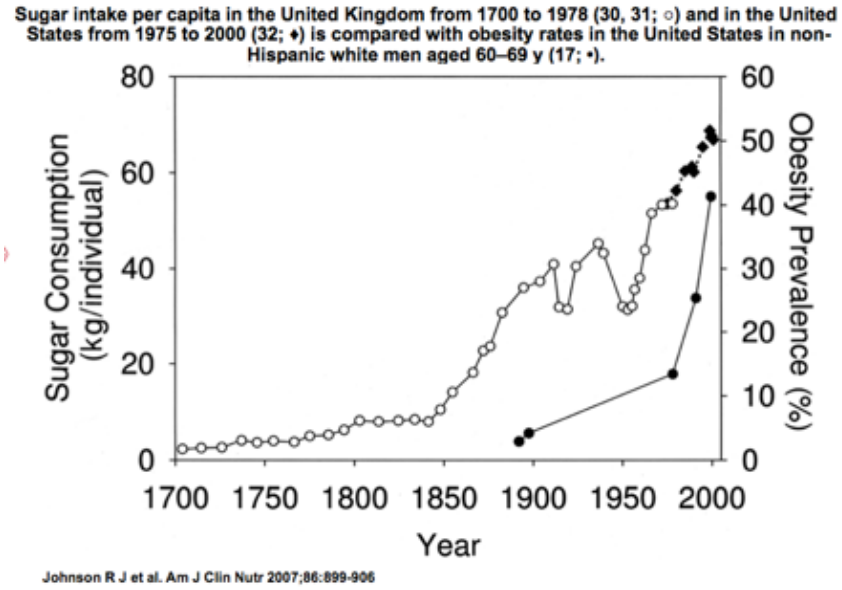
More than forty years later, his concerns have been realized. Several recent meta-analyses have raised questions regarding the etiologic role saturated fats play in promoting CVD . While no one would question the health-risks of trans and hydrogenated fats as promoting inflammation and disease risk, there has been a significant increase in our consumption of sugar, fructose, and refined grain-based flours over the last two generations. Eating saturated fats have been unquestionably demonstrated to raise total cholesterol and circulating saturated fats. If however one restricts sugar and refined carbohydrate without changing saturated fat intake, circulating levels drop considerably as they become a fuel source compared to those consuming lower saturated fat amounts. Fats are more of an issue in a glucose metabolizer i.e. one who consumes large amounts of sugar, high-glycemic refined flour foods and fructose, a critical stimulus for lipogenesis. In addition, there is some recent evidence to suggest that substituting healthy sources of saturated fats e.g. from pasture raised eggs, meats, and dairy with highly touted vegetable-based polyunsaturated fats does not lower cardiovascular risk as long thought.

In 1890 one in thirty adults (3.4%) were obese. Today 35% of adults are obese and almost 20% of children are overweight-obese. In 1890, 1/50,000 adults were known to be diabetic. Today one out of ten adults are diabetic and up to a third have evidence of insulin resistance, pre-diabetes, or features of metabolic syndrome. These are changes of epidemic proportions! Haven Emerson (1874-1957), NYC Health Commissioner, noted an increase in diabetes in NYC from 3/100,00 cases to 20/100,000 cases, a seven-fold increase between 1880 and 1920. This was a public health attention-getter at that time.

The risk factors he associated this concerning trend with included:

- Sugar consumption
- Affluence
- Sedentary states
- Caucasian
- Merchants in the food industry

Figure 1: Association between sugar consumption and obesity

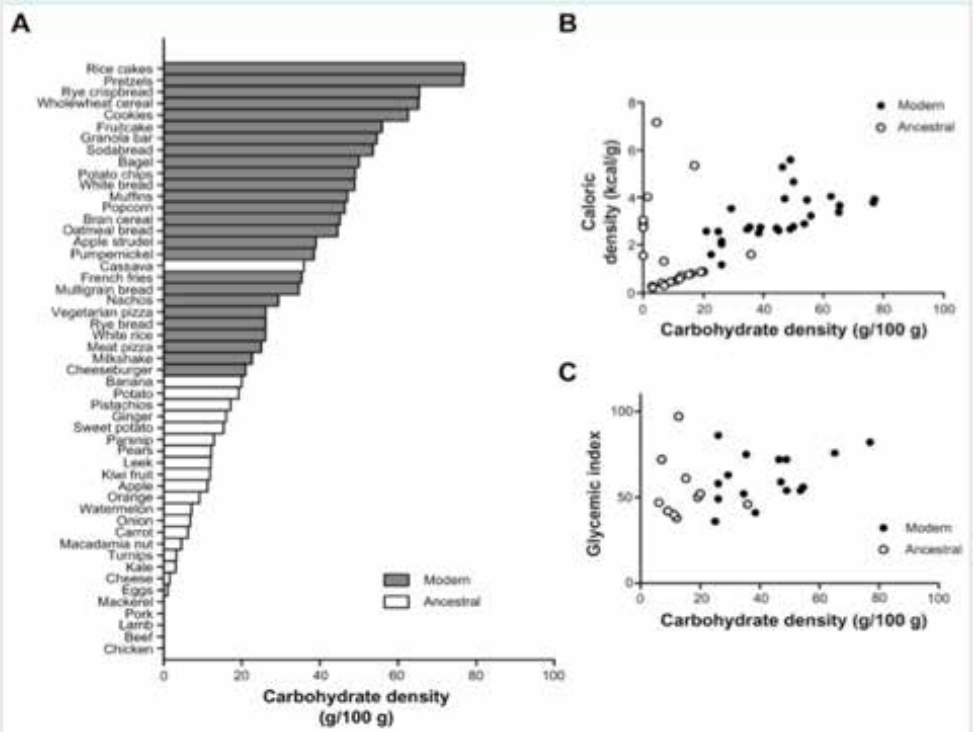


Ninety years later the association between sugar intake and cardiovascular disease and cardiovascular mortality was reported in The Journal of The American Medical Association.

Ian Spreadbury, a microbiome researcher in the GI Disease Research Unit at Queen's University in Ontario published a review that examined the diets of scores of modern ancestral hunting-gathering societies around the globe . These societies have a very low prevalence of chronic complex disease. Their average BMI is 23! While there were many variations on the percentages of macronutrients and plant vs. animal-based sources, what jumped out was what they shared i.e., what they did not consume. The single most significant shift from ancestral food consumption (including that of your great grandparents) to the standard American diet is our ubiquitous incorporation of "carbohydrate dense foods". Spreadbury's analysis examines carbohydrate density as a percentage of the weight of the food composed of carbohydrate. The epidemiologic threshold beyond which one sees more chronic complex disease risk is the consumption of foods with a carbohydrate density at or above 24% (figure 2). In addition, he noted that the most dangerous carb sources were largely "acellular", namely sugar and refined grain-based flour foods. Americans consume 50+% of their daily total energy from these foods. This was unheard of just 3+ generations ago! Examples of acellular carb-dense foods include:

- Rice cakes, pretzels, cookies, cakes, muffins, potato chips, pancakes, waffles, bagels, whole wheat bread, cereals, multi-grain bread, French fries, hamburger and hot dog rolls, pumpernickel bread, rye bread, white bread, oatmeal, white rice, pizza, pasta, granola, granola bars, candy, soft drinks, crackers, etc.

Figure 2 (Spreadbury, I. Comparison with ancestral diets suggest dense acellular carbohydrates promote an inflammatory microbiota, and may be the primary dietary cause of leptin resistance and obesity. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. Dove Press. July 4, 2012)



Foods commonly consumed by ancestral cultures with a much lower carbohydrate density as well as foods our recent ancestors consumed include:

- Most fruits (seasonal from an ancestral perspective) and vegetables
- Sweet potatoes and root vegetables, e.g. radishes, onions, turnips
- Beans, legumes, lentils
- Eggs, cheese, fish, nuts, beef, lamb, chicken, pork, organ meats

There is growing interest in the interaction of these carbohydrate-dense foods with our gut's ecosystem or microbiome. As it would appear we are not just what we eat, we are what our microbiome does with what we eat. While this fascinating area of research will be the topic of a forthcoming review, these processed grain-based carbohydrates, in addition to promoting obesity and insulin resistance, promote an up regulation of inflammatory cytokines. In addition, they interfere with leptin signaling in the hypothalamus. Leptin sensitivity is critical to promote satiety and to prompt movement.

David Ludwig MD at The Brigham and Women's Hospital in Boston raised an interesting question regarding the impact that refined, processed carbohydrates are playing in the epidemic of obesity. Is obesity a consequence or a cause of overeating and under activity? In his proposed model, the fundamental changes in our diet have led to an increase in insulin activity often worsened by insulin resistance. As basal and post-prandial insulin levels remain high, the biologic mandate is to store more fat. High insulin levels make mobilization of fat stores as a source of free fatty acid fuel impossible. As more consumed energy is stored as fat there is less circulating energy. The impact that insulin excess and inflammation have on the brain is to diminish leptin sensitivity. The combination of leptin resistance and diminished circulating fuels in a carbohydrate-dependent metabolism lead to increased appetite and diminished activity. In this model the changes in biology lead to changes in behavior. More refined, processed carbohydrates lead to more body fat, more robust appetite, and a mandate to minimize activity as

the brain senses energy deprivation. We are in essence creating a biology that is tricked into saving for a rainy day that will never come. We are tricked into moving less when in fact we should be doing just the opposite. This hypothesis is a departure from a more simplistic calories in-calories out paradigm, to one that places more emphasis on quality, not quantity of calories. While quantity is important, the first law of thermodynamics is not as straight forward when applied to human biologic systems.

A conservative, fat-storing biology may be further exacerbated by our avoidance of healthier fats e.g. olive oil, grass-fed meats, fatty fish, nuts, pasture-raised eggs, butter, coconut oil, etc. Healthier fats are known to suppress insulin and raise satiety. Individuals who consume more fat and less sugar, fructose, and refined carbohydrates actually burn or expend more calories per day compared with those on a more traditional "low-fat diet". Despite equal amounts of caloric consumption, altering the macronutrient composition toward less carbohydrate and more fat resulted in a resting energy expenditure (REE) of 330 more calories per day! This is the equivalent of almost one hour at a moderate pace on a treadmill!

Based on the NHANES III data (10,628 participants), sugar and high-fructose corn syrup comprise 14.9% of total calories consumed and over 25% of total calories consumed in 9.0% of participants in the survey. If one includes grain-based flour or acellular (grain-based) carbohydrate-dense foods average intake is approximately 55% total calories. The amount is even higher in Hispanic whites, blacks and Mexican Americans. No generation of Americans has ever consumed these foods to this extent. One third of sugar-fructose intake is from soft drinks though fructose is hidden in many foods including salad dressings, hamburger buns, ketchup, peanut butter, etc. This is a staggering amount that no generations before the last few have known.

From an evolutionary biologic perspective, nature made sugar hard to get. Fructose from seasonally ripened fruits had limited availability each year and honey was usually well protected and a more rare treat. It is estimated that our ancient hunting-gathering ancestors consumed approximately 15 grams per day from ripened fruits. We evolved to consume these fructose-containing fruits as an effective way to induce fat storage for the energy-depriving winter season to come. Prior to WW II the average American intake of fructose was 20-24 grams per day. This was particularly important as we migrated from a more tropical environment to one more temperate. Currently (NHANES III) fructose intake ranges from 54-70 grams per day with highest intakes in adolescents and young adults.

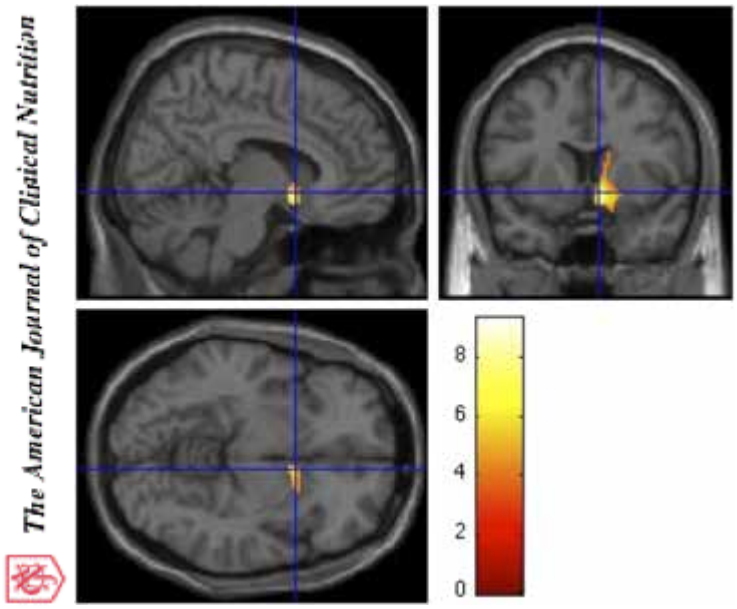
Fructose is a simple sugar; similar to glucose though has a very different metabolic fate. Unlike glucose, which is readily used as a fuel throughout our bodies, the liver exclusively metabolizes fructose. Fructose stimulates de novo lipogenesis in the form of triglycerides (fatty liver), depletes ATP (in its metabolism to uric acid), interferes with insulin and leptin signaling (bad boys of obesity and metabolic syndrome), and is known to up regulate JNK-1 expression, a pro-inflammatory pathway. The primary concern with fructose is not that it is inherently toxic as humans have long been in a health relationship with it. The concern is that with an increasing availability-consumption of sugar (fructose and glucose) and high fructose corn syrup (ubiquitous in our food supply e.g. condiments, peanut butter and hamburger buns), a cheaper super-sweetener introduced from Japan in the 1970s, Americans are consuming "toxic" amounts that are fueling obesity, fatty liver, metabolic syndrome and it's many features.

The Neurobiology of Craving Sweets

It can be said that we are heavily "under the influence" of the food industry whose food chemists have created the perfect foods to hack our capacity to disengage. Palatable and inexpensive it is hard to avoid the temptation to free-base sugar. There is a growing body of evidence that higher glycemic foods play a major factor in disrupting human metabolism that increases risks of metabolic syndrome, cardiovascular disease, adverse outcomes in pregnancy e.g. gestational duration, head circumference, inflammation, and brain reward-motivation craving-addiction. The more sugar one consumes, the more they crave it. A growing body of evidence would suggest that the more dopamine we produce in response to these carbohydrate-dense foods, the more we down-regulate our dopamine receptors. This is an adaptive response to diminish over-stimulation. This has the effect of requiring more sweet foods and beverages to produce the same response. Eating sweet foods (a phenomenon well understood by food scientists) causes a potent reward in the brain and mesolimbic pathways (Figure 3). Rodents will consistently choose sugar over cocaine and the former produces a more robust response.

Figure 3: Effects of high-glycemic foods on brain reward centers

Lennerz B S et al. Am J Clin Nutr 2013; 98:641-647



While some still question the legitimacy of food addictions, the neuroscience research demonstrates clear pathways similar to those found in "well-established" addictions i.e., cocaine, heroin, alcohol, and gambling. Grains and in particular gluten (found in wheat, rye, and barley) are metabolized to molecules known as gluteomorphin. These molecules have potent effects on craving, pleasure, and mood and cognitive alteration. These effects can be reduced with naltrexone, a CNS opiate inhibitor.

Many people now use artificial sweeteners with the false assumption that because they are calorie-free they are a better choice. While perhaps a bit overstated, this is like switching from heroin to methadone. Artificial sweeteners are at least 200 times sweeter than sucrose (table sugar) and people who consume them crave them and are likely to find they are more at risk to gain weight, not lose it. The similarities between sugar and opiates are interesting even at a molecular level. Sugar-dependent rats (probably similar in humans) have alterations in dopamine and opioid mRNA levels that are similar to rats dependent on morphine.

What I have described is the perfect storm: a diet that commonly promotes a fat-storing biologic imperative, is self-perpetuating, creates the hypothalamic drive to eat more and do less, and as if that was not unfair enough, produces a powerful reward that "hooks" naturally, rendering "free-will" not so free after all.

Taming the Sweet Beast

In summary, many of the current challenges we confront with respect to the rapidly growing burden of chronic, complex disease, can be traced to changes in our modern food supply that we, as modern Homo sapiens, are not well adapted for. We have evolved to survive by fully leveraging our "thrifty genes" that have helped us store away needed fat during times of abundance e.g. seasonal ripened fruits-food availability to manage an often long and hostile winter of deprivation, particularly as we migrated out of the African savannah 35-40,000 years ago. As more palatable and rewarding sugar, fructose (from processed sucrose and high-fructose corn syrup), and carbohydrate-dense refined grains entered our food supply, we have seen a distorted metabolic trajectory that leaves us saving for a rainy day that will never come and wanting more nonetheless. We find it more difficult to create health because our fine-tuned metabolic pathways become high jacked. We become hungry all the time and find it almost impossible to foster the energy to move more. Instructing someone to eat less and move more, important though that advice is, will not fix this dilemma. Until the biology is addressed it is hard to fix the behavior.

So what is a modern day human to do? Here are a few suggestions from a nutritional science perspective that can, at least in part, restore a metabolic trajectory more aligned with one were are highly evolved for. The results are likely to produce loss of inches around the mid-section, reduce inflammatory burden, improve insulin sensitivity, reduce disease risk, and improve both quality and quantity of life!

1. The most effective nutritional strategy for reducing visceral fat, improving insulin sensitivity and reducing inflammation is to lower unhealthy carbohydrate consumption e.g. sugar, fructose and processed refined grain based carbohydrate-dense foods.

   A Recent meta-analysis suggests dietary carbohydrate restriction as the first approach for individuals with established diabetes and insulin resistance.

2. Reduce-eliminate artificial sweeteners.

3. Vegetables are the focal point. Eat as many as desired with an emphasis on variety and seasonal availability. Frozen are equally good. Moderate, if insulin resistant, starchy vegetables e.g. white potatoes, white rice, corn.

4. Introduce healthier fat sources e.g. pasture-raised meats, eggs, pasture-raised butter, nuts, seeds, fish e.g. salmon, sardines, mackerel, anchovies, coconut oil, tallow, etc. Healthier fats will reduce cravings, improve satiety, and reduce lipogenesis!

While moderate elevations in total cholesterol and LDL may be seen with this strategy, the shift will be toward less Apo b (small-dense LDL particles, the most atherogenic) and more Apo a (larger, buoyant LDL which is less atherogenic); much improved HDL levels, perhaps the most consistent predictor of CV risk across a wide range of LDL levels; and dramatic reduction in triglycerides. Most of the features of metabolic syndrome mitigate in time, depending on the magnitude of restriction as well as other factors e.g. sleep and stress management.

In summary, many of the rapid epidemiological trends toward higher burdens of chronic complex disease and diminished functional capacity can be traced to changes in our food supply over the last three generations. These changes create environmental "new to nature" challenges that our stone-age biologic mandate struggles to effectively adapt to. Sugar and by extension fructose, in addition to unprecedented exposure to processed, refined grain-based carbohydrate-dense flour, along with a reduction in healthy fats and a skyrocketing increase in consumption of processed omega-6 seed-based oils…have created the perfect storm of metabolic disruption.

While there are surely other significant environmental changes that I will elaborate on in future BMJ submissions that contribute to our epidemic of chronic complex disease, none are as profound or as remediable as this.

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Dr. Mark Pettus is a triple-board certified Internist, Nephrologist, and Integrative Medicine physician practicing for over 25 years. He received his A.B. from Boston University and his M.D. from the University of Massachusetts Medical School. His postdoctoral training was at Harvard Medical School. He completed his renal fellowship at The Massachusetts General Hospital in Boston. Dr. Pettus is also an alumnus of The Advanced Program for Conflict Resolution, Negotiation, and Mediation at The Harvard School of Public Health.

Dr. Pettus currently serves as the Director of Medical Education, Wellness and Population Health at Berkshire Health Systems in western Massachusetts. In addition he serves as The Associate Dean of Medical Education at The University of Massachusetts Medical School. He also serves as The Medical Director for Functional Formularies. He is former Chief of Medicine at St. Peter's Hospital in Albany, NY. He is a Clinical Associate Professor of Medicine at the University of Massachusetts Medical School. He is the former the Medical Director of The Kripalu Institute for Integrated Healing. He is the author of two books, The Savvy Patient: The Ultimate Advocate For Quality Health Care and It's All in Your Head: Change Your Mind, Change Your Health. He serves on the teaching faculty at The Center for Mind-Body Medicine in D.C. and The Meditation Institute in Averill Park NY.

Dr. Pettus has appeared on numerous TV and Radio venues nationally including the 700 Club, Good Morning America, NPR and PBS. His podcast, The Health Edge is heard by people all over the world.

P. MICHAEL STONE
MD, MS, IFM-CP

CATHY SNAPP
PhD

RUTH M. DEBUSK
PhD, RDN

Innovative Mindfulness Based Therapeutic Lifestyle Change for Chronic Disease

P. Michael Stone MD, MS, IFM-CP1, Cathy Snapp, PhD2, Ruth DeBusk, PhD, RDN1,2
Medical Director: Ashland Comprehensive Family Medicine1
Adjunct Faculty: Institute for Functional Medicine1
Family Medicine Residency Program at Tallahassee Memorial HealthCare2
Tallahassee, Florida

Healthcare is in transition, from the primary focus being on acute care to better addressing an escalating increase in the prevalence of lifestyle-driven chronic disease. Cardiometabolic syndrome in particular is burgeoning as a major health morbidity that affects over 30% of the adult population in the United States. Elevated blood pressure, blood lipids, blood sugar, and inflammatory visceral body fat are all tied to many lifestyle choices and responses.

The new era of healthcare is accompanied by major advances in science, particularly in neuroscience, genomics, epigenetics, and nutrition. These advances are facilitating the discovery of the underlying mechanisms of chronic disease, the molecular basis for these mechanisms, and the influence on neural and behavioral outcomes. The intersection of worsening chronic disease and the major advances in science offers an opportunity to look at health, diseases and lifestyle in a new way. By understanding chronic disorders at their root cause and identifying the primary system imbalances that lead to dysfunction and disease there is a different leverage point. From this knowledge base, healthcare professionals on chronic care teams can develop therapeutic interventions that can help prevent disease and restore health to those with existing conditions. Significant progress has been made in understanding the process of effective behavioral change and provides practitioners with options for helping individuals develop and sustain daily habits that support health rather than disease. Behavioral professionals will increasingly be incorporated into chronic care teams and will play valuable roles in 1) educating patients on the key lifestyle factors that trigger chronic disease and 2) assisting patients in making behavioral changes that can be sustained long-term.

Systems medicine and the emerging disciplines of genomics, epigenetics, and neuroscience; the importance of patient education and behavioral therapy with respect to key modifiable lifestyle domains; and the integration of mindfulness in chronic disease care have been integrated into a Mindfulness-based Therapeutic Lifestyle Change (MBTLC) model that has been piloted in academic, residency, and community health systems. The core principles have been used to address patient care and community needs and physician and employee well-being. An overview of the core principles will be discussed, with a cardiometabolic case presented as an example of how the MBTLC program can be applied to the management and prevention of chronic disease and overall well-being.

Healthcare and the Challenges of Chronic Disease

Chronic disease is a growing concern in the U.S. and globally. The prevalence of chronic behavioral, metabolic, and physiological disorders has been escalating steadily over the past several decades (http://www.weforum.org/reports/global-economic-burden-non-communicable-diseases). Examples of common chronic disorders include heart disease, stroke, cancer, diabetes, overweight and obesity, high blood pressure, arthritis, osteoporosis, asthma and allergy, digestive disorders, sleep disturbances, and a variety of behavioral health disorders, with depression and anxiety particularly common. According to the Centers for Disease Control and Prevention, chronic

disorders are among the most common, costly, and preventable of all health conditions (http://www.cdc.gov/chronicdisease/overview). Within the United States, chronic disease is the leading cause of death and disability. One in every 2 Americans has one or more chronic diseases, one in 4 has two or more, and 70% of Americans die from complications of chronic disease (Ward et al., 2014).

Chronic disease is accompanied by significant costs in terms of decreased quality of life and economic burden for individuals and for societies. For three of the more prevalent chronic diseases, the economic burden was estimated in 2010 to be $315.4 billion for heart disease and stroke (Go et al., 2014), $157 billion in 2010 for cancer (National Cancer Institute, 2013; http:costprojections.cancer.gov/), and $245 billion for diagnosed diabetes in 2012 (American Diabetes Association, 2013; American Diabetes Association. The Cost of Diabetes. http://www.diabetes.org/advocacy/news-events/cost-of-diabetes.html). Such costs are becoming unsustainable and potential solutions are needed.

Systems Medicine

Systems medicine is a revolutionary approach to viewing chronic disease through a lens distinct from acute disease, a lens that recognizes the complex interconnectivity of the human organism and its health and disease ramifications. This type of approach is called "systems medicine" or "functional medicine" as it focuses on the influence on how well an organism functions—its functional ability. In its simplest form, systems medicine is always asking "Why?" Why does this patient have these symptoms? What do the symptoms tell us about the clinical imbalances that exist? What are the root causes of these symptoms and the key underlying mechanisms that are in play? This type of information provides the basis for targeted interventions that can potentially restore health to those with chronic disorders and ultimately prevent chronic disease.

The theory behind systems medicine is that chronic disease is a complex web of systemic imbalances, with multiple interconnections throughout the body such that an imbalance in one area typically influences other areas and often sets the stage for additional chronic disorders to develop. Left unaddressed, in time these imbalances move the body far from its natural state of balance (homeostasis) and set the stage for dysfunction and disease. A systems medicine approach recognizes that the symptoms of chronic disease are only the tip of the iceberg in terms of the myriad systemic imbalances taking place below the surface. Underneath are physiological disturbances that result from metabolic imbalances. These imbalances are in turn generated by the interaction of the individual's genetic material with messages received from the internal and external environments that in turn influence gene expression and, ultimately, the organism's functional ability. Seeing the patient through a systems medicine lens requires consideration of root causes and identification of underlying mechanisms so that appropriately targeted interventions can be applied.

Furthermore, as seen through a system medicine lens, chronic disease is lifestyle-triggered disease—the result of lifelong inappropriate choices concerning nutrition, physical activity, thoughts and emotions, relationships and system of meaning, and sleep and relaxation. Collectively, these factors are responsible for the environmental cues that convey messages to our genetic blueprint that then influence the expression of our genes, ultimately influencing how well we are able to function within the environment in which we live.

From a behavioral health focus, systems medicine helps us to work in a model wherein the goal is to intervene on this chain of events leading to chronic illness. Each step in the process to the development of chronic disease is modifiable and such modifications can be learned, practiced, and sustained long-term through effec-

tive behavioral therapy. Doing so offers the promise of prevention of future chronic disease and more effective management of existing chronic disorders, with the associated improvement in quality of life.

The Brain-Mind-Body Connection

Although it is common in healthcare today to think in terms of organ systems in isolation (e.g., heart disease, brain trauma, etc.), neuroscience research reminds us that the brain, mind, and body are components of a complex, interconnected system that work seamlessly together to produce health and overall well-being. Activity, particularly imbalances, in one part of the system has consequences to other parts that may be quite distant from the originating event. Living organisms have complex mechanisms designed to maintain homeostasis, a physiological state characterized by balance and stability. Upon detecting system imbalances, the organism will do its best to restore homeostasis. How successful it is influences whether we find ourselves functioning at the healthy or unhealthy region of the homeostasis continuum.

A major source of imbalances of importance in behavioral health is the contribution of the brain. As we will see, the brain plays a significant role in receiving signals and translating them into molecular, biochemical, physiological and behavioral responses. However, the brain often interprets signals inappropriately, termed deceptive brain messages by neuroscientist Jeffrey Schwartz (1997), and generate inappropriate physiological and behavioral responses that create system imbalances that in turn decrease health and well-being. This section reviews the basic characteristics of the brain-mind-body connection and how this knowledge can be useful in behavioral health with respect to chronic disease. It will also explore the basics of psychoneuroimmunology as an excellent example of this interconnectivity and the consequences of system imbalances.

The Brain

For our purposes of understanding how the brain-mind-body connection works and the consequences of imbalances on behavior and overall health, we will position the brain as the physical organ that receives the signals, real or perceived, and is responsible for regulating the molecular, biochemical, physiological and behavioral responses.

The human brain has evolved over time and consists of three main segments, each having developed at different times in human evolution and having contributed to our behavioral patterns in different ways. Neuroscientist Paul MacLean (1990) coined the term "the triune brain" to describe these three segments: the reptilian brain, the paleomammalian brain, and the neomammalian brain, which their ancestral relationships to reptiles, early mammals, and later mammals, respectively. Although today's advances in neuroscience suggest that this characterization of the complex mammalian brain is an oversimplification, it remains a useful way to conceptualize the workings of the brain and provides clues as to the brain's relationship to behavior.

The reptilian brain is the oldest of the brain segments and is present in many types of organisms. This segment encompasses the brainstem and cerebellum and is focused on ensuring the survival of the organism so that it can perpetuate the species. It is responsive to environmental cues that elicit fear, particularly in relation to the safety of the organism. The paleomammalian brain is the next oldest segment and is motivated by satisfaction and reward. This segment houses the limbic system, which is considered to be the emotional center of the brain and that part of the brain that is essential for bonding/attachment and for emotions (Nieuwenhuys et al., 2007). The newest segment to evolve is the neomammalian brain, which is responsible for the higher order functions

that characterize humans, such as language, reasoning, abstract thinking, compassion, empathy, cooperation, altruism. This segment is motivated by attachment to others, feeling part of the tribe.

From a behavioral standpoint, each of these segments appears to have ancient adaptive strategies that served the organism well in the evolutionary past but are not always appropriate for 21st century living. Understanding what these strategies are and the cues that elicit responses can be helpful in changing behaviors to ones that are more appropriate for today's world. Rick Hanson, PhD, a neuropsychologist at the University of California at Berkeley, uses visual imagery to help distinguish the three segments and remind us how each segment relates to behavior (Hanson, 2013). The reptilian brain is motivated by a sense of safety. The Hanson imagery for quieting the reptilian brain is to "pet the lizard." Providing a safe environment (nonjudgmental, supportive) for patients to be in helps calm them so that they can focus attention on other aspects of their lives. The paleomammalian brain is motivated by feeling a sense of satisfaction and contentment. The Hanson imagery is to "feed the mouse." Within a safe environment, helping patients to feel a sense of contentment with themselves and their place in the world helps to quiet this segment of the brain so that attention can be focused elsewhere. The neomammalian brain is motivated by love and a sense of belonging. The Hanson imagery here is to "hug the monkey".

Having an understanding of the various parts of the brain and their contribution to behavior can be useful when working with behavioral change. By assessing which brain segments appear to be dominating a person's behavior, it becomes possible to develop therapeutic approaches that will resonate with individual patients and meet their needs, which increases the probability that a patient will make the desired changes and sustain them long-term.

The HPA Axis

Psychosocial stress has long been known to affect physiological systems.

Hans Selye (reviewed in Neylan, 1998) first described the "fight-or-flight" stress response and is further credited with the discovery that the nervous system responds to both actual threats and perceived threats with the same physiological responses. Investigations by various research teams into the underlying mechanisms of these physiological responses to perceived stress have provided insight into the cascade of events that ensues.

The stress response occurs within the limbic system, which is formed by components of the paleomammlian brain. The limbic system controls functions necessary for self-preservation and species-preservation that relate to emotions, memory, arousal, and motivation and reinforcing behaviors. Think of the limbic system as connecting the parts of the brain responsible for low and high function, essentially a feeling and reacting region that bridges the reptilian brain that receives input from the nervous system and the thinking brain (neomammalian brain) that's responsible for higher order executive functions.

Of particular importance to the stress response is the HPA axis, formed by the hypothalamus and pituitary within the paleomammalian brain and the adrenal cortex glands that sit on top of each kidney. Through hormones secreted by these glands, a threat (real or perceived) is conveyed to the brain and to multiple regions of the body. , which influences a number of physiological processes such as the digestive, cardiovascular, immune, reproductive, and central nervous systems. Corticotropin-releasing hormone (CRH) is secreted by the hypothalamus, which then stimulates the pituitary gland to secrete adrenocorticotropic hormone (ACTH), which then stimulates the adrenal glands to secrete mineralocorticoid and glucocorticoid hormones. In humans the primary

mineralocorticoid is aldosterone, which promotes water and sodium retention and influences blood pressure. In humans the primary glucocorticoid secreted is cortisol. Together these adrenal hormones help prepare the body for the "fight-or-flight" response through actions such as increasing adrenaline levels and nutrient supplies and conserving water.

Cortisol is a major stress hormone that affects many tissues in the body, including the brain. Its purpose is to sound the alarm and then retreat as sustained levels of high cortisol have multiple negative effects of physiology. The body has a feedback mechanism by which elevated cortisol levels are detected and signals are sent to the hypothalamus and pituitary to reduce the secretion of CRH and ACTH, respectively, ending the immediate stress response. However, cortisol remains in the body until it has been degraded and excreted, a process that may take hours to days to complete. Untamed stress leads to prolonged exposure to excess cortisol, which has been linked to damage to regions of the brain, excess body fat, poor sleep quality, low libido, anxiety, digestive upset, and depressed immune function, which increases vulnerability to respiratory and other infections. The more frequent the triggering of the stress response and the greater the magnitude of the response, the more cortisol circulates throughout the body, the longer it takes for clearance from the body, and the longer exposure to this powerful hormone.

In ancient times the stress response served the organism well by alerting it to physical dangers that threatened survival. In today's environment, however, this process continues to respond to what the organism perceives as danger but the threats tend to be mental rather than physical. The end result, however, is the same: a negative influence on one's health. In spite of our common perception of living in a stress-filled world, neuroscience research offers considerable hope that we can tame our stress response, minimize our vulnerability to chronic disease, and enjoy vibrant health and a high quality of life. One of the major hopeful outcomes of neuroscience research has been the concept of neuroplasticity, that the brain's neural circuits are "plastic" and can be dismantled and rewired. Further, neuroplasticity can be self-directed, which gives healthcare practitioners new ideas for how to approach chronic disease.

The Primary care landscape is inundated with patients impacted by inflammatory imbalances. These imbalances are directly related to lifestyle choices resulting in complex, idiosyncratic epigenomic changes in the organism. These systemic changes, like sea oats on a sandy dune, move and shift in concert with 'the breezes' of ones unique genetic makeup and epigenetic expressions. Successful interventions in the next generation of personalized medicine models will require physicians operating through a root-cause, systems based lens and an integrated behavioral health team to assist patient's in making the appropriate genetic and neural anatomical changes that will lead to long-term health promotion. The next part of this chapter will identify key components for understanding and treating one of the largest chronic disease populations seen in primary care today: patients with multiple connected inflammatory processes called cardiometabolic syndrome (imbalances in: blood sugar, blood pressure, blood dyslipidemia, body visceral fat).

HPA Axis- Autonomic Neurologic Balance Applied to Cardiometabolic Syndrome:

To effectively treat cardiometabolic syndrome, one must 'look upstream' to see how the inflammatory cascade of cardiometabolic imbalance is influenced by autonomic neurologic balance and the central hypothalamic-pituitary-adrenal (HPA) axis. At the level of causation, there is a confluence of nutritional, environmental, and psychological stress factors and chronic low-grade inflammatory processes flowing into visceral adipose tissue (Lemche 2016). As a result, there is increased oxidative stress in the cells, subcellular organelles, mitochondria

and the endoplasmic reticulum. The resulting oxidative stress increases nutrient requirements or in situations of insufficiency these oxidative imbalances bias steroidogenesis and eventually impair glucose uptake and insulin resistance. During periods of stress there are discrete, step-wise changes in cortisol production impacting the central HPA axis and degrading certain regions of hippocampal brain tissue over time and through repeated exposure. Impaired activity in this part of the brain associated with emotional regulation and resiliency primes and sensitizes the brain for stress-filled perception. This sets up a virtual 'cortisol cascade', deleteriously influencing visceral adipose and hepatic tissue via

11-beta-hydroxyl-steroid-dehydrogenase-1 action. These psychological and nutritional 'imbalances' lead to post translational modifications in specific at-risk gene loci that, in turn, leads to genotype-environmental interactions that shape the "Metabolic Syndrome Phenotype" (Lemche et al., 2016).

Additional brain structures involved in the stress physiology of metabolic syndrome include the POMC (proopiomelanocortin) neuron populations in the hypothalamus, which are under influences of histone methylation, lysine acetylation and other epigenetic processes. This POMC population, found mostly in the arcuate nucleus, helps process environmental stress signals with direct influences of the basolateral amygdaloid and central amygdaloid nuclei. This primed and habituated reflexive response to stress develops triggering sympathetic-excitation, launching the cascade of inflammatory physiologic responses (Lemche et al 2016, McEwen 2013).

Hunger and satiety homeostasis and its central regulation interact with the arcuate and paraventricular nuclei, and possibly leptin, MC4R (melanocortin-4 receptor) and NPY (Neuropeptide Y) systems (Lemche et al., 2016). Neurons that secrete NPY are targeted by ghrelin in the hypothalamus. Leptin desensitizes the brain to hunger signals and inhibits NPY-secreting neurons. There is HPA dysfunction in metabolic syndrome that is markedly influenced by the synthesis of glucocorticoids in a peripheral corticotropin-releasing hormone (CRH) system that is active in the adipose tissue and the liver. The peripheral CRH system biases the susceptibility of the central hypothalamic pituitary regulation (Lemche et al., 2016).

In evaluating responses to stress and teasing out compartmental influences: psychological stress measures accounted for 37% explained variance of the correlation between metabolic syndrome and adrenaline metabolite normetanephrine, heart rate variability, cortisol and interleukin-6. It is widely believed that health behaviors explained 18% of the neuroendocrine variance (Chandola 2006, Chondola 2008). The data is clear, to effectively address the meteoric rise of cardiometabolic syndrome innovative long-term behavior change models and systems based physician root-cause analyses are required. What to do?

A Need for Innovative Behavioral Change Models: Focus on the Brain and Self-directed Neuroplasticity

In contrast to earlier thinking that the brain, once formed, was not able to synthesize new neurons, we now know that neurons can be synthesized and that they are "plastic", able to adapt to their environment (FitzGerald, Folan-Curran, 2002). Old neural circuits can be dismantled and new ones developed. From Hebb's law (Hebb, 1949), which is now a main principle of neuropsychology, we know that neurons that "fire together, wire together." Neural circuits are shaped by experiences throughout life. It stands to reason, then, that specific experiential interventions could positively influence the development of neural circuits and, by extension, behaviors that support health and well-being. This is indeed what has been observed over the past decade or so. Davidson and McEwen (2012) review existing data from animal and human studies that document the relationship of plasticity

to behavioral change.

Although we may have a genetic predisposition towards a negativity bias or have acquired a number of habits that are not serving us well, self-directed neuroplasticity provides the basis for our choosing to change our neural circuits and thereby our behaviors to ones that support our life goals. Through self-directed neuroplasticity, these behaviors become hardwired as neural structures that are critical for our sustained well-being (Kabat-Zinn, 2003; Schwartz, 2012).

Neural circuits are shaped by experiences throughout life. It stands to reason, then, that specific experiential interventions could positively influence the development of neural circuits and, by extension, behaviors that support health and well-being (reviewed in Maier, 2015). In fact, mindfulness (to be discussed in a subsequent section) offers such an approach. Neural installation, accomplished through mindfulness-based interventions, appears to be an important tool in making sustainable behavior changes (Hanson, 2013).

Mindfulness

Mindfulness is defined as a state of focused attention, where one pays attention "on purpose, moment to moment and nonjudgmentally" (Kabat-Zinn, 1994).

It is reported to have been a part of Eastern cultures for at least 26 centuries, with positive effects on quality of life (Cayoun, 2005). Mindfulness was successfully introduced into clinical practice in the U.S. in the 1990s by John Kabat-Zinn for stress reduction. Mindfulness training has subsequently been adapted by a number of researchers and clinicians to a variety of clinical applications, such as mindfulness-based cognitive therapy and mindfulness-based eating. See the works of Kabat-Zinn (1992); Kristeller, Hallett (1999), Miller et al., (2012), Segal, et al., (2002), Schwartz (1997, 2012) and Siegel (2007, 2012) for an introduction to these adaptations.

Mindfulness training enhances our ability to focus our attention, which is reflected in changes throughoøut the organism. Research has shown mindfulness training to improve immune function, strengthen equanimity and clarity, reduce pain and potentially increase empathy and relational satisfaction (Davidson et al., 2003; Siegel, 2007; Gard et al., 2012). Using current research on mindfulness-based stress reduction as an example, Baer et al. (2012) found in 87 adults with chronic stress due to lifestyle-associated disorders that skills developed through mindfulness training preceded changes in perceived stress. Creswell and colleagues (2012) showed that mindfulness-based stress reduction reduced loneliness in mature adults and was correlated with changes in gene expression, particularly in the reduction in pro-inflammatory cytokines.

The changes in focused attention resulting from mindfulness training have been correlated with changes within the neomammalian brain by a number of researchers. Davidson and colleagues (2002) were among the first to map the effects of mindfulness to specific regions of the brain and were able to show in healthy individuals that the experimental group that had been trained in mindfulness showed increased activation in the left prefrontal cortex whereas the control group did not. Further, the effects of mindfulness training were still evident upon re-screening at four months. These and similar studies have solidified the concept of neuroplasticity as well as the value of mindfulness in promoting changes in neural circuits (Hölzel et al., 2011; Marchand, 2014). Hölzel and colleagues also reported that mindfulness interventions targeted to stress reduction correlated with decreased gray-matter density in the amygdala, which plays an important role in anxiety and stress. Davidson and McEwan (2012) supply further documentation for neuroplasticity changes within the brain and the value of mindfulness

training.

Figure 1-1 illustrates how practicing mindfulness can convert myriad sensory and emotional inputs into positive outputs in terms of physical and emotional well-being.

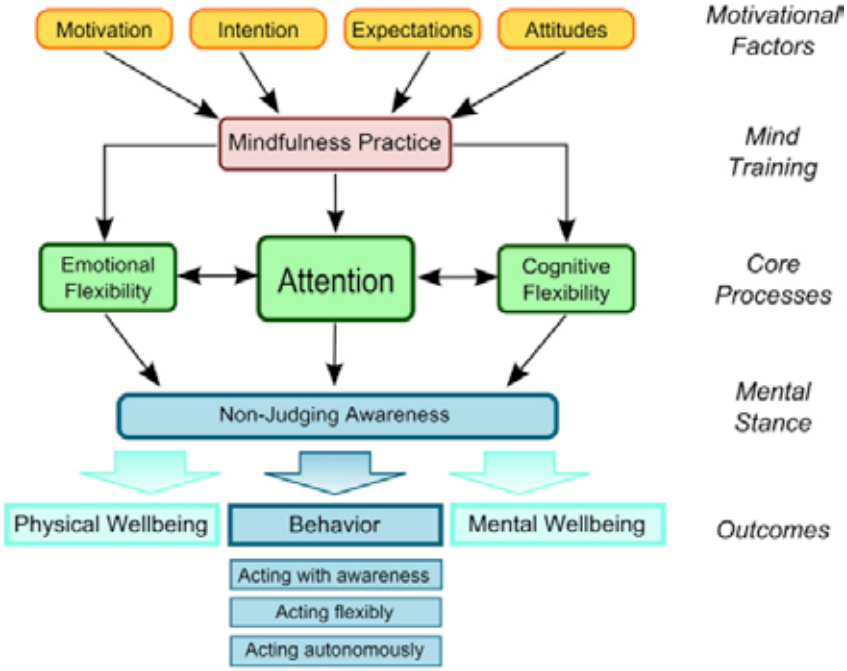

Fig. 1-1. Liverpool Mindfulness Model. Allen, et al., 2012 – used with permission

Why is achieving this level of focused attention of interest? Mindfulness training promotes balance (homeostasis) throughout the organism, which in turn increases resilience. These outcomes are desirable because a balanced system is thought to be more resistant to pathology, including psychopathology (Allen et al., 2012). Developing proficiency in paying attention to the present moment without judgment lays the foundation for self-directed neuroplasticity. As we learn to become mindful of the messages we are receiving from our brain and body, we cultivate the capacity to identify deceptive brain messages that have arisen through conditioning and have become entrained in our brain but that may not be serving us well. In fact, many promote system imbalances and resultant disease. We are then in a position to choose to focus on what we want to have more of in our life and to install these changes within our brains through the process of self-directed neuroplasticity. Through a daily mindfulness practice, we can become adept at choosing behaviors that support our life goals.

The importance of mindfulness cannot be over emphasized as it relates to recognizing our capacity to make choices for the good in our lives, and it also provides a sound foundation for developing an approach to behavioral change that allows the individual to choose where to place their attention and thus the outcome of their self-directed neuroplasticity efforts while simultaneously supporting the development of diet-and-lifestyle programs in which desirable behavioral change can be sustained for the long-term. In this way it becomes possible to cultivate new habits that lead to enhanced health and well-being.

Mindfulness is a primary principle underlying the systems medicine-based Mindfulness-based Therapeutic Lifestyle Change program (to be discussed in a later section). Being able to observe our lived experience in the present

moment without judgment facilitates our developing the capacity to choose what we want more of, such as happiness, creativity, equanimity. Operating in such a state enables the organism to rebalance and move towards health and overall well-being.

Psychoneuroimmunology

Ever wonder how a psychological event could make you sick? Although it's long been known that biological, behavioral, and social factors influence health and disease, how this occurs has only been coming to light over the past 25 years. The interdisciplinary field of psychoneuroimmunology (PNI) is providing answers by using a systems approach to understanding the interactions among the nervous system, endocrine system, and immune system; how stress influences these interactions; and the resultant implications for health (Vedhara et al., 2013; see Irwin, 2015 for an overview of the historical development of PNI). Key disciplines represented include neuroscience, psychology, immunology, endocrinology, genetics, and behavioral health. Using animal models initially and then human subjects, researchers have sought to identify the interactions and define the health outcomes along with the mechanisms by which stress can have discrete influences on the immune system plus many other physiological systems, such as the cardiovascular, respiratory, and digestive systems.

Before considering how stress-induced suppression of the immune system might occur, it's helpful to review a few immune system basics. The role of the immune system is to protect the body against invasion from foreign cells and organisms that are potentially harmful, which is essentially any type of cell that's different from the host's cells, such as bacteria, fungi, virus, parasites or cancer cells, for example. The immune system produces an innate/nonspecific (early phase) and an adaptive/highly specific (later phase) response to the threat of invasion. The innate response happens right away in direct response to the threat, real or perceived, of the presence of foreign cells in the body. The adaptive response happens more slowly (days) because it requires immune cells to be synthesized with specific antibodies on their surface and in sufficient numbers to attack the foreign cells.

In terms of how psychosocial stressors can influence immune function, there are two systems that are primarily involved: 1) the central nervous system and its triggering of the HPA axis and 2) the sympathetic nervous system, which elicits the arousal response and increases heart rate, constricts blood vessels, and raises blood pressure. Together these systems prepare the body to fight the threat. The HPA axis elicits the classic stress response and the sympathetic nervous system, orchestrates the release of neurotransmitters and hormones. Within the first couple of hours the nonspecific immune response (also called the "sickness" response) has been mobilized, which includes the mobilization of macrophages (first-on-the-scene immune cells) and their secretion of pro-inflammatory cytokines, such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor alpha (TNFalpha). These cytokines are small proteins that communicate the threat to the nervous system and promote inflammation, which is a normal part of the immune response to infection. This response enables the body to focus its resources on fighting infection and is characterized by both physiological and behavioral changes, such as fever, alterations in liver metabolism, suppression of appetite and libido, and activation of the stress response with its release of cortisol and other stress hormones.

Both real and perceived threats of infection can trigger the nonspecific immune response. When this response is chronically triggered, critical energy and nutrient resources are shifted away from the immune system, which can impair immune system function and leave the body with increased vulnerability to infection. The end result is typically a decreased quality of life due to outcomes such as depression and anxiety, social withdrawal, sleep disturbances, limitations to motivation and productivity, and cognitive impairment.

Behavioral professionals are familiar with the behavioral abnormalities characteristic of stressed patients, such as depression, anxiety, and disturbed sleep patterns. Depressed patients typically have elevated CRH, which leads to activation of the HPA axis. CRH triggers the pituitary to release ACTH, which triggers the adrenal cortex to secrete cortisol. Elevated CRH, ACTH, and glucocorticoid levels are correlated with decreased immune cell activity in animals and humans, which sets the stage for a suppressed immune response and increased risk of inflammatory and infectious disease (reviewed in Irwin, 2015).

The key mechanisms discussed here apply to virtually all stress-induced changes to the immune system and the behavioral changes that typically ensue. Details of the various types of cytokines, neurotransmitters, and environmental (epigenetic) influences on immune system function can be found in the scientific literature for those interested in a more detailed discussion of PNI and of specific immune-related disorders that appear to be influenced by these interconnected triggers and responses. A recent meta-analysis by Morgan et al. (2014) is helpful.

Genomics and Epigenetics

The advances in genomics and epigenetics that have resulted from the Human Genome Project (http://www.genome.gov) have provided the foundation for looking at chronic disease through a systems medicine lens. Although the genetic material is relatively stable throughout an individual's lifespan, the environment can be highly variable. Changing the environment provides a therapeutic approach for changing gene expression, which in turn influences physiological function and, thus, one's personal health continuum between wellness and illness. Further, several categories of modifiable lifestyle factors have been identified that affect gene expression and influence the development or prevention of chronic disease. This section will provide a brief overview of how genomics, epigenetics, and modifiable lifestyle factors provide the foundation for an effective approach to changing the trajectory of chronic disease.

Genomics is the study of an organism's DNA, its genetic material, which contains the blueprint for the operation of the organism—in other words, its operating system. The information for this operating system resides in the linear sequence of nucleotide building blocks that comprises the DNA. To be useful to the organism, the information encoded in the nucleotide sequence must first be translated into the proteins that do the work of the trillions of cells that collectively make up the organism. Examples of these proteins include enzymes, receptors, transport systems, hormones and other types of communication molecules, and structural and contractile components. Proteins are synthesized from genes, which are sequences of nucleotides whose encoded information ultimately generates the amino acid sequence of a protein. Just as words must be appropriate and in the right order to form a sentence that conveys meaning, the nucleotides within a gene are ordered such that their information can be used to order the amino acid building blocks of a protein that, when synthesized, is able to carry out its role in cellular health.

Changes to the DNA sequence occur and make each of us unique in our physical appearance and our functional abilities. These changes typically occur slowly over evolutionary time, with little change during the lifetime of an individual. For humans, the DNA sequence is estimated to have evolved only slightly over the past 40,000-50,000 years (Konner and Eaton, 2010). The changes ("mutations" in genetic parlance) in the nucleotide sequence can cause changes in the proteins that result when genes are expressed. These changes within the genome may result in positive, negative, or neutral effects on how well an individual functions in his or her environment. In terms of clinical applications, genetics to date has typically focused on the negative effects on function, those changes

that provide our genetic susceptibilities to disease.

In contrast, epigenetics is a process that does not affect the nucleotide sequence of the DNA, but instead alters the expression of the information encoded in the sequence (i.e., whether a gene is expressed and its protein is synthesized). As an example, by attaching chemical groups such as a methyl group to nucleotides, gene expression can be turned on or off. The sum total of all these changes throughout the genome is referred to as an individual's epigenome, which is unique to each person, even to siblings with an identical DNA nucleotide sequence, such as identical twins. Tammen and colleagues offer a comprehensive overview of how epigenetics is a key link between nature and nurture (2013). As an interesting aside, the uniqueness of our epigenome is responsible for the fact that, over time, genetically identical siblings begin to look different and have different traits (Fraga et al., 2005).

Both an individual's genome (DNA sequence) and its epigenome (set of molecular tags) are of critical importance in chronic disease. We now know that, like the genome, the epigenome can be inherited. The genome contributes genetic susceptibilities through the structure and, thus, function of the proteins it encodes and the epigenome contributes control over gene expression, whether those proteins are expressed at all and at appropriate times during development and throughout the ensuing lifespan of an individual. Although many of the details remain to be elucidated, ancestors back at least two generations contribute to our epigenome. For a more detailed exploration of epigenetics and its influence on functional outcomes, see the following classic references for this field: Wolff et al., 1998; Joven and Jirtle, 2003; Cooney, 2006; Remely et al., 2006; and Waterland et al., 2006. For overviews of research studies pertaining to the role of epigenetics in behavioral health, see Guitivano and Kaminsky, 2016; Hing et al., 2014; McEwen and Getz, 2013; Reul, 2014; Stankiewicz et al., 2013; Tammen et al., 2013; and Zannas et al., 2014.

Genomics and epigenetics are particularly relevant to the development of chronic disease because they provide the foundation for how internal and external messages communicate with the body, brain, and mind and influence outcomes throughout the organism (Mazzio and Soliman, 2014). Think of genomics as "loading the gun" by endowing us with genetic susceptibilities and epigenetics as "pulling the trigger" by controlling the expression of our genes in response to messages received from the internal and external environment that washes over our genes throughout our lifetime. These messages can turn genes on and off, appropriately or not, depending on the messages received and their timing. When the timing of the genes' expression is appropriate for the organism's needs, the influence on function is positive; when inappropriate, the influence is negative. These environmental messages appear to fall into only a few discrete "buckets" or "domains" that directly relate to our lifestyle choices: nutrition (the foods we eat and toxins we ingest), physical activity (whether we choose to exercise), thoughts and emotions (how we handle our positive and negative thoughts and emotions), sleep and relaxation (the quality and quantity of our sleep and rejuvenation), relationships with ourselves and others (our system of meaning and whether our relationships support or detract from our ability to thrive and flourish).

What is emerging is an understanding that each of the major lifestyle domains has an epigenetic influence on gene expression. It is through epigenetics that each of us becomes the product of the interaction between our individual genetic capabilities and limitations and our lifestyle choices. The earlier argument of whether a disease is the result of "nature vs. nurture" has given way to our understanding that traits, including susceptibility to a particular disease, are seldom due solely to nature (our genome). In the case of chronic disorders, nurture plays a particularly central role in health.

Fortunately, these key lifestyle choices are modifiable and provide practitioners with leverage points for using education and behavioral therapy to help patients live at the health end of their personal health continuum rather than at the disease end. Ongoing research into the most appropriate choices in each of the lifestyle domains gives practitioners a basis for educating patients. Coupling lifestyle education to behavioral change therapy can be a powerful approach for preventing chronic disease and for restoring health to those who have already developed such disorders.

Modifiable Lifestyle Factors and Chronic Disease

Over the past 3 decades, numerous studies have been conducted that demonstrate the health benefits of lifestyle intervention. Among the earliest pioneering work was that of Dean Ornish and colleagues working with men who had cardiovascular disease (Ornish et al., 1983; Aldana et al., 2003; Dod et al., 2010; Silberman et al., 2010). These researchers were able to show that diet and lifestyle modifications—nutrition, movement, thoughts and emotions, relationships, and sleep were powerful promoters of health, even in the face of existing cardiovascular disease. In 2010 the Centers for Medicare and Medicaid began including the Ornish lifestyle program as an approved program for reversing heart disease (CMS memo available at www.cms.gov).

In a cohort from the Look AHEAD trial of 5,000 overweight or obese adults with type 2 diabetes, researchers found significant reductions in hospitalizations, medication use, and healthcare costs (Espeland et al., 2014). At the 10-year follow-up there was a 10% reduction in hospitalizations, 7% reduction in medication use, and a cost-savings of $5,280 per patient over the 10-year period.

More recently lifestyle interventions for chronic disorders have been demonstrated to have positive effects on gene expression. Ornish and co-workers elegantly demonstrated the influence of lifestyle on gene expression in men with prostate cancer (Ornish et al., 2008a). The Prostate Cancer Lifestyle Trial was a one-year randomized controlled clinical trial of 92 men with early-stage prostate cancer. The experimental arm opted not to undergo surgery or radiation therapy but instead to adopt a plant-based diet, exercise regularly, practice stress management techniques, and attend group support sessions. At the 2-year follow-up, only 5% (2 of 43) of the experimental subjects had undergone conventional prostate cancer therapy compared with 27% (13 of 49) of the control patients (Frattaroli et al., 2008).

Ornish and coworkers further demonstrated that diet and lifestyle therapy was effective in increasing telomerase activity, measured in peripheral blood mononuclear cells (immune system cells) from men with prostate cancer (Ornish et al., 2008b). Telomeres are the protective DNA-protein "caps" at the end of chromosomes that enhance chromosome stability, similar in concept to the cap at the end of a shoelace that prevents the shoelace from unraveling. The length of telomeres in human beings is becoming a prognostic indicator of longevity (longer telomere length being associated with longer longevity) and shortness being associated with disease risk and progression in several types of cancer. In a 5-year follow-up to this initial study, Ornish and colleagues found that both telomerase activity and telomere length increased in the experimental subjects but decreased in the controls (Ornish et al., 2013).

Since this groundbreaking work that has elegantly demonstrated the important connection between mindfulness, lifestyle choices, regulation of gene expression, and positive health outcomes, numerous research laboratories worldwide are now engaged in building a strong foundation for a systems approach that works through personalized modifiable lifestyle factors to change the trajectory of chronic disease. The significance of these

findings to healthcare, and to behavioral therapists in particular, is that our lifestyle choices provide us with significant tools that we can use in determining where on our personal health continuum we operate: at the wellness end or the illness end. Below is a brief discussion of each of the major lifestyle domains and our current understanding of how they influence chronic disease.

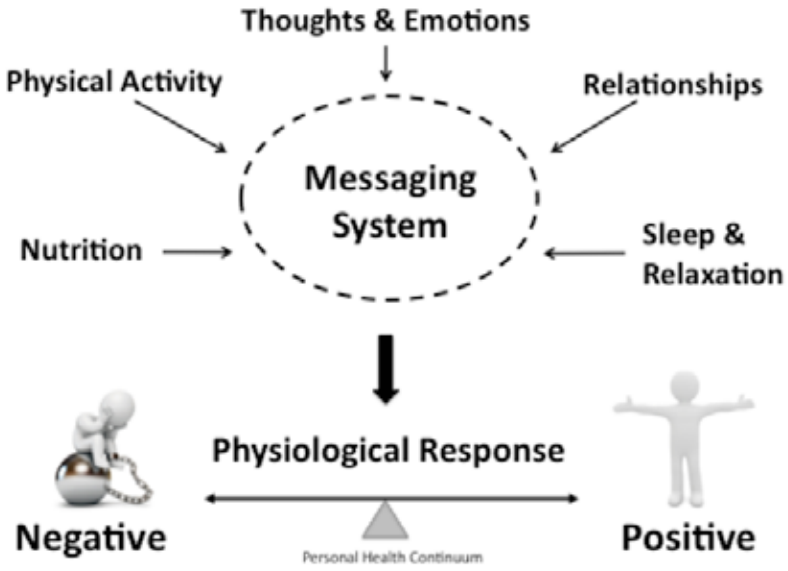

Fig. 1-2. Key Modifiable Lifestyle Domains that Influence Health Outcomes

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Lifestyle Domain: Nutrition

The Academy of Nutrition and Dietetics, the largest organization of nutrition professionals in the U.S., addresses the role of nutrition in health promotion and chronic disease prevention in its official position and practice statements (Slawson et al., 2013; Rosenbloom et al., 2013). These publications summarize the strong association between dietary choices and chronic diseases and the economic and quality of life costs of these disorders. Micha et al. (2012) succinctly summarize the central role of nutrition in health promotion and chronic disease prevention as so:

"It is expected that by 2020, almost 75% of all deaths worldwide and 60% of all disability-adjusted life years will be attributed to chronic diseases… Considering that most chronic diseases are premature and can be prevented or delayed, identifying and targeting the modifiable risk factors with the greatest potential for reducing risk is of major scientific and public health importance. Suboptimal dietary habits are a major preventable cause of many chronic diseases."

The science of nutrition concerns how the nutrients present in food are used to fuel and nourish the cells of living organisms. Much of the research in human beings over the past half-century has focused on nutritional deficiency states, their health consequences, and the use of the diet to supply the missing nutrients. Although genetic changes were known to result in deficiencies of various nutrients or critical metabolic intermediates, these situations were thought to be rare disease states. Thus, genetics was not a major emphasis within nutrition research or

practice. However, with the current advances in genomics and epigenetics, it has become clear that food not only supplies nutrients missing from the diet or that are suboptimal as a result of genetic susceptibilities, but also conveys information from the internal and external environment to the genetic material and influences gene expression, which in turn influences function (Jiménez-Chillarón et al., 2012; Bacalini et al., 2014; Jang and Serra, 2014; Vickers, 2014).

What is emerging is a new systems biology focus for nutrition called nutritional genomics, which seeks to identify the genetic susceptibilities in one's genome and to tailor diets to maximize health and minimize disease (Fenech, 2014; Sales et al., 2014). Once genetic susceptibilities have been identified, it becomes possible to develop a diet that can fill the metabolic gaps that result from one's particular set of genetic variations. For example, humans lack the genetic machinery to synthesize key nutrients, such as vitamin C or essential amino acids or fatty acids. For survival, these nutrients must, then, be supplied by the diet.

Alternatively, one's genetic makeup may result in an impaired enzyme that interferes with the ability to clear some toxic chemicals from the body. Broccoli and other cabbage family vegetables contain glucosinolates, compounds that are able to influence gene expression of the family of enzymes responsible for clearing these toxins. Eating broccoli regularly becomes a therapeutic strategy for these individuals and increases their protection against certain toxic chemicals that they are exposed to in their food or environment. See Remely et al. (2014), Henning et al. (2013); Joven et al. (2014), Miceli et al. (2014), and Milenkovic et al. (2014) for examples of the types of gene, diet, epigenome interactions that are being investigated and the anticipated applications to chronic disease management and prevention.

Using food in this way is part of the systems medicine approach that uses therapeutic interventions targeted to a chronic condition's underlying mechanisms. The technology is in place for this approach but a deeper nutrition research foundation must be developed so that it is clear which gene alteration is associated with which dysfunction and what the appropriate nutritional intervention options are for restoring homeostasis. In the meantime, clinicians familiar with a systems approach and well-versed in metabolic pathways and their associations with various food components are increasingly thinking of food as an appropriate way to improve health and prevent chronic disease.

Of more immediate application are the many ways that food components influence the complex structures and reactions of the brain (McEwen and Getz, 2013; Stankiewicz et al., 2013; Virmani et al., 2013; Hing et al., 2014). As with molecular nutrition, neuroscience is a young field and much research lies ahead before the mechanisms by which food influences brain activity and behavior are well understood. However, it is clear that food plays an important role in brain health. Food supplies the building blocks needed to make neurotransmitters, for example. The precursors for the synthesis of the complex neural circuits that transmit information and respond to neurotransmitters, hormones, and other chemical messengers through gene-encoded protein receptors also originate from the food we eat. At a minimum a diet built on a healthy base of overall nutrient sufficiency and generous levels of omega-3 fatty acids and protein is needed.

Nutrition Applied to Cardiometabolic Syndrome- Cardiometabolic Food Plan

The Cardiometabolic Food Plan is designed for individuals at risk for cardiovascular disease, dysfunctional metabolic conditions including metabolic syndrome or type 2 DM, and cardiovascular disease with high blood pressure, dyslipidemia, or dysglycemia (Institute for Functional Medicine 2016). It focuses on high quality complete

protein and healthy fats (monounsaturated, essential fatty acids) minimizing transaturated partially hydrogenated vegetable oils. The low glycemic index and load carbohydrates found in many vegetables and fruits are more beneficial. The incorporation of the full range of phytonutrient rich foods (the colorful vegetables and fruits) and fermented foods which have so many diet-microbiome interactions are emphasized. The foods rich in the macro- and micronutrients affecting cardio-metabolic disease have been reviewed (Mozaffarian 2016).

The Mediterranean diet way of eating favorably incorporates many of the focused dietary and food changes which alter the parameters of metabolic syndrome (decreasing waist circumference, raising high density lipoprotein, decreasing triglycerides, glucose and lowering systolic and diastolic blood pressure. This has been confirmed in over 50 studies (Doménech, 2014; Estruch et al, 2013; García-Fernández, et al 2014; Jones, 2012)

The Cardiometabolic food plan is a modified Mediterranean food plan which is low glycemic impact. There are two ways to assess the impact of food on blood sugar: Glycemic load and glycemic index. The goal of the cardiometabolic food plan is to encourage low glycemic index foods (foods scoring 55 or lower on the glycemic index), with moderate glycemic index foods (56-69) eg most startchy vegetables eaten occasionally and finally high glycemic foods eaten rarely (>70) (Brand-Miller, 2009). The cardiometabolic plan balances blood sugar, is high in fiber, low in simple sugars, contains balanced quality fats (monounsaturated, essential fats), and encourages condition specific phytonutrients which all help with blood sugar regulation, lower LDL cholesterol and improve blood pressure. The decision to encourage specific phytonutrients in a food plan utilizes the powerful physiologic modulators in the diet. See Table 1.

Table: 4B's of Metabolic Syndrome: Blood Sugar, Blood Pressure, Blood Dyslipidemia, Body Visceral Fat1

Abnormality and Desired Metabolic Rx	Molecules	Foods	Encouraged Foods	Limited Foods
Elevated Blood Glucose				
Rx:Improve Blood sugar regulation	4-hydroxyisoleucine Chaantin Cinnamaldehyde Isoflavones Beta glucan	Fenugreek Bitter melon Cinnamon Soybean Oats and Barley	Olive oil Cinnamon Green Tea Mixed nuts Omega 3 rich foods Fiber rich legumes	Sucrose Fructose Processed foods Saturated Animal fat Fast foods Overcooked meats Large meals Fruit juices >1 egg/d
Blood Dyslipidemia				
Rx: Reduction of LDL Cholesterol Oxidation	Carotenoids Lycopene Polyphenols	 Tomatoes, grapefruit, watermelon	Fish Green leafy vegetables Low glycemic	Sucrose Processed foods Fast foods

	Hydroxytyrosol ECGC Isoflavones	Dark chocolate, pomegranate Extra virgin olive oil Green tea Soybeans	index fruits Tomatoes Extra virgin olive oil Green tea Soybeans Dark Chocolate Pomegranate Seeds and nuts (seseme) Garlic Rice Bran oil	Refined carbohydrates Trans Fats High saturated fats Margarine
Elevated Blood Pressure				
Rx: Reduction of Blood Pressure	Quercetin Sulfur compounds Beta glucan Isoflavones Polyhenols	Onions Garlic Whole oats Soybeans Pomegranate juice, dark chocolate	Protein-soy Whey Legumes Cold water fish High Arginine food Lentils, Walnuts… Blueberries Seaweed Garlic Mushrooms Celery High lycopene fruit Flaxseeds	Sodium >2g/d Processed foods Frozen meals Fast foods Soft Drinks Caffeinated Beverages Alcohol Oils in high heat cooking
Body Visceral Fat				
Rx: Reduction of Visceral Fat	Low Glycemic Index Low Glycemic Load Foods. Adequacy of vitamin D Firmacutes/ Balance EFA balance	Non root vegetables 3:1 ratio vegetables/fruit Protein each meal Omega 3,6,9 Fatty Acids Spice Rich Food Plan	As Above	As Above

The modified lifestyle domain of nutrition focuses on food and places emphasis on the three main areas of macronutrients (Protein, Fat, and Carbohydrate (PFC)) and Micronutrients (Minerals, Vitamins and Phytonutrients (MVP)). The impact of each of the six component areas are reviewed below.

Protein

The cardiometabolic effects of dietary protein has been the subject of many randomized trials. The meta-analysis of these randomized trialed of only increasing protein intake has shown little effect on cardiometabolic risk factors (dysglycemia, adiposity, hyperlipidemia or hypertension).(Schwingshackl 2013). But protein does stabilize blood sugar and should be included in every meal unless the person has chronic renal insufficiency, renal failure or other medical conditions that restrict protein (IFM-Cardiometabolic Food Plan). Protein content of food varies extensively. It's role in altering metabolism and underlying imbalance often rests with the other macronutrients of total fat and carbohydrate in the specific foods (Iso,2011; Schwingshackl, 2013; Nilsson 2012; Institute for Functional Medicine 2016). There have been studies showing a decrease risk of hemorrhagic stroke with the addition of animal protein with the protective effects decreasing vascular fragility (Van Damm, 2012; Haring, 2014). The timing of protein intake can modulate genetic expression and cellular function rapidly. The substitution of high dairy diet with a high red meat diet changes increases insulin resistance (Turner, 2015). The consumption of branched chain amino acids within 60 minutes following an anaerobic exercise session can turn on proteogenesis and the formation of muscle where the consumption of the same protein spaced over 1-3 hours has less effect than a bolus of the same amount of protein in the first 60 minutes on muscle formation (West, 2011).

In fish eaters, moderate consumption provides good quality protein with omega 3 fatty acids and is associated with lower risk of fatal coronary heart disease (2+ servings a week) compared to little or no fish consumption (Mozaffarian, 2011; Zheng, 2012). Higher intake of fish does not seem to be protective (Larsson, 2012; Leung, 2014)

Through this lens, the macronutrients located in health enhancing foods provide essential 'medical' components comparable to pharmaceuticals in treatment. It can be said, 'The right food, at the right time, in the right situation, in the right dose leads to healthy change'.

Fat

Limiting fat has been a focus in industry and many diet plans in the United States for the last 50 years. Low-fat diets have no benefit for major chronic disease if that is the only intervention (Alhazmi, 2012; Mente, 2009). When the endpoint of heart disease, stroke, cancer, diabetes or insulin resistance is considered in the 50,000 US women followed for a decade, there is no benefit of the low fat diet(Howard, 2006; Tinker, 2008; Micha, 2010). In fact when diets higher in healthy fats over 35% of the diet, there is a reduction of cardiovascular disease and diabetes (Appel, 2005; Gadgil, 2013; Estruch, 2013; Chowdhury,2014 ; Roncaglioni, 2013). It is noted in the healthiest traditional diets they are rich in vegetable oils, seafood and nuts (Mozaffarian, 2011). Mozaffarian and his colleague have extensively reviewed the role of diet and cardiovascular disease prevention and treatments (Mozaffarian, 2016).

Monounstaturated Fat

Monounsaturated fat (predominantly oleic acid, 18:1) improves blood pressure and cholesterol when it is substituted for saturated fat and indeed lowers glucose in people predisposed to insulin resistance (Schwingshackl 2014; Schwingshackl, 2011; Schwingshackl, Sasser 2011). Monounsaturated fat intake is associated with trends toward greater CVD (Jakobsen) and is not associated with lowering the incidence of diabetes (Micha 2010).

Extra-virgin olive oil and mixed nuts, and perhaps high-oleic canola oil, are good dietary choices to improve cardiometabolic health (Appel, 2005; Gadgil, 2013).

Polyunsaturated Fatty Acids (PUFA)

Examples of omega 6 polyunsaturated fatty acid linoleic acids are in walnuts, flaxseed, chia seeds, and soybeans. The most common are n-6 linoleic acid (LA, 18:2n-6) and n-3 alpha linolenic acid (ALA, 18:3n-3), which are principally in vegetables and their oils. Seafood is the major source of the long chain n-3 polyunsaturated fats eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). These fats help reduce risk factors for heart disease, including hypercholesterolemia, hypertriglyceridemia and hypertension.

Saturated and monounsaturated fats are synthesized from carbohydrate in the liver (hepatic de novo lipogenesis) however humans cannot synthesize linolenic acid or alpha linoleic acid. Linoleic acid lowers both LDL cholesterol and triglyceride rich lipoproteins and raises HDL cholesterol (Mozaffarian et al., 2010).

High biomarker levels of arachidonic acid and linoleic acid are linked to lower risk of CHD, and consumption of n-6 rich vegetable oils (15% of calories) in place of animal fats reduces CHD (Chowdbury 2014; Farvid, 2014: Mozaffarian, 2015, 2016).

TransFats

When a double bond in the fat is in the trans position versus the cis position it is a trans fatty acid. Mammals synthesize predominantly cis fats. Partially hydrogenated vegetable oils are 30-60% trans fatty acids. Trans fats have advantages for commercial deep frying, backed goods, packaged snacks and shortening but not for the normal life of a mammalian cell.

There are small amounts of trans fatty acids in meats and milks of cow, sheep, and goats formed by their gut microflora but account for less than 5% the total fat (Mozaffarian, 2009). The mammalian trans fats are not associated with increased cardiovascular disease risk and in fact are associated with a lower diabetes risk (Mozaffarian, 2009, 2015). However, the higher level of trans fats from processed oils is associated with raising LDL cholesterol, ApoB, triglycerides, and lipoprotein (a) and lowering HDL cholesterol and ApoA1 levels (Mozaffarian, 2006). The 18:2 trans fatty acid isomers influence pathways related to adipocyte dysfunction and insulin resistance (Micha 2009, 2012). They promote inflammation, endothelial vasodilator dysfunction, insulin resistance, visceral adiposity and arrhythmia seen associated with cardiometabolic syndrome (Micha 2010; Wallace, 2009).

Carbohydrates (sugar, fructose)

Food plans and eating habits that are rich in legumes, vegetable, minimally processed grains, and fruit are protective of health and minimizes cardiovascular disease risk. While foods rich in white bread, white rice, crackers, cereals, baked deserts, white potatoes and other sources of high glycemic index foods increase cardiac risk. The risk of cardiometabolic disease is modified by the quality and quantity of the carbohydrate. The consumers of low fiber, refined grains, starches, added sugar, forming a high glycemic index, high glycemic load diet suffer from the metabolic pertubations of glucose and lipid dysregulation (Mozaffarian, 2016).

The high doses of rapidly digested glucose or fructose induces postrandial hyperglycemia and resultant hyperinsulinemia. The glycogen stores in the liver fill, and once filled excess glucose is converted to fat by way of normal

hepatic de novo lipogenesis. Fructose (half of the sucrose molecule or predominant component of high fructose corn syrup) does not stimulate blood glucose or insulin rise but rather stimulates hepatic lipogenesis, hepatic and visceral adiposity and uric acid production which becomes significant when the intake becomes greater than 25-50 grams in the diet (Basaranoglu, 2013; Stanhope, 2015; Malik, 2015). High doses of rapidly digested glucose and fructose are each harmful, via both distinct and partly overlapping pathways. In contrast, low doses of slowly digested glucose or fructose (e.g., as found in fruit) would each have minimal cardiometabolic harms (Mozaffarian, 2016).

Minerals

Sodium

In North America and Europe, most sodium (~75%) comes from packaged foods and restaurants, and little from home cooking or table salt. In Asian countries most sodium comes from soy sauce and salt added during cooking or at the table (Brown, 2007). The more salt above 4 grams a day someone eats the greater chance of cardiovascular events or stroke, and there also is an increased risk if the sodium level is too low. (Aburto, 2013; O'Donnell, 2014; Whelton, 2012) The DASH diet has a set goal of 2 grams of sodium a day.

Magnesium and Potassium

The major sources of minerals in the diet include vegetables, fruit, grains, legumes, nuts and dairy. Adequacy of potassium, calcium and magnesium help prevent hypertension in the setting of higher dietary sodium intake. Potassium and sodium excretion are controlled by the aldosterone pathway. When potassium supplementation to lower blood pressure is initiated, the effect is greater when the dietary sodium intake is high. This relates specifically to the balance of sodium and potassium excretion and the sodium/potassium ratio modulated by the aldosterone pathway (Adrogue and Madias, 2007). There are few high sodium foods in nature. Simple flipping the diet intake from a high sodium/potassium ratio to a high potassium/sodium ratio by decreasing added salt and processed foods, there is an improvement in blood pressure, modulation of the immune TH2 to TH1 balance and resulting less inflammation. By converting someone to a western diet, which is higher in sodium, there is a resultant raising of blood pressure, worsening incidence of stroke, and worsening cardiovascular disease (Mozaffarian, 2016).

Diets rich in potassium attenuate while diets low in potassium exaggerate the blood pressure effects of sodium. By just converting someone from a western diet to a Mediterranean or DASH type diet (more fruits, vegetables, and nuts) there is improvement in blood pressure (Mozaffarian, 2016; D'Elia,2011). In observational analyses, dietary and blood Mg inversely associate with CVD, especially fatal CHD (Del Gobbo 2013). In a recent metanalysis the magnesium status is inversely correlated to metabolic syndrome (Sarrafzadegan 2015). Interestingly for every 100 mg/day increase in dietary magnesium intake there is an associated with a 22% reduction in the risk of heart failure and a 7% reduction in the risk of stroke and a 19% decreased relative risk of mortality due to stroke in type 2 diabetics (Fang 2016). Increasing dietary magnesium intake is associated with a reduced risk of stroke, heart failure, diabetes, and all-cause mortality, but not CHD or total CVD (Fang 2016).

In diabetic patients with magnesium levels low normal who were given 300 mg of magnesium oxide for three months there was significant improvement in total cholesterol, lowering triglycerides and LDL, increasing HDL lipid fractions and improved hemoglobin A1c 30% (Shahbah, 2017). In populations with metabolic syndrome adequa-

cy of magnesium should be encouraged. The incorporation of high magnesium rich vegetables is consistent with the cardiometabolic food plan or modified Mediterranean food plan.

Vitamins

The focus on vitamin supplementation and controlled trials over the years have shown little effect on atherosclerosis progression or cardiovascular events (Mozaffarian, Appel 2011, Mente 2009, Ye 2013). The B vitamins, folate, beta-carotene and the mineral and vitamin antioxidants selenium, vitamin C and E have been studied extensively. Diets high in antioxidants are rich in vegetables and fruit, whole grains and nuts. These foods are encouraged in the cardiometabolic food plan and are consistent with a modified Mediterranean diet. The focus on single components of food vs. the symphony of molecules found in whole foods may be folly and is not likely to have similar effects (Mozaffarian, Ludwig 2010;Jacobs 2007).

Vitamin interventions for discrete biomarkers have been studied. Homocysteine is a biomarker which increases when there is inadequacy of many B vitamins. The most commonly recognized influencing B vitamins include riboflavin, niacin, pyridoxine, folate, and cyanocobalamin. Recently recognition of genetic single nucleotide polymorphisms common in the populations studies influence the Km of the enzyme and the cofactor requirements for the normalization of metabolic pathways. For example, if an individual has a homozygous recessive single nucleotide polymorphism for methylenetetrahydrofolate reductase, the daily requirement of folate doubles from 400 to 800 mcg/day for adequate balance of this single step in one carbon metabolism (Kohlmeier 2013). As homocysteine rises the oxidative stress increases, endothelial dysfunction increases as does the resultant blood pressure. Multiple metabolic markers in cardio metabolic syndrome are followed with the appreciation that the family of biomarkers are influenced by the family of cofactors for the enzymes which metabolically balance the physiologic perturbations in metabolic syndrome.

Vitamin D adequacy has been linked to decreasing incidence of hypertension, endothelial dysfunction, inflammation, and improved insulin sensitivity. The more obese the individual the more difficult it is to bring balance and adequacy to serum markers of vitamin D, 25 OH vitamin D3. Over the last 30 years there has been increased focus on vitamin D adequacy since there have been so many associated disease conditions with lower levels, and populations are deficient by current standards. Vitamin D's role in skeletal and non skeletal conditions are well documented. Deficiency is associated with pain hyperesthesia, neurotransmitter imbalance and seasonal affective disorder, hypertension, insulin resistance, increased intestinal permeability and its associated immune dysregulation, innate immune system balance, atherosclerotic disease, osteoporosis, increased fall risk, and cognitive changes of aging. This partial lists attests to the multifactorial and multimodal effect of the cascade of vitamin D metabolites. Adequacy of sun, vitamin D2 (mushrooms), and vitamin D3 in the diet all play a role in the balanced adequacy in populations and the incidence of cardiometabolic syndrome.

Phytonutrients (Colors of the Rainbow)

Phytonutrients include a diverse group of up to 10,000 molecules which are potent cell metabolic modulators whose activity crosses species. Plant phytonutrients modulate human physiology. One of the categories of phytonutrients are bioactive polyphenolics which include flavones (eg. Celery chamomile tea, and parsley), flavonols (broccoli, onions, tea, and fruits), flavanones (citrus fruits), flavanols such as procyanidins (apples, cocoa, grapes, red wine, tea), anthrocyanidins (colored berries) and isoflavones (soy). The effects are far ranging, multifactorial and include epigenetic, post translational modulation, enzyme cofactor kinetic impacts, and receptor mod-

ulating influences. In cardiometabolic syndrome endothelial function, insulin resistance, and dyslipidemia are abnormal and with flavonoid-rich cocoa has measurable benefits in all these areas when consumed in as little as 6 grams a day (30 kcal/d) (Shrime 2011, Corti 2009, Perez-Vizcaino 2010, Hooper 2012 ;Buitrago-Lopez 2011). Some of the activity of the phytonutrients is through the specific modulation of nitric oxide at the endothelial level (Taubert).Tea and red wine, grapes and berries, nuts and extra-virgin olive oil all rich in phenolic compounds have had positive observational studies showing lower risk of developing cardiometabolic syndrome (Afshin 2014 ;Basu 2012).

Lifestyle Domain: Physical Activity

Regular physical activity is recommended for health promotion for all age groups. The benefits are well-documented in the prevention, management, and rehabilitation of chronic conditions, particularly for cardiovascular-related outcomes (Gupta et al., 2011; Barlow et al., 2012). Further, low levels of activity are associated with increased risk for all-cause mortality as well as for chronic disorders, such as heart disease and stroke, high blood pressure, insulin resistance and diabetes, and behavioral health conditions such as anxiety, depression, impaired cognition, and overall diminished quality of life (reviewed by Park et al., 2014). Research with animals and humans suggests that physical activity results in greater neuroplasticity through multiple avenues, which in turn improves cognitive function and the capacity to respond to potential stressors with positive behavioral adaptations (Gary and Brunn, 2014; Hötting and Röder, 2013). Improving and sustaining neuroplasticity, requires cardiovascular fitness, further supporting the idea that physical activity needs to be regular and lifelong.

In addition to the conventional recommendations for aerobic, resistance, and stretching activities, the ancient practice of yoga has become a popular movement modality in the U.S. Gentle forms of yoga have particular advantages for the elderly and those with limited mobility or chronic pain. In a meta-analysis of 18 studies, Patel and coworkers (2012) found that for elderly participants a regular yoga practice was at least equal to other forms of exercise in terms of overall health benefits, aerobic fitness and muscular strength. Additional benefits of improved executive function and other aspects of cognition have also been reported for those engaging in a regular gentle yoga practice (Gothe et al., 2014). Bikram yoga ("hot yoga") has become popular for younger participants, particularly for weight loss and weight maintenance, and appears to be a beneficial physical activity option (Pate and Buono, 2014). Research correlating yoga with changes in gene expression are in their infancy but promising, particularly with respect to reduction in pro-inflammatory signaling (Black et al., 2013; Bower, et al., 2014).

Research into the molecular basis for the various health benefits of regular physical activity is being conducted in numerous laboratories and across multiple chronic disorders. The focus is on the identification of gene variants and their roles in various chronic diseases as well as on the epigenetic influences on gene expression. Using insulin resistance-related conditions as just one chronic disease example, studies have found that the muscle contractions that occur during physical activity result in translocation of the GLUT4 receptor from the interior of cells to the cell membrane where it assists in blood glucose entry and facilitates energy production (reviewed in Richter and Hargreaves, 2013; Strasser and Pesta, 2014). Further, exercise lower the number of methyl groups attached to the region of DNA that controls the synthesis of the GLUT4 receptor, which increases the production of this receptor protein and further enhances glucose entry (Rowlands et al., 2014). A second important component, the PGC1 (peroxisome proliferator-activated receptor γ coactivator-1γ) gene, has also been found to respond positively to exercise in ways that benefit glucose usage (Santos et al., 2014). This gene is a master regu-

lator of mitochondrial activity, which is key to energy production. Its expression is essential for proper glucose disposal and is subject to epigenetic modification by high-energy diets and reduced physical activity. The resultant decreased expression of the PGC1 gene contributes to insulin resistance. Exercise appears to attenuate the epigenetic effects, thereby increasing expression of this gene and reducing insulin resistance. In this way exercise's effects on PGC1 expression can help to prevent the development of insulin resistance-related chronic conditions such as metabolic syndrome and type 2 diabetes and more effectively manage existing disease.

In spite of the well-documented benefits of regular exercise, physical activity is not routinely prescribed within the health care system (Dacey et al., 2014; Vuori et al., 2013). The Healthy People 2020 guidelines include a strong statement of the need for increased physical activity among Americans, based on the discovery that greater than 80% of adults do not meet current guidelines for aerobic and muscle-strengthening activities and greater than 80% of adolescents do not meet the youth guidelines (http://www.healthypeople.gov/2020/topic-sobjectives2020/overview.aspx?topicid=33).

Given the well-documented health benefits of physical activity, a significant contribution could be made through effective behavioral change therapy. A recent recommendation from American College of Sports Medicine (Garber et al., 2014) recommends prescribing exercise interventions and promoting their adoption and adherence by combining behavioral change therapy, the inclusion of an experienced fitness instructor, and a focus on activities that are enjoyable to the participant.

Lifestyle Domain: Thoughts and Emotions

This lifestyle domain is particularly important to behavioral change as it can enhance emotional regulation, cognitive flexibility, cognitive reappraisal to stress and to re-contextualize perception by targeting neural growth in the parts of the neomammalian brain associated with these outcomes (Keyworth, 2014). Additionally, there is a growing body of literature that supports a mindfulness-based foundation to working with thoughts and emotions (Kashdan and Ciarrochi, 2013). A meta-analysis of 39 studies and over 6,000 participants exposed to positive psychological interventions found that these strategies were impactful in increasing subjective well-being, psychological well-being and in reducing depressive symptoms (Bolier, et al., 2013). A mindfulness-based positive psychological approach teaches skills in working with painful, maladaptive cognition and feelings and trains the mind in developing a positive, flexible, open, self-controlled, receptive and goal-directed stance towards life (Hanson, 2009). Cheung and coworkers (2014) have demonstrated that those skilled in mindful meditation practices can accelerate the growth of neural substrates associated with greater trait self-control (TSC), which positively correlate with experiencing greater life satisfaction and happiness. Promising findings by Kaliman et al. (2014) suggest that mindfulness-based lifestyle interventions may impact inflammatory processes known to underlie chronic disease through the epigenetic regulation of pro-inflammatory gene expression.

Thoughts and Emotions- Impacting Cardiometabolic syndrome

Chronic stress leads to maladaptive physiology (Guarneri, Bradley 2015). The stress alters underlying physiology leading to changes in cardiometabolic markers affecting numerous organ systems (Table 2).

Chronic stress leads to maladaptive physiology (Table 2)

Stress and Physiologic Pathways[1]	Cardiometabolic Marker	Organs
Impaired glucose metabolism via chronic cortisol elevations and aberrant gluconeogenesis	Hyperglycemia	Adrenals, Liver, Pancreas
Weight gain from disrupted diurnal cortisol rhythms	Elevated BMI, Obesity Visceral adiposity	Visceral Fat, Adrenals
Cardiac arrhythmia via imbalanced sympathetic to parasympathetic nervous tone	Hypertension, palpitations	Heart electrical conduction system, Carotid Bodies
Hypertension from elevated catecholamines increasing vascular tone	Hypertension	Adrenals, Peripheral vasculature
Hyperlipidemia and excess circulated free fatty acids from lipolysis	Hyperlipidemia- High LDL and Low HDL, increased small LDL particle number	Mitochondrial dysfunction with inadequate reserve for transfer of free fatty acids via the carnitine shuttle
Increased Inflammation with increased TNF alpha from elevated catecholamines	Elevation in hsCRP, TNF alpha	Immunologic upregulation with resultant cytokine modulation of inflammation- Brain, Intestine, Musculoskeletal system
Coronary spasm from imbalanced sympathetic and parasympathetic nervous tone	Increased oxidized LDL, assymetric dimethylarginine, Increased hsCRP	Heart, vascular endothelial dysfunction.
Immune suppression from excess cortisol	Weight gain-increased BMI	Immune system- brain, lungs, intestines, skin, mucosa
Increased anxiety from excess catecholamines	Hypertension	Brain, intestines, nervous system
Hypersensitivity to pain from increased inflammatory modulation	Weight gain due to decreased mobility	Brain, musculoskeletal, skin

Stress and physiologic pathways [1]Guarneri, Bradley 2015; [2]Crettaz 2013

Lifestyle Domain: Relationships with Self and Others

This domain focuses on the influence on health of developing positive relationships with oneself and with others and of being grounded within a system of meaning. Cultivating self-compassion, self-appreciation, self-acceptance, insight and an awareness of one's strengths appears to enhance health and well-being. It is well documented that self-affirmation improves psychological functioning and recent studies have further identified self-compassion as a potential stimulator for self-affirming beliefs that appear in turn to enhance pro-social, relational behaviors (Lindsay & Creswell, 2014). In fact, pro-social behaviors in adolescents have been correlated with decreasing inflammatory indicators, such as overweight and obesity, proinflammatory cytokine levels, and cholesterol levels (Schreier, Schonert-Reichl & Chen, 2013). These results are encouraging because inflammation is a common promoter of chronic disease. In contrast, there is strong evidence suggesting that socially isolated individuals have significantly increased indicators for stress and chronic inflammation (Copertaro, et al., 2014).

Becoming a "benefit-finder" of oneself and of others is yet another practical approach in this domain. Researchers are finding that focusing attention on positive traits in oneself and others and increasing the attention one pays to things for which one is grateful can yield positive health outcomes. There are robust data validating that the brain is turbo-charged to create neural connections wherever focused attention is placed (Hanson, 2013). There is strong evidence that this type of 'benefit finding' correlates with positive chronic disease outcomes by changing negative perceptions driving underlying inflammatory processes (Meyerson, et al., 2011) and potentially modulating neuroendocrine and neuroimmune processes of significance to development and management of chronic disease (Antoni, et al., 2009). Increasingly enhanced states of happiness and flourishing are being correlated with a host of positive health-based outcomes, including significantly less chronic disease. It is suggested that those who routinely train their mind to see, value and appreciate pleasant daily events (i.e., helping others, creating, interacting, playing, learning, spiritual activity, nature) experience greater heartfelt positivity and physical well-being as well as an enhanced capacity for mindfulness (Catalino & Frederickson, 2011).

Overall this domain is concerned with promoting neuroplasticity in ways that benefit health, such as developed enhanced resiliency, social support, inner acceptance, stable attention, and equanimity. Simple practices such as focusing on the strengths of oneself and others, looking for the good in one's life, being grateful for one's experiences, and engaging in activities that are meaningful to oneself appear to have profoundly positive influences in terms of enhancing health and well-being.

Lifestyle Domain: Sleep and Relaxation

Sleep plays a restorative role for the brain and for the body in general. Given the importance of sleep, of increasing concern from a health perspective are the changes in the sleep/wake cycle that industrialized societies are experiencing in association with escalating chronic stress. Currently the sleep period is estimated to have decreased by approximately 2 hours per day over the past 50 years (Misra and Khurana, 2008; Lucassen et al, 2012). Numerous studies have demonstrated that insufficient quality or quantity of sleep can lead to a variety of behavioral, neurochemical, endocrine, immune, cellular, molecular, and metabolic changes throughout the body (Anafi et al., 2013; Kurien et al., 2013; Buxton et al., 2012; Hanlon and Van Cauter, 2011; Van Cauter, 2011, Chrousos, 2009, Knutson et al., 2006). Exactly how an impaired sleep/wake cycle compromises health is not yet known but promising research over the past decade suggests there is are complex interactions among environmental cues (such as chronic stress), the sleep/wake cycle, and gene expression (Orozco-Solis and Sassone-Corsi, 2014; Archer et al., 2014).

Much of the experimental work to date involves the use of animal models but extrapolation of the findings to humans has proven to be helpful in understanding the human sleep process. As with animals, humans have a 24-hour circadian rhythm and this internal clock mechanism is important to our personal sleep pattern. The circadian clock mechanism is a key component of homeostasis and controls the timing and quality of both sleep and wakefulness (Franken, 2013). Researchers have discovered an intersection among circadian rhythms, metabolic pathways, and the altered sleep patterns commonly associated with chronic diseases. Anxiety, depression, and cognitive dysfunction, all conditions frequently seen in the clinic, have been linked to disruption of circadian rhythms (Chrousos, 2009).

Several of the genes that encode components of the human biological clock have been identified, and epigenetic markings have been detected. When the clock mechanism is impaired, whether through genetic mutations or metabolic cues that affect epigenetic control of gene expression, circadian rhythms are impaired and promote the development of many of today's chronic disorders (Aguilar-Arnal and Sassone-Corsi, 2013). The ongoing research efforts of numerous laboratories is expected to provide insight into the details of the interactions among genomics, environmental cues, and healthy sleep/wake cycles and to provide recommendations for health-promoting sleep hygiene.

To date, mindfulness and the relaxation response have been primary approaches used to counter the negative influence of chronic stress on healthy sleep patterns (Bhasin et al., 2013). In a recent randomized controlled trial of 54 adults with chronic insomnia, mindfulness was found to be effective in improving sleep (Ong et al., 2014). Gross and colleagues (2011) found mindfulness to be more effective than pharmacotherapy for insomnia. In a meta-analysis, Winbush and colleagues (2007) found that mindfulness techniques were associated with improved sleep patterns and that mindfulness-based stress reduction was especially helpful in reducing worry and other cognitive processes that interfered with quality sleep.

A Systems Approach to Health and Well-being Facilitated through Mindfulness Training: The Mindfulness-based Therapeutic Lifestyle Change Program

As behavioral health practitioners and educators, the salient question then is how can we best teach and guide physicians and their patients to become the captains' of their own health and well-being? Physicians will need to develop knowledge and skills in the applications of systems medicine to medical practice as discussed in earlier sections. For physicians and patients alike, the behavioral aspects of systems medicine will provide increased focused attention, self-regulation and self-awareness, which are beneficial in virtually every aspect of one's personal and professional endeavors. When both physicians and patients practice mindfulness, a deeper capacity for an enhanced doctor-patient relationship is realized.

The first step for the behavioral specialist working with patients is to use the behavioral aspects of systems medicine to deliver an effective behavioral change program for chronic disease. Such a program focuses on the key external factors that communicate with our cells and influence our molecular, biochemical and physiological responses: nutrition, physical activity, thoughts and emotions, relationships, and sleep and relaxation. Using mindfulness training as the foundation for effective lifestyle interventions, the behavioral health specialist can educate patients on which lifestyle choices are appropriate for each modifiable lifestyle domain and facilitate their developing the mindfulness skills that will allow them to make needed behavioral changes that can be sustained long-term.

The Mindfulness-based Therapeutic Lifestyle Change program (MBTLC) was developed to facilitate education and behavioral change useful to individuals with chronic disease. Each patient is assessed by the chronic care team, from a thorough medical evaluation to nutritional counseling to psychological counseling at the beginning, end, and midpoint of a 12-week program. In weekly classes of 2.5 hours duration, participants learn about and practice mindfulness as a critical foundation for developing the benefits of self-regulation and self-awareness that will in turn assist them in managing their chronic conditions and preventing future chronic disease. The format for each weekly class consists of an overarching theme that reflects the principles of the MBTLC program, didactic and experiential learning that addresses each of the 5 modifiable lifestyle domains as relevant to the week's theme, and a short practice that guides participants in using their own neuroplasticity to install the learning into their brains. We use the Let be, Let go, Let in approach of Rick Hanson, PhD (Hanson, 2013), who is masterful in applying neuroscience in practice (Hanson, 2013). Significant class time is devoted to experiential learning and participants are responsible for practicing the learned skills outside of class for approximately 45 minutes per day. In our experience, the necessary knowledge and skills of mindfulness and making appropriate lifestyle choices must be experienced in order to be effective. A summary of key points for each of the major modifiable lifestyle factors is presented below.

For the nutrition domain, the major focus is on using food to manage existing chronic disorders and to prevent additional co-morbidities. The diets used were developed by a team of medical and nutritional experts working with the Institute of Functional Medicine, a nonprofit medical education institute of healthcare professionals and scientists with expertise in a systems medicine approach to chronic disease that includes diet-and-lifestyle approaches. The food plans are nutritionally sufficient, balanced in overall nutrient content according to current guidelines, high in plant foods, water, fiber, healthy fats, phytonutrients, and low in simple sugars and other high glycemic carbohydrate foods, saturated fat, and sodium and moderate in lean meats. The core food plan is readily adaptable for particular chronic diseases. Through the weekly classes participants learn the basis for making appropriate dietary choices in terms of both the quality and quantity of food; how to plan menus, shop, and prepare foods appropriately for their needs; how to make appropriate choices when away from home; and are charged with the responsibility for practicing these guidelines daily and to log their food intake.

For the physical activity domain, participants learn about body composition and the health benefits of achieving and maintaining a healthy level of weight, body fat, and lean muscle mass. In addition to the dietary support, physical activity is an essential component for achieving these goals. The program explores various aerobic, resistance, and stretching options appropriate for various life stages, mobility limitations, and interests. Participants log their activity daily. Additionally, yoga is included in each class for both the activity and the mindfulness training benefits.

For the thoughts and emotions domain, participants spend additional time focusing on the Let be, Let go, Let in process that, although used in all the domains, is described here in more detail since the Thoughts & Emotions domain lends itself readily to explaining how this approach works. To become skilled in the Let be step, participants are taught how to accept mental and emotional content present in each moment through the lens of non-judgmental awareness, which allows them to steep themselves in the often-negative feelings without judging themselves and their reactions. When ready, the next step is to Let go of any stress-filled mental and emotional content and to then move on to the final step in the process: Let in. This step uses self-directed neuroplasticity strategies to train the mind for Letting in positive experiences that, over time, can change neural circuits. This step is not a superficial feel-good substitution for the often-times painful feelings that triggered the

need for the Letting in experience. Through mindfulness-based positive psychological practices and interventions (Tal Ben-Shahar, 2014), neuroplasticity can be harnessed to promote nonjudgmental awareness, emotional regulation, mental flexibility and goal-directed behavior. Additionally research suggests that epigenetic processes may also be activated so that these beneficial states can synergistically bring a positive influence on health and well-being. In keeping with the importance of focusing on what works, participant keep a daily gratitude log and journal about moments in their day in which they were benefit-finders.

The relationship with self and others (RSO) domain addresses the need to develop a loving relationship with oneself through greater self-compassion, self-appreciation, self-acceptance, insight and valuing one's strengths. It has been our experience that self-love today is often at a low level, particularly in those struggling with chronic disorders. The degree to which we can increase our self-esteem and sense of innate worth is a critical factor in being able to impart these values to others, which serves to increase our and their for healthy, strong relationships and support systems.

In the work with the RSO domain, participants are encouraged to train their minds to focus on the good in their lives and in their relationships. Positive psychologists describe this process as "becoming a benefit finder" (Tal Ben-Shahar, 2014). A foundational maxim used in the MBTLC program is that `"focusing on what works, WORKS." As we noted in the neuroplasticity section, the brain appears to readily develop new neural circuits in response to where we focus our attention (Hanson. 2013). Therefore, the program teaches knowledge and skills needed for focusing attention on our strengths, on things for which we are grateful, and on our supportive relationships. There is strong evidence that this type of "benefit finding" correlates with positive chronic disease outcomes by changing negative perceptions that are driving underlying inflammatory processes (Meyerson, et al., 2011) and potentially modulating neuroendocrine and immune processes (Antoni, et al., 2009). Researchers have found that enhanced states of happiness and flourishing are correlated with multiple positive health outcomes, including a reduction in chronic disease. It is suggested that those who routinely train their mind to see, value and appreciate daily events that generate pleasure for us experience greater heartfelt positivity and physical well-being as well as enhanced capacity for mindfulness (Catalino & Frederickson, 2011. Through the weekly classes participants learn goal-setting, identifying role models and learned optimism. These lessons are reinforced in the home practice through coaching calls with classmates, which serve as a means for building supportive community and safety to practice newly acquired skills.

In the final domain, sleep and relaxation, a combination of education and practice are again used to help participants assess their sleep pattern and, as needed, to achieve a better quality and quantity of sleep and relaxation. Not surprisingly, sleep is closely tied to the other four lifestyle domains. Appropriate nutrition and physical activity, regular practice of mindfulness, and attention to appreciation and gratitude help to create a supportive environment for restorative sleep. Participants log their daily sleep experience as to number of hours slept and the degree to which they feel rested when they awaken.

The following is a case is illustrative of how the overall MBTLC program is being implemented with patients.

Case Example- MBTLC and Cardiometabolic Syndrome- Uncovering Root Cause

The patient is a 42 year-old never-married African-American woman with multiple medical and psychiatric complaints. Early childhood trauma and abuse. Compliant with medications. Complains of worsening extreme fatigue leading to vocational absenteeism/social isolation/heightened frustration with coworkers/friends/family.

Increased weight gain. Lack of motivation for self-care. Lack of exercise or motivation for physical activity of any kind. Patient has been treated for dysthymic depression, with a variety of SSRIs and SNRIs for 13 years. In behavioral therapy for 3 years. Diagnoses include hypertension, major depression, hyperlipidemia, morbid obesity, diabetes, vitamin D deficiency, fatigue, insomnia, constipation

The patient was referred to the MBTLC program for lifestyle therapy. The outcome of the chronic care team's assessment of the patient, coupled to the patient's health goals led to the following treatment plan.

Medical: ***(Cardiometabolic Syndrome Markers)***

- Depression: slowly reduce psychiatric medications
- ***Hypertension:*** diet-and-lifestyle therapy, continue medication until blood pressure improves
- ***Hyperlipidemia:*** lifestyle therapy
- ***Morbid obesity:*** lifestyle therapy
- ***Diabetes:*** lifestyle therapy
- Vitamin D deficiency: 2,000 IU vitamin D3 daily
- Fatigue: lifestyle therapy; vitamin B12 testing (methyl malonic acid)
- Insomnia: lifestyle therapy; continue trazadone 50 mg daily, prn
- Constipation: lifestyle therapy

Lifestyle:

- Nutrition: nutrition counseling; cardiometabolic food plan (addresses weight, hypertension, diabetes, hyperlipidemia, constipation); log of foods, quantity, and emotional state while eating; 1,000 mg mixed EPA-DHA essential fatty acids twice daily
- Physical activity: walking program initiated with an ultimate goal of 10,000 steps/day self-monitored using a pedometer and recorded on an activity log; patient also engaged in resistance and stretching exercises; home yoga program using MBTLC yoga CD
- Thoughts and emotions: daily mindfulness practice to improve self-acceptance, benefit-finding, self-esteem, optimism, courage, self-appreciation, perseverance
- Relationships with self and others: attendance at weekly 2.5 hour MBTLC program and active engagement with other participants; encouraged to resume her church activities and personal friendships as her health improved; encouraged to reflect on her system of meaning and move toward aligning her life with her highest principles
- Sleep and relaxation: commitment to adequate hours of sleep; improved sleep hygiene to improve

quality, self-regulatory breath practice,

At the end of the 12-week program, these changes were noted:

Biomarkers

- Reduction in blood pressure
- Reduced weight and body fat
- Constipation resolved
- Decreased fasting glucose; no change in HbA1c (6.1 mg/dL)
- Decreased total cholesterol, LDL-cholesterol, and triglycerides
- Increase HDL cholesterol
- Medication reduction: discontinuation of medications for hypertension, diabetes, and depression, insomnia

Lifestyle Parameters

- Patient had active nutrition, physical activity, thoughts and emotion, relationships with self and others, and sleep programs and planned to continue each one
- Patient affect noticeably improved, "brain fog" lifted, not depressed, no longer fatigued
- Dietary supplementation to be continued: vitamin D3 at 1000 mg/day, essential fatty acids at 2000 mg/day, a multiple activated B complex (Thiamine, Riboflavin, Niacin, Biotin, Pantothenic acid, Pyridoxine 5 phosphate, Methyl Folate and Methyl B 12) 1 capsule/day to support one carbon metabolism and the low vitamin B 12 was initiated at week 8).
- Quality of Life assessment-determined: improved overall health, improved energy level, reduced anxiety, reduction in emotional reactivity, improved ability to work and carry out daily activities, improved feeling of calm and peacefulness, much improved sleep, increased focused attention, decreased emotional reactivity, increased ability to "step back" from distressing thoughts and emotions and observe non-judgmentally

Conclusion

Systems approaches, such as MBTLC and functional medicine, provide important advances in mapping the future of prevention and health promotion through root cause analysis leading to integrated treatment strategy. MBTLC is a transformational lifestyle approach leading to long-term behavioral change through its focus on neuro-sculpting and installing specific neuro-anatomical changes in the brain. By employing the 5 modifiable lifestyle domains as levers for neuroplasticity, significant anti-inflammatory brain-heart-gut alterations are made that allow for transformation of perception, behavior and overall health and happiness. This innovative and comprehensive mindfulness-based lifestyle approach is successfully being applied to populations with cardiometabolic syndrome and other inflammatory chronic conditions as well as for health promotion within employee and

physician cohorts.

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P. Michael Stone, MD, MS, IFM-CP is medical director of Ashland Comprehensive Family Medicine-Stone

Medical in Ashland Oregon. With Cathy Snapp PhD and Ruth DeBusk PhD RDN he has worked on bringing functional medicine clinical application to Residency Programs and hospital settings. Through the application of Mindfulness Based Therapeutic Lifestyle Change to Cardiometabolic syndrome using the group medical visit model, the disease burden of hypertension, hyperlipidemia, insulin resistance and obesity is decreasing. As a team they the vision to bring mindfulness based therapeutic lifestyle change programs to primary care using the group medical visit model and virtual platforms to promote health.

He is a faculty member for the Institute for Functional Medicine and involved in Cardiometabolic teaching and curriculum development.

He received his MD at University of Washington Seattle and His Graduate Degree in Nutrition at Washington State University. He completed Residency and Fellowship at UCLA Ventura in Family Medicine. Additional Certification in Functional Medicine. mstone@ashlandmd.com

Cathy Snapp, PhD, is an Assistant Professor of Family Medicine at the Florida State College of Medicine

and a Co-Developer/Director of the Mindfulness-based Therapeutic Lifestyle Change Program (MBTLC). She served for 13 years as the Director of Behavioral Health at the Tallahassee Memorial HealthCare Family Medicine Residency Program. Over the past 10 years, Dr. Snapp (PI) and her co-director, Dr. Ruth DeBusk, have been awarded over $8 million dollars to develop epigenetic, multigenerational behavior and therapeutic lifestyle change programs and resident training curriculum in functional medicine and systems approaches to health and well-being.

Ruth M. DeBusk, PhD, RDN

Ruth DeBusk is a geneticist and clinical nutritionist with expertise in the genomics and nutrition aspects of

systems medicine. A former professor and researcher at Florida State University prior to entering clinical practice, she has extensive research, teaching, and clinical experience and is the author of numerous journal articles, textbook chapters, books, and patents. Dr. DeBusk has been a key contributor in the Institute for Functional Medicine's integration of nutrition and genomics into the Institute's medical education offerings. As part of the fabulous team of Drs. Cathy Snapp, Michael Stone and Geralyn Russell, she has helped to develop the behavioral and systems medicine aspects of the Mindfulness-based Therapeutic Lifestyle Change program.

JOEL M. EVANS
MD

ALEXANDRIA L. GESING
BA

Sociogenomics: Using Food to Reverse the Gene Expression of Unhealthy Relationships

The interplay of our social environment, genetic makeup and the food we eat have a dramatic affect our overall health dramatically in a multifaceted mechanisms which we are just discovering and are continuing to explore. By studying the changes that occur as a result of genetic modifications (epigenetics) together with the emerging field of human social genomics (sociogenomics); we have gained an increased understanding of the influence each of these three factors have on our overall health. Through continual research and conducted studies within both fields; we've become closer to preventing and finding solutions to the development of chronic health conditions such as metabolic syndrome, cardiovascular disease and Alzheimer's, to name a few. Within this chapter, I will first provide a general understanding of the field of sociogenomics in order to next explore recent findings pertaining to the influence our genes, social environment and diet/nutrition have on the development of chronic diseases. Lastly, I will demonstrate the potential nutritional ways to reverse or even prevent such factors from influencing our health in a negative way.

Understanding Epigenetics

In order to understand the field of sociogenomics, we must first address the way in which the the field of epigenetics has changed our understanding of our biological makeup: our DNA. The dominating perspective regarding the influence a person's DNA has on developing a chronic disease throughout their lifetime has been that "we inherit the basic building blocks of human potential, DNA, from our parents and that our DNA remains largely unchanged over our lifetimes" (Slavich & Cole, 2013.331). Although DNA is widely regarded as the unchangeable carrier of genetic information; genes themselves need instructions for what to do, as well as where and when to do it. We now know that certain genes can be "turned on" or "turned off" by certain social-environmental conditions we may encounter. Put a different way, it is not about what genes we carry but rather, which genes are turned on. Transcription factors are the proteins that help determine whether a gene is "turned on" or "turned off" by whether they do or do not bind to DNA. The gene is activated when binding happens, and "our body upregulates the transcription of DNA into mRNA, which is then decoded, or translated, to produce proteins that mediate bodily processes that affect our mood, cognition, behavior, and health" (Slavich & Cole, 2013.333). Transcription factors can work in two ways; Some work within the cell to maintain its cellular identity, while others respond to extracellular signals, such as hormones, neurotransmitters, or growth factors to alter the expression of a gene. An example of the latter function would be how in the context of stress, for instance; signals from glucocorticoids or catecholamines are detected by receptors on the surface of cells. These signals then initiate a complex set of interactions intracellularly, which results in activation of transcription factors such as CREB (cAMP response element-binding protein) or glucocorticoid receptors. These epigenetic modifications, also known as "tags," therefore provide the instructions our genes require.

Although there have been thousands discovered, the two primary tags are:

1. ***methyl groups,*** which are of carbon and hydrogen makeup.

2. ***histones,*** types of proteins.

As demonstrated below, methyl groups act as a switch that turns a gene on or off, while histones provide more of a regulation function through which they turn up or down gene activity. Thus, these tags both turn our genes on and off and regulate their activity. What is exciting is that we now know that lifestyle and environmental factors impact methyl groups and histones influencing the activation of specific epigenetic modifications. This is where

the exciting role of sociogenomics comes into play.

Understanding Sociogenomics

Although it is true that some people are more prone to develop a chronic disease due to their genetic make-up; research has revealed that the "human genome is not a static blueprint for human potential. Instead, our genome appears to encode a wide variety of 'potential biological selves,' and which 'biological self' gets realized depends on the social conditions we experience over the life course" (Slavich & Cole, 2013.331). Thus, gene expression is influenced by our social interactions. Until recently, research on the social-environmental effects on health has been focused primarily on understanding the "biological mechanisms involved in sensing and responding to stressful social environments" (Gudsnuk & Champagne, 2013). Such an approach has led to a strong understanding on how the social-environment affects the ***limbic system (part of the brain that deals with fear, anxiety, and emotion) as well as the hypothalamic– pituitary–adrenal (HPA) axis (plays a central role in the brain responding to stress).*** The knowledge we have gained through this perspective has been lucrative in understanding how social-environmental conditions affect our central nervous system, neural and endocrine processes; however, on the other hand, there is a lack of understanding "about the molecular intermediaries that mediate social environmental effects on neurological, endocrinological, or immunological traits, especially at the level of gene regulation" (Gudsnuk & Champagne, 2013). The mechanism known as ***social signal transduction*** is a dynamic that reveals an understanding of both approaches, which has led to a more comprehensive understanding of the effect specific social-environmental conditions have on our bodies.

Social signal transduction is the process in which social conditions influence genome-regulation and thus exemplifies the influence social-environmental conditions have on our central nervous system, neural and endocrine processes at a genomic level. This process begins by an individual experiencing a social-environmental condition and perceiving such as either "safe" or "threatening." Based on the subjective perception of the condition, the body accordingly transduces this information into changes in "hormone and neurotransmitter dynamics that in turn modulate gene expression changes throughout the body including the brain" (Slavich & Cole, 2013.336). The central nervous system's mediated perception of a social-environmental condition as threatening or safe plays a vital role in whether dynamics such as the leukocyte **CTRA *(Conserved Transcriptional Response to Adversity)*** are activated. In the case that a social-environmental condition is perceived as threatening, the activation of CTRA creates a proinflammatory response in the body, which aids in infection and wound healing. This proinflammatory skewing of the leukocyte basal transcriptome is an adaptive response to physical threat, given the fact that historically such threats were associated with increased risk for wounding and bacterial infection.

In this modern day and age we no longer encounter the same type of physically threatening social-environmental conditions that we faced when such an adaptation originated. Put into perspective the vast difference between physical threats within a hunting and gathering lifestyle, compared to threats associated with an urbanized and industrialized society such as the one we live in now. For example, our lifestyles no longer require us to catch, kill and cook our own food, nor are we forced to frequently travel long distances on foot. Although the human race no longer faces considerable physical threats as we had in the past; findings within the field of sociogenomics have revealed that, "social, symbolic, or imagined threats occurring in the contemporary social environment can also activate the CTRA" (Slavich & Cole, 2013.335).

Put in a different way, though today humans face more social threats as opposed to physical threats, the activation of the CTRA can occur when we encounter either. Current social-environmental stressors such as divorce,

bad grades, arguments, or a death are just a few conditions humans face (often on a daily basis), which may be subjectively perceived as threatening and therefore lead to the activation of the CTRA.

The problem with the activation of CTRA in the absence of actual physical threat (and therefore the absence of potential wounds and infection) is that it "deflects host defenses away from the now more prevalent threat of socially mediated viral infections and toward the now diminished threats of injury and bacterial infection" (Slavich & Cole, 2013.335). When the CTRA is activated, the upregulation of inflammation is a sign of a healthy body reacting in a normal way to injury; however, without any injuries (and therefore serving no real function) inflammation can become harmful to our bodies. For instance, repeated activation of the CTRA can lead to chronic inflammation, which becomes a very real possibility when we take into consideration the large number of social-environmental conditions we encounter daily that may be perceived as threatening or even potentially threatening. The consequence of too much inflammation within the body is the development of several inflammation-related chronic conditions, such as:

- **Asthma**
- **Metabolic syndrome**
- **Rheumatoid arthritis**
- **Cardiovascular disease**
- **Neurodegenerative disorders**
- **Certain cancers**
- **Depression**

Proinflammatory/anti-antiviral skewing of the leukocyte basal transcriptome has also been found for people diagnosed with breast cancer (Antoni et al., 2012; Bower, Ganz, Irwin, Arevalo, & Cole, 2011) and PTSD (Posttraumatic stress disorder) (O'Donovan et al., 2011). In consequence, a proinflammatory response within the body may occur in the absence of physical danger, which gives these dynamics the ability to affect risk for certain diseases.

It is important to note that the activation of the CTRA during the process of social signal transduction is not the only way in which our bodies may develop certain diseases as a result of chronic inflammation. For example, the activation of ***cytokines*** play a vital role in reacting to infection, inflammation and other injuries to the body; however, certain cytokines are proinflammatory when activated by specific transcription factors. Frequent activation of proinflammatory cytokines may result chronic inflammation, which increases the risk of developing certain diseases as well as make all kinds of already existing diseases worse.

In summation, the processes presented above provide "a biologically plausible explanation for how social adversity may elicit the wide range of neural, psychological, and behavioral alterations that characterize mental and physical health problems that have been associated with adverse social-environmental circumstances" (Slavich & Cole, 2013.335), which aid in forming the empirical basis for human social genomics.

Now, with a general understanding of this field of research, I will present a few recent studies conducted on both animals and humans that provide better insight into how sociogenomics can help in understanding how to prevent the development and reduce the rate of chronic diseases within this country.

Prenatal Social-Environmental Studies

Research within the field of sociogenomics has revealed recent findings specifically pertaining to the ways in which our relationships influence our overall health. Through increasing knowledge on how our social environment affects our biological makeup, we are thus able to play a more active role in our own well-being as well as the well-being of those around us.

Our first, and most significant environment is the womb, which is also our very first relationship (mother and child). Several studies within the field have therefore concentrated on the prenatal environment and how conditions within this environment are carried into adulthood. The documentary In Utero (2015), for instance, addresses how different changes within prenatal development affect the overall development of the baby's genetic makeup. There are a few ways in which this may happen. First, as stated before, it's not about the genes we carry but rather which genes are activated or not. Recent findings have shown that if a gene is turned on, it will continue to be activated from one generation to the next until a social-environmental condition is experienced that then turns the gene off. This means that we inherit certain genes that have already been activated by specific social-environmental conditions prior to our existence in the outside world.

A second way in which our genetic makeup may be affected prenatally is through our mother's experiences of social-environmental conditions while we are in utero. For example, a study was conducted in which pregnant women were briefly made to feel stress and the child's biological reactions were monitored. The findings showed that the fetuses whose mothers' were exposed to stress showed an increase in heart rate, while those who faced no stressors showed no change or a decrease in heart rate. Within the same study, they also monitored pregnant women who met a depression criteria. What they found within this subgroup was not only an increased heart rate for the child, but an increased breathing rate and blood pressure as well. Through this experiment, one can clearly see a direct relationship between the biological effect a pregnant woman's social-environmental experience has on her fetus by such a small and brief stressor.

On a much larger scale, a child whose mother experiences chronic stress and anxiety while in the womb has shown an effect on the child's ability to cope and deal with stress or anxiety into adulthood (even though they weren't the one's necessarily experiencing the specific stressors). For instance, studies have been conducted on adults who were born during traumatic periods of American history such as the Holocaust. These findings showed that if the offspring were to be born into a similar social-environmental context, their bodies would benefit by being better prepared for conditions such as extended periods of starvation or a better ability to cope with overwhelming stress. This biological change that is passed from mother to child (and potentially many generations after that) could be helpful; however, it may also be detrimental to the offspring's health in the case that their social-environmental context is not similar to the conditions their mother faced (ie starvation, violence, etc.). The presence of biological adaptations that serve no purpose within the body, may therefore result in chronic anxiety or stress.

Dr. Gabor Maté, a Hungarian-born Canadian physician who specializes in neurology, psychiatry, and psychology, was born during WWII. Within In Utero (2015), Dr. Maté explains that the chronic stress and anxiety she experienced while carrying him, led to the development of chronic anxiety, depression and ultimately ADD (Attention Deficit Disorder) in his adult life. Dr. Maté's development of ADD at the age of 50 he strongly attributes to the exposure to chronic stress in the early environment as opposed to a genetic disorder, as argued by experts. His personal experience, along with the findings of studies on adults born under similar conditions, demonstrate the

way in which one's social-environmental conditions while in the womb affect one's health status well into their adult life.

Within the prenatal environment is where a fetus's brain begins to become organized as well as the place in which thousands of neurons make initial connections and organize into functional networks. This puts into perspective just how vulnerable the fetus is in utero and therefore how exposure to social-environmental conditions (though external to womb), as the ones mentioned above, ultimately can create a large-scale imprint on the child for the rest of it's life.

Influence Unhealthy Relationships Have on Our Overall Health

By presenting the social-environmental conditions such as those I have discussed thus far, it should be clear how the relationships we experience throughout our lifetime contribute to a healthy social-environment or an unhealthy social-environment, which in turn influences our overall health.

For example, a study that compared socially integrated people to those who experience chronic social isolation found that those who fit into the latter group showed an enhanced expression of proinflammatory immune response genes and a reciprocal downregulation of antiviral immune response genes (Slavich & Cole, 2013). In another study, this time with macaques (a type of monkey), maternally reared macaques' peripheral blood mononuclear cells were compared to surrogate and peer reared macaques peripheral blood mononuclear cells. The cells of the second group showed significantly greater expression of proinflammatory immune response genes and reduced expression of antiviral immune response genes (Slavich & Cole, 2013). The experimental groups that would be categorized as experiencing "unhealthy relationships" (chronic social isolation and surrogate and peer reared macaques) within each of the two studies reveal the same two findings:

1) Increased activity of proinflammatory ***NF-kB*** transcription factors

2) Decreased activity of ***interferon response*** factor transcription factors

Through studies such as these, we can see the correlation between unhealthy relationships or social adversity and leukocyte gene expression. These two effects have been found in several instances and "are believed to be mediated by chronic social stress resulting from prolonged exposure to social adversity" (Tung & Gilad, 2013). The types of chronic diseases people develop who have faced long-term unhealthy relationships and chronic social adversity are those that involve heightened inflammatory activity, which makes sense now that we better understand the biological response to such conditions through findings within the field of sociogenomics.

Nutritional Solutions/Recommendations

Thus far, I have presented some of the biological mechanisms involved in the development of chronic diseases that we as Americans are increasingly facing, in addition to what recent findings within the field of sociogenomics reveal about how unhealthy relationships and one's social-environment contributes to this problem. Within this section, I will demonstrate how although the American diet contributes to this problem, there is a way in which it can be managed in order to become the solution.

The dominant perspective pertaining to the way in which certain diets may lead to chronic diseases such as metabolic syndrome is that eating foods either we have allergies/sensitivities to or that are categorized as pro-in-

flammatory foods causes chronic inflammation within the body, which increases the risk of developing of metabolic syndrome and other chronic diseases alike. However, through epigenetic research, we have most recently come to find that it's more about the excessive amount of sugar, fructose and refined grains that makes up the American diet. High-glycemic foods such as these increase inflammatory pathways, which can lead to chronic inflammation and diseases such as metabolic syndrome when consumed in large amounts and over a long period of time. My first nutritional recommendation for those who face chronic diseases and are looking to reverse such a result of their social-environment is therefore to reduce and ideally remove the amount of high-glycemic foods in their diet. By replacing these foods with low-glycemic foods like vegetables, legumes and healthy fats such as nuts and fatty fish the results have shown significant reverse effects specifically of high blood pressure and blood sugar rates as well as insulin resistance. These reversal effects thus reduce a person's development of chronic diseases such as diabetes, cardiovascular disease and metabolic syndrome.

The second recommendation I present to my own patients who face high risk or have already developed chronic diseases and are unable to absorb necessary nutrients from their diet alone, is the additional incorporation of specific nutritional supplements that address certain deficiencies. For example, ***DHEA (dehydroepiandrosterone)*** is a hormone produced by your body's adrenal glands, which production of peaks in your mid-20s and for most people gradually declines with age, especially for women when going through menopause. For patients who fit this criteria, I prescribe a DHEA replacement in order to reverse certain negative effects aging has on our health such as:

- Adrenal fatigue and stress
- Weakening immune system
- Reduced bone density and muscle strength
- Lack of energy
- Reduced mood and memory loss

Glutathione is an important antioxidant compound, which similar to DHEA, diminishes with age. Food sources rich in glutathione include, whey protein, avocado, asparagus and parsley; however, most people are unable to absorb sufficient amounts of glutathione from food sources alone, especially those with a glutathione deficiency. A person's ability to generate this compound may be affected by their exposure to chronic stress, extended states of high oxidation, and toxins, which most people within this country face. From my experience in treating patients using Functional Medicine, nearly all patients who face chronic diseases such as arthritis, asthma, cancer, diabetes and Alzheimer's have shown a deficiency of glutathione. Because glutathione is found in nearly all tissues of the body, our body's production and maintenance of sufficient levels is critical in promoting optimal organ function as well as our body's recovery process of chronic illnesses and diseases. As a result, I recommend several nutritional supplements that include the following ingredients:

- **Milk thistle**
- **Selenium**
- **Vitamins B6, B9, B12, and biotin**
- **Vitamins C and E**

Each of these ingredients promote the production of glutathione within the body and thus aid in ensuring optimal overall health for my patients.

In treating symptoms of fatigue, stress, depression, and asthma caused by reduced adrenal functions, I also prescribe supplements that include ingredients such as, ***Adrenal Concentrate, Rhodiola rosea Root Extract, and Licorice Root Extract.*** In doing so, I have found significant results in the reversal of the adverse health effects my patients face. Rhodiola and Licorice extracts are both plant based supplements, which promote in increasing energy, stamina, strength and mental capacity. As an ***"adaptogen,"*** Rhodiola also aids the body in adapting to and resist physical, chemical, and environmental stress, which as we have discussed, are major influencers in the development of chronic diseases. Also a member of the adaptogen family, Licorice extract, which in addition to the health benefits above, additionally acts as an anti-inflammatory to reverse the copious ways in which our social-environment generates the up regulation of inflammation within the body.

My final recommendation in reversing the negative gene expression of our social-environment is to practice daily physical exercise along with some form of meditation. Both of which are incorporated in my own daily regimen and facilitate in reducing inflammation within the body, which may otherwise lead to the development of chronic diseases that our stressful social-environment inversely contributes to.

In Summation

Based on what has been gathered thus far through research within the field of sociogenomics and epigenetics, I have demonstrated the possible ways in which a person's social-environmental conditions may lead to the increasing trend of developing a chronic disease in this country. Based on such influencing factors, I have presented my own recommendations (with an emphasis on nutrition) to aid in reversing and avoiding such trends.

The most influential aspect of what these studies have shown thus far is the clear role our diet, social-environment and genetic makeup collectively play in determining our own health status. From what we eat, smoke, and drink, all the way to the relationships and experiences we encounter over the course of our lifetime; studies show that we have the ability to actively play a role ourselves in optimal health outcomes by changing our behavior and thus altering our biology. With the movement in healthcare towards that of more personalized medicine, it is an ideal climate to educate the general public on the research being conducted within fields such as sociogenomics; and ultimately integrate such findings into the care we receive from healthcare practitioners to the care we provide for ourselves throughout our lifetime. In doing so, I strongly believe that by continuing to actively educate oneself as well as others on future findings within this field in addition to focusing on lower glycemic diets, nutritional supplements, healthier relationships, increased physical activity, and integrating daily methods of stress relief, we can significantly become both individually and collectively healthier beings.

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Joel M. Evans, M.D., a board-certified OB/GYN and international physician educator, is the Founder and Director of The Center for Women's Health, where he practices Integrative Gynecology and Functional Medicine. He is also the Chief Medical Officer of HealthPointe Solutions, which specializes in the use of Artificial Intelligence in Health Care. Dr. Evans was honored to speak at the United Nations in March 2013 on the topic of Prenatal Origins of Violence, and he serves as UN Representative and Chief Medical Advisor for OMAEP – World Organization of Prenatal Education Associations. His book on the holistic approach to pregnancy, The Whole Pregnancy Handbook (Gotham, 2005), has received widespread critical acclaim and media attention. He currently is the Medical Director of the Association for Prenatal and Perinatal Psychology and Health. Dr. Evans was an Assistant Clinical Professor in the Department of Obstetrics, Gynecology and Women's Health at the Albert Einstein College of Medicine from 2002 to 2014. He is a Founding Diplomate of the American Board of Holistic Medicine and is recognized as the first physician in Connecticut to be Board Certified in both Integrative Medicine and Obstetrics and Gynecology. He has a special interest in Hereditary Breast and Ovarian Cancer, and as a National Speaker for both Phenogen Sciences and Myriad Genetics, brings the latest information on cancer risk assessment and prevention to his patients. Dr. Evans serves as a peer reviewer for the journals Alternative Therapies in Health and Medicine and Global Advances in Health and Medicine and served on the editorial advisory board of Bottom Line/Women's Health for its entire publication run. He is a member of the senior faculty of two of the most recognized and prestigious teaching institutions in integrative medicine: The Center for Mind/Body Medicine and the Institute for Functional Medicine. In 2011 he was the external lead physician in the creation of the IFM Advanced Practice Module in Hormone Health and continues to serve in that role. He is a former Director of two nationally known organizations focused on pregnancy, Childbirth Connection and the Association for Prenatal and Perinatal Psychology and Health. Dr. Evans also helped create a clinical study at Columbia University Medical Center on the use of the herb black cohosh in breast cancer, which was presented at the 2001 Annual Meeting of the American Society of Clinical Oncologists and later published in their journal. He recently co-authored (2014) a chapter in the textbook Women's Mental Health across the Lifespan. Having pursued studies in spirituality, metaphysics, and personal transformation for many years, Dr. Evans has recently created a core curriculum designed to share ancient spiritual wisdom with others in order to help bring health and happiness into their lives.

Alexandria L. Gesing is the Research Assistant for Dr. Joel Evans. She supports his writing and public speaking by researching medical literature and copy editing his work. Ms. Gesing is a recent graduate, magna cum laude, of Union College where her studies focused on medical research and policy. She received the John H. Jenkins Award for excellence in project research. Ms. Gesing spent a term studying and comparing healthcare systems in Amsterdam, Netherlands; Cambridge and London, United Kingdom; and Kingston, Canada. This experience ignited her passion and dedication to reforming the US healthcare system.

LISA DORFMAN

MS, RD, CSSD, LMHC, FAND

Integrative Sports and Performance Nutrition

Introduction

Nutrition for sports and performance requires optimal physical training, nutrition, hydration, and adequate rest. Understanding sport specific physiological requirements for training and competition is integral for obtaining sufficient energy, macronutrient and micronutrients and fluids. Healthy, balanced eating and lifestyle habits are necessary for training hard, achieving performance goals and reducing the incidence of illness and injury.

The integration of pertinent information such as lifestyle habits and behaviors including age, gender, culture, health, living conditions, economics are essential for realistically assessing, guiding, counseling and coaching athletes whether or not the goal is to fuel recreational fitness regimens or prepare for the Olympic Games.

This chapter will provide physicians with an integrative sports dietitian's approach to working with athletes; formulas used for assessing nutrition needs; training and competition fuel options; sports supplement considerations; tools and resources.

An Integrative Approach to Working with Athletes

Sports and performance nutrition is not limited to exercise physiology or nutrition—psychological, cultural, emotional, social, and economical factors require an interdisciplinary approach to provide a broader and more comprehensive understanding, assessment and application of the nutritional requirements for athletes.

One needs to consider everything that could potentially impact optimal health and performance in an athlete's life including: genetics & individualized differences, exercise modalities and environments, food beliefs aka trajectories, and life stress which can all effect the athlete's tolerance, assimilation and metabolism of specific nutrients.

In order to prevent nutrient deficiencies, anthropometric, biochemical, dietary data and feedback from athletes are needed to determine if additional factors such as gut dysbiosis, food allergies and/or intolerances, dietary preferences/aversions, or disease processes may affect the overall absorption, assimilation, digestions, biotransformation and transport of specific macronutrients, micronutrients or fluids and ultimately impact performance potential.

Muscle Fuel

To be successful in sport, the body must be continuously supplied with energy. To generate power for exercise, the body relies on ATP (adenosine triphosphate) found within the cell's mitochondria. Although ATP is the main currency for energy in the body, the body is not actually capable of storing very much of it. In fact, there is only about 3 ounces of stored ATP, enough energy for several seconds of exercise at any one time. Therefore, ATP must be continually resynthesized to provide a constant energy source during exercise.

With ATP as fuel, the body utilizes three metabolic systems to provide the energy one need. Two (the Immediate Energy System and the Glycolytic Energy System) are devoted to high intensity activities like all-out sprinting, weight lifting, boxing, martial arts, tennis and intermittent high intensity team sports like football and soccer. The third energy system (aerobic metabolism) fuels moderately paced endurance sports like distance running, swimming, or cycling.

All three of these systems at some point during training, regardless of the sport. However, how much is used of each system, as well as the amount of calories and fat one uses with each session, depends on the duration, intensity, type, and frequency of the workouts. This amount of energy also varies with diet, fitness, stress level, sleep status, age, gender, and genetics.

Calculating Energy Requirements

The most important component of successful sport training and performance is to ensure adequate calorie intake to support energy expenditure and maintain strength, endurance, muscle mass and overall health. Energy and nutrient requirements vary with age, gender, weight, height, training/sport type, frequency, intensity and duration; typical diet, diet history, history of restrictive and disordered eating; endocrine and environmental conditions such as heat, cold and altitude.

Estimating energy intake is challenging to accomplish especially in sports that are less well studied. Calorie needs can range from 25 to 35 kcal/kg/day or roughly 1800 to 2400 calories a day for the 30-40min/day exerciser to 45 to 50 kcal/kg/day and in certain sports even more. For elite athletes or heavier athletes, daily calorie needs can reach 150 to 200 kcal/kg, or about 7500 to 10,000 kcal/day depending on the volume and intensity of different training phases.

Resting metabolic rate (RMR) can be calculated using indirect calorimetry or by using predictive equations. Indirect Calorimetry involves using a hand-held device like the MedGem® calorimeter or metabolic cart typically used in exercise physiology or research settings, to measure a person's oxygen consumption and carbon dioxide production to determine RMR/BMR. Measuring RMR/BMR is more accurate than using prediction equations.

Predictive equations are used to estimate RMR/basal metabolic rate (BMR) when technical equipment, such as a metabolic cart, is not available. The Cunningham Equation has been shown to be the best predictor of RMR for active men and women followed by the Harris Benedict. RMR = 500 + 22 (fat-free mass, or FFM) (kg)

Once the RMR has been calculated, the total energy expenditure (TEE) can be estimated once energy expenditure from physical activity is considered. Since metabolic equipment is expensive, requires considerable training to use and is not practical outside research settings, indirect methods can be employed and include: heart rate monitors, pedometers or accelerometers, or by using indirect methods such as a daily activity factor and adding exercise calories expended by multiplying the calories expended per minute of exercise times the amount of time spent in that activity.

Multiplying total daily RMR energy expenditure x Activity Factor based on the following

activity factor category definitions:

1.2 = sedentary: Little or no exercise and desk job

1.38 = lightly active: Light exercise or sports 1-3 days/week

1.55 = moderately active: Moderate exercise/sports 3-5 days/week

1.73 = Very active: Hard exercise or sports 6-7 days/week

1.9 = extremely active: Hard daily exercise/sports and physical job

Meeting caloric needs for many fitness-minded and or elite; intensely training individuals can be a challenge regardless of the accuracy of the formulas used to predict energy needs. For high school and college athletes disruptive sleep patterns, accommodating academic, social and training schedules often leads to skipped meals, high frequency of unplanned snacking, use of sport shakes and bars in lieu of whole food meals, and late night snacking while studying, socializing online or with friends.

Adult athletes with family and work responsibilities are also meal challenged when juggling daily training schedules with carpools, work deadlines and accommodating children's eating schedules which can ultimately compromise the quantity, quality, and timing of meals, and greatly affect energy, strength levels, and overall health.

In elite athletes, consuming enough food at regular intervals without compromising performance is challenging, particularly when professional athletes are traveling abroad, are at the mercy of airport food, foreign food schedules, unfamiliar training facilities, delays and unforeseen events such as in climate weather postposing game and competition schedules.

All athletes regardless of age and lifestyle demands can be better prepared by packing snacks and ready to eat meals and essential for keeping energy intakes adequate to support overall health and performance. Meeting the daily energy needs and the appropriate macronutrient distribution for active individuals may necessitate the use of sports bars, drinks, and organic convenience foods and snacks in addition to whole foods and meals.

Organic Portable Snacks

Grass fed whey or plant based or Sport bars or shakes
Almonds, walnuts, pistachios, or trail mix
Breakfast bars
Single portion whole grain cereal boxes
Baby Food Fruit and Veggie "Pouches"
Fresh fruit such as apples, bananas or pears
Fruit leathers or dried fruits
Grass fed meat or veggie "jerkies"

Weight Management

Although lean body mass has been associated with positive health benefits, negative health outcomes are associated with excessive loss or gain of body mass. In efforts to maximize performance or meet weight criteria determined by specific sports whether it is in the case of "making a lower weight" in sports such as martial arts, sailing, rowing, or wrestling , or reaching a higher weight for power lifting, football or baseball many athletes alter normal energy intake to either gain or lose weight.

Although such efforts are sometimes appropriate, weight-reduction or weight gain programs may involve elements of risk especially when the pressure to lose or gain weight is expected in an unrealistic short amount of time. For some young athletes achievement of an unrealistically low weight can jeopardize growth and development or conversely a high weight with the use of weight gainer or other supplements.

The goal weight of an athlete should ultimately be based on optimizing health and performance based on the athlete's best previous performance weight and body composition. Adequate time should be allowed for a

slow, steady weight loss of approximately 1 to 2 pounds each week over several weeks. Weight loss should be achieved during off season or preseason when competition is not a priority.

When no standard exists participants would be required to remain above a certain minimal body fat Highest safe weight should be calculated using a value no higher than the highest end of the range satisfactory for health: 10-22% body fat in males and 20-32% in females

Body fat (%) Standards by Sex and Age

Body fat standard	Males	Females
Lowest reference body fat adults	5	12
Lowest reference body fat adolescents	7	14
Healthy body fat ranges	10-22	20-32

Weight Gain

To accomplish a healthy weight gain of lean muscle tissue, 500 to 1000 additional calories per day can be added in addition to strength training which will dually increase muscle strength. The rate of weight gain will be dependent on the athlete's genetic make-up, degree of positive energy balance, number of rest and recovery sessions a week and exercise type.

Athlete Weight Related Challenges

Disordered Eating

Athletes who are more vulnerable to disordered eating are those who participate in "lean-build" sports such as cross country running, swimming, gymnastics, cheerleading, dance, yoga and wrestling who may think they need to be a certain weight or body type often far less than what it is realistic to attain and maintain to be competitive in their sport. This desire to be unrealistically light or lean may lead to restrictive eating, binging and purging, and excessive training far beyond what is required for their sport.

Female Athletic Triad

Chronic dieting by female athletes can lead to the female athletic triad otherwise known as FAT which consists of three interrelated health disorders: low energy availability with or without an eating disorder, osteoporosis and amenorrhea. The prevalence of FAT for athletes participating in lean verses non lean team sports has been shown to be range from 1.5% to 6.7% and from 0% to 2.0%. Also known as Athletic Energy Deficit (AED) can lead to an increase in bone fractures and lifelong consequences for the bone and reproductive health of developing adolescent girl.

Evidence suggests it is energy availability that regulates reproductive function in women, not exercise nor body composition and that ensuring adequate calorie intake is imperative to the overall health of the athletic women. Low energy consumption paired with ovarian suppression aka amenorrhea has been associated with poor athletic performance.

Muscle Dysmorphia

Muscle Dysmorphia (MD), also known as "bigorexia" or reverse anorexia nervosa (AN) is a disorder in which individuals are preoccupied with the concern that their bodies are not muscular or big enough. It is marked by a mix of symptoms that are similar to and opposite of anorexia nervosa symptomatology in that the intense dissatisfaction with their bodies and related distress and maladaptive behavior can occur at all phases of body weight/body fat spectrum while with females in females the extent to which the desire to be smaller is typically indicative of the extent of psychopathology.

Research suggests that with this preference for a muscular physique already evident in boys as young as six years old and may affect up to 95% of college age American men who may be dissatisfied with some aspect of their body and up to 25% of college men engaging in negative body talk

Planning Athlete Diets

According to the United States Olympic Committee (USOC) sports dietitians and other sports dietitian experts, keeping guidelines simple for athletes is imperative for compliance. http://www.outsideonline.com/fitness/nutrition/The-Secret-Food-of-Athletes.html. The United States Olympic Committee Sports Dietitians created The Athletes Plate as a guide for advising athletes diets based on easy, moderate and hard training regimens. Another tool from The Food Swiss Society for Nutrition is the Food Pyramid and Guide for Athletes. This tool helps athletes training more than 5 hours a week modify servings and portion sizes from each food group based on their training

MACRONUTRIENTS

According to the Position Paper of the Academy of Nutrition and Dietetics, Dietitians of Canada, and the American College of Sports Medicine most Individuals engaging in a general fitness program can typically meet their macronutrient needs by consuming a normal diet of 45% to 55% of calories from carbohydrates (3 to 5 g/kg/day), 10% to 15% from protein (0.8 to 1 g/kg/day) and 25% to 35% from fat (0.5 to 1.5 g/kg/day).

This composition prescription is not static and depends on the training "cycle;" season-pre, active, post; and personal food desires of the athlete whether they want to follow vegan, paleo, keto or intermittent fasting. As an integrative practitioner, the most important factor when planning athlete diets is about listening to the athlete's goals and helping them to make their preferences as balanced and healthy as possible in order not to compromise overall health.

The second most important factor to be considered when planning athlete diets is strategizing the diet in concert with training needs and goals called nutritional periodization.

Nutritional periodization is a concept that involves altering one's diet to match the intensity, volume, and specificity of training as it changes throughout the year. Periodization involves taking into account different training cycles, including the exercise load, recovery, peak, and conditioning. These cycles are implemented according to the athlete's sport demands and competition schedules. This requires manipulating the percentage and amounts of carbohydrates, protein, and fat to work in tandem with training to maximize strength, muscle mass, and endurance.

Sports Fuel: Carbohydrates

Carbohydrates are one of two main fuels used for sports. The first source of glucose for the exercising muscle is its own glycogen store. When this is depleted, glycogenolysis and then gluconeogenesis (both in the liver) maintain the glucose supply. The relationship between carbohydrate intake, muscle glycogen content and endurance exercise capacity is well documented and has become widely accepted that a high carbohydrate diet before combined with carbohydrate supplementation during prolonged submaximal exercise can postpone the development of muscular fatigue and enhance performance.

During endurance exercise that exceeds 90 minutes, such as marathon running, muscle glycogen stores become progressively lower. When they drop to critically low levels, high-intensity exercise cannot be maintained. In practical terms the athlete is exhausted and must either stop exercising or drastically reduce the pace. Athletes often refer to this as "hitting the wall."

Carbohydrate Rx

The amount of carbohydrate required depends on the athlete's total daily energy expenditure, type of sport, gender, and environmental conditions with the ultimate goal of providing adequate energy for performance and recovery and by exhibiting a protein sparing effect.

Recommendations should provide for daily carbohydrate intake in grams relative to body mass, and allow flexibility for the athlete to meet these targets within the context of their energy needs and other dietary goals. Carbohydrate intake of 5 to 7 g/kg/day can meet general training needs, and 7 to 10 g/kg/day will likely suffice for endurance athletes, although elite athletes training 5-6 hours a day or more will probably need between 7 to 12 grams per kilogram a day or a range of 420 to 720 grams of carbohydrates a day for the 60kg athlete.

Good sources of carbohydrates include whole grains, vegetables, fruits and low fat dairy options such as low fat organic cow or goat milk; flax, almond or soy yogurt.

Types of Carbohydrate

Even though the effects of different sugars on performance, substrate use, and recovery have been studied extensively, the optimal type of carbohydrate for the athlete is debatable. Studies concerning whether the glycemic index of carbohydrate in the pre-exercise meal affects performance have been primarily performed in endurance sports, compared with fasting conditions and/or are inconclusive.

Sports Fuel: Protein

For athletes interested in building muscle, it appears that either lean animal or plant-based are acceptable as long as the day's total amount is within the recommended range for resistance-training athletes of 1.2 to 2 grams (2.4 grams maximum) of protein per kilogram of body weight per day, depending on many factors including age, size, gender, lean body mass, activity level and intensity and overall health. One study suggests that 2.3 grams per kilogram bodyweight (or about 35 percent) protein is more effective than 1.0 gram per kilogram bodyweight (or 15 percent) protein for maintaining lean body mass in athletes during short term, low calorie weight loss.

Protein experts suggest that 20 to 25 grams of a high-quality, complete protein containing 2.5 grams of the

branched chain amino acid (BCAA) leucine per meal maximizes the response of protein synthesis following strength workouts. No differences have been shown between 20 and 40 grams, suggesting more is not better. Smaller protein portions consumed throughout the day, rather than large 20-ounce steaks, may be more beneficial for maintaining and building muscle.

If the athlete is vegetarian, consuming a diet of primarily incomplete plant based protein sources (for example, vegetables, beans, nuts, whole grains, soy or hemp), or if one is an older individual, more protein may be required to maximize the response of muscle synthesis.

Pre-workout essential amino acid fuel also appears to enhance the anabolic response. And while essential fat Omega 3s foods (such as fish, soy, and some nuts) and carbohydrates may not contribute to protein synthesis, they have been shown to play a role in the prevention of muscle breakdown (catabolism).

Sports Fuel: Fats

Fat is the major, if not most important, fuel for light- to moderate-intensity exercise. Although fat is a valuable metabolic fuel for muscle activity during longer aerobic exercise and performs many important functions in the body, more than the usual recommended amount of fat is not indicated. In addition, athletes who consume a high-fat diet typically consume fewer calories from carbohydrate.

Even though maximum performance is impossible without muscle glycogen, fat also provides energy for exercise. Fat is the most concentrated source of food energy, supplying 9 kcal/g. Essential fatty acids are necessary for cell membranes, skin, hormones, and transport of fat-soluble vitamins. The body has total glycogen stores (both muscle and liver) equaling approximately 2600 calories, whereas each pound of body fat supplies 3500 calories. This means that an athlete weighing 74 kg (163 lb.) with 10% body fat has 16.3 lb. of fat, which equals 57,000 calories.

Exercise intensity and duration are important determinants of fat oxidation. Fat oxidation rates decrease when exercise intensity becomes high. A high-fat diet has been shown to compromise high-intensity performance even when a high-fat diet regimen is followed by carbohydrate loading before high-intensity performance. The mode and duration of exercise can also affect fat oxidation; running increases fat oxidation more than cycling.

The diet content also determines which substrate is used during an exercise bout. If an athlete is consuming a high-carbohydrate diet, he or she will use more glycogen as fuel for the exercise. If the diet is high in fat, more fat will be oxidized as a fuel source. Fat oxidation rates decline after the ingestion of high-fat diets, partly because of adaptations at the muscle level and decreased glycogen stores. Fasting longer than 6 hours optimizes fat oxidation; however, the ingestion of carbohydrates in the hours before or at the beginning of an exercise session augments the rate of fat oxidation significantly when compared with fasting

Fats, Inflammation and Sports Injury

When athletes get injured, they want to heal and get back to training as soon as possible. Specific foods at the right time can help to provide energy for rehabilitation, rebuild strength, and ensure a complete, healthy, and faster recovery.

Stress to muscle leads to inflammation, bruising and tissue breakdown. Failure to decrease inflammation can lead to scar tissue, poor mobility, and delayed recovery times. The inflammatory stage is impacted by foods, especial-

ly the types of dietary fat consumed. A diet high in trans fats, saturated fats, and some omega-6 vegetable oils has been shown to promote inflammation while a diet high in monounsaturated fat and essential omega-3 fats has been shown to be anti-inflammatory.

Monounsaturated fats like olive, peanut, canola, and sesame oils as well as avocado also inhibit and reduce inflammation by interfering with pro-inflammatory compounds such as leukotrienes, which are produced naturally by the body. Diets high in omega-3s have been shown to increase collagen deposition and promote healing. There is also evidence suggest a strong connection between omega-3 status, neuroprotection and supplementation to accelerate recovery from Traumatic Brain Injury including concussion.

Supplemental omega-3 fat has been recommended during the inflammation stage especially when the diet is deficient. However, there are also concerns regarding the usual source of omega-3 fats and fish oils since some have been found to be contaminated with mercury and polychlorinated biphenyls (PCBs.)

Fruits and vegetables are also good sources of alpha linolenic acid, an omega-3. However, the conversion to the more active forms of omega-3s, DHA and EPA, in the body is very low. Plant-based foods rich in ALA include: kidney beans, navy beans, tofu, winter and summer squash, certain berries such as raspberries and strawberries, broccoli, cauliflower, green beans, romaine lettuce, and collard greens. Wheat germ and free-range beef and poultry are also good sources of omega-3 fats since they are fed with omega-3 rich food.

Sports Fuel: Fluids

Experts still debate the ins and outs of fluids—the best methods for assessing fluid needs. There is not general agreement on how much or what type of fluids athletes' need, under what conditions athletes need additional amounts, or even about whether or not dehydration makes any difference for sports performance. When possible, fluid should be consumed at rates that closely match sweating rate. It appears that plain water is not the best beverage to consume following exercise to replace the water lost as sweat. Although specific recommendations differ slightly, the intent is to keep athletes well hydrated

A 2012 study on endurance athletes suggests mild dehydration during workouts of one hour or less does not affect performance. Drinking too much water can work against the athlete. Water alone actually dilutes the blood rapidly, increases its volume, and stimulates urination! Blood dilution also lowers the electrolyte, sodium and volume-dependent part of the thirst drive, removing much of your drive to drink and replace fluid losses. However, pre-workout losses of three percent or more have been shown to negatively affect performance for longer than one-hour sessions. If one weighs 150 pounds, a fluid loss of three percent means at least a fluid loss of four to five pounds.

Fluid Replacement

Proper fluid balance maintains blood volume, which in turn supplies blood to the skin for body temperature regulation. Because exercise produces heat, which must be eliminated from the body to maintain appropriate temperatures, regular fluid intake is essential. Any fluid deficit that is incurred during an exercise session can potentially compromise the subsequent exercise bout. Imbalance between fluid intake and fluid loss during prolonged exercise may increase the risk for development of dehydration. Dehydration may enhance the development of hyperthermia, heat exhaustion, and heat stroke.

Environmental conditions have a large effect on thermoregulation. Humidity affects the body's ability to dissipate heat to a greater extent than air temperatures. As humidity increases, the rate at which sweat evaporates decreases, which means more sweat drips off the body without transferring heat from the body to the environment. Combining the effects of a hot, humid environment with a large metabolic heat load produced during exercise taxes the thermoregulatory system to its maximum. Ensuring proper and adequate fluid intake is key to reducing the risk of heat stress.

How Much is Enough?

Daily fluid intake recommendations for sedentary individuals vary greatly because of the wide disparity in daily fluid needs created by body size, physical activity, and environmental conditions. The DRI for water and electrolytes identify the adequate intake for water to be 3.7 L/day in men (130 oz. /day, 16 cups of fluid/day) and 2.7 L/day for women (95 oz. /day, approximately 12 cups/day.) Active adults who live in a warm environment are reported to have daily water needs of approximately 6 liters and athletes have been reported to have markedly higher values (>6 L).When individuals work, train, and compete in warm environments, their fluid needs can increase to more than 10 L/day.

Men appear to have higher sweat rates that might lead to more fluid loss during exercise as compared with women. Studies have also shown that men have higher plasma sodium levels and a higher prevalence of hypernatremia than women after prolonged exercise which suggests larger fluid losses in men. In contrast, it is also reported that women have an increased risk for overdrinking, which could lead to exercise associated hyponatremia.

Approximately 20% of the daily water can be provided by water found in fruits and vegetables, more if the athlete is vegetarian. The remaining 80% is provided by beverages such as water, juice, milk options-organic, almond, flax or soy; coffee, tea, soup, and sports drinks and shakes.

Fluid Intake for Training

Several Position Statements and recommendations are published by a variety of professional organizations that address fluid and electrolyte replacement before, during, and after exercise. A summary of these recommendations can be found in Table # The groups that developed these statements include the American College of Sports Medicine (ACSM), the National Athletic Trainers Association (NATA), the American Academy of Pediatrics (AAP), Australian Institute of Sports (AIS), the Academy of Nutrition and Dietetics (AND) and the Dietitians of Canada, the International Olympic Committee (IOC) International Marathon Directors Association (IMDA), the Inter-Association Task Force on External Heat Illnesses, and USA Track and Field (USA T&F).

Before

Drink approximately 14 to 22 ounces of water or sports drink (approximately 17 ounces) two to three hours before the start of exercise.

During

Drink six to 12 ounces of fluid every 15 to 20 minutes, depending on exercise intensity environmental conditions, and tolerance. Drink no more than one cup (8 to 10 ounces) every 15 to 20 minutes, although individualized recommendations must be followed.

After

Drink 25 percent to 50 percent more than existing weight loss to ensure hydration, four to six hours after exercise. Drink 16 to 24 oz. of fluid for every pound of body weight lost during exercise. If you are participating in multiple workouts in one day, then 80 percent of fluid loss must be replaced before the next workout.

Sports Fuel: Fluid and Electrolytes

Electrolytes are minerals involved in the movement of water in and out of cells and in nerve and muscle transmission. Electrolyte depletion can be even more serious and detrimental to performance than dehydration itself! Electrolyte depletion can cause leg cramps or gut "stitches" painful contractions in the gut. It can also cause the misfiring of information between the stomach and the brain and from the muscles to the kidneys.

The replacement of electrolytes as well as water is essential for complete rehydration. It is important to include sodium in fluid-replacement solutions, especially with excessive intake of plain water. For events lasting more than 2 hours; sodium should be added to the fluid to replace losses and to prevent hyponatremia. Rehydration with water alone dilutes the blood rapidly, increases its volume, and stimulates urine output. Blood dilution lowers both sodium and the volume-dependent part of the thirst drive, thus removing much of the drive to drink and replace fluid losses.

Sodium

Water replacement in the absence of supplemental sodium can lead to decreased plasma sodium concentrations. As plasma sodium levels fall below 130 mEq/L, symptoms can include lethargy, confusion, seizures, or loss of consciousness. Exercise-induced hyponatremia may result from fluid overloading during prolonged exercise over 4 hours. Hyponatremia is associated with individuals who drink plain water in excess of their sweat losses or who are less physically conditioned and produce a saltier sweat.

Fluid overloading during prolonged workouts lasting more than four hours can cause hyponatremia (low blood sodium). Athletes who are less conditioned or prepared often produce a saltier sweat. If blood sodium levels fall below 130 mEq/L, you can become confused, have seizures, or lose consciousness. To avoid this, about 500 to 700 mg sodium is recommended for each liter of fluid consumed.

Sodium sweat losses differ from individual to individual, so one sport formula may not fit everyone. While leaner and also large athletes seem to sweat more, it's my experience that leaner, fitter athletes seem to cramp up faster. Typical losses are around 900 to 2,600mg sodium per liter of sweat lost.

Potassium

As for potassium, it's also an important major electrolyte inside the body's cells. Potassium works in tandem with sodium and chloride (salt) in maintaining body fluids, as well as in generating electrical impulses in the nerves, muscles, and heart. While one does not lose as much potassium as sodium in sweat (about 150mg/liter fluid) most athletes don't meet the four-gram-plus daily recommendation through food. (Five to 10 servings of fruits and veggies a day is where it's most often found.) Therefore, a good source of potassium is the 80 to 125 mg contained in most sports drinks.

Coconut water is even better than sports drinks for replacing potassium losses, with 500 to 600 mg of potassium

typically found per serving. Foods also rich in potassium include bananas, kiwi, oranges, tomatoes, and potatoes—all also great carbohydrate boosters to fuel active muscles.

Fluid Absorption

Healthy hydration is not simply reliant on drinking the right amount of fluid or the right amount of electrolytes. I often hear athletes say they ordered the best blend of products from Company ABC, or their friend suggested xxx for their Ironman Distance race and sadly, the fluid choice didn't get them to the finish. Instead, it caused GI distress, cramps, and nausea. Not a simple issue, the speed at which fluid is absorbed depends on a number of different factors, including the amount, type, temperature, and osmolality (density of compounds) of the fluid consumed and the rate of gastric emptying.

Cold water is preferable to warm water because it attenuates changes in core temperature and peripheral blood flow, decreases sweat rate, speeds up gastric emptying, and is absorbed more quickly. In one recent study, sweating response was influenced by water temperature and voluntary intake volume. Cool tap water of 60 degrees appeared to replace fluids in dehydrated individuals when compared with warmer fluids.

While ingestion of cold beverages is preferable, an ergogenic benefit was also seen from the effect of ice slushy ingestion and mouthwash on thermoregulation and endurance performance in the heat. Precooling with ice slushy solution may also have beneficial effects to cold fluid ingestion during exercise and performance. One study compared ice slushy to cold water in moderately active males running and showed prolonged running time to exhaustion and reduced rectal temperature supporting possible sensory and psychological effects of ice slushy beverages whether consumed or as a mouthwash on performance

Children

Children differ from adults in that, for any given level of dehydration. While their core temperatures rise faster than those of adults probably due to a greater number of heat activated sweat glands per unit skin area than adolescents and adults, they sweat less even though they achieve higher core temperatures.

Children who participate in sports activities must be taught to prevent dehydration by drinking above and beyond thirst and at frequent intervals, such as every 20 minutes. A rule of thumb is that a child 10 years of age or younger should drink until he or she does not feel thirsty and then should drink an additional half a glass (cup to cup).

Older children and adolescents should follow the same guidelines; however, they should consume an additional cup of fluid (8 oz.). When relevant, regulations for competition should be modified to allow children to leave the playing field periodically to drink. One of the hurdles to getting children to consume fluids is to provide fluids they like. Providing a sports drink or ice slushy drink as described in previous section that will maintain the drive to drink and rehydrate them may be the key.

Older Athletes

Older, mature, or masters-level athletes are also at risk for dehydration and need to take precautions when exercising or staying fit. Hypohydration (water loss exceeding water intake with a body water deficit) in older individuals can affect circulatory and thermoregulatory function to a greater extent and may be caused by the lower skin blood flow, causing core temperature to rise. Because the thirst drive is reduced in older adults, they need to

drink adequately before exercise, well before they become thirsty.

Fluid "Extras"

Sugar

Sugar is important, since it is actively absorbed in the intestines and can "escort" and increase both sodium and water absorption. A carbohydrate-electrolyte solution enhances exercise capacity, preventing brain drain and perceived exertion by elevating blood sugar and by maintaining a high rate of carbohydrate use by muscles.

Some experts suggest a 6 percent carbohydrate drink, which contains about 14 to 16 grams of carbohydrate per 8 ounces (1 cup) as the ideal amount. A 2013 study suggests a cold drink (about 60 degrees F) cools the body, inspires peripheral blood flow, decreases sweat rate, speeds up gastric emptying, and is absorbed more quickly when compared with warmer fluids. Iced slushy drinks and/or mouth rinses have also shown to prolong running time to exhaustion and reduce rectal temperature, supporting possible sensory and psychological effects of ice slushy beverages on performance, whether consumed or used as a mouthwash.

Magnesium

Magnesium, the underestimated and overlooked mineral, supports more than 300 metabolic reactions in your body. For athletes, the energy, immune, hormonal, and muscle contraction/relaxation functions are the most pressing. Cause for concern, about 70 percent of my recreational to Olympic level athletes and the general population are deficient in magnesium. Magnesium deficiency causes muscle spasms, increasing heart rate and oxygen use even for the easiest of workouts.

Endurance training, excessive sweating while training, not eating enough whole grains, beans, nut and green veggies, and drinking too much alcohol are the top reasons athletes don't get enough magnesium. Fresh greens with black bean and whole grain brown rice salad, a hand full of nuts at snack time, or a training formula with added magnesium can help fill the gap and cover needs of about 300 to 400mg/day.

Branched-Chain Amino Acids

The BCAAs: leucine, isoleucine, and valine, which make up 35 to 40 percent of our essential amino acid (EAA) "pool", 14 percent of total muscle AAs. During training and competition stress, the body gets energy by breaking down muscle and BCAAs "fund" the cause more than any other EAA.

Research suggests BCAAs included in the pre/post workout formulas may decrease exercise-induced protein breakdown and muscle enzyme release (a sign of muscle damage) and increase protein synthesis and muscle gains beyond normal adaptation. Whey and egg protein are good sources, taken at mealtime or included in the hydration and recovery foods you whip up.

Beet Juice

Studies suggest natural sources of inorganic nitrate found in beetroot juice and powders, consumed immediately before, during, and after long-duration, endurance exercise for peak concentration may enhance performance by increasing vasodilation (blood flow) and muscular sugar uptake and reducing blood pressure and the oxygen cost of everyday workouts. In one cycling study, ½ liter beetroot juice daily for four to six days reduced the effort

of steady training by five percent and extended the time to exhaustion during high intensity training by 16 percent. Nitrate levels peak within three hours and remain elevated for six to nine hours before returning to baseline which is ideal for athletes training or competing in multiday and or endurance events like the Ironman triathlon, adventure races, or ultramarathon running.

While there is a possibility that uncontrolled high doses of nitrate salts from processed meats such as hot dogs may be harmful to health, natural food sources also found in spinach, lettuce, and celery are most likely to promote health.

Caffeine

In addition to an energy boost, research suggests caffeine can also improves strength and endurance, reduces rates of perceived effort, and improves hydration and recovery. Some of the ergogenic benefits include improving cognitive performance; mobilizing fat; sparing glycogen from muscles during exercise; increasing intestinal absorption and oxidation of ingested carbohydrates to speed the rate of glycogen resynthesis during recovery; and best of all, reducing perceived exertion and pain of training!

For most healthy adults who have a normal tolerance of caffeine, studies suggest a dose of 1.5 to 3 mg of caffeine per pound body weight (3.3 to 6.6 mg/kg) is enough to have an energy-enhancing effect. This is the equivalent of just a 10-oz cup of java for the 150-lb athlete. Knowing ones threshold is critical as more is not better. At worst, too much caffeine can cause headaches, shakiness, GI irritation, reflux and bleeding, heart palpitations, increased urination, insomnia, and withdrawal, and may certainly limit performance in sport, health, and life.

No doubt, we are all affected differently—knowing ones threshold, and knowing the difference between how it feels to be energy-, water-, or electrolyte-depleted (which feel very different from one another), will ensure that hydration will never be the weak link again at any distance.

Training & Competition Fuel: Pre-Training

The pre-training or pre-event meal serves two purposes: (1) it keeps the athlete from feeling hungry before and during the exercise and (2) it maintains optimal levels of blood glucose for the exercising muscles. A pre-exercise meal can improve performance compared with exercising in a fasted state. Athletes who train early in the morning before eating or drinking risk developing low liver glycogen stores that can impair performance, particularly if the exercise regimen involves endurance training.

Carbohydrate feedings before exercise can enhance liver glycogen stores. Although allowing for personal preferences and psychological factors, the pre-event meal should be high in carbohydrates, non-greasy, and readily digested. Fat should be limited because it delays gastric emptying time and takes longer to digest. A meal eaten 3.5 to 4 hours before competition should be limited to 25% of the kilocalories from fat. Closer to the event, the fat content should be less than 25%.

Exercising with a full stomach may cause indigestion, nausea, and vomiting. Thus the pregame meal should be eaten 3 to 4 hours before an event and should provide 200 to 350 g of carbohydrates (4 g/kg). Allowing time for partial digestion and absorption provides a final addition to muscle glycogen, additional blood sugar, and also relatively complete emptying of the stomach. To avoid gastrointestinal (GI) distress, the carbohydrate content of the meal should be reduced when the meal is close to the exercise time. For example, 4 hours before the event it

is suggested that the athlete consume 4 g of carbohydrate per kilogram of body weight, whereas 1 hour before the competition the athlete would consume 1 g of carbohydrate per kilogram of body weight.

Commercial liquid formulas providing an easily digested high-carbohydrate fluid are popular with athletes and probably leave the stomach faster. Foods high in fiber, fat, and lactose will cause GI distress for some (e.g., bloating, gas, or diarrhea) and should be avoided before competition. Athletes should always use what works best for them by experimenting with foods and beverages during practice sessions and planning ahead to ensure that they have these foods available when they compete.

Pre Training Fasting

Some athletes either rise too early for workouts to consume a meal or snack or feel nauseous when consuming food before exercise. Overnight fasts of 8 to10 hours or longer are normal for most people, athletes or not. While some evidence suggests a metabolic advantage of endurance training in a fasted state to increase fat oxidation in trained muscles, other evidence supports the intake of nutrients, primarily carbohydrates before during and after training sessions.

Pre-Workout Meals

A pre-workout meal can improve performance compared with exercising in a fasted state. Athletes who train early in the morning before eating or drinking risk developing low liver glycogen stores that can impair performance, particularly if the exercise regimen involves endurance training.

The pre-workout snack helps to maintain optimal levels of blood sugar for muscles, and can help restore suboptimal liver glycogen stores. If one trains first thing in the morning and they cannot imagine eating anything first thing, then the last meal or snack the night before will serve as the pre-workout snack. If that's the case, the evening meal needs to be carb-loaded—a tennis ball or two serving sizes of 100 percent whole grain pasta, brown rice, potatoes, beans, peas, or corn with additional carbohydrate servings from fruit, vegetables, or low fat dairy.

If the pre-workout snack is within one hour of training, keep it simple—leave the fibers, fat, and spices for other mealtimes to avoid indigestion. Exercising with a full stomach may cause indigestion, nausea, and vomiting. (Gut distress addressed later in this section.)

One can calculate how much one needs by multiplying the kilogram body weight by the number of hours before the workout you're eating, to get how many grams of carbohydrates they need. As a reference, a slice of toast, ½ cup of unsweetened cereal, or 6 saltines has about 15 grams of carbs; 14 grams for every 8 oz of sports drink; 30 to 45 grams for a banana, and 21 to 40 grams for some of the more popular, high carbohydrate sport bars.

Fuel During Exercise

Eating carbohydrates during longer workouts also improves performance, speeds recovery, and may help to prevent post- race respiratory illness. Although it can't prevent fatigue, it can definitely delay it. Eating during exercise can also spare muscle protein and carbohydrates so you'll recover faster and feel more energized for the next workout.

During the final minutes of exercise, when muscle glycogen is low and athletes rely heavily on blood glucose for energy, their muscles feel heavy, and they must concentrate to maintain exercise at intensities that are ordinarily

not stressful when muscle glycogen stores are full. Studies show carbohydrates consumed during exercise can also spare endogenous protein help to maintain blood sugars, and improve performance.

Physiologically, the form of carbohydrate does not seem to matter in terms of staying fueled, although some athletes do better with some forms of sugars than others especially if they are FODMAP sensitive. Some athletes prefer a sports drink, while others like orange slices or a sports gel with water. Regardless, training is a great time to practice the workout fuel since not every choice works for every athlete, even if the fuel is designed for sports training. Trying different brands and flavors will help to find the best one for the athlete to sort out any GI challenges and compete without issues on race day.

The recommended amount of carbs to consume during training is about 25 to 30 grams every 30 minutes. Sixteen ounces of most sports drinks have this amount unless they're diluted. Sip a few ounces every 15 to 20 minutes after you start your second hour of training.

Post workout/Recovery Fuel

Recovery fuel strives to accomplish several goals—enhance recovery from the negative effects of exercise; promote more effective training adaptation; and enable one to return faster to training. The resulting improvement in training efficiency can lead to significant performance benefits and sport career longevity by supporting repetitive training and competition over time, helping to maintain immune status, and enhancing long term health.

On average, only a small percent (5 percent, to be exact) of the muscle glycogen used during exercise is resynthesized each hour following exercise. At least 20 hours will be required for complete restoration after all-out training sessions, and this will happen only when one replenishes and consumes carbohydrates throughout the remainder of the day. Delaying the consumption of carbohydrates for too long after training reduces overall muscle glycogen resynthesis.

The highest capacity of muscle glycogen synthesis has been shown with the equivalent of 1 to 1.85 grams carbohydrates/kilogram/bodyweight/hour, consumed immediately after training and at 15- to 60-minute intervals thereafter, for up to five hours after a workout out. That means snacking on carbs throughout the remainder of the day and at main meals.

It also appears that the consumption of carbohydrates with a high glycemic index results in higher muscle glycogen levels 24 hours after exercise compared with the same amount of carbohydrates provided as foods with a low glycemic index. Adding approximately 5 to 9 g of protein with every 100 g of carbohydrate eaten after exercise may further increase glycogen resynthesis rate, provide amino acids for muscle repair and promote a more anabolic hormonal profile.

Recovery Supplements

Many athletes find it difficult to consume food immediately after exercise. Usually when body temperature or core temperature is elevated, appetite is depressed, and it is difficult to consume carbohydrate-rich foods. Many athletes find it easier and simpler to drink their carbohydrate or to consume easy-to-eat, carbohydrate-rich foods such as fruit pops, bananas, oranges, melon, or apple slices. That's when sports recovery shakes, bars, and fuel steps in.

Sports supplements may include easy-to-carry, easy-to-consume, and easy-to-digest meal-replacement pow-

ders, ready-to-drink supplements, energy bars, gummies and energy gels. They provide a portable, easy-to-consume fuel that can be used before during or after training; while traveling; at work; in the car; or throughout the day at a multi-event meet such as in track and field, swimming, diving, or gymnastics.

These products are typically fortified with 33% to 100% of the recommended dietary allowances (RDAs) for vitamins and minerals; provide varying amounts and types of carbohydrates, protein, and fat; and are ideal for athletes on the run. They provide a portable, easy-to-consume food that can be used pericompetitively; while traveling; at work; in the car; or throughout the day at a multievent meet such as in track and field, swimming, diving, or gymnastics.

Many fitness-minded and athletic individuals use these products as a convenient way to enhance their current diet. These products are generally regarded as safe. However, if they are substituted in the place of whole foods on a regular basis, they can deprive the athlete of a well-balanced diet. They may also contain excesses of sugars, fats, and protein and banned substances such as herbs, stimulants and other botanicals prohibited by USADA in and out of competition. Safe brands can be found at Informed Choice or NSF for Sports Certification websites (supplement safety later in chapter.)

What to look for in Sports Fuel

1. Include:

- Organic products which contain a blend of high and low glycemic carbohydrate sources.
- Bars, gels, and energy chews with sugars or sweeteners such as: honey, beet sugar, date sugar, brown rice syrup, black strap molasses, organic corn syrup, and calorie-free stevia and Monkfruit.

2. Avoid all sport drinks with artificial flavors, obvious artificial colorings, and brominated vegetable oil (BVO).

BVO is actually a flame retardant which was banned in Europe and Japan, but is still included in some of the most popular sports drinks here in the US! BVO is associated with:

- Reproductive and behavioral problems.
- Skin lesions
- Memory loss
- Nerve disorders

3. Avoid sports drinks and products that contain:

- High fructose corn syrup,
- Artificial colorings or flavorings, preservatives, and hydrogenated oils.

4. Watch out for other potentially questionable ingredients

- Unfamiliar herbs
- Caffeine in which no amount has been provided
- Added vitamins and minerals above 100 percent of the DVs

Performance Fuel Challenges

Gut Distress

Gut issues affect 45 to 85 percent of athletes and can include upper GI (as in the case of heart burn, chest pain, nausea, vomiting, gastritis, peptic ulcers, or stitches) or the lower GI (as in the case of gas, bloating, urge to defecate, diarrhea, hemorrhoids, and colitis/inflamed colon). In addition to the pre-training/competition diet, stress, climate, dehydration, and non-steroidal anti-inflammatory drug (NSAIDs) use can affect gut health. Additional factors can include the obvious mechanical force of running, and less-obvious nuances like the stress of competition causing altered gut blood flow and changes to gut movement and neuro-endocrine (brain/hormone) balance in response to desiring a first place finish.

Ruling out food-related issues may require a thorough dietary analysis; food sensitivity/allergy blood testing to determine if food intolerances to gluten, lactose, or other foods and spices exist; stool testing; or more invasive gut testing to see if there is a more serious issue like a bacterial infection like H. Pylori's, which causes chronic inflammation of the inner lining of the stomach. Supplementation advice such for probiotics, enzymes, and electrolytes/ multivitamins may also be necessary. If the athlete is plagued by gut distress especially before competitions, then try the following:

- A low fiber/residue diet especially for three days prior to a competitive event. That means skipping all the Grande vegetable salads, fresh fruits with skin, and high fiber cereals!
- Eat small meals throughout the day rather than three big squared
- Go lactose free, the milk sugar often responsible for gas and bloating for those who are sensitive or lactose intolerant.
- Get tested for celiac or gluten intolerance as you may be effected by the wheat protein component called gluten in your bread, cereals, pasta and snacks.

Overtraining Syndrome

When the training diet fails to keep up with the demands of training, competitive season, or the accumulating physical demands of school, work, and life, overtraining syndrome can result. When one becomes overtrained and get burned out, they're likely to hit the wall (or "bonk") before they ever really get started.

The "bonk" is a term to describe a physical breakdown in sports. It can be short term, due to poor training, nutrition, and fluid replenishment, or long term, due to overtraining. Short term bonking happens when the brain either shuts down from lack of carbohydrate fuel, not enough fluids, or from mental fatigue. Some say the short term bonk feels like the athlete has gotten hit on the head with a ton of bricks.

Difficult to diagnose and treat, the consequences of attempting to train for and recover from endurance activities without adequate nutrition can be devastating. Long-term effects of bonking may include same emotional features such as depression, anxiety, and fear. Research shows the symptoms are the same as those experienced by stressed, overworked men and women and by students taking exams.

The causes for long-term bonking are too much exercise, and an increase in training/overload too quick-

ly, or even a combination of too much exercise with emotional stress. Research shows that overtrained athletes with stress are actually susceptible to more sports injuries than those without emotional stress.

Some of the signs of overtraining and poor recovery are:

- Premature fatigue
- Decline in performance
- Mood changes
- Emotional instability—anger, anxiety, and depression
- Decreased motivation
- Increased early morning heart rate
- Slow recovery of heart rate after exercise
- Postural hypotension
- Increased resting blood pressure
- Decreased performance
- Poor wound and injury
- Disturbed sleep, depression, loss of drive and enthusiasm
- Increased fluid intake at night, muscle and joint pain, heaviness in legs
- Decreased appetite, weight loss
- Loss of libido, due to decreased testosterone levels
- Amenorrhea, due to decreased LH and FSH hormone levels in women

A short term bonk is quickly reversible with the peri-training/competition fuel and fluids and recommended eating plans discussed in this chapter. Long-term bonking requires rest and recovery. The extent of that rest and the treatment, whether medical, nutritional, or psychological, dependent on the severity of the overtraining syndrome.

The best way to treat overtraining syndrome is to prevent it by adhering to a well-nourished performance nutrition program, and by slowly and methodically increasing training volume and intensity.

Supplemental Fuel

Athletes who fail to consume a diet with adequate vitamins and minerals can lead to deficiencies which can impair training and performance. High training volume, exercise performed in stressful conditions including hot conditions, altitude, or training with substandard diets may promote excessive losses of micronutrients because of increased catabolism or excretion. There is good evidence of a benefit for some athletes in some specific circumstances as in the following:

- Athletes with dietary deficiencies
- Athletes with clinical issues such as anemia
- Athletes taking medications
- Older, master level athletes
- Vegetarians, vegans or athletes on restrictive diets
- Allergies, sensitivities where whole food groups such as dairy and grains and or FODMAP foods are excluded
- Gut Dysbiosis—IBS, Crohn's disease .

- genetic snp i.e. MTHFR
- Imbalanced diets—no vegetables or fruits
- Eating disorders

High proportions of elite female athletes have been shown not to meet the Recommended Dietary Intake (RDI) including iron (51% and 43%), zinc (4% and 35%), calcium (36% and 25%), and vitamin E (17% and 75%). In one study, female athletes failed to meet the estimated average requirement (EAR) for folate in 48% of cases, calcium (24%), magnesium (19%), and iron (4%) (Heaney et al., 2010). In a recent study of male athletes, significant deficiencies were observed in the following: Vitamin A (44% of group below EAR), vitamin C (80% below EAR), vitamin D (92% below EAR), foliate (84% below EAR), calcium (52% below EAR) and magnesium (60% below EAR).

Training and work schedules, low-nutrient snacks, infrequent nutrient-dense meals, and overall low calorie intakes may cause inadequate intakes of vitamins and minerals. Also impacting the intake of micronutrients are athletes who adopt popular diets which eliminate whole food groups such as meat, dairy, grains and fruits as in the case of vegetarians or Paleo enthusiasts. Micronutrients such as calcium, zinc, iron, vitamin B12 and others may be of concern.

Performance Supplements

While supplements may assist athletes in achieving optimal health and peak performance under specific circumstances (such as deficiency conditions or at certain times of high intensity or endurance training and competition), poor regulation of the supplement industry allows athletes to be bombarded with marketing hype that exaggerates or completely invents unproven benefits arising from the use of supplements.

Consequences of unsubstantiated supplement use:

- Distraction from the factors that can really enhance optimal health, recovery, and performance—FOOD!
- Money invested in supplements instead of equipment to prepare healthier foods such as homemade, process-free, organic and grass-fed, hormone-free lean protein
- Diversion from working on performance eating for training, competition, and recovery
- The possible risk of a positive doping outcome

How to make educated decisions about the efficacy, safety, and sound use of supplements as part of the optimal health and performance eating plan depends on understanding the science and sorting out fact from fiction on several of the most popular supplements.

Why Food First?

First consider that the athlete may be getting enough vitamins and minerals through their daily diet. After all, athletes are nutritionally savvy taking advantage of the latest fortified foods on the market—wholesome foods which already have a high level of nutrients and which also have extra vitamins, minerals, and compounds added for health-minded people and athletes alike, such as antioxidants, electrolytes, omega 3 essential fats, energy boosters etc.

The more foods one consumes with these extras, the more likely one is not only be meeting daily needs, but potentially exceeding them, increasing the risk for adverse reactions from excessive amounts. In addition,

interactions between nutrients can interfere with the absorption and metabolism of each. For example, calcium binds iron, so combining a fortified calcium-rich beverage with a bowl of iron-rich whole grain cereal for breakfast may compromise the ability to get enough of the iron to meet daily needs.

A similar example involves using tea as a healthy drink to maintain hydration. Tea contains trace minerals; including manganese, copper, and zinc, which are used by the endogenous antioxidants. A single bag of black tea provides nearly twice as much of the daily recommendations for manganese, which may compete with other minerals, such as magnesium and iron, in enzymes and other metabolic functions.

"Assess" the Next Steps

Assess the diet using a 3-5 day "typical" dietary intake and analyze by using a computerized nutritional analysis program along with traditional and/or functional tests to determine level of adequacy, deficiency and/or absorption.

Bottom line is about justifying the means; determining if a deficiency exists, replacing the deficient nutrient by determining which supplement is best in terms of efficacy, safety, purity, dose, modality, and consumption timing and ensuring that supplementation is the only and best way to replace the nutrients of concern.

Supplements for Optimal Health and Performance

Supplements used to achieve optimal health and performance fall into several categories, depending on the intended purpose and objective. Some of the supplement categories overlap. For example, probiotics are used both for general health and for gut health.

A thorough physical exam, medical history, and biochemical testing (blood, urine, stool, salivary) can help discover nutrition deficiencies which may warrant the use of a vitamin, mineral, or any other food or beverage supplement only under the supervision of a licensed health professional. This is because serious side effects can occur if certain supplements are combined with each other or with medications, and also because some supplements are contraindicated with certain health conditions.

Selected Supplements Used to Achieve Optimal Health and Performance *

Objective	Examples
General health	vitamins, minerals, antioxidants, quercetin, glutathione, probiotics, omega 3, fish oils
Gut health	probiotics, enzymes
Immune function	antioxidants, zinc, glutamine, phytonutrients, herbs (e.g., Echinacea)
Fuel replacement/competition	liquid meals, sport drinks, bars, gels, chews snacks
Fluid and electrolytes	electrolyte supplements, sports drinks
Joint health	glucosamine, chondroitin, MSM
Muscle growth and repair	protein powders, amino acids (essential EAA, Branched Chain (BCAA), HMB
Fat reduction	caffeine, carnitine, pyruvate
Exercise metabolism	carbohydrates, nitrates, bicarbonate, beta alanine, and betaine

Promoting recovery	protein powders, amino acids, carbohydrate bars/drinks
Central Nervous System (CNS) stimulants	caffeine, taurine

**Please note: This supplement list is NOT a recommended or complete guide. All athletes need to be evaluated prior to taking any dietary supplement and prior to changing their diet, exercise, or lifestyle pattern.*

If the athlete is competitive year-round, it may be necessary to reevaluate the supplement needs seasonally. For example, during pre-season the requirements will be significantly different than during the season, because of different training regimens and goals. For pre-season, the aim might be to increase or to lose extra mass; supplements consumed for building muscle mass or losing weight which are very different from those used during the season when continuous competitive energy is the priority and supplemental carbohydrate fuel, electrolyte replacement, or lactic acid buffers may be the priority.

Also consider that the need for a supplement may pass. For example, the athlete was found to have a vitamin deficiency, detected by a dietary analysis and blood test at your office, and after a few weeks or months of improved diet and supplementation, the deficiency appears to have been reversed by improved energy levels, strength or performance. Time to Reassess! Why continue to take the supplement if the deficiency has passed? Perhaps there are other deficiencies that require attention.

Questions used to determine supplemental needs:

1. Will this supplement help to overcome dietary deficiencies?
If the athlete cannot eat or drink and/or absolutely detest or desire to eliminate whole food groups from your diet (i.e. dairy, grains, fruits, or vegetables) and miss out meeting your daily recommended requirements of vitamins, minerals, and nutrients, it may make sense to consider supplements.

2. Will this supplement help achieve the athlete's personal goals and the physiological requirements for THEIR sport?
As you know, different sports have different energy needs. If the athlete is a bodybuilder or Cross Fitter, the energy sources and requirements are going to be significantly different than a marathoner or ironman triathlete. Knowing the science behind the muscle fuel, knowing how and when to fuel, and what compounds impact the ability to use the fuel, MAY help to enhance performance.

3. Will this supplement offer a true ergogenic effect, which will directly enhance performance?
Sometimes a supplement helps one to reach, increase, or even saturate levels of substrate, nutrient, or compound levels. However does it enhance performance? The truth is, even though a compound may have a specific function in the body, taking more of that compound doesn't necessarily mean it will actually exert a performance enhancing-effect.

4. Will this supplement enhance performance during this specific phase of training?
It's all about nutrition periodization—in other words, athletes need to "go seasonal" when it comes to supplements. When selecting a supplement, it needs to match the training and competitive season.

5. Is the Supplement Safe?
Since dietary supplement certification is voluntary, and not all companies pursue independent testing and certification. For some companies, financial reasons are sometimes the obstacle for certification, while for others,

either the manufacturing facility has difficulty passing the Good Manufacturing Practices (GMP) audit or there is a processing, contamination, purity, and standardization problem with the actual product.

Some products cannot pass the certification process for other reasons, such as: the stated label nutrient content doesn't match what is actually in the product; they may fail because they have heavy metal or microbial contamination; or, in the case of sports supplements, the product does not pass the banned substance portion of the testing.

Here are some of the organizing bodies that conduct certifications with their criteria and seals of approval and the certifications required for athletes competing in Olympic, professional, collegiate sports in which testing is mandatory and disqualification or banning the athlete from competition is at risk and their career at stakes.

Good Manufacturing Practices (GMPs)

http://www.fda.gov/Food/GuidanceRegulation/CGMP/ucm110858.htm.

GMP requirements include: provisions related to the design and construction of physical plants that facilitate maintenance, cleaning, proper manufacturing operations, quality control procedures, testing of final product or incoming and in-process materials, handling of consumer complaints, and maintaining records.

US Pharmacopoeia http://www.usp.org/

USP offers verification services for dietary supplement finished products, dietary ingredients, pharmaceutical ingredients, and excipients. Participation is voluntary and available to manufacturers worldwide.

Sport Specific Certifications

Although there is no such thing as a "100 percent guarantee" that tested supplements are free of all banned substances, which include drugs of abuse, anabolic agents, stimulants, beta-2-agonists, masking agents, etc. the following certification programs have been validated and accredited to examine powders, bars, liquids, capsules, tablets, etc., with defined method capabilities/reporting limits.

NSF http://www.nsfsport.com A program that focuses primarily on the sports supplement manufacturing and sourcing process provides preventive measures to protect against adulteration of products, verify label claims against product contents, and identify athletic banned substances in the finished product or ingredients. Program designed for manufacturers and their products, includes product testing for more than 180 banned substances, label content confirmation, formulation and label review, production facility and supplier inspections, as well as ongoing monitoring in line with substance prohibitive lists. Program is recognized by NFL, NFLPA, MLB, MLBPA, PGA, LPGA, and CCES.

List of certified products: http://www.nsfsport.com/listings/certified_products.asp .

Informed Choice, www.informed-choice.org

A quality assurance program for sports nutrition products, suppliers to the sports nutrition industry, and supplement manufacturing facilities is a world-renowned sports doping control and research laboratory. Registered products: http://www.informed-choice.org/registered-products.

Banned Substances Control Group

http://www.bscg.org/

Banned Substances Control Group (BSCG) offers the BSCG Certified Drug Free® independent third party supplement certification to responsible dietary supplement manufacturers to ensure finished products are free of more than 145 drugs on the WADA prohibited list and banned by sports organizations including the IOC, NFL, NHL, MLS, NCAA, MLB and others. BSCG includes additional testing for many drugs not banned in sport like pain killers, muscle relaxants, weight loss drugs and more. Label claim verification, contaminant testing and a toxicology review is conducted on each product.

Integrative Sports Nutrition for Optimal Health and Performance Chapter Summary

Working with all athletes, whether young or mature, recreational or professional requires personalization, patience, perseverance and persistence while addressing training and competition goals and considering all factors which influence the nutrition prescription.

The performance nutrition diet is never static, constantly in motion like our athletes who are continually striving to attain and maintain new goals. It is our role to understand, appreciate and respect the athlete by taking into consideration their age, gender, health and dietary history and desires, food trajectories, social, cultural and religious factors and all variables which could potentially effect optimal health and performance such as genetic, epigenetic, lifecycle, medical and environmental factors.

For three decades as an integrative sports and performance nutritionist I have embraced this exciting and fulfilling career and invite you to join me to help athletes reach their personal best in health, sport and life.

Resources:

Sample Sports Menus

1800 calorie Sample Menu

Pre-workout AM (1 hour before): 1 cup green tea with half of a sport bar or 1 slice of 100 percent whole grain toast with 1 tsp nut butter

During workout: Less than one hour: water, electrolytes as needed. More than one hour: coconut water or low sugar electrolyte-rich, naturally sweetened sports drink as needed. Organic energy chews, gels, or bar as needed for beyond 90 minutes (See more information later in this chapter.)

After workout: Recovery beverage to include a natural source of simple sugar with high-quality protein such as a NSF or Informed Choice approved protein powder (for example, a fruit smoothie with whey scoop)

Breakfast
Whole egg plus 4 Egg white omelet with spinach, mushrooms, onions, and a side of sliced tomatoes, topped with low-fat shredded cheese and salsa
1 mini whole grain bagel with 1 teaspoon of almond butter.
1 lowfat Greek yogurt
½ cup strawberries

Snack
1 ounce lowfat string cheese with a sliced apple

Lunch
1 cup gazpacho soup
4 ounces lean, antibiotic-free turkey breast \
2 slices whole grain toast
Add deep greens, tomato slices and sprouts
1 teaspoon extra virgin olive oil or low-fat, olive-oil-based dressing
1 cup mixed tropical fruit salad with diced kiwi and citrus sections (for a potassium kick)

Snack
100 % whole grain, high fiber, low-added-sugar breakfast bar and watermelon chunks

Pre-Afternoon-Workout Snack (if required)
(45 minutes to 1 hour before)
1 lite natural sport drink and banana
Or 12-ounce coconut water with 1 ounce of oat bran pretzel nuggets

Dinner
Kale salad with shredded carrots, tomatoes, chickpeas, mushrooms
And grilled corn topped with 1 ounce lite lowfat Feta cheese crumbles
5 ounce grilled turkey burger or veggie burger
1 whole grain bun
Handful of baked fried potatoes
1 cup stir fried mixed veggies

Snack
Frozen natural fruit pop or ¾ cup berries with light whipped cream

3500 Calorie Sample Menu

Morning
1 cup 100% orange juice
1 bowl vitamin fortified 100% whole grain cereal
1 cup lowfat "milk" group option
½ cup strawberries and sliced banana in cereal

Snack
1 lowfat string cheese snack
6 whole grain crackers
1 apple

Afternoon
1 spinach salad with carrots and tomatoes
1 ounce olive-oil-based salad dressing

12-inch turkey (6 oz.) sub on whole grain bread, loaded with veggies, lite cheese
1 bag baked potato chips
12 ounces low fat milk
1 orange

Snack

Pre workout: 1 whole grain breakfast bar or sports bar
During workout: water and sports drink, as needed
Post workout: recovery drink or fruit smoothie with fresh fruits and whey isolate protein powder

Evening

1 cup vegetable soup
1 whole grain roll, 1 tsp butter
8 ounces grilled fish
1 Cup of brown rice and beans or 1 large baked sweet potato
1 Cup of peas and corn
1 cup steamed broccoli with parmesan cheese
1 Cup of mixed berries with whipped cream

Snack—1-2 hours before bedtime
12 ounces low fat "milk" option

Sports Nutrition Resources:

Academy of Dietetics and Nutrition (AND)
Sports Nutrition Care Manual
https://sports.nutritioncaremanual.org/vault/sports/WeightLossAthletes1.pdf
(CDR) Board Certification Specialists in Sports Dietetics (CSSD)
http://www.scandpg.org/sports-nutrition/be-a-board-certified-sports-dietitian-cssd/
Collegiate and Professional Sports Dietitians Association (CPSDA)
http://www.sportsrd.org/
International Society for Sports Nutrition (ISSN)
http://www.sportsnutritionsociety.org/
Sports and Cardiovascular and Wellness Dietitians Dietetic Practice Group of the American Dietetic Association
www.scandpg.org
United States Olympic Committee Sports Dietitian Registry (USOC)
http://www.teamusa.org/About-the-USOC/Athlete-Development/Sport-Performance/Nutrition/Sport-Dietitian-Registry
Australian Institute of Sport
www.ausport.gov.au

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As The Running Nutritionist®, Lisa is leader to industry, academia, the public & press for more than three decades Lisa has built a global Integrative Sports Nutrition & Performance Practice, consulting to Olympian, Professional, Collegiate & Junior athletes. She served as the US Sailing Olympic and Paralympics Team Nutritionist for the 2008 Beijing Olympics & Nutrition Expert for Zumba® Plate program. A consultant to Sony Entertainment, Lisa is known as the Celebrity Nutritionist working with some of Hollywood's Award winning actors/actresses who have appeared in Avengers, Gone Girl, Iron Man 3, Book Thief, 13 Hours, The Glades, Hatfield's & McCoy's, soap operas & commercials & to young artists at Julliard School in New York City.

An Integrative Nutritionist, Lisa is Board Certified Specialist in Sports Dietetics, Board Certified Professional Counselor, certified USAT&F & USA Triathlon Coach, Certified Reiki Practitioner, and Certified Horticulturist & Fellow of The Academy of Nutrition & Dietetics. She currently teaches online sports nutrition courses @ https://mysportsduniversity.com/aboutus/.

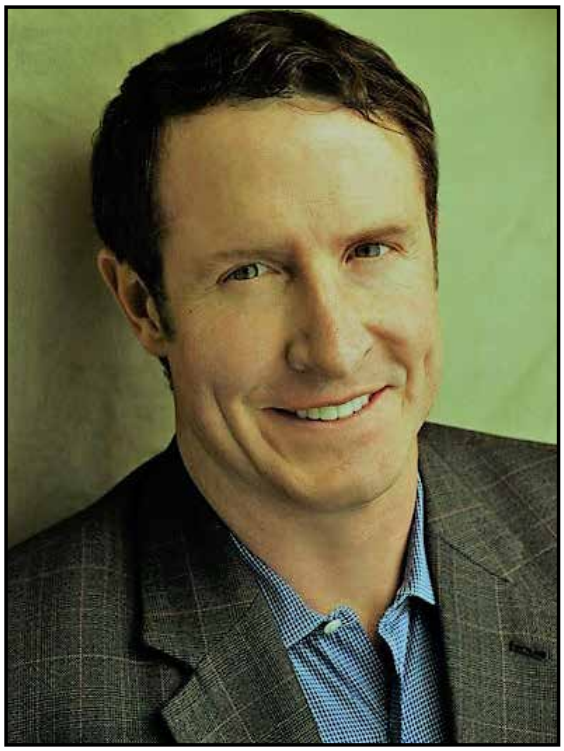
A culinary consultant and educator, Lisa has taught culinary nutrition at Johnson & Wales University & Miami Culinary Institute (MCI) & serves as Chairperson of the MCI Advisory Board. In 2014, Lisa & Miami organic restaurateurs launched Miami's first Farm to Table Performance Nutrition Delivery Service. In 2014, she cofounded the award winning global mobile app called cTHRUNutrition to help consumers find and select optimal foods at groceries and restaurants worldwide.

The author of 8 books, including her most recent, Legally Lean: Sports Nutrition Strategies for Optimal Health & Performance. Lisa has appeared on 20/20, Dateline, Good Morning America Health, FOX News, CNN, MSNBC and ESPN and has been featured in numerous publications including: USA Today, Newsweek, Wall Street Journal, New York Times, Men's Fitness, Outside & Runners World magazines. Lisa was a National Media Spokesperson for the Academy of Nutrition & Dietetics (AND) & was selected as a Recognized Young Dietitian of the Year. She serves as Country Representatives Director for the American Overseas Dietetic Association (AODA), representing more than 70 countries & 1000+ Nutritionists/Dietitians worldwide.

Lisa is a competitive runner and triathlete who has competed in more than 34 marathons (PR 2:52:32), Ironman USA Lake Placid, and hundreds of running and multisport races. In 2004, she competed for the United States on Team USA at the World Long Distance Duathlon Championships. Lisa resides in Miami, Florida with her husband and is the mom of 3 children.

MARIA E. LEVADA

OB/GYN



JONATHAN ORBAN

CEO IGS

INTEGRATION OF OPTIMAL CHEMICAL, HORMONAL, NUTRITIONAL BALANCE WITH SOFTWARE TECHNOLOGY

The Evolution of Medicine over the past 50+ years has made impressive gains in lifespan and communicable diseases but is overshadowed by the rapid growth of chronic and non-communicable illness. The current model of medical practice using prescriptions, surgeries and treatments can cure disease but it is not designed to create health.

Fortunately, we are now at a time of a great convergence in medicine with new tools and operating systems enabling the creation of new, functional and personalized models of medical practice to eliminate the epidemic of lifestyle-driven chronic illness and to create health.

The decoding of The Human Genome (Dr. Craig Venter) and subsequent identification of (millions of) single nuclear polymorphisms (SNPs) and the emergence of epigenetics has shown that our lifestyle and environment

influence our gene expression patterns and play a major role in predicting individual responses to drugs (pharmacogenetics). This, in turn, leads to the concept of "personalized medicine".

I Gene Adaptation Response (GAR) and Its Relationship to Body Chemistry

Genetic Adaptation Response (GAR) is in part an individual's physiological response to a series of internal and external environmental factors. This genetic or "epigenetic" response is the cumulative effect of multiple gene pools, individual genes and gene mutations activated as a result of these factors. Some internal factors that can drive an adverse epigenetic responses include deficient blood serum levels of vitamins, minerals, electrolytes and hormones. An adverse GAR can have a draconian impact on critical functions such as sleep, energy, libido, etc. (In the Ranger Assessment and Selection Program (RASP) study (Genes and Immunity, 2013), gene expression changes occurring in leukocytes collected from soldiers before and after undergoing 8 weeks of grueling, battlefield-like training were assessed. Post RASP leukocytes showed a markedly impaired immune response to infection (with super-antigen Staph. enterotoxin B). The results suggest that suppression of antigen presentation and lymphocyte activation pathways, a negative GAR response, in the setting of reduced (yet still low normal range) blood cell counts, contributes to poor immune response (impaired wound healing, infection susceptibility, poor vaccine response) associated with chronic intense stress. After 2 months of intense stress of the RASP, the numbers of leukocytes (of soldiers) were reduced but still within normal limits despite the poor gene expression changes (GAR) causing the obviously impaired immune response. However, by targeting important blood serum levels to the approximate 70th percentile (optimal level instead of WNL level) of each patient's gender, age and phase-of-cycle based normal ranges, a patient is likely to have a more favorable GAR; highlighted by a noted improvement in their physical, mental and emotional aptitude. In other words, balanced and improved body chemistry will minimize a patient's adverse physiological response to unfavorable external factors. When body chemistry imbalances are identified and treated (or optimized) a patient will generally see an improvement across a full spectrum of faculties.

A standard blood test compares a specific blood serum level (i.e. estradiol) against a reference range commonly referred to as "WNL" (within normal limits). These WNL reference ranges vary based on gender, age and a woman's phase of cycle. The downside to this approach is the broad characterization of what is considered "normal" and which blood serum levels warrant treatment.

Traditionally, a WNL reference range will encompass the middle 95% of a specific patient demographic (i.e.

postmenopausal women or an entire gender). Any patient who falls within this range is considered "normal" leaving only 5% of that entire demographic, 2.5% above and below the normal range, as considered outside of normal limits. Optimal values for each WNL are NOT referenced. Age, genetic mutations (variations) and other factors are rarely considered. In most cases (and according to the current 'standard of care' model) a physician's decision to treat a patient (based on their result) can be binary. If the patient's blood serum level is above or below normal limits, they are treated. If the patient is within the specific reference range, they are commonly not treated.

For example, normal reference ranges for male total testosterone include blood serum values from 300 to 1,000 ng/ml. A serum level of 320 ng/ml would not dictate treatment according to general standards of care. However, a modestly lower serum level of 280 ng/ml, would most likely be treated. Effectively, a patient just inside the normal range (320) could go untreated, whereas a patient just below the normal range (280) would be treated (but with a standard, guessed at dose, not taking into account any other possibly aberrant factors/imbalances)!

Obviously, signs and symptoms do not appear suddenly at the lower bound of a normal range; in this case 300 ng/ml. Rather, these symptoms increase as a blood serum level moves further away from an optimal value within each range. Typically, that optimal value is the approximate 70th to 80th percentile of a specific normal reference range. Today's practitioner rarely, if ever, takes this into account because it is not part of the medical treatment model they were taught (and it takes too much time to evaluate and calculate). This is particularly evident when treating thyroid and menopausal hormone imbalances yet hormone balance is crucial to a good, healthy quality of life. Women and their hormones are very controversial subjects in our current medical establishment and very few physicians (including gynecologists) want to or are comfortable with prescribing hormone replacement. Current lab standards of "within normal limits" estradiol levels in a postmenopausal woman is <=32 pg/ml! How can a hormone (estradiol) that keeps a woman young and healthy (cardioprotective, prevents osteoporosis, promotes collagen production, maintains vaginal health, keeps HDL levels up, etc) be so bad for her 1 year into menopause (and after)? At the turn of the last Century, women barely lived beyond menopause years but now we are living 1/3 to ½ of our lives in menopause! Hormone therapy supplementation is often needed to maintain optimal balance and the question of how much and how to monitor is now made simple with the use of new software technology.

Certain health agencies like the National Institute of Health (NIH) do recommend some optimal blood serum levels. These are rarely (if at all) included with standard lab results. Without this more personalized analysis, treatment decisions made by the healthcare providers (HCPs) are more reliant on intuition and experience when trying to gauge treatment for known and observable symptoms. Moreover, this "general" approach is compounded by the lack of time HCPs spend with each patient, which now averages less than 8 minutes.

With this decline in how much time a practitioner has to evaluate and treat a patient, the end result usually involves the treatment of one or two key symptoms with a single diagnosis and treatment. In most cases, treatments are standardized with dosing recommendations that do not take into account or adjust for age, gender, genetic variations, and even more complexly, how hormonal interconversions into each other can also radically affect what is considered an appropriate and personalized recommended dose.

The method developed in 20th Century medicine for treating patients is referred to as the differential diagnosis (to include all feasible disease possibilities) which is then reduced to a single most likely diagnosis by a process of elimination.

The shortcoming of this process is that it does not accommodate for the more realistic scenario of two or more disease states contributing to a patient's suboptimal health. Furthermore, HCPs rarely have the time and the experience to treat a comprehensive series of interdependent hormone, vitamin, and mineral imbalances. Many of these imbalances may actually be within a given "normal" reference range but far from optimal.

With the strain on today's healthcare resources, combined with the complexities of balancing body chemistry, it is nearly impossible for a practitioner to accurately diagnose and treat dozens interconnected blood serum imbalances. The good news is that the implementation of this time consuming and data-intensive process can be radically improved through the integration of lab testing and software that is now available from Silicon Valley so that the practitioner can easily move on to the 21st Century Medical Practice Model.

In contrast to the process of differential diagnosis, current 21st Century Integrative Medicine theory not only recommends treating a more comprehensive spectrum of patient symptoms but also treating with increasing personalization and specificity. Instead of the binary treatment decision of whether or not a lab result is within a reference range, advanced integrative practitioners compare lab results to their respective "optimal values". But the treatment of multiple blood markers that are out of balance is a process that can take many hours; especially when the computation takes into account normal ranges that are adjusted for a specific age, gender, phase of cycle, as well as the complexities of hormone therapy recommendations given their interconversions and cross reactions. Not accounting for these interdependences can easily result in over-prescribing or under-prescribing of important hormone and all medical treatment recommendations (especially when the margin between therapy and toxicity is narrow).

Personalized dosing accuracy becomes even more complex when a patients genetic profile is introduced; specifically, their unique combination of genetic mutations or nuclear polymorphisms (our life's typos). Despite the rising tide of new science and research related to genetics and gene mutations, most of this work is descriptive (meaning no defined treatment protocols) instead of prescriptive (having defined treatment protocols). The vast majority of research in the genetic space today is based on small sample sets often providing unreliable or statistically insignificant data. For most practitioners, trying to absorb all of this new information is akin to sipping from a firehose shooting dirty water.

Despite this proliferation of genetic based research, advanced integrated practitioners are focusing on fewer but more reliably researched genes and their mutations. An example of this is the MTHFR mutation. With this specific mutation, a patient's ability to convert (or methylate) folate into active folate (L-methylfolate) is reduced 40% to 70%. This can lead to myriad complications, impairing the body's immune function response, ability to detoxify, and to synthesize and repair DNA.

A patient can have multiple MTHFR mutations and the more mutations they have, the more impaired their methylation process will be. An MTHFR mutation is commonly treated by introducing L-Methylfolate (or active folate) as a supplement. However, many practitioners do not personalize or adjust their recommended dose of active folate based on a patients weight, the number of mutations they have, or any other related genetic mutations. When a patient is on a large dose of active folate, commonly 5,000 mcg per day (or more), it is important to determine if they are also positive for the COMT (catechol-O-methlytransferase) mutation. Not addressing this combination of genetic mutations, along with active folate supplementation, can influence (worsen) severe anxiety, mood swings, and introduce cardiac-related risks. In fact, a COMT mutation would contraindicate any SSRI (Serum Serot0nin Reuptake Inhibitor) treatment.

Predicting individual responses to drugs (pharmacogenetics) will be essential to integrative practitioners to help mitigate potentially adverse health outcomes when treating patients: clotting events (Factors II and V), cardiovascular disease, strokes and heart attacks (Apolipoprotein E and ApoA1, MTHFR), under-dosing or over-dosing with chemotherapy, statins, opioids, blood thinners, anti-depressants (Cytochromes P4502D6, P4502C19, P4503A4, P4503A5, P2B6, P1A2, SLCO1B1 OPRM1, VKORC1, ANKK1/DRD2). There is a lot of research right now looking into antipsychotic medications (clozapine for instance) that are very useful but for some people can have some very bad, emergency-type effects. Research has been able to identify clusters of genetic variants (cytochromes P450 and P2D6 enzymes) that can lead to rapid or slow metabolism of psychiatric medications. Slow metabolizers can experience serious side effects if the drug remains in the bloodstream longer. This possible outcome is even more lethal with chemotherapy treatments where there is a very narrow margin between therapy and toxicity.

This personalized approach, combining optimal values and genetics, is nothing less than a fundamental shift in modern medicine. Integrative practitioners are rapidly shifting away from a linear one diagnosis/one standard treatment protocol, which is insufficient, to a more comprehensive and holistic approach. Consider the image of a complex woven tapestry or a spider web. If one string is pulled, it will affect all other strings that are directly and indirectly connected. Patients today are now being treated for multiple deficiencies simultaneously with more personalized recommendations with the help of new, reliable software technology. As a result, this more inclusive and proactive form of treatment can generally improve a patient's overall health, mental acuity, energy levels, and body composition.

Rebalancing body chemistry is not a singular event, however. There are a wide range of dynamic factors that necessitate continual optimization over time. These include: age (declining hormone production), physical and emotional stressors, sleep quality, exercise levels, exposure to heavy metals and contaminants, and nutritional quality etc. All of these factors will alter a patient's epigenetic and physiological response. The best doctors are re-measuring blood values on a regular basis, typically every 90 days, with the goal of helping each patient maintain optimal levels over time with the use of current software.

This initial "rebalancing" or "calibration" process can take six months to one year. Once a patient undergoes this initial process and responds well, then each follow up analysis can be taken every six months to one year unless the patient experiences a radical environment shift or adverse medical event.

II GAR, Exercise and Nutrition

Nutritional genomics is a more recent offshoot of the genetic revolution that includes (1) nutrigenomics: The study of interaction of dietary components with the genome, the resulting changes in proteins, and other metabolites; and

(2) nutrigenetics: Understanding the gene-based differences in response to dietary components and developing nutraceuticals that are most compatible with health for individuals based on their genetic makeup.

Since the dawn of personal exercise, the metric for success has often been the number of calories burned. It was thought that burning calories was the most efficient way to burn fat and secondarily to add muscle mass. This logic has framed the common approach taken by many exercisers, that of maintaining a caloric deficit.

The concept of a caloric deficit is to burn more calories through exercise than are consumed as a way to burn

fat and lose weight. An example of this approach would target daily deficit of 500 calories designed around exercise duration and intensity along with nutritional intake. With the assumption that one pound equals 3,500 calories, one would expect to lose about a pound per week on such a program.

The issue with this approach is one of adaptation. The human's body is remarkably efficient at adapting to internal and external environmental factors. If one maintains a caloric deficit with the goal of losing weight, the approach will yield results over the short term, but yield adverse results over the long term. (http://www.montignac.com/en/the-failure-of-low-calorie-diets) Why? The answer is adaptation.

Adaptation is the premise that the human body will have an epigenetic and physiological response to certain factors. One may lose weight through various forms of nutritional starvation, but over time the body will interpret this state as a threat and will respond by slowing down metabolism and any further weight loss. Typically, a person's metabolic rate will slow down, in turn burning fewer calories. The body will also store more food as fat. As a result, in order to maintain a constant state of weight loss, an individual will have to work out more and eat much less, in order to maintain a true caloric deficit over time. This approach usually turns out to be an unmitigated failure.

If maintaining caloric deficits to lose weight yields minimal success over time, how should we approach achieving sustainable health over the long term? The answer is actually quite simple: maintain a sensible and healthy nutritional program balanced with consistent and moderate exercise.

A sensible and healthy nutritional program has a few simple rules: eat enough calories to avoid an adaptive starvation response and avoid specific food types that can result in a negative physiological response; i.e. processed foods, foods high in saturated fats or high on the glycemic index.

Dr. Stacey Sims is considered one of the most respected nutritional experts in the world. Her nutritional advice is remarkably pragmatic: eat fruit in the morning, eat as many vegetables as possible through lunch and dinner, focus on eating lean sources of protein, and avoid any form of fried or processed foods. The cornerstone of Dr. Sims guidelines is to make sure the body is never starved of important nutrients.

Even with consuming healthy nutrients, processed foods can still have a net-negative affect on our bodies. These are effectively foods made in a lab, filled with chemicals and preservatives, with the perfect blend of artificial flavors meant to stimulate our brains and deliver negligible nutrient quality. Our body literally reacts to these foods as poison, causing a negative shift in our GAR, which, in turn will diminish your body's ability to respond to various factors (stresses) which, in turn will lead to chronic illness.

A moderate exercise program is also crucial to maintain optimal health: a balanced mix of resistance (weight-lifting) and aerobic (walking or running) training; try to lift weights or engage in some form of resistance training three times per week, try to engage in some form of running, cycling, or walking several times per week, and try to be active twice per day with enough exertion to sweat at least once per day.

There are many PhDs dedicated to the fine tuning of these concepts. It really comes down to being this simple:

1) Be active, preferably twice a day for 30 or more minutes. Work hard enough to sweat at least once a day.
2) Lift weights 3 times a week.
3) Eat real food

4) Avoid processed, fake food.
5) Always use common sense around portion control but never starve yourself.

In summary, optimal body chemistry is defined by a patient's unique genetically determined levels of hormones, prehormones, vitamins, minerals, enzymes, proteins, and electrolytes that a body relies on every moment of every day to regulate almost everything they do. The variables in this complex ecosystem are all highly interdependent: even a small change in one can have substantial ripple effects to many others. Due to age, stress or trauma, a patient's body chemistry falls out of balance. Maintaining a patient's optimal body chemistry will deliver better health, better aesthetics, better levels of energy and stamina, sharper mental acuity, better memory and a longer more fulfilled life.

New software technology from Silicon Valley allows a practitioner to measure each individuals unique body chemistry through scientific mathematical analysis of DNA and blood panels, and, to offer a tailored solution based on a patient's deficiencies from combinatory optimal levels and their genetically driven responses to their prescribed medications and supplements. The resulting data and analysis allows doc tors to identify and treat any imbalances through prescriptions of medications, NSF GMP-certified supplements, and nutraceuticals. Using this software results in a level of precision that's impossible to achieve in a medical practice today.

New technology (from Silicon Valley) has taken genomics and epigenetics along with extensive biochemical analysis data to create an invaluable system available to physicians, enabling them to practice Predictive, Preventive, Personalized and Participatory Medicine (P4M) with just the click of a mouse.

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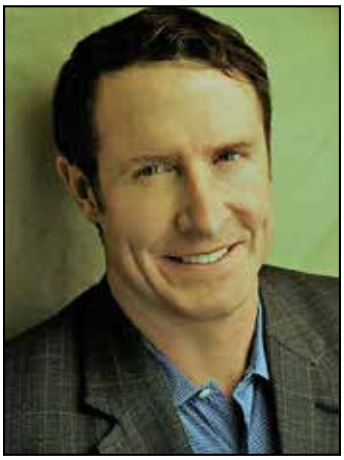
Dr. Maria E. Levada is a graduate of New York University and SUNY Downstate College of Medicine. She is a Board Certified OB/GYN and is a Fellow of the American College of Obstetrics & Gynecology, American College of Surgeons and the Nassau Academy of Medicine.

Dr. Levada founded and maintains an active clinical practice devoted to women's health for over 30 years. As past President of the Nassau County Ob/Gyn Society and former Director of Gynecology at Franklin Hospital Medical Center, she was an administrator involved in teaching residents as well as other physicians. A gifted surgeon who combines the art of medicine with the most advanced technologies to achieve the finest outcomes, she is voted into America's Top Gynecologists and World's Leading Physicians.

For the past 15+ years her specialty has focused on Natural Bioidentical Hormone Therapy and counseling for Men and Women. She was co-founder and Medical Director for the International Hormone Institute in Westchester. With its in-house compounding pharmacy, Dr. Levada researched the benefits and risks of synthetic versus natural hormones and developed therapeutic dose regimens for compounded bioidentical hormone extracts.

Dr. Levada is currently on the Medical Advisory Board and consultant for Integrated Genetic Solutions (IGS), a software company designed to help Doctors personalize and optimize their patient's health care by measuring a patient's comprehensive blood chemistry and DNA then with an unmatched level of precision, prescribe a custom tailored program of medications, vitamins, nutraceuticals, nutrition and physical activity designed to make patients perform, look and feel their best.

Presently, Jonathan Orban is the CEO of Integrated Genetic Solutions (IGS). IGS is the world's leading software for precision healthcare in the medical body chemistry space providing health care providers with a specific



numerical diagnostic tool. Previously he was the founder and CEO of GeneSolve, a series of clinics focused on calibrating and optimizing the body chemistry of patients. Jonathan Orban was the founder and CEO of Third Pillar Systems for twelve years. Third Pillar provided underwriting and risk analytics software to the World's leading banks and commercial lenders, and processed over 100 billion in loans and leases. Jonathan learned about banking while working in investment banking where he made partner at the age of 27. He served five years in the US Army and in 7th Special Forces Group. He graduated second in his class at Special Operations Medical School at Ft. Sam Houston and did his clinical rotations at Reynolds Hospital.

CORIE EDWARDS
ND

ZAHRA MEHDIZADEH KASHI
PhD

Introduction:

Genetic testing is on the rise as research identifies significant connections between certain allelic variations in the genetic code and disease states. Through improved understanding of certain medical conditions on a deeper level, it is now possible to relate the uniqueness of patients to an informative test result. Genetic testing identifies individual potential biochemical interactions and thus allows practitioners, in conjunction with reported symptoms, to develop targeted treatment plans. This is an exciting time to be working with patients and clients for improved outcomes; as more significant clinically useful information is becoming available, medicine is at the cusp of a new way to meet and treat people as individuals.

Understanding this advancing technology is the first step. Combining concepts of genetics, biochemistry, physiology and emerging scientific research is a new approach for many practitioners. Genetic testing can sometimes be a controversial topic as questions have arisen over the quality of testing laboratories and the general ability to keep genetic information secure. However, mastering this use of science can provide a benefit not just for a practice, but more importantly, for the patient. This chapter aims to review the concepts of basic genetics so the practitioner is confident in ordering, reviewing, and discussing genetic testing with a patient; and to illustrate how medical genetic testing is a powerful tool for working with a varied patient population.

The starting point for medical genetics is in understanding the definition and role of an allele. Every person has two copies of every gene; one from the mother and one from the father. Together these two genes form what is called a base pair. The gene base pairs code instructions for the manufacture of proteins, enzymes and more. These genes can be exactly the same, meaning each base pair within the genetic sequence is identical, or they can have subtle differences that cause production of slightly different protein or enzyme products.

A perfect example of this is eye color; everyone has two copies of a gene that encodes for a product that determines eye color, but not everyone has the exact same gene. This is why there is such a variety of eye colors. These various versions of the same gene are called alleles: in this example - a brown eyed allele, blue eyed allele, and so on. The same is true for all genes, and it is these differences that cause all the variations in humans.

Genetic variation is fundamental to evolution, it is what allows a species to survive and continue generation after generation in an ever-changing environment. This genetic variation arises through mutations which can have a number of effects on the offspring. Mutations can cause death, disease, improved health, or have no effect whatsoever on the organism. The outcome depends completely on how the change in the genetic code affects the end product, the protein. If there is a mutation present, then this mutation will be passed on from generation to generation. Often times the type of mutation passed on to offspring is subtle, and consists of one single change to the base pair sequence of a gene. These are known as Single Nucleotide Polymorphisms or SNPs. Most alleles are created from SNPs; therefore, the majority of genetic research and testing has focused on detecting as well as quantifying them.

Genome wide association studies search the genomes of many people to find genetic markers that are thought to be associated with a particular disease. These studies help to develop the growing database of information of genetic disease and are used to select which genetic markers a laboratory will test for. There will soon be a dizzying array of genetic data to make sense of. Just because it is possible to get a full genetic profile on a patient, it does not mean that all that information will be helpful. There are for example, many genetic mutations which have zero impact; there are other mutations with limited impact because the body had evolved to have back-up systems that counterbalance a harmful mutation. This is why research is important, as is working with a laboratory that has combed existing research to understand which alleles have the most impact on health. As this scientific technology progresses the effect a person's genetic code has on their health will become clearer. Medical genetic testing allows for specific targeted testing to identify disease proclivity. While some practitioners are wary of genetic testing to evaluate risk for serious life threatening disease, a growing number of practitioners are recognizing that genetic testing linked to lifestyle factors can be a powerful

tool in identifying the right treatment protocol for a particular patient. This chapter content goes on to provide examples to illustrate just how powerful this selective genetic testing can be. As this new medical technology is gaining ground, practitioners are learning how to integrate it into their practice. Understanding when to test, how to use the test results to maximize benefit to the patient, and the potential outcomes that can increase treatment success. An example of how genetic testing can be used successfully in practice is outlined in the following case study.

A 39-year-old female informs the clinic with her concerns of an inability to lose weight after the birth of her second child 11 months ago. The patient has a history of being overweight on and off, with the symptom presenting itself in early childhood. However, for the majority of her adult life she had been able to maintain a healthy BMI through diet and exercise. Her current health history is unremarkable other than occasional low back pain that she has struggled with for approximately 15 years. Her sleep is broken up into 1 to 3 hour stretches as her new baby does not sleep through the night. She is not currently breast feeding. Her energy level is 6-7/10 (10 = the highest energy). Mood is good. Her menstrual cycle is regular, every 26-28 days, medium flow lasting 3 days with little to no cramping. Current diet is paleo for 10 months with no weight loss. She exercises 5-7 days a week, 30 minutes a day at moderate intensity with the main goal of preventing an increase in back pain. She was on no pharmaceutical medications, but took a multi-vitamin, probiotic, fish oil, and vitamin C 500 mg BID. Past medical history includes appendectomy at age 17, two previous pregnancies with both children being born healthy with no complications, and low back pain. Family medical history positive from breast cancer (mother), auto immune (father) and heart disease (father). Review of systems was unremarkable accept for a history of dry skin and hair with an intolerance to cold.

Physical exam was unremarkable and revealed normal blood pressure of 101/72, pulse 85, temperature 98.1, height was 5 feet and 7 inches with a weight of 175 pounds (BMI 27.4). Lungs, heart and neurological exams all within normal limits (WNL), thyroid was palpable, normal size, 0 lesions. Tests ordered: CBC, comprehensive metabolic panel, thyroid panel with (free T4, free T3 and TSH) and the following genetic testing was ordered through Kashi Health Laboratories: Weight Management, Nutritional Deficiencies and Cardiac Health panel. Results of these tests revealed no anemia present though the MVC was on the upper range of normal at 94 fl/red cell indicating a tendency towards low B12 or folate levels. Triglycerides, and fasting blood sugar levels were within normal range, however total cholesterol was low at 120 mg/dl. TSH was suboptimal but within the normal range at 3 ulU/ml, Free T4 and Free T3 WNL as well.

Results of the genetic testing revealed much more. This patient had risk alleles for three out of the five genetic markers associated with an increased BMI; FTO, ADRB2, and SH2B1. Cardiac Health panel revealed no presences of related risk alleles. The Nutritional Deficiencies panel also revealed that the patient was positive for three risk alleles associated with vitamin D deficiency (VDR, NADSYN1/DHCR7, and CYP2R1) and the risk allele for vitamin B 12 deficiency (FUT2). Follow up testing for serum vitamin D levels was preformed and a severe vitamin D deficiency was confirmed.

The treatment plan was compiled based on the patients presenting symptoms, physical exam results and laboratory test results. Genetic testing revealed that this patient has trouble feeling full after a meal and prone to crave high calorie foods and to over eating. In addition, she was less likely to lose weight in response to medium to high intensity exercise. SH2B1 revealed that this patient was prone to both insulin and leptin resistance.

The Vitamin Deficiency panel revealed that the patient was prone to vitamin D and B12 deficiencies. Specifically, the patient had a mutation in the CYP2R1 gene that caused a decrease in the conversion of cholecalciferol (D3) to calcitriol by the enzyme vitamin D 25 hydroxylase. Based on these test results a treatment plan was formulated to help this patient lose weight. Her current diet was to be maintained, however modifications were made. Patient was recommended to eat one serving of her meal and then wait 10 minutes until deciding if she would need a second serving. Her exercise regime was changed to add low intensity exercise for longer periods of time. Patient worked hard to increase low calorie fiber rich foods as her primary source of nutrition, and instructed to eat small frequent meals throughout the

day to decrease cravings. Increased supplementation was recommended, vitamin D was prescribed in the form of calcitriol and B12 in the form of injections.

After 6 months of the prescribed treatment plan the patient reported improved weight loss with an average of 2-5 pounds a month for a total of 23-pound loss. Serum vitamin D levels where increased to low normal range and MCV was reduced to an optimal level of 90 fl/red cell. The patient reported an increase in mood and energy level, though her sleep was still being disrupted by her young child. Most importantly the patient was very pleased with the lifestyle modifications; she stated that she found them easy to integrate into her life and that finally seeing results increased her level of motivation greatly. Genetic testing allowed for a targeted treatment plan that made basic but powerful modifications to an already healthy lifestyle. Because of this, the patient was able to achieve her desired weight of 150 pounds without severe calorie restriction.

Deciding on the best tests for a specific patient can have its challenges, and yet genetic testing can now add a wealth of knowledge to decisions about a particular treatment plan. Understanding the options in genetic testing is the next step. Some testing facilities can offer the patients' entire genetic profile which has an overwhelming amount of information and very little help in deciphering it. Practitioners find it hard to know which genetic markers are well researched and strongly correlated to disease. Other concerns arise in regards to the safety and confidentiality of the test results. Certain genetic markers tested for can have a wealth of research supporting their correlation to disease, while others can have less or conflicting studies to support their use in genetic testing. With over 20,000 genes in the human genome, knowing which ones are significant within the seemingly endless amount of code is vital. This chapter will cover some of the most clinically relevant genetic markers that have been found to be correlated to some key areas of health: weight management, cardiac health and behavioral health.

According to the CDC the average adult is 26 pounds heavier than in the 1950, with the United States having an obesity rate of 35%.[1] Many theories have arisen concerning the cause of this increase: higher calorie food with lower nutrition, decrease in physical activity, increased environmental pollutants, change in eating habits and more. In addition, studies have found that certain genetic markers play a role a person's ability to lose and maintain their weight. Some of the most well researched genes are the FTO, MC4R, FABP2, ADRB2, and SH2B1. These markers are important not only in that they are well researched, but they also have clinical relevancy. It is important to focus on detecting genetic markers that have a disease pathology that can be either treated or that can warn of the need for early surveillance. This chapter will cover various genetic markers, their pathology and recommended treatment protocols and or additional testing.

FTO

FTO, also known as the human fat-mass and obesity associated gene, is found on chromosome 16. Discovered in 2007 it is one of the strongest genetic risk factors for obesity. Frayling et al, found a significant association between weight, Body Mass Index and the FTO risk allele in over 38,000 participants.[2] It was determined that adults who have two copies of the risk allele weighed an average of 6.6 pounds more and had a 1.7-fold increased risk of developing obesity when compared with those not carrying a risk allele.[2] The association has been confirmed in multiple populations of differing ethnicities.[3-10] FTO carriers appear to have a higher amount of FTO expression in the brain and body which has been shown to result in an imbalance that increases the risk of becoming overweight.[11-14] This risk may result in a preference for high-calorie foods or low feelings of satiety.[14] It has been recently shown that individuals with this variant do respond equally well to dietary, physical activity, or drug base weight loss interventions.[15]

MC4R

Melanocortin4 Receptor refers to a gene found on chromosome 18 and the receptor that this gene creates. The MC4R is located in the hypothalamus, a region of the brain responsible for appetite (among many other functions).[16] Mutations in and near the MC4R gene account for

up to 6% of severe early-onset obesity cases, suggesting an important role for the central melanocortin system in the maintenance of normal body weight.[17-22] The MCR4 risk allele has been linked to obesity, diminished insulin response in the brain, altered eating behaviors, and is believed to impair MC4R function.[23] There is a tendency for increased appetite and a preference for calorie-dense foods. However, studies in children and teens show that even though carriers of the high-risk allele near MC4R are more prone to weight gain, homozygous variant carriers may be even more responsive to lifestyle modifications than non-carriers or heterozygotes.[24]

FABP2

Fatty Acid Binding Protein 2 is the intracellular protein product of a gene found on chromosome 4. The FABP2 protein helps in fat transportation and absorption, specifically in mobilizing fat from the small intestine into circulation for downstream deposit and storage in fat cells and the liver. FABP2 variants result in increased absorption and transportation of fats in the body.[25-27] This variant has also been linked to type 2 diabetes mellitus risk in certain ethnic populations.[27-29] Controlling the amount and types of fat, particularly saturated fat, is critically to working successfully with this variant.

ADRB2 The Beta-2 adrenergic receptor is a gene found on chromosome 5 that codes for a receptor located on cells of various tissues including liver and fat cells.[30] Research suggests that mutations in the ADRB2 gene may be important risk factors for the development of obesity and may affect how an individual's weight changes in response to exercise or a carbohydrate rich diet.[31-33] Women in particular who have this risk allele could benefit from lower carbohydrate intake.[31] Some studies suggest that the ADRB2 variant may lower the rate of fat metabolism during workout recovery phase although this is currently not conclusive.[31]

SH2B1

The Sarcoma homology 2B adaptor protein 1 refers to a gene found on chromosome 16 and the protein that the gene produces. This protein is critical in maintaining the balance of insulin and leptin in the body. Insulin helps control blood sugar (glucose) and is strongly influenced by dietary fat and carbohydrate.[34-36] Insulin is well known as a factor in diabetes. The hormone leptin is important in regulating appetite and the feeling of hunger through its impact on ghrelin. The body can become leptin resistant in the same way it can become insulin resistant. The SH2B1 risk allele can have an altered form of the adapter protein that impairs insulin and leptin signaling resulting in increased appetite and associated weight gain.[37-42] Controlling intake of fat and carbohydrate is important along with regular exercise to improve leptin signaling.

Behavioral Health

Nutritional deficiencies are now common in America as food quality and the ability to absorb nutrients has become impaired. Because nutrients are key to making and maintaining proper levels of neurotransmitters, these deficiencies can be related to mental health. Approximately 1 in 5 adults in the U.S (43.8 million) experience mental illness in a given year.[43]

MTHFR

An important marker gaining ground with practitioners treating behavioral health issues is the MTHFR gene. The MTHFR (methylenetetrahydrofolate reductase) gene produces an enzyme that helps in processing folate and regulating homocysteine levels. Folate is a critical nutrient involved in methylation, DNA synthesis and amino acid metabolism. Impaired folate metabolism due to MTHFR enzyme inactivity, or decreased folate, results in elevated plasma homocysteine which has been linked to depression.[44-46] The first of two common mutations in the MTHFR gene is the C677T polymorphism.[47] The second mutation is a substitution of adenine (A) with cytosine (C) at mRNA position 1298.[48,49] There is no evidence to suggest that the A1298C mutation alone affects plasma homocysteine levels, however, it has been demonstrated that

individuals who are compound heterozygotes for both the C677T and the A1298C mutations have increased plasma homocysteine concentrations.[48] Elevated homocysteine levels are inversely associated with memory score[50] and directly related to brain atrophy[51] and depressive symptoms.[52] Folate levels are directly related to memory scores,59 and inversely related to depressive symptoms in women.[53]

COMT

The COMT (catechol-O-methyltransferase) gene codes for an enzyme that is essential for the breakdown of several mood-associated neurotransmitters, most notably dopamine.[54-58] Scientific research has demonstrated that a common mutation in COMT results in the conversion of the amino acid valine to methionine at position 158, and causes a dramatic reduction in the enzyme's ability to break down neurotransmitters. The enzyme is predominantly active in the prefrontal cortex, or PFC; the area of the brain that gives rise to what we perceive as our personality, emotions, behavior inhibition, abstract thinking, and short-term memory.

Genes of Interest Table

Gene	Function	Impact
FUT2 – Vitamin B12	B12 Levels also affect mood and behavioral health. Genetic variants of the FUT2 gene give rise to a non-functional FUT2 enzyme resulting in an inability to synthesize Vitamin B12. Vitamin B12 supports the synthesis of a molecule known as S-adenosyl methionine (SAM) which is critical in regulating levels of neurotransmitters in the brain.	Behavioral Health
CYP2R1	Low vitamin D levels are associated with decreased cognitive function and the development of depression.[59-60] Hepatic enzyme 25-hydroxylase is responsible for the conversion of Vitamin D3 (found in most supplements) to Calcitriol.[61] Impaired function of this enzyme results in low levels of vitamin D in the body.[62,63]	Behavioral Health
GC	Vitamin D binding protein is responsible for the transportation of vitamin D to various tissues. Several studies have shown that vitamin D serum levels differ significantly depending on the genotype of the person.[63,64]	Behavioral Health
VDR BsmI	Vitamin D receptor (VDR) is essential for promoting both calcium absorption and maintenance of adequate serum calcium and vitamin D. [65,66] Maintaining adequate levels of vitamin D may be beneficial to patients not only for optimal bone health, but also for reducing cardiovascular and autoimmune disease, cancer risk, and increasing life expectancy.[67,68]	Behavioral Health Cardiovascular Health General Health
NADSYN1/DHCR7	Responsible for converting the vitamin D precursor (7-DHC) to cholesterol.[69] By converting the 7-DHC into cholesterol the needed substrate used by the body to generate vitamin D is removed, leaving the individual at a higher risk of vitamin D deficiency.[64] Low vitamin D levels are associated with decreased cognitive function and the development of depression.[59,60]	Behavioral Health
CYP450 enzymes: CYP2D679-80 CYP2C19 (79, 81)	CYP450 enzymes are necessary for the metabolism of drugs. Variant alleles usually encode a CYP450 enzyme that has reduced or no activity.[70] These enzymes are critical for processing several common medications prescribed by mental health professionals.	Behavioral Health
carotene 15,15'-monooxygenase 1	Vitamin A is a fat-soluble vitamin crucial for proper vision, immune response, and cellular differentiation.[71] The first step in the metabolic conversion of the carotenoids is their cleavage by the enzyme carotene 15,15'-monooxygenase 1 (BCMO1).[72] A polymorphism located upstream of the BCMO1 gene has been reported to result in the reduction of	Nutritional Health

	the BCMO1 enzyme's catalytic activity by up to 48% in homozygous variant carriers, which can then lead to a vitamin A deficient state.	
transmembrane protease serine 6 (TMPRSS6) Iron	Scientists have found that a mutation in the gene coding for transmembrane protease serine 6 (TMPRSS6) is associated with several clinical indicators of anemia.[73,74] Evidence suggests that carrying even one copy of the risk allele can negatively impact your iron status.	Nutritional Health

Cardiac Health

Coronary heart disease and stroke remain the leading causes of death and disability for individuals of most ethnicities within the United States.[75,76] Coronary artery disease (CAD) risk is approximately 40-60% genetically determined.[77] Several genetic markers have been found to be strongly correlated to an increase risk of developing heart disease.

Gene	Function
9p21	9p21 exhibits anti-proliferative activity in the vascular endothelium[78] and genetic variants may cause the development of atherosclerosis.[79]
AGT gene and Angiotensinogen	The precursor to the active peptide angiotensin II (Ang II), a hormone that causes blood pressure to increase through vasoconstriction and sodium retention.[80] The more precursor available in the blood, the more Ang II is produced, and increased levels of the hormone are significantly correlated with blood pressure in patients with hypertension.[81] Certain alleles of this gene increase levels of precursor.
Endothelial nitric oxide synthase (eNOS/NOS3)	The key enzyme responsible for maintaining baseline vascular nitric oxide (NO) levels is encoded in the eNOS gene.[82] Nitric oxide is responsible for vasodilation, or the relaxation of vascular smooth muscle cells allowing greater blood flow and reduced blood pressure.[83] Variants of this gene cause increased risk of ischemic heart disease, ischemic stroke, and myocardial infarction in young patients, while the risk for hypertension seems to be dependent upon ethnicity.[84-87]
Prothrombin gene or coagulation Factor II (F2)	Prothrombin is the precursor protein of thrombin, a component of the coagulation cascade.[88] Individuals with this particular mutation in F2 have a 2-3-fold increased risk for developing thrombosis and venous thromboembolism (VTE).[89-91]
Factor V Leiden thrombophilia	Factor V Leiden is a rare variant of the human factor V protein that causes an increase in blood clotting (hypercoagulability).[92] In a comprehensive meta-analysis it was determined that individuals that are heterozygous for the factor V mutation have a fivefold increased relative risk for idiopathic venous thromboembolism (VTE), while those who are homozygous for the mutation have a nine to tenfold increase in risk.[91]
ApoE	There are three possible types of ApoE protein, called E2, E3 and E4.[93,94] For the majority of people, the E2 ApoE variant confers a decreased risk of cardiovascular disease and promotes a more optimal cholesterol profile. however, those with two copies of E2 (E2/E2) are at a slightly increased risk (less than 10%) for a rare hereditary condition called hyperlipoproteinemia (III HLP).[95] E3 is considered normal. E4 allele carriers are at an increased risk for cardiovascular disease, elevated triglycerides,[96]elevated total cholesterol and elevated LDL.[95]
SLCO1B1 gene	Encodes the organic anion transporting polypeptide B1 (OATPB1). This protein mediates the liver's uptake of many compounds, including the class of medications called statins.[97] Presence of the variant allele markedly reduces the uptake of certain statins which in turn reduces the efficacy of the statin medication and allows statin accumulation in the bloodstream. Due to the adverse effects of statin-induced

	myopathies and myalgia's being dose dependent, it may be advisable to avoid high dose statin therapy in these variant allele carriers.[97]

As the body of research concerning genetic markers and their effect on health grows through genome wide association studies, so will our need for genetic testing. Understanding the patient's genetic blue print will allow a practitioner to provide targeted treatment plans while achieving larger results. It is important to focus on utilizing genetic markers that research has proven to be clinically relevant and that can be affected by treatment and/or monitoring. Keeping abreast of new and exciting research is important, a testing laboratory that has up to date information can be invaluable partner. Focus on partnering with a trusted laboratory that is fully accredited, and has physicians and scientists on staff working to stay current on the growing body of genetic information.

Every patient is different, how they react to medications, food, and or exercise can vary greatly. Genetic testing can explain the biochemical cause for these long-observed differences. Knowledge is power and this knowledge can wield strong results in an otherwise difficult situation. Utilizing genetic testing as a tool is the wave of the future in medicine, and increasing clinical proficiency with this resource can greatly benefit any practitioner.

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Corie Edwards, ND

Staff Physician

Dr. Corie Edwards graduated from the University of Oregon with a bachelor's degree in biology, and received a doctorate in Naturopathic Medicine with honors in research from the National University of Natural Medicine in Portland. In the past, she has worked in private practice offering primary care, nutritional counseling, weight loss, pain management, and vitamin injections. Currently she is adjunct faculty at the National University of Natural Medicine were she teaches genetics through their undergraduate program. Growing up in Eugene, Oregon, Dr. Edwards has a deep appreciation for the Pacific Northwest, its natural beauty, culture, and creative atmosphere. In her professional life, she takes an interest in functional medicine with a focus on the role genetics plays in health. Outside of work, she loves her role as a mother and wife, as well as spending time with friends and family.

Zahra Mehdizadeh Kashi, PhD

Founder and CEO

Zahra Mehdizadeh Kashi, PhD, HCLD, is a board-certified molecular immunohematologist with nearly 25 years of experience in clinical laboratories, biologics, and pharmaceuticals. Dr. Kashi also has extensive leadership training, having completed more than 1,000 hours in areas such as clinical development and trial protocols, quality system auditing, GMP development and process, project management, inspection, regulatory agencies, strategic planning and business development. Dr. Kashi is a highly-sought clinical laboratory consultant, with dozens of peer-reviewed publications and abstracts, as well as numerous invited presentations. Over the years, Dr. Kashi has been a consultant for many Northwest and western state laboratories including LABS Inc., Fanno Creek Clinic, Portland Family Practice, Pediatric Associates of the Northwest, the Portland Clinic, VRL Laboratories, Portland Pain and Spine Clinic and the American Red Cross.

She is active in the American Society of Histocompatibility & Immunogenics where she is an inspector, and a liaison for the Relationship Testing Standards Program, and previously was a commissioner. She is currently an inspector for the College of American Pathologists and an expert witness on genetic identity. In addition, Dr. Kashi has served as a clinical assistant professor in the department of pathology/CLS at Oregon Health & Science University and has also held a number of other education and research positions at local universities, hospitals, and corporations. Dr. Kashi holds a doctorate degree in molecular immunohematology from Portland State University. She completed her doctoral thesis under the mentorship of Dr. Michael Heinrich at Oregon Health Sciences University. She also completed the Michigan Ross Executive Program at the University of Michigan in 2005.

COREY SCHULER

RN, MS, LN, CNS, DC, DBM, FAAIM

Small Intestinal Bacterial Overgrowth (SIBO): Integrative Approaches

Small Intestinal Bacterial Overgrowth (SIBO) is a clinical entity in which we are improving our understanding. While bacterial overgrowth can be thought of as an infectious condition, it is most appropriately understood as a condition of improper gastrointestinal motility. At the root of SIBO is the concept that commensal bacteria that normally colonize in the large intestine migrate proximally into the small bowel. This translocated overgrowth allows for premature bacterial exposure to the host's food which results in fermentation. For the host this means symptoms. For the bacterial colonies this means substantial growth and overgrowth beyond typical numbers. SIBO can subsequently be a contributor or causal factor to a variety of maladies including but not limited to malnutrition, diarrhea, nausea, bloating, vomiting, weight loss, joint pain, fatigue, skin conditions, and depression as reported by patients. It is also common in those diagnosed with irritable bowel syndrome and may in fact be a cause of that clinical entity. Causes of SIBO are thought to include decreased pancreatic enzyme function and/ or stomach acid or lack of stimulation of migrating motor complexes. Reflux medications, antibiotics, oral contraceptives, and acute gastroenteritis may either contribute or be a causative factor for SIBO. Also a diet high in fermentable carbohydrates may be the cause or a contributor to SIBO.

There are typically four main "lanes" of treatment for SIBO. These include dietary change, antibiotics, herbal antimicrobials, and the elemental diet. Dietary changes are designed to eliminate fermentable foods from the diet until gastrointestinal motility can be restored. A nutritional professional with experience in this area is key to the success of dietary approaches. Herbal antimicrobial approaches vary based on the needs of the client and the experience of the practitioner. Antibiotic therapy is typically limited to luminal agents and those that support gastrointestinal motility. The elemental diet is both an evidence based as well as non-pharmacologic approach.

The Elemental Diet: Clinical Applications and Protocols

An elemental diet is a diet consisting of pre-digested or elemental nutrients designed to be used as dietary management and sole source of nutritional intake for limited periods. They are often used by patients who have a limited capacity to digest, absorb, or metabolize ordinary foods or certain nutrients. This eBook will review the clinical application of an elemental diet for patients with moderate to severe GI dysfunction, including SIBO and Crohn's disease.

What is an Elemental Diet?

An elemental diet is a diet consisting of pre-digested nutrients designed to be a sole source of nutrition for limited periods (generally for 14-21 days). They are liquid dietary products, which are available through a few delivery methods, including orally, gastric tube feeding, or intravenously. They can be in a ready-to-drink package or as a powder reconstituted with water. The nutrients of an elemental diet are in their simplest form, allowing them to be easily assimilated by the body, while allowing the gut to rest.

History of Clinical Use

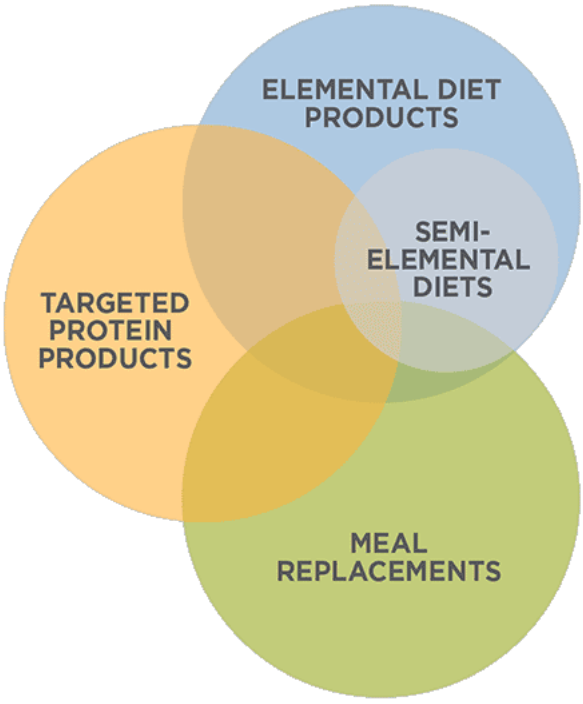
The elemental diet has been used in hospital settings since the 1940's; however, research has resurfaced the benefits of using it as a dietary intervention for patients with moderate to severely compromised digestive systems in outpatient settings. Clinical evidence supports the use of elemental formulas for the dietary management of gastrointestinal/digestive dysfunctions including SIBO and irritable bowel and Crohn's disease.[1-12] Nutrients from an elemental diet are believed to be primarily absorbed in the proximal small intestine, limiting the digestive function needed to absorb the necessary nutrients.[7]

Macro and Micronutrient Composition

- 14-18% of calories from protein in the form of amino acids
- 42-76% of calories from carbohydrates in the form of monosaccharaides
- 6-43% of calories from fat in the form of fatty acids

The micronutrient composition of an elemental formula is complex because as the single source of nutrition, it must be sufficient for up to 4 weeks, but not exceed safe levels of ingestion even for individuals with GI impairment.

It's important to understand what an elemental diet is, and what it is not. Meal replacement products, using intact protein sources, are often used to support body composition whereas elemental diets are used under medical supervision for a spectrum of health concerns. Targeted protein products also contain whole proteins. Targeted protein products are not designed to be a sole source of nutrition for an individual and are not indicated for severely impaired GI function.



Clinical Applications of the Elemental Diet

In the current guidelines of established gastroenterology, the dietary management strategies widely approved in the care model for inflammatory bowel/Crohn's disease are parenteral and enteral nutrition. Oral elemental diet is enteral nutrition.

Small Intestinal Bacterial Overgrowth (SIBO)

Background of SIBO

SIBO was first described in 1939, in association with intestinal strictures.[13] Indeed, SIBO is more likely to occur as a complication of gut motility disorders, including strictures, scleroderma, or diabetic enteropathy.[13] Recently, however, the association between SIBO and irritable bowel has piqued the interest of clinicians. In 2000, Mark Pimental, MD, and his colleagues at Cedars-Sinai Medical Center reported a 78% prevalence of SIBO in patients with irritable bowel.[14] Since that time, SIBO has been identified more frequently in patients with irritable bowel than in healthy controls.[15]

Assessing SIBO

The upper portions of the small intestine normally contain minimal numbers of bacteria. Gastric acid, intestinal motility, biliary secretions, and immunoglobulins keep bacterial growth in check. With the loss of any of these protective mechanisms, bacteria can thrive.[1] One standard for SIBO assessment is a culture analysis of duodenal aspirates, but a less costly and less invasive test that has gained favor is the lactulose breath test.
Lactulose is a sugar not digested by the body, meaning that it is able to travel all the way through the small in-

testine without modification in normal physiology. The lactulose breath test thus allows detection of abnormally increased numbers of bacteria located in the distal small intestine. Patients consume lactulose syrup and samples of their breath are collected over a 2-3 hour period. The lactulose is taken up by bacteria in the small intestine which digest and ferment it, producing different types of gases such as hydrogen and methane. Similarly, when dietary intake includes fermentable carbohydrates such as lactulose and poorly digested oligosaccharides, it feeds bacteria present in the small intestine producing gases that can be measured in the breath. Elemental diets do not contain such fermentable carbohydrates and provide safe nutrition for the patient. Another type of breath test uses glucose as a challenge substrate and, on the other hand, is completely absorbed by the body, typically within the first few feet of the GI tract. A glucose challenge test is highly specific meaning that if it is positive, SIBO is very likely present.

Application of an Elemental Diet in Patients with SIBO

Use of an elemental diet is thought to place commensal bacterial overgrowth into a hypometabolic state by essentially starving them. Using highly bioavailable and essentially monomeric versions of macronutrients, there is a greater chance for absorption to occur before arriving in the distal small intestine where bacterial overgrowth is common. Some of the colonies in the distal small intestine would not sustain the duration of inadequate fuel and die, and total overgrowth would decrease. Many of the human clinical trials used two-four weeks duration for the elemental diet, so that is commonly recommended, but some people benefit from shorter and others need longer periods of time.

Crohn's Disease

Background of Crohn's Disease

Crohn's disease is a chronic disease characterized by patchy inflammation of the intestines and relapsing and remitting symptoms. Crohn's disease and inflammatory bowel disease more generally is increasing worldwide, with the highest rates seen in Europe and North America.[16] Unlike other chronic diseases, the incidence of inflammatory bowel disease does not increase with age.

The intestinal inflammation of Crohn's disease is driven by an altered immune response that activates nuclear factor (NF)-κβ, tumor necrosis factor (TNF)-alpha, and pro-inflammatory cytokines.[17] Numerous genes and polymorphisms have been associated with Crohn's disease, but environmental signals are thought to play a key role in triggering disease onset.[18]

Application of an Elemental Diet in Patients with Crohn's Disease

The value of elemental enteral feeds in Crohn's disease was reported over 30 years ago.[6] The colonic microflora is abnormal in Crohn's disease, which may lead to production of toxic chemicals such as alcohols, aldehydes, and the ethyl esters of fatty acids.[20] It is believed that this is the reason for the loss of normal immune tolerance to the gut flora in Crohn's disease, which results in the coating of fecal bacteria by immunoglobulin.[21] Enteral feeding acts directly on the microbiota. The elemental diet has been shown to reduce the production of bacterial metabolites within two weeks and to significantly reduce bacterial coating with immunoglobulin.[20] Overall, the results of elemental enteral feeding are excellent within two-three weeks.

A study provided an elemental diet as a sole source of nutrition for to 28 consecutive patients with active Crohn's disease. Mucosal biopsies were obtained from the distal small intestine and colon and compared against a control group. 71% of patients were reclassified in regards to disease status.[11] A half elemental diet was also found to be a promising dietary management approach to Crohn's disease. In one clinical trial patients were recommended a half elemental diet for, on average, 11.9 months and found to be better managed than those who ate typical foods.[19]

Elemental Diet Protocols

Protocols:

- Full Elemental Diet
- Half Elemental Diet
- PRN (pro re nata) Elemental Diet

Regardless of which protocol is applied, medical supervision throughout the duration is critical. Supervision should include

- Evaluating if the proper caloric need is being met (as assessed by monitoring a patient's weight)
- That symptoms do not exacerbate or new symptoms are reasonable given the patient's clinical context
- That the patient is adhering to the prescribed protocol

Full Elemental Diet
Using an elemental formula as the sole source of nutrition
Timing: Two week duration (longer or shorter periods can be used as determined)
Caloric Need: Elemental formula fulfills 100% of daily caloric need
Patient Cases: Patients diagnosed with SIBO or Crohn's Disease

Use of an elemental diet for a period of two weeks is considered the most evidence-based protocol as it has commonly been used in clinical trials. It can also be extended out an additional week or two based on clinical need. Clinical need can be determined by symptom monitoring or breath test for microbial overgrowth.

Protocol:
1: Determine patient's daily caloric need
2: Define consumption schedule based on caloric need and consumption rate
3: Monitor patient throughout the duration of the program

Half Elemental Diet
Using an elemental formula as a partial-source of nutrition.
Timing: Two-four week duration (longer or shorter periods can be used as determined)
Caloric Need: Typically 50% of daily caloric intake from an elemental formula, and 50% from well-tolerated foods.

Patient Cases: Patients with moderate to severe GI dysfunction who are unable to complete or tolerate a full elemental diet, during food re-introduction, or for use following other protocols.
Half-elemental diets are used when patients cannot, or will not, adhere to a full elemental diet protocol OR when practitioners are not as comfortable with full elemental diet or are desirous of utilizing additional nutritional therapies – such as nutritional supplements. Reasons for adherence vary, though most often is attributed to cost and palatability. In a published use of the elemental diet, patients were started on a partial element diet before commencing a full elemental diet as well as transitioning to food re-introduction.[6]

Protocol:
1: Determine patients daily caloric need
2: Define daily dietary schedule based on consumption of well-tolerated foods, and of the elemental formula based on caloric need and consumption rate
3: Monitor patient throughout the duration of the program

PRN (pro re nata) Elemental Diet
Using an elemental formula as a full or partial-source of nutrition, as needed.
Timing: One-three days, but varies
Caloric Need: Varies
Patient Cases: Most often during food re-introduction, during exacerbations, following a prior full or half elemental diet protocol.
Some practitioners utilize a half elemental diet with patients intermittently, or on an as-needed basis, primarily during times of exacerbations following a prior full or half elemental diet protocol. If a patient has been on a complicated protocol of supplements and/ or medications in which a washout period may be useful, transitioning

from one protocol to a new one may be supported using a short duration elemental diet. In this way, interactions between the previous and new protocol are minimized.

Protocol:
1: Determine patients daily caloric need
2: Define daily dietary schedule based on consumption of well-tolerated foods, and of the elemental formula based on caloric need and consumption rate
3: Monitor patient throughout the duration of the program

Type of Diet	**Timing of Diet**	**When to use:**
Full Elemental Diet	2-3 Weeks* *based on clinic trials, though longer periods may be appropriate in some patients.	Patients diagnosed with[1-12]: - SIBO - Crohn's Disease
Half Elemental Diet	2-4 Weeks or longer	When patients are unable to complete or tolerate a full elemental diet or if continued use of GI Support Supplements is desired.
PRN (pro re nata) Elemental Diet	1-3 Days	To begin or follow up on a full or half elemental diet protocol. This approach can also be used to provide the gut with rest during exacerbations.

The Patient Experience

An elemental diet is a significant change for most patients, as such, impact to well-being, both physically and emotionally, should be considered for additional evaluation.

- Physical Effects: As with any change in diet, the introduction of an elemental diet may bring on new symptoms, some of which are challenging for patients to distinguish between the exacerbation of an existing symptom, a reaction to their elemental diet product, or in the case of SIBO, a Herxheimer reaction. Hence, your monitoring is required. Most commonly, this includes

    - **Cramping**

      Elemental diet products are typically concentrated, resulting in a high osmolality, which can result in intestinal cramping. Two approaches can be taken: reduce the rate of consumption and, if applicable/depending on the product being utilized, increase dilution (note: follow the manufacturers' instructions as not every elemental formula allows for dilution. If the effects are still noticed, you may also consider reducing the meal load (while still keeping overall caloric need in mind).

    - **Constipation**
      Individuals consuming a full elemental diet may report constipation. Constipation is best defined as when bowel movements occur less often than usual or consist of hard, dry stools that are painful or difficult to pass. While the first part of this definition is often applicable to those consuming an elemental diet, the latter part of the definition is not. Some people are accustomed to several bowel movements per day and a reduction in this frequency may be reported as constipation. It is helpful to note that decreased motility is not necessarily constipation. The macronutrients of an elemental diet are easily absorbable and contain no fiber. Fiber typically stimulates goblet cell production of mucus resulting in bowel movements.

An elemental diet is also not feeding microflora the way a typical diet may, so a reduction in colony counts may occur. The mass of stool contains a fair amount of bacterial materials. The formula, however, reduces the feeding of the commensal bacterial overgrowth. In this hypometabolic state, there is less division and reproduction leading to subsequently less microbes and less fecal mass. For these reasons, slow bowel motility is common and not typically a cause for concern.

It is common practice to use prokinetic agents in conjunction with an elemental diet to maintain the stimulation of migrating motor complexes. Some common prokinetic agents include

- Ginger (100-300 mg TID)
- 5-HTP (50-150 mg TID)
- Artichoke extract (320 mg TID)
- NAC to tolerance
- Other prokinetic agents

- **Social & Emotional Effects:** It's not surprising that patients with chronic conditions, such as severe GI impairment, may report a reduced quality of life, or that their emotional well-being, social functioning, and/or their self-concept is diminished. Introducing an elemental diet protocol, though with the intent of an improved outcome, is a significant change, and some patients may have a social or emotional reaction. While an elemental diet is not considered a fast because it is calorically and nutrient replete, some patients may report social and emotional effects consistent with fasting. Continued evaluation of a patient's well-being with these aspects in mind is imperative.

An elemental diet is a significant change in routine for patients. It is recommended that patients start their journey in the evening prior to their first full day on the elemental diet. During this time patients tend to be more relaxed, and the change in schedule allows them time to better understand the experience. They learn behavioral cues regarding the time it takes to prepare the elemental diet product and the rate of consumption that is recommended and required. These are small details that all impact adherence and are best learned while in a relaxed state versus rushing through it in the morning where they may have a busy schedule.

After the Elemental Diet: Food Reintroduction

One concern that has been raised by using an elemental diet is what does the patient do once they have completed the selected protocol? The answer is best described in the form of what not to do.
One research group found that symptoms can return if the foods that were causing challenges for the individual are returned immediately to the diet, therefore other options should be attempted. Beginning with broths and soups is one recommended option as they are nutrient dense foods, but have low allergenic potential. The volume added by these high water content foods can support stimulating migrating motor complexes. In some instances, soups and broths can be high in histamine and patients will not tolerate that approach. Alternative recommendations for these patients are a low FODMAP diet, Specific Carbohydrate Diet (SCD), Fast Tract Diet, LOFFLEX (Low Fat, Fibre Limited Exclusion), or SIBO Guide. The type of food reintroduction plan used should be consistent with the amount of support able to be provided as well as patient preference.

The half elemental diet can also be used as a reintroduction of normal food. While this use is still based entirely on clinician experiences and empirical reporting, the value of detecting specific food intolerances and building up a personalized exclusion diet for long-term care is well established. A diet low in fat and fiber (LOFFLEX) or diets with low fermentation potential (low FODMAP, Fast Tract, SIBO Guide) may be considered. Foods involved vary from patient to patient. The process of food testing involves trial and error and requires patience. It is therefore essential that nutrition professionals are available to ensure diets remain nutritionally adequate. If well tolerated foods are to be reintroduced, this suggests that a patient has created a "well-tolerated foods" list or has provided one.

Elemental Diet Product Formulations

There are several elemental diet product formulations on the market, ranging from prescription-only to home-made. Patient preference is a key consideration, including convenience, ingredient sensitivities, flavor, and cost. Regardless of the selected product, your supervision is required.

Elemental Diet Usage Guidelines

Consume Slowly

Slow consumption allows the digestive system to assimilate the nutrients rather than acting on a large bolus of nutrients which can interact with several different physiologic systems. Slow consumption allows the body the time it needs to effectively use the elemental diet product. Fast consumption, on the other hand, can stimulate an insulin response and/ or allow the carbohydrate components of the medical food to traverse too far into the digestive system without proper absorption. This is especially important for patients who respond to the higher glycemic load.

One technique used to help a patient understand how slowly to drink the elemental diet is to have them consume their first meal (which may be between 150 and 600 calories) during a sixty minute television or radio program with commercials. The patient is instructed to take a sip or single gulp at the beginning of the program and to drink a sip or gulp during each commercial break.

Medical Evaluation & Supervision

An all liquid diet, even with a hypoallergenic medical food, is not a "set it and forget it" procedure. It is a diet that requires medical supervision. Variation to your original instructions may be required. Therefore, recommendation to remain on the diet without checking in or evaluating the patient is inappropriate. It is reasonable to make recommendations to change the rate of consumption or change the number of scoops required per day based on weight or activity level.

Monitor for Constipation or Cramping

If intestinal cramping occurs, two things can be done immediately: further reduce the rate of consumption and/or further dilute the formula. The first task, reducing the rate of consumption, can be done by instructing the patient to consume a single meal in as long as one, 45-60 minute sitting. During consumption increasing the dilution by adding 6-8 ounces of water per 150 kilocalories of powder can also be instructed.

For constipation, consider a prokinetic agent to maintain the stimulation of migrating motor complexes.

Common Patient Questions

Q: I'm bored with the protocol, how can I change up the experience?

First, remind patients that speaking with YOU, the practitioner, is key before altering their plan of action. Things such as flavor fatigue are common, a few suggestions include:

1- Encourage patients to maintain an active and healthy social life while exploring activities that don't involve food (think mini-golf, pottery, and more). Leaning on friends and family for support and staying positive are important elements of adherence.

2- Related to flavor or formula fatigue, encourage patients to:

- Add ice in a blender along with elemental diet or add ice after reconstituting the product in water to reach the coldest temperature possible, or pre-mix a pitcher and refrigerate in advance.
- Mix up the powder in a Mason jar or favorite beverage carrier to ensure the product is portable.

Q: Can I add more water to the powder?

Yes. An elemental diet is not a fluid-restricted diet. If a patient prefers less sweetness, more water can be added to the elemental diet. This increases dilution, decreases sweetness, and also decreases the osmolality. Some

practitioners use 6-8 ounces of water as the standard, per 150 kilocalorie of powder.
Additional water can be consumed beyond what is used to reconstitute the elemental diet powder as well.

Q: When can I eat whole foods again?
Food reintroduction requires patience. Foods should be reintroduced one at a time, and in a very deliberate order. It is not advised to revert to the diet that was consumed before their elemental diet protocol. Reintroducing tolerated foods over the course of two-four weeks should take precedence over introducing questionable or new foods. Using a period of time of tolerated foods is thought to provide three important functions:

1. Keep inflammation low as foods not well tolerated can stimulate various immune cascades and inhibit healing.
2. Provides gut rest to allow normal turnover to occur.
3. Prevents major shifts in microbiota which may have deleterious effects on various systems.

Reintroduce uncomplicated foods one at a time for two-four months, just like an elimination diet (every one-three days). Some elimination diets recommend a 24-hour observation period which may be acceptable. However, since an elemental diet is a more aggressive approach than an elimination diet, a more conservative approach may be required in the reintroduction phase. Prudent reintroduction greatly expands diet choices for the individual well beyond their initial list of tolerated foods. Nourishing and healing foods that are well tolerated also reduces dependence on supplementation.

Unique Patient Cases

Prescription-Induced Glycemic Responses
From time to time, patients may have or be prescribed a medication which causes glycemic sensitives. This can occur if a patient is taking corticosteroids as an example as they can raise blood sugar and a high glycemic formula may add to the glycemic load.

Recommendation: MCT (medium chain triglyceride) oil is a component of elemental diet formulas and can be added to the elemental diet. This lowers the glycemic index, increases the macronutrient ratio between fat and carbohydrates, and may stimulate bowel activity. The individual's caloric needs would have to be reconfigured if this technique is employed.

For example, if an 1800 kilocalorie daily need is required, instead of using 1800 kilocalories of elemental diet, you may consider recommending 1500 kilocalories of elemental diet powder and three tablespoons of MCT oil. MCT oil is approximately 100 kilocalories per tablespoon so this combination would also equal 1800 kilocalories. Continue to monitor, to ensure the patient tolerates this type of change to the base product.

Patients with Proximal SIBO
For patients with proximal SIBO, bacterial growth is located in the GI tract proximal to the distal small intestine.

Recommendation: Hold off on introducing an elemental diet until later in the dietary management process. You may want to first consider using antimicrobials or luminal agent antibiotics.

Patients with Fungal Propensity
Patients who have a personal history of fungal overgrowth are most likely to have a fungal overgrowth. Either objective or subjective reports may be useful. A significant history of antibiotic use may also be an indication of fungal propensity.

Recommendation: Consider anti-fungal interventions used for 1-2 weeks prior to introducing an elemental diet, and for the first week of the elemental diet.

Patient Adherence

As mentioned earlier, adherence is a common concern with the elemental diet. A few core areas of this are

- **Taste.** Always important, but even more-so in the case of a full elemental diet. Some practitioners encourage their staff to sample a variety of products as well, in order to better relate to the patient experience.

- **Cost.** Share the costs upfront to prevent sticker-shock. Elemental diet formulas are not inexpensive, but they do replace daily intake of food which offsets other costs they may have.

- **Communication.** Ensure the patient is well-informed about their condition, the pros and cons of your recommended protocol, and an understanding of their action plan.

An everyday action plan worksheet can be a useful tool for complex protocols to aid in adherence.

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Corey Schuler, RN, MS, LN, CNS, DC, DBM, FAAIM serves as the Director of Clinical Affairs for Integrative Therapeutics and is adjunct assistant professor at the School of Health Sciences and Education at New York Chiropractic College. He practices integrative and functional medicine in Greater Minneapolis-St. Paul, Minnesota. He is a member of Institute for Functional Medicine and American College of Nutrition. Corey is a registered nurse, licensed nutritionist, Certified Nutrition Specialist and earned a Master of Science degree in Human Nutrition from the University of Bridgeport, as well as degrees in chiropractic medicine, botanical medicine, and chemistry. He is a fellow of the American Association of Integrative Medicine. He routinely speaks to physicians and healthcare practitioners at scientific conferences and symposia.

KIRAN KRISHNAN

RESEARCH MICROBIOLOGIST

METABOLIC ENDOTOXEMIA
A Driving Force Behind Chronic Illness

Introduction

Metabolic endotoxemia is a condition that is estimated to affect approximately 33% of the western population. The conditions is characterized by increased serum endotoxin (typically lipopolysaccharide) concentration during the first five hours of the post-prandial period following consumption of a meal. Meals that are high in fat and dense in calories seem to impact the condition more so than low fat and low calorie meals. This increase in serum endotoxin concentration is followed by elevated inflammation that is marked by measurable increases in interleukin-6, interleukin-1-alpha, interferon-gamma, triglycerides and post-prandial insulin. Chronic metabolic endotoxemia and the associated inflammation has been shown to have significant correlation to increases in the risk of developing a variety of chronic diseases. To date, studies support a strong correlation between metabolic endotoxemia (ME) and the risk or onset of conditions such as cardiovascular disease, diabetes, obesity, hypogonadism, autoimmunity and even mood disorders such as anxiety and depression.

Causes and Pathophysiology of Metabolic Endotoxemia

ME is essentially an innate immune response that becomes a sub-clinical, persistent, low-grade inflammation because of increased, circulating endotoxins. The primary endotoxin of concern is lipopolysaccharide (LPS); LPS is a major component of the outer cell membrane of gram-negative bacteria. LPS contains 3 major components; a hydrophobic lipid section (lipid A), a hydrophilic core polysaccharide chain and a repeating hydrophilic side chain called the O-antigen. The Lipid A portion is responsible for the toxicity of LPS and the O-antigen is specific to specific bacterial serotypes. LPS endotoxemia was originally studied as high-dose endotoxemia in cases of sepsis and septic shock, this has allowed for the accumulation of a sizable body of information on the immune signaling pathways associated with LPS. It is important to note that a majority of the microbes in the digestive tract are gram negative bacteria, for example, clostridium sp., enterococcus sp., escherichia sp., and bacteroides sp. Trillions of commensal bacteria in the gastrointestinal tract contain LPS and as you will come to learn, they are the primary source of this toxin in chronic, low-dose endotoxemia and low-grade inflammation. Low-dose endotoxemia may be a more significant version of ME due to a suppressive mechanism that will be discussed in this chapter.

As previously mentioned, LPS endotoxemia is an innate immune response and this response begins with a ubiquitous signaling protein called toll-like receptor 4 (TLR4). TLR4 is an immune receptor that is part of a class of immune receptors called pattern-recognition receptors. TLR4 is a membrane-spanning receptor found on the surface of innate immune defense cells such as macrophages and dendritic cells. An important accessory protein to mention in this signaling pathway is CD14. CD14 exists in a complex with TLR4 and is responsible for recognizing patterns on both gram negative and gram positive bacteria cells. Circulating LPS first gets bound by a binding protein called LPS-binding protein or LBP. LBP is a lipid and a phospholipid transfer protein that carries the LPS to the CD14-TLR4 complex, which is found on innate immune cells in tissues all over the body. Once LPS has bound to the CD14-TLR4 complex, it initiates one of two immune pathways, both of which end up with the expression of NFKγ. The activation of NFKγsubsequently leads to the increased expression of pro-inflammatory mediators TNFγ, IL-1γ, IL-6 and MCP-1. As a defense against dangerous endotoxin exposure, the body has devised a mechanism to suppress the inflammatory response of endotoxins like LPS. This response is facilitated by the PI3K pathway which is a cellular compensatory, anti-inflammatory response that is mediated through MKP-1 and CREB, both of which are cellular transcription factors. What makes the low-dose, chronic LPS endotoxemia more dangerous

is that it has been shown to suppress this PI3K anti-inflammatory, protective mechanism. Although the low-dose, chronic LPS is not as potent at inducing the inflammatory response, it seems to play a significant role in suppressing the suppression mechanisms designed to minimize damage to tissue from endotoxemia. For this reason, the low-dose ME, could be the more dangerous version of this condition.

We now understand that circulating LPS can trigger a potent inflammatory cascade via the innate immune system and TLR4 activation. We know that the innate immune activation and subsequent inflammation can occur anywhere in the body and even at sites very distal to the intestines, such as the blood brain barrier. We also know that chronic, low-dose endotoxins can suppress the cellular anti-inflammatory protective mechanisms and thus lead to more damaging consequences compared to high-dose LPS endotoxemia. These pathological consequences are a result of LPS from the intestinal tract entering the circulatory system. This means that the LPS had to pass through the mucosa and the intestinal barrier (intestinal epithelium cells) to enter the basolateral space, where it gains access to our circulatory system. The logical question here is what causes LPS to "leak" from the intestinal lumen into the circulatory system? With high-dose ME, the cause is typically a systemic bacterial infection. However, there are 6 lifestyle choices that have been linked to low-dose, chronic ME and they are:

- Chronic alcohol consumption
- Diet induced low microbial diversity in the microbiome
- Chronic smoking
- Obesity and high fat diet
- Periodontal disease
- Aging

y *Chronic Alcohol Consumption* – Alcohol abuse is known to lead to cardiomyopathy, liver disease and even brain injury, but the mechanisms behind the causation if often not well understood by clinicians. Research is showing the conditions are driven by increased levels of circulating endotoxins in people that abuse alcohol. Although it is not clearly understood how alcohol abuse leads to elevated circulating endotoxins, recent studies have pointed towards the possible disruption of the intestinal microflora by alcohol. Studies have also shown that chronic alcohol feeding has been shown to increase the permeability of the intestinal lining to larger molecular weight molecules. The intestinal epithelium (the barrier) ends up with increased permeability due to altered controls of the paracellular pathway. With a more "open" intestinal epithelium, LPS from the lumen is allowed to pass through into the basolateral space more readily. Some studies have also been able to demonstrate a direct dose dependency on this phenomenon, the degree of alcohol consumption is directly correlated to the amount of circulating endotoxin. This direct correlation has been shown to be independent of any disease manifestation. To further support the relationship between alcohol consumption and free, circulating endotoxins, studies have shown that halting alcohol consumption leads to an decrease in circulating endotoxin levels.

y Diet Induced Low Microbial Diversity in the Microbiome – Numerous studies on the human microbiome have concluded that a diverse microbiome is more protective to the host and thus favors better health outcomes. A study comparing subjects who suffer from chronic rhinosinusitis vs. those that do not suffer from chronic rhinosinusitis revealed that the sufferers simply had lower microbial diversity in their sinus and nasal cavities. A review paper by Lloyd-Price, et al (2016) concluded that a relative lack of microbial diversity was clear and apparent in the microbiomes of individuals suffering from diseases such as obesity, inflammatory bowel disease, type 1 diabetes, type 2 diabetes and even skin disorders like atopic dermatitis and psoriasis. Low diversity is also associated with increased circulating endotoxin and increased intestinal permeability. A diverse microbiome

seems to play a role in protecting the gut from increased permeability. Although the mechanisms are not yet well understood, it is hypothesized that a diverse microbiome increases protective secretory IgA, improves the barrier function of the mucosa and likely stimulates the expression on tight-junction proteins, which help close up the paracellular pathways. The average western diet is very low in macronutrient diversity, thus the food sources do not favor a diverse microbiome. Early humans consumed as many as 600 different types of foods each year, at best a "healthy" individual on an standard American diet consumes 8-10 different types of foods.

y *Chronic Smoking* – The hazards of smoking are well known and are typically associated with exposure to carcinogens. However, what is less known is that smoking directly exposes the individual to harmful bacteria and high levels of endotoxins. With the use of DNA/RNA sequencing techniques, researchers have been able to detect and characterize the presence of a wide number of bacterial species on tobacco. Some of these organisms are pathogens that cause pneumonia and food poisoning. High levels of endotoxins are also detected on unburnt tobacco and in cigarette smoke. A single smoked cigarette contains 75-120 ng of active LPS and indoor smoking has been shown to increase the concentration of airborne endotoxins by nearly 120x. The increased presence of LPS in the lungs of smokers leads to chronic immune activation in pulmonary endothelial cells, this compromises the integrity of the endothelial barrier and leads to persistent inflammation. The persistent inflammation dramatically increases the risk of tumor development and leads to tissue damage.

y *Obesity and High Fat Diets* – A diet rich in fat, especially saturated fats, will increase free fatty acids in the circulation and will shift the microbial population to contain higher levels of gram-negative bacterium. As mentioned before, LPS is a component of the bacterial cell membrane structures in gram-negative bacteria, thus this shift in population can increase circulating LPS by 2-3 fold. The increase in circulating LPS is also due to disruptions in the tight-junctions that control the epithelial paracellular pathways and increased chylomicron-facilitated transport of LPS. Fats stimulate the release of chylomicrons and studies have demonstrated that LPS is effectively transported across the epithelial lining by chylomicrons. A clear relationship between high fat intake with increased LPS and inflammation was demonstrated in a study on CD14 knockout mice. A knockout of CD14 on mice reversed the increase in pro-inflammatory markers seen with a high fat diet. Another relationship between dietary saturated fat and LPS becomes clear when you examine the molecular structure of LPS. LPS contains a Lipid A portion which confers the toxicity of the compound, this Lipid A portion is produced from saturated fats. This may be the reason that saturated fats seem to increase LPS more than other fats.

y *Periodontal Disease* – Periodontal disease is associated with the risk of developing diabetes, arthritis and atherosclerosis. Understanding this strong association, it becomes apparent that LPS may have a connection with periodontal disease. In periodontal disease, gram-negative bacteria colonize the oral cavity and typically form biofilms, which makes them impervious to antiseptics and mechanical removal. These oral colonizing organisms have direct access to the circulatory system through minor abrasions in the oral cavity from daily activities like eating. Studies have shown that subjects with periodontal disease have elevated serum levels of LPS. The persistence of periodontal disease and the easy access to the circulation means that people with the condition can constantly be shedding the gram-negative bacteria into the circulatory system.

y *Aging* – Immune dysregulation, immunosenescence, is a hallmark of aging. This condition results in the increased risk of developing inflammation related conditions such as cardiovascular disease, neurological disorders and infections. This immune dysregulation is marked by 2-4 fold increases in circulating inflammatory mediators such as TNF-alpha, IL-6 and C-reactive protein. You will recall that these are the same markers associated with elevated LPS in the serum. With aging related immune dysfunction, macrophages and neutrophils are particular-

ly compromised and display weaker ability to respond to chemotactic signals and decreased expression of TLR. In addition to the documented increase in inflammatory markers, several studies have also shown a significant elevation in circulating endotoxins among the elderly. Considering the elevation of TNF-alpha, IL-6 and CRP with the documented increase in LPS, metabolic endotoxemia is clearly associated with aging and likely cause of the increased disease risk. It has also been documented that as an individual ages, the diversity of their microbiome decreases, this decrease could be a factor in the increased metabolic endotoxemia.

Disease Consequences of Low-Dose, Chronic Endotoxemia

Numerous conditions are known to be associated with metabolic endotoxemia, some are well studied are others are just now being elucidated. This review will focus on the 3 most well understood conditions associated with ME and will list the other conditions, with mechanisms in Table 1. The 3 most well studied conditions associated with ME are atherosclerosis, diabetes and obesity.

- *Atherosclerosis* – The vascular endothelial influences vessel tone, vessel permeability and manages coagulation status. It has been clearly established that dysfunction in the endothelial is the first step to developing atherosclerosis. A variety of conditions have been shown to create this dysfunction, i.e. infection, free-radical damage, oxidized LDL, hypertension, diabetes and chronic inflammation. In the case of chronic inflammation, the nitric oxide system of the endothelium is disrupted, where endothelium cells lose the ability to secrete nitric oxide, which is important for its anti-thrombotic and anti-inflammatory functions. This loss of ability to secrete nitric oxide leads to the expression of endothelin-1 (Et-1) and also encourages leukocyte adhesion. Et-1 is a vasoconstrictor and has been shown to have increased expression in atherosclerotic plaques. Chronic inflammation from ME also leads to the expression of intracellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1), both of these compounds enhance the adhesion of monocytes and T cells to the endothelium. Once these immune cells attach, they migrate to the intima of the vessel due to the expression of a powerful chemokine called MCP-1. Once in the intima, macrophages take up a pro-inflammatory confirmation and convert into foam cells. These foam cells lead to a gradual accumulation of lipids in the intima. This accumulation leads to classical endothelium dysfunction, then apoptosis and necrosis, which becomes the core of a atherosclerotic plaque. This lethal progression that starts with inflammation and leads to a monolayer of activated foam cells as well as activated T cells is called the "fatty streak". With a strong understanding of the mechanism by which ME can lead to plaque formation, the larger cohort studies on circulating endotoxin level and cardiovascular risk really begin to make sense. A large Italian cohort study found that subjects with circulating endotoxin levels of 50pg/ml had a 3-fold greater risk of cardiovascular disease than those with concentrations below 50pg/ml of LPS. A further study revealed that increased circulating endotoxin levels among different ethnic groups correlated strongly with differences in risk for the development of cardiovascular disease. A more revealing connection between ME and atherosclerosis is the fact that several studies have demonstrated that TLR4 up-regulation can be caused by abnormal blood flow in the endothelium which leads to mechanical stress. Interestingly, not all endothelia cells express TLR4 from mechanical stress, the ones that do are found in the aortic trunk and arch, which are the more common sites for atherosclerotic plaque formation. Subsequent studies have shown that even healthy endothelium cells will express TLR4 when LPS concentrations are at 100pg/ml or higher. The expression of TLR4 in this case is followed by increased expression of MCP-1, which leads to the "fatty streaks" described above.

The fatty streak develops into an atherosclerotic plaque when the adhered T cells begin to secrete TGFγ growth factors and fibrogenic mediators that lead to migration and proliferation of smooth muscle cells into the area. A thick extracellular matrix develops as well. This process continues with further chemokine secretion and further

migration of smooth muscle cells. An abundance of fibrous tissue develops over the growing core of apoptotic macrophages, toped with the thick extracellular matrix, referred to as the "cap". The cells responsible for forming the plaque are also the initiators of plaque rupture. The macrophages at the core continue to secrete inflammatory mediators which include matrix metalloproteinases (MMPs) which are responsible for degrading the extracellular matrix (the cap), which can lead to the rupture of the plaque. Further inflammation in the area is mediated by Th1 cells which secrete IFNγ which causes a decrease in collagen formation, this weakens the matrix that holds the plaque together and can lead to rupture. Thus, chronic inflammation from circulating LPS causes the formation of the plaque and the same chronic inflammation increases the risk for the rupture of the plaque, an event that leads to severe morbidity or mortality.

- *Diabetes and Insulin Resistance* – A significant number of studies have clarified the role of the inflammatory state, elevated plasma endotoxin (as in ME) and risk for to type II diabetes. In particular, pro-inflammatory cytokines interleukin 1 beta (IL-1β), IL-6 and TNFα which happen to be the key cytokines that are chronically elevated in ME. Insulin is a multifunctional hormone produced by pancreatic β-cells. Insulin decreases liver glycogenolysis, decreases gluconeogenesis, decreases lipolysis, promotes the breakdown of VLDL to free fatty acids and promotes glucose transport to tissues in need of it. Insulin functions by binding to insulin receptors and causing the activation of insulin receptor substrates (IRS). Studies have demonstrated that low-grade chronic inflammation due to ME and the subsequent activation of pathways downstream of TLR4 activation, disrupts insulin function through inactivation of the IRS. It's important to note that type II diabetes does not develop with obesity if TLR4 is inhibited, emphasizing the importance of the downstream components of TLR4 in the development of glucose intolerance and diabetes.

- *Obesity* – Obesity is a self-perpetuating problem as it is well understood that obesity increases chronic, low-grade inflammation, however, recent evidence has suggested that chronic low-grade inflammation can be causal in the development of obesity. Thus, once obesity develops, it becomes an increasing source of inflammation. The continued propagation of inflammation by adipocytes is likely the link between obesity and type II diabetes. In activated adipose tissue composed of macrophages, necrotic adipocytes and some extra-cellular fat droplets, TNFα secreted by the macrophages causes the release of MCP-1 in the adipocyte. As previously shown, MCP-1 is a powerful chemokine that recruits further innate immune cells and inflammatory mediators to the region. Additionally, free fatty acid accumulation in the liver, which occurs in obesity, causes hepatocytes to release the pro-inflammatory mediators IL-1β, IL-6 and TNFα which leads to systemic inflammation and an exacerbation of the condition. Which comes first? Does the chronic inflammation result from obesity or does it cause obesity? To answer this question, Patrice D. Cani et al (2007) conducted a series of experiments with high fat feeding in normal weight mice to induce ME. She found that high fat feeding made significant changes to the gut microbiome, in favour of an obese profile, where bacterium in the genus bifidobacterium and bacteriodes saw drastic reduction. These organisms are associated with a more lean body mass and their loss could begin the process of obesity. Furthermore, Patrice D. Cani et al studied chronic, experimental ME by administering LPS and found that administered LPS with a normal diet produced the same weight gain and metabolic syndrome results as chronic high fat diet. This study suggests that the elevated LPS is the driving force behind the weight gain. Once weight is gained, adipocytes perpetuate the low-grade inflammation and a vicious cycle begins.

There are several other conditions associated with elevated serum LPS (ME) that have good scientific support. These conditions are listed in Table 1 below.

Table 1: Conditions Associated with Increased Serum LPS – Metabolic Endotoxemia

CONDITION	MECHANISM
Leptin Resistance	LPS enters and causes inflammation in the enteric nervous system leading to a disruption in the gut-brain axis of communication.
Chronic Constipation	LPS enters the enteric nervous system and causes disruption in signals for gastric emptying and bowel motility.
Mood and Appetite Disorders	LPS disrupts ghrelin function which has a direct impact on appetite and mood,
Depression	LPS can migrate to the blood-brain barrier and cause inflammation along with inhibition of dopamine receptors.
Cognitive Decline	Inflammation in the blood brain barrier leads to cognitive decline
Loss of Memory and Recall	LPS can get into the amygdala and hippocampus which disrupts memory function
Depression	LPS can increase the turnover of serotonin in the synapse and CNS reducing the concentration in those regions
Anorexia	The reduction of serotonin in the synapse and CNS is proposed as a possible mechanism for anorexia.
Anxiety	LPS disrupts key communication between the hypothalamic-adrenal-pituitary axis thereby increasing the expression of corticosteroid releasing hormone
Chronic Pain	Elevated LPS in sensory neurons in the dorsal root stimulate nociceptors.
Parkinson's	Intra-cranially LPS causes microglial activation and neuronal loss
Hypogonadism (low testosterone)	Increased circulating LPS and the subsequent chronic immune activation has feedback inhibition of testosterone production. GELDING theory.
Autoimmunity	Chronic activation of the innate immune system in various tissues leads to the by-stander effect where self-tissues inadvertently become targeted by the immune system.

Metabolic endotoxemia could very well be the primary driver of most chronic illnesses plaguing the western world. The causes of ME do not seem to be genetic or congenital, but rather due to lifestyle choices. The promise here is that there is significant opportunity to change health outcomes for millions of patients by making different lifestyle choices. A 2015 published review paper in Frontiers of Immunology, Karin de Punder et al (2015) concluded the following;

"In combination with modern life-style factors, the increase in bacteria/bacterial toxin translocation arising from a more permeable intestinal wall causes a low-grade inflammatory state. We support this hypothesis with numerous studies finding associations with non-communicable diseases and markers of endotoxemia, suggesting that this process plays a pivotal and perhaps even a causal role in the development of low-grade inflammation and its related diseases."

They further went on to conclude;

"Chronic non-communicable diseases (NCDs) are the leading causes of work absence, disability, and mortality worldwide. Most of these diseases are associated with low-grade inflammation."

This paper perfectly summarizes the impact of metabolic endotoxemia on our communities and the health of the general public. It is becoming increasingly clear that ME has to be addressed in order to attain better prognosis of most chronic illnesses.)

Solutions for Metabolic Endotoxemia

There are some basic lifestyle choices that will help reduce the risk and incidence of ME. Minimizing alcohol consumption, cessation of smoking, expanding the diversity of dietary macronutrients and reducing fat intake can all have a drastic impact on ME. All of the listed behaviors have been closely correlated to increased circulating LPS.

In addition to the above lifestyle modifications, there are some interventional targets that could help with decreasing ME, the following are the most promising interventions to date:

1) Increasing Secretory IgA – Secretory immunoglobulin A is the first line of defense against free LPS liberated in the lumen of the intestines. This liberated LPS will eventually make its way through the mucosa and the paracellular pathways in the intestinal epithelium thereby causing ME. sIgA has the capability to bind and neutralize LPS in the lumen and mucosa itself. Many of the conditions associated with ME are also associated with low production of sIgA. Thus, increasing sIgA production could have a meaningful impact on ME. Nutrients that have been shown to have a positive impact on the production and secretion of IgA are omega essential fatty acids, glutathione, glycine, glutamine, phosphatidylcholine, vitamin C, zinc and colostrum.

2) Increasing Mucin Production – The mucosa is a key barrier to the entry of luminal LPS into the basolateral layer. When the mucosa suffers from inadequate production of mucin, inadequate viscosity, it fails to perform its barrier function and thus allows for the migration of LPS. Increasing mucin production can be a benefit to restrict the movement of LPS towards the intestinal epithelial. Nutrients that have been shown to support increased mucin production are L-threonine, L-serine, L-proline, and L-cysteine.

3) Modulating the Microbiome – Probiotics hold great promise to modulation the microbiome and confer protection in conditions like ME. It is clear that dysbiosis drives ME, thus, a healthy microbiome has the capability to protect the body from ME. The major issue with most probiotics is that they do not survive gastric passage to enter the small or large intestines intact and viable. There are however probiotic spores that have the capability to survive the harsh gastric passage and enter the intestines completely viable. To date, bacterial spores are the only strains that have been shown to treat metabolic endotoxemia. The following is a description of a study conducted on bacterial spores and metabolic endotoxemia.

Probiotic spores in the product MegaSporeBiotic® were the subject of a University, double-blind, placebo controlled trial to evaluate the ability of the product to reduce or prevent metabolic endotoxemia induced by dietary challenge. In addition to assessing changes in dietary endotoxemia, the researchers also measured how this probiotic altered transient changes in cardiovascular disease (CVD) risk factors, other novel disease risk biomarkers, and the immune system itself following a high-fat challenge meal.

Healthy volunteers were screened for the metabolic endotoxemia response to the challenge meal. If they showed the response, they were enrolled into the study and randomized into either the placebo group or treatment group. They consumed the placebo or treatment product for 30 days, with no other interventions or dietary/lifestyle changes. After the 30 days, they reported back to the lab for their "post-treatment" response and were given the challenge meal again. All the same blood work was run to access their levels of endotoxemia. The data shows a clear change to a protective microbiome with just 30 days of supplementation of the spores. The post-test challenge on all subjects showed a drastic and significant reduction in endotoxemia whereas in the placebo group there was no change or the toxic response increased. This is likely the most promising therapy for metabolic endotoxemia as no other probiotics or compounds have demonstrated this effect.

The following are data tables and graphs from the study:

The effect of 30-days of probiotic supplementation on post-prandial responses to a high-fat meal: An Expanded Pilot Study

Principal Investigator: Brian K. McFarlin, PhD, FACSM, FTOS University of North Texas

Figure 2: Baseline and 30 days of Megasporebiotic on serum LPS response to a challenge meal

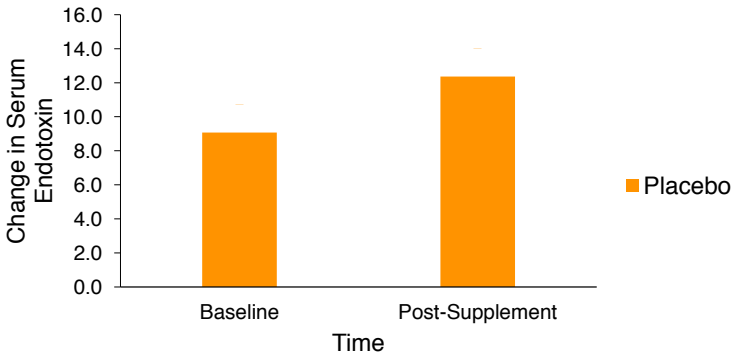
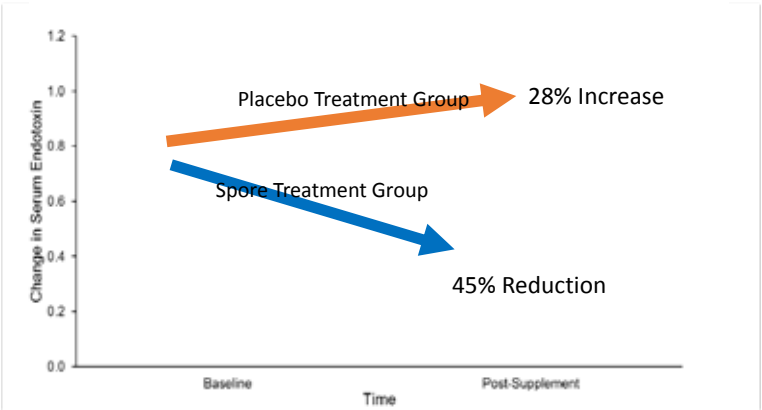
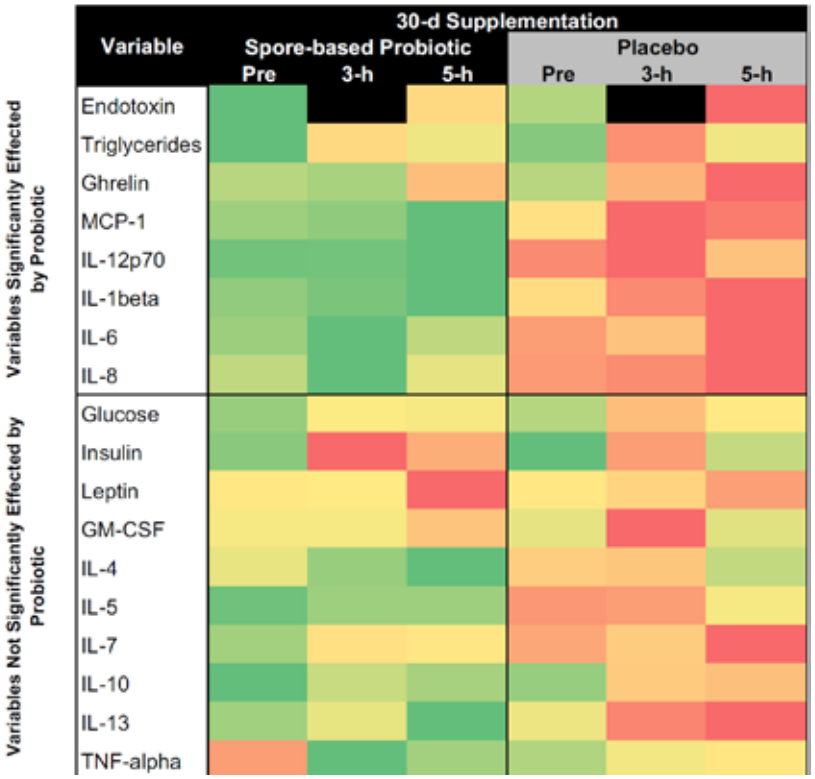


Figure 3: Comparison of Baseline and 30 days of placebo vs Megasporebiotic on serum LPS response to a challenge meal





Collectively, the findings of the present study demonstrate a significant blunting of metabolic endotoxemia, triglycerides, and systemic inflammatory markers IL-6, IL-8, MCP-1, IL-1yand IL-12 following a 30-d period of probiotic supplementation. To our knowledge, the present study is the first to report that a short-term probiotic intervention altered dietary endotoxemia in human subjects,

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Kiran Krishnan is a Research Microbiologist and has been involved in the dietary supplement and nutrition market for the past 17 years. He comes from a strict research background having spent several years with hands-on R&D in the fields of molecular medicine and microbiology at the University of Iowa. He left University research to take a position as the U.S. Business Development and Product Development lead for Amano Enzyme, USA. Amano is one of the world's largest suppliers of therapeutic enzymes used in the dietary supplement and pharmaceutical industries in North America. Kiran also established a Clinical Research Organization where he designed and conducted dozens of human clinical trials in human nutrition. Kiran is also a co-founder and partner in Nu Science Trading, LLC.; a nutritional technology development, research and marketing company in the U.S. Dietary Supplement and Medical Food markets. Most recently, Kiran is acting as the Chief Scientific Officer at Physician's Exclusive, LLC. and Microbiome Labs. He has developed over 50 private label nutritional products for small to large brands in the global market. He is a frequent lecturer on the Human Microbiome at Medical and Nutrition Conferences. He conducts the popular monthly Microbiome Series Webinars through the Rebel Health Tribe Group practitioner training program, is an expert guest on National Radio and Satellite radio and has been a guest speaker on several Health Summits as a microbiome expert. He is currently involved in 7 novel human clinical trials on probiotics and the human microbiome. Kiran is also on the Scientific Advisory Board for 3 other companies in the industry. Kiran offers his extensive knowledge and practical application of the latest science on the human microbiome as it relates to health and wellness.

SUSAN BLUM
M.D. MPH

Healing the Gut to Repair Immune System

You've probably heard and even used the expression to "trust your gut" or said that you had a "gut feeling," "gut instinct," or "gut reaction" to or about a situation in your life. These expressions refer to an instinctive feeling or intuition that you have deep within your core. In the world of medicine, "gut" is a slang term that includes your whole digestive tract, including your stomach, small intestine, and large intestine. The gut is literally at the center of your body and it plays a central role in your health, just as your "gut feeling" plays a central role in your instinct. But before I go into detail about the gut and its impact on your health, let me first explain its crucial link to your immune system.

What's Gut Got To Do With It?

Every day, you expose your body to things that may cause infections or illness such as viruses, bacteria, mold, parasites, and foreign proteins in food. These outside agents are typically brought into the body through your mouth and nose. As your first line of defense, the immune system in your gut is faced with the task of clearing out the bad agents, while keeping what your body requires to stay nourished and healthy. It also has the job of repairing any damage caused by these foreign substances and any reactions they've caused in your body, such as inflammation or infection.

To carry out these important tasks, the immune system is divided into two systems. Each one plays a role in protecting you from the invaders that come into your body every day. The first is called the innate immune system, which is the front line of defense. These cells are always alert and ready for action and need no priming or prep time. Antigen presenting cells are one type of cell from the front line and here's how these cells get their name: an antigen is a substance, like a bad bacteria, yeast, parasite, or virus, that is recognized as foreign when it meets up with these cells. To simplify, I often call the bad bacteria, yeasts, parasites, and viruses "invaders" or "foreigners." An important type of antigen presenting cell that makes its home in your gut are the dendritic cells and they live right under the surface of your intestinal lining in large numbers. There, they lie in wait, their cell surface filled with receptors like antennae, ready to touch and then react to any foreigners that come their way. If the dendritic cells touch something they see as foreign, their job is to spread the word to the cells that make up your immune system's second line of defense. As you can see, the two important roles of your immune system's front line of defense are first to recognize what is foreign, and then to sound an alarm by telling other cells in the immune system to react.

The group of cells that make the second line of defense is formally known as the adaptive immune system, because they are cells that adapt to the alarm that's been sounded. In the gut, the dendritic cells sound the alarm and activate your immune cells (more formally known as lymphocytes), which include your T cells and B cells. Both groups of immune cells live within and underneath the lining of your intestines. The dendritic cells respond immediately and then it takes a bit of time, anywhere from hours to days, for the lymphocytes to mobilize to either make more killers cells or to make antibodies to attack the foreigner.

When this process goes smoothly, there are signals and messages sent between the dendritic cells and T cells that keep the immune system in balance. T regulator cells help turn the alarm off when the immune system's job is done. For example, let's say that there was salmonella, a type of bacteria, in something you ate for dinner last night. If things are working correctly, your dendritic cells recognize the salmonella as foreign, and sound an alarm to the T cells and B cells, which then attack the bacteria and clear it out of your system. But if the T regulator cells are not working correctly the killer cells and/or antibody producing cells can get stuck in overdrive and become confused about what is foreign and what is not. This confusion can then cause autoimmune diseases. All of the steps in this book are aimed at balancing your killer cells and your antibody producing cells, and to do so we must focus on fixing your T regulator cell function.

So now you can see that your digestive system has a lot of influence on your immune system. **(In fact, seventy-percent of your immune system actually lives in your gut.)** Yes, you read that correctly! Seventy percent. It sounds surprising at first, but actually makes sense if you think about it. After all, you bring the outside world into your body through your mouth every day so your front line of defense needs to be in your gut. Because so much of your immune system is in your gut, it's critical to keep your gastrointestinal system healthy and in balance. It is also one reason why in Functional Medicine, we look at the gut first when it comes to any chronic disease. These

immune cells release many, many inflammatory molecules when they are activated, traveling around the body and causing inflammation in your joints, hands, blood vessels, brain, you name it! Since there is always inflammation at the root of all chronic disease, the gut is the place to start.

START BOX

The immune system within your gastrointestinal system is called the gut-associated lymphoid tissue, or GALT for short, and this is one of the places in your body where new immune cells are constantly growing and maturing. A lot of research is now focused on understanding what influences the maturation of T cells in the GALT because abnormal balances in these cells is an underlying problem in all autoimmune diseases. (1)

END BOX

The Role Of Intestinal Bacteria

The good bacteria that live in your intestines have the most important influence on the function of the T cells that are located there. Besides immune cells, the gut is also home to an estimated 70 to 100 trillion beneficial bacteria of various species. Though the word "bacteria" typically has a negative connotation, flora are a natural part of us and are critical for so many of your body's functions. You may recognize the names of some of these good bacteria, like lactobacillus acidophilus and bifido bacteria, because they're some of the most popular and in recent years their presence in certain things like yogurts and probiotic supplements has been highly marketed. Experts are conducting ongoing research to understand the differences between the various species of these beneficial bacteria and the importance of each one. But for the purposes of this book, we'll discuss the good bacteria in general (rather than differentiating between the various kinds) and detail the health benefits they offer, especially when it comes to the development and maintenance of your immune system.

As I have mentioned, there is an epidemic of autoimmune diseases today. (It is believed that imbalances in gut flora are a big part of the problem, causing both autoimmunity and making your symptoms and antibodies worse if you already have a diagnosed autoimmune disease.(2,3,4,5) How does the gut flora get out of balance? One theory is called the hygiene hypothesis and it suggests that we have been so focused on fighting germs –with things like antibiotics and antibacterial wipes, cleansers, hand sanitizers, and more – that we've sterilized our environments too much.(6) Many children today live in concrete jungles instead of being surrounded by dirt, trees, and grass the way most children were generations ago. As a result, they are not exposed to the bacteria, parasites, and molds that naturally exist when children play outside all day, every day. Because of this city living and our culture's obsession with banishing germs, our children live in worlds that are too clean and without enough germs to fight, their immune systems don't develop properly. After all, it is exposure to germs when you are young that helps teach your immune cells what is bad and what is not. Then when you get older, your immune system remembers and recognizes the dangerous germs and reacts against them. Exposure to germs also brings in many good bacteria and the gut immune system has to learn how to live with these trillions of bacteria and not attack them. Learning the difference between good and bad bacteria is called tolerance and this tolerance is something that develops in your body when you are very young. Tolerance is very, very important because without it your immune cells get confused and begin to overreact and attack your own good flora and your tissues, which is exactly what happens in autoimmune diseases.

When you are born, your body is sterile, meaning your skin, lungs, and intestines don't contain any bacteria at all. When you pass through your mother's birth canal, you are exposed to bacteria in the outside world and your gut begins a harmonious and beneficial relationship with over 1000 strains of good bacteria. The point is that when you are born, you need to be exposed to the many bacteria that will later live within you. In fact, the hygiene hypothesis has recently been renamed the Old Friends Hypothesis, with the "old friends" being the good intestinal bacteria, and suggests that many people have lost these "old friends" who have always lived within us humans. Some people joke that the answer to the hygiene hypothesis is that our children need to eat dirt, but that is not the way to expose them to the old friends that are beneficial. Instead, the most widely used approach is to re-balance the gut with herbs and probiotics (also called healthy flora supplements), which we will do in the next chapter, Healing Your Gut Workbook, but first it is important to understand what's going on in your gut and why the bacteria that live there, or should be living there, are so crucial for a strong immune system and robust health in general.

For a healthy immune system, your body is dependent on a good relationship with the beneficial bacteria that live in your digestive tract. Although there is much evidence that other things trigger autoimmune diseases, and I discuss these things like toxins, stress, infections and food elsewhere in this book, the epidemic rise in autoimmune diseases in the last few decades suggests that there is something inside our bodies that has changed. One of these recent changes is the balance of good bacteria. Whether you have had an imbalance of good bacteria since childhood, or whether it happened later in your life from things like taking too many antibiotics and antacids, drinking too much alcohol, or experiencing too much stress, we need to focus on what we can do now, today, to bring your gut back into balance. A huge part of this healing includes making sure you have enough beneficial bacteria. But first let's talk about what these good bacteria are actually doing inside of you.

Healthy Flora and The Immune System

There is a lot of research looking at the bacteria that live in the gut and how they grow, develop, and help our immune systems function properly. As I mentioned before, it appears that gut flora play a huge role in early infancy in helping your immune cells develop properly and in the right balance. Beneficial bacteria also seem to help the immune system learn the difference between something like your own tissue that is a natural part of you (which I also refer to as "self") and a foreign substance (which is also called "not self"). Thus, the immune cells develop tolerance to these bacteria rather than try to kill them.

Good bacteria are key players in the relationship between your immune system cells in both the first line of defense and the second. Changes in your good bacteria can have a significant influence on your body's T helper cells that, as we discussed in Understanding the Stress Connection, help accelerate your immune system's response to a foreigner. I describe these T helper cells as the gas in a car because they help turn on your body's immune response. However, these cells can get stuck in overdrive, keeping your immune response going on and on without stopping. Sometimes they get stuck making more killer cells (which is called Th1 dominance). Sometimes they get stuck making more B cells and antibodies (which is called Th2 dominance). Good bacteria help unstick the gas peddle, and help the breaks (the T regulator cells) work better. Ideally, we want the gas and brakes to be working in balance.

Beneficial bacteria also stimulate the production of a protective antibody that's one of the main defenses in your gut. It's called immunoglobulin A, a compound made by the immune system to fight off foreign substances. (This compound is so important that one way to tell if your gut immune system is working properly is to have the levels of this antibody measured in your blood, stool, and saliva.)

Good bacteria make something called short chain fatty acids, which feed and strengthen all the cells that line your digestive tract, keeping them healthy. They also help form the protective barrier (also called your intestinal lining) that helps keep the outside world in your intestines and not in the rest of your body when you eat. And creating this barrier is no small task considering that the surface area of your intestines, when if opened up and spread out, would be greater than that of a tennis court. These good bacteria interact with your immune cells to directly protect you from harmful infections and maintain the function of that barrier so that unwanted foreign proteins and infectious agents can't seep into the blood stream. If this barrier is compromised, you can develop what is called leaky gut syndrome, a condition that can lead to autoimmune diseases. (But more on that later in this chapter.)

We are constantly exposed to toxins like cleaning products, pesticides, and additives in the food we eat and the air we breathe. Our good bacteria help us begin the process of metabolizing these toxins, which means changing their form to make them less harmful. They also make enzymes that improve digestion. In particular, they help the body break down gluten, a protein found in wheat, barley, spelt, and kamut. As we discussed in Chapter 2 Using Food As Medicine, gluten is a very toxic protein that often causes an allergic reaction or other immune response and is a big problem for people with autoimmune diseases. Properly digesting and breaking down this gluten protein decreases the chance that your immune system will react when you eat it. **(It is entirely possible that impaired digestion and a leaky gut due to a lack of beneficial gut flora is the reason why some people develop gluten issues in the first place.)** Lastly, good bacteria also help the body process vitamins such as B12 and K so they can be better utilized and absorbed by the body. **(The bottom line: Having enough friendly flora in your gut reduces the incidence of allergies and autoimmune diseases)** and restoring and balancing these flora in the gut can treat and reverse these conditions as well. (Something else we'll discuss later in this chapter.).

START BOX

So what does it feel like when you don't have enough good bacteria in your gut? You can have:

- constipation
- diarrhea
- gas
- bloating after eating
- abdominal cramping or discomfort
- upper stomach problems like reflux and indigestion.

Fixing the bacteria imbalance is critical not only to alleviate all these gut symptoms, but also for you to heal your immune system, and we will do that in the next chapter, Healing Your Gut Workbook.

END BOX

Belly Out Of Balance

Before we move on to healing your gut, let's look at all the things that can go wrong in the gut that harm your immune system. We will start at the top with your stomach.

Your Digestive Power

I like to describe the entire digestive tract as a river. The stomach is at the top of that river and has a major influence on what the balance of good bacteria, and thus your immune health, will be downstream. The contents of the stomach empty into the small intestine, which flows into the large intestine and then out of the body. As the river flows, the stomach secretes acid and the enzyme pepsin, which begins the digestion of protein. It also secretes messengers that tell the pancreas and gall bladder to release enzymes and bile to help the digestion process even further. Without adequate amounts of these acids and enzymes, food doesn't break down properly so it sits in your stomach, refusing to leave. This poor digestion can cause reflux or heartburn.

The Importance of Acid

Speaking of heartburn, another important part of your stomach is the acid it contains. If you think back to high school chemistry, you may remember that pH is a measure of how acidic or alkaline something is. There is a pH scale that goes from 0.0 to 14.0. Anything less than 7.0 is acidic, anything more than 7.0 is alkaline, and 7.0 is neutral. Many people take antacids to reduce the acid in their stomachs, yet the pH of your stomach needs to be 1.5, an acid pH, for several important reasons. First, a pH of 1.5 kills any viruses and bacteria that you might ingest and prevents unwanted infections from coming into your body and stressing your immune system. (Think of it as your own personal food sterilizer!) An acid pH also helps the food in your stomach digest quickly and move forward, instead of refluxing backward into your throat. Good bacteria are very tolerant to acid, while unfriendly flora and yeast are not, and so an acid pH will help the bacterial balance in your small intestine, which is downstream from your stomach, stay in favor of good bacteria.

The right pH is also necessary for the digestion and absorption of many vitamins and minerals, which is key because certain vitamin deficiencies can cause an array of health problems. For example, a B12 deficiency can harm your ability to make red blood cells, which you need to bring oxygen to tissues throughout your body. This is a condition called anemia where you tend to feel very tired as a result. Calcium and magnesium deficiencies can contribute to osteoporosis, a disease where your bones become very porous and at risk for fracturing. In fact, many studies link antacids to an increase in fractures believed to be caused by the poor absorption of minerals like calcium and magnesium in an alkaline pH. The absorption of other minerals like zinc, which is a key player in the immune system, is also affected. Low stomach acid can really impair your digestion of protein, which provides the body with amino acids that are critical for the creation of new tissue especially immune cells. To have

enough amino acids for a healthy immune system, you need to be eating enough protein. But you also need to digest protein properly so it can be absorbed; stomach acid helps activate your digestive enzymes so this can happen. After leaving the stomach, the food you eat moves into the upper part of the small intestine called the duodenum. This area is where the enzymes from your pancreas and the bile from your gall bladder meet up with the food to further digest proteins, carbohydrates, and fats. These enzymes need a low pH to work well. If your stomach acid or digestive enzymes aren't doing their best, they don't finish their job and partially digested foods make their way further down into the intestines. These particles traveling where they don't belong adds to the problem of leaky gut syndrome (an issue we'll discuss shortly) and increases the risk of food sensitivities and autoimmune reactions, in fact studies have shown people who take antacids and proton pump inhibitors have an increased risk of developing food sensitivities.

(Now you can see why antacids, which many people think help their stomachs actually do the opposite and harm your immune system.(7)) So if you regularly pop them, we need to get you off of them. But don't worry. You don't have to choose between having heartburn and your stomach having the right pH. There are other ways to treat heartburn.

What's commonly known as heartburn is caused by a stomach lining (which is called the mucosa) that has worn away, making it raw and sensitive to the amount of acid that should be in your stomach. As we discussed, this acidic environment is normal; it's the worn stomach lining that is not. Many things can cause this lining to wear away, including stress, alcohol, a stomach bacteria that causes infections called H.pylori, aspirin, and medications. Once the lining is damaged, you feel the acid that is normal to have in your stomach, but which you wouldn't feel if your lining were strong, thick and healthy. Because acid is so important, the answer is not to kill it. The answer is to heal the lining, something we will do in the next chapter, the Healing Your Gut Workbook.

Surprisingly, many people with reflux or heartburn actually have too little stomach acid, a condition called hypochlorhydria. Acid is made in special cells in your stomach called parietal cells. If your stomach lining is constantly irritated, these cells can become damaged and produce less acid. It is also possible to develop antibodies to these stomach cells, a common condition called autoimmune gastritis that affects up to 2% of the population and is even more common among those living with autoimmune diseases. For example, researchers at the University of Antwerp in Belgium, found that people with type 1 diabetes and autoimmune thyroid disease were three to five times more likely to have autoimmune gastritis than those who did not have either of these conditions. Low stomach acid is also caused by H. pylori infection, getting older (acid levels decrease as you age), and chronic stress-related gastritis. (8) But whatever the cause, low stomach acid has been associated with many autoimmune diseases including Addison's disease, lupus, myasthenia gravis, celiac disease, dermatitis herpetiformis, Graves' disease, pernicious anemia, rheumatoid arthritis, Sjogren's syndrome, and vitiligo.

Let me give you an example from my practice. My patient Linda, a 40-year-old African American woman, came to see me four years after she was diagnosed with Sjogren's syndrome. Sjogren's is an autoimmune condition where antibodies attack and damage your salivary glands and tear ducts. Linda was a classic case of Sjogren's syndrome with the common symptoms of dry mouth and eyes and joint pain (Most patients have some sort of inflammation, usually arthritis or muscle tenderness.) Linda had also been living with constipation and abdominal pain that she said had been going on "forever," probably since her mid 20's. She also had a persistent cough and reflux that she remembers began when her mother died five years prior. A year before coming to see me, an endoscopy revealed signs of a chronically irritated stomach lining and inflammation in her stomach. Her doctor prescribed a proton pump inhibitor (PPI), which is a medication that reduces the amount of acid in the stomach and is commonly used to treat acid reflux and heartburn. But she didn't want to stay on the medication because she was worried about developing osteoporosis and the risk of fracturing a bone because as I mentioned earlier, numerous studies link PPI's to an increased fracture risk. She also wanted to get off the medication because her persistent, bothersome cough, which is one of the medication's possible side effects, still lingered. As a result, she came to see me for help with her digestive issues.

One of the first things I did was to put Linda on the elimination diet that we discussed in Chapter 3 Using Food As Medicine Workbook removing gluten, dairy, soy, and corn for three weeks. Almost immediately, the joint pain she'd been living with for four years disappeared, a result that is pretty typical. (When we talk about leaky gut syndrome later in this chapter, I will explain how some of the foods you eat can cause inflammation in your joints). However, we needed to go further because a stool test showed an overgrowth of yeast and bad bacteria and lack of good bacteria in her gut. (A stool test is when a sample of your stool is sent to a laboratory for analysis.)

After treating Linda's gut with herbs like berberine and oregano and probiotics, which are live cultures that help balance the flora in your gut, her abdominal pain and constipation were gone.

However, Linda still had reflux and, although she was free of any physical symptoms of Sjogren's syndrome (her dry eyes and mouth were gone), a blood test showed that her antibody levels for this condition were still high. So I decided to focus on her stomach and her digestive power and added two supplements to her regimen. One was a digestive enzyme and the other something called betaine, which is stomach acid in a pill form. Just two weeks after she started taking these supplements, the reflux Linda had lived with for five years was finally gone. Making her stomach more acidic so that the pH was close to 1.5, activated the digestive enzymes. Linda was finally able to properly digest the foods she ate . The fact that these enzymes and extra stomach acid worked showed me that Linda's reflux was caused by poor digestion, a poor production of stomach acid, and a chronically irritated stomach lining due to stress. Just to note, there are foods you can eat instead of taking supplements to boost your enzymes and stomach acid, like apple cider vinegar and ume boshi plums, and you will learn more about these foods in the Healing Your Gut Workbook.

Six months after her first appointment, Linda repeated her initial lab tests and her results had reversed, meaning there was no sign of Sjogren's syndrome and her antibody levels were now normal. For her, all the answers to changing her health (and thus, her life) sat right in her gut! The same could be true for you, as it often is for those with autoimmune conditions, which is why this part of The Immune System Recovery Plan is so important.

Dysbiosis: An Imbalance In Your Gut's Good Bacteria

When the amount of healthy bacteria in your gut is too low, a condition called dysbiosis occurs. Sometimes you might also have an overgrowth of harmful bacteria, yeast, or parasites and this makes the dysbiosis more severe. The severity of dysbiosis can cause a lot of intestinal symptoms, and as I mentioned before, many people are given a diagnosis of irritable bowel syndrome because they have chronic constipation and/or diarrhea, gas, and/or bloating after they eat, and sometimes also don't feel good after they eat any food at all. In addition to your digestive symptoms, these changes in your gut flora have such profound effects on both your immune system's first and second lines of defense, and so it is not surprising that an imbalance has been linked to autoimmune diseases.

Researchers at the University of Arizona College of Medicine recently reviewed the literature on this topic and found good evidence that dysbiosis plays a role in rheumatoid arthritis and, in animal studies, multiple sclerosis. (4) Because we are just now beginning to understand this relationship, research in this area should really explode in the years to come.

There are five types of dysbiosis. All of them have many symptoms in common such as:

- Constipation
- Diarrhea
- Gas
- Bloating
- Abdominal cramps
- Nausea
- Feeling sick after eating

Unfortunately, you can also have more than one kind of dysbiosis at the same time! The mildest form of dysbiosis is insufficient good bacteria. Here you have a lack of the beneficial bacteria needed to balance the gut.

Next is small intestinal bacterial overgrowth (SIBO), which occurs in the upper part of the small intestine when bacteria from the colon grow in the wrong place. People with SIBO might also have stomach symptoms like heartburn and reflux.

The third type is immunosuppressive dysbiosis. Here toxins from harmful bacteria, yeast, or a parasite lower your levels of good bacteria and give off toxins that weaken or break down the gut wall lining and cause leaky gut syndrome. People often get this form of dysbiosis when they have an overgrowth of yeast in the body called candida, which is what happened to Linda. I discovered this after seeing the results of her stool test. Though a

stool test is helpful, you do not need to do one to diagnose yourself. I'll show how using the self-assessment in the next chapter, the Healing Your Gut Workbook. People with this kind of dysbiosis often have sensitivities to many different foods, feel tired and puffy and have difficulty concentrating right after eating or even the next day.

A fourth type is inflammatory dysbiosis, which is when the body has an exaggerated response to your body's imbalance of good bacteria. Physical symptoms of this type of dysbiosis include muscle and joint pain in addition to digestive symptoms like gas and bloating. This form of dysbiosis is often seen in autoimmune diseases.

The last type is parasites, which can infect the digestive tract and put stress on the population of good bacteria. Parasites often cause diarrhea, cramping, and bloating. But they can also be silent, causing no obvious gut issues, but hives for no clear reason or food and environmental allergies that you have never had before. The only way to diagnose a parasite is to do a stool test.

All types of dysbiosis except the first one require the removal of bad bacteria, yeast, or parasites. And all of them can be thought of as infections that aren't detected by routine medical tests or procedures. Dysbiosis can be caused by an overuse of antibiotics and antacids, including proton pump inhibitors that lower the production of acid in the stomach; gastrointestinal infections; gastrointestinal surgery; chronic digestion problems (because undigested foods wreak havoc in the intestines); chronic constipation; eating the standard American diet, which is very low in the fiber that your beneficial flora need to thrive and be healthy; and eating foods that your body's immune system is reacting to. A good example of this is gluten, which causes many different kinds of reactions in the body, one of which is celiac disease, as we discussed in detail in Chapter 2 Using Food As Medicine. Chronic stress, which can lower the levels of the friendly flora in your gut can also cause dysbiosis.(9)

What's really important to note is that even a small disruptive event in your gut, for example taking a short course of antibiotics for a sinus infection, can create a severe or chronic condition like yeast overgrowth or small intestinal bacterial overgrowth. That said, a relatively minor change— if carefully conceived—can sometimes restore that balance and, as a result, your gut health. For example, simply taking a daily probiotic supplement can create or stimulate major changes in your good bacteria, which ultimately decrease an allergic reaction or other symptoms that you may be having.

(The bottom line: dysbiosis can trigger or promote an autoimmune disease because the lack of healthy flora and influence of toxic, harmful flora cause the immune system to malfunction.) Dysbiosis can also lead to leaky gut syndrome, a problem on its own that we'll discuss shortly. My point here is that finding out if you have dysbiosis and treating it is a foundational part of how I work with patients in my office and in the program I'm sharing in this book. Research shows that restoring healthy flora to the gut helps improve immune function, and I am continually amazed at how balancing the good bacteria in the gut helps almost everyone feel better! (10, 11, 12)

What Is Leaky Gut Syndrome?

I've mentioned leaky gut syndrome a few times already, so let me finally explain it in some detail. Normally, the cells that line your intestines stick tightly together and form a protective barrier that is hard to penetrate. Sitting on top of the cell lining, is a layer of mucus that is also an important part of the barrier. This barrier's job is to regulate everything that passes between the environment within your intestine and your body. Together with the immune cells located in your gut, this barrier helps control how your immune system reacts to anything foreign. When this barrier is weak or compromised, you have a condition called leaky gut syndrome. The problems caused by this condition are easier to understand if you imagine the barrier like a brick wall made of intestinal cells and what is called intercellular tight junctions, which are the "glue" that holds these cells together and forms the rest of the barrier. When the glue breaks down, there are cracks in between the cells that allow food particles and bacteria to literally leak into your bloodstream. (Hence the name "leaky gut syndrome.") Researchers at the University of Maryland School of Medicine recently identified a molecule called zonulin, that is part of the glue. They found that when the zonulin is damaged, the result is leaky gut syndrome. (13)

Leaky gut allows anything that is inside your intestines to be "seen" by the immune system that is lying beneath your intestinal lining - like food proteins, good bacteria, harmful bacteria, yeast, and parasites. When this exposure is chronic, meaning it goes on and on for months, the immune reaction over time begins to malfunction, putting you at risk for an autoimmune disease. The researchers who identified zonulin found that in people who have a genetic predisposition to autoimmune disease, damaging zonulin and the glue that holds the cells to-

gether, caused them to develop an autoimmune disease more often than people who had normal zonulin and glue, meaning a normal intestinal barrier.

This "glue" in between the cells gets damaged from things like dysbiosis from yeast, parasites or bad bacteria, severe stress, alcohol, certain medications, or after a virus or chemotherapy. When this happens, in addition to putting you at risk of developing an autoimmune disease, you are likely to develop food sensitivities. And these food sensitivities can happen not only in childhood, but later in life, too, something that comes as a surprise to most people especially if they had no food sensitivities or allergies as children. Maintaining a strong barrier is the best way to keep your immune system healthy, which as I have said, means that it knows when to turn on and off, knows the difference between self and foreigners and has tolerance to the good bacteria lining the digestive tract.

Some things that can cause leaky gut syndrome include:

- Antibiotic use. Typically this means taking antibiotics multiple times over multiple years, but taking them only one time can also be an issue.
- Acute trauma, emotional or physical, like surgery or food poisoning.
- Chronic stress
- Infections or exposures that were never resolved like traveler's diarrhea or a parasite.
- Chronic dysbiosis. Bad bacteria can secrete enzymes that destroy the glue between the cells.
- Non steroidal anti-inflammatory (NSAID) medications like ibuprofen and other prescriptions
- Toxins, like those secreted by the yeast candida. These can bind to part of the protective barrier breaking it down. They also can create pores across the membranes of the barrier.
- Alcoholism

What Does Leaky Gut Feel Like?

People with leaky gut syndrome often have digestive symptoms like constipation or gas and bloating after they eat. But it is also possible to have leaky gut syndrome and have absolutely no digestive symptoms at all. Instead, you might feel your hands and feet swell up after you eat, your muscles are tight and stiff in the morning, and you have brain fog and difficulty thinking after eating certain foods. These symptoms are a result of what's called systemic inflammation, which simply means that there are irritating molecules running around your body after you eat certain foods. Sometimes it is hard to know which food is the culprit because it seems like you react to so many. I hear this story from my patients with bad leaky gut syndrome very often. Also, when you get symptoms that are nowhere near your stomach, like joint pain or headaches, you may not realize they are even related to your diet.

How Does Leaky Gut Cause Autoimmune Disease?

Let's go into a bit more detail about how you can get autoimmune disease from leaky gut syndrome. The latest research and literature about leaky gut syndrome and autoimmune disease shows that almost every one with an autoimmune disease has leaky gut syndrome, even if they don't have any gut symptoms. (14, 15) This lack of symptoms is why, with all my patients, I do a comprehensive digestive stool analysis to make sure their gut flora is healthy. But what is the link between leaky gut and autoimmune disease?

As we discussed, when your intestinal barrier is weak or broken down partially digested food or antigens from bacteria and yeast can seep out, bump into the lymphoid tissue and immune cells in your gut, and then also get into your bloodstream. Your immune cells react by making lots of T helper cells, which are directly in charge of revving up the killer cells and antibody producing cells to attack anything they don't recognize as an invader. However, problems can occur when your body starts producing an abundance of T helper cells, especially if the T regulator cells don't do their job to turn this attack off. These extra T helper cells can:

- rev up the killer T cells too much, prompting them to mistake your own tissues for foreign invaders.
- tell the killer cells to make inflammatory molecules that are sent out all over your body causing inflammation and pain at distant places.
- tell immune cells, called B cells, to make antibodies that bind to the foreigner and form something called an immune complex. These immune complexes can circulate throughout the body and build up in tissues, causing irritation, inflammation, and swelling. Since food is a big trigger for these kinds of reactions when you have leaky gut syndrome, I always recommend eliminating gluten, dairy, soy, corn, and eggs from your diet. (I haven't told you to eliminate and test your sensitivity to eggs, yet, but don't worry, it's coming!) This can really improve symptoms dramatically. While you will still actually have a leaky gut when you are on an elimination diet, you are no longer eating the foods that trigger inflammation and worsen symptoms, so you begin to feel better immediately. Once you fix the leaky gut, you will be able to eat those foods again, but this will take at least six months. (I will show you how to heal your gut in the next chapter)
- tell the B cells to make antibodies to the foreigner; these antibodies can make a mistake and attack your own tissue instead, which is called "molecular mimicry" and is believed to be one of the ways that a viral infection and a food like gluten, can trigger autoimmune disease.
- get stuck "on" and so the immune response keeps going without stopping

Hopefully, you now understand that in order to reverse your immune disease or illness and have the healthiest immune system possible, we need to find what is causing the T cell imbalance, so that we can turn off the revved up T helper cells and calm down the killer cells, or the antibody producing cells. Helping your T regulator cells work better is important to help this balance. I know the way to do this and I will show you.

Both in my practice and in the latest research and scientific literature, I see that in order to fully heal and balance your immune system, we must heal your intestinal lining and make sure you have a good, intact barrier. Otherwise, your immune imbalance and your reactions to food and other antigens will not be cured and will come back again and again. The first step is to treat the cause, which is usually dysbiosis or impaired digestion.

Now you can see why it is so important to figure out what's going in your gut and heal your dysbiosis and/or leaky gut syndrome if you have them. To do so, let's move on to the Healing Your Gut Workbook in the next chapter where you will find self-assessments for these conditions and a treatment plan based on the results. Just think: you're getting closer and closer to healing your gut and feeling better.

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A true pioneer in Functional Medicine, Susan Blum, MD, MPH an Assistant Clinical Professor in the Department of Preventive Medicine at the Icahn School of Medicine at Mount Sinai, has been treating, healing and preventing chronic diseases for nearly two decades. Her passion and dedication for identifying and addressing the root causes of chronic illness through the groundbreaking whole body approach known as Functional Medicine, has helped thousands of people and is transforming our healthcare system.

A Preventive Medicine and Chronic Disease Specialist, Dr. Blum is a member of the Medical Advisory Board for The Dr. Oz Show, and the Institute for Integrative Nutrition. She has appeared on The Dr. Oz Show, Fox 5 News, ABC Eyewitness News, and is regularly quoted in Real Simple, Harper's Bazaar, Redbook. Through Dr. Blum's medical practice, education efforts, writing, research, and advocacy, she empowers her patients to stop covering up symptoms in order to actually treat the underlying causes of illness, thereby combating—and most often curing—the chronic-disease epidemic.

As the Founder and Director of Blum Center for Health in Rye Brook, New York, Dr. Blum leads a large and well trained multi-specialty team of physicians, nurse practitioners, nutritionists and health coaches, all providing cutting edge Functional and Integrative Medicine services to all who need it. Dr. Blum brings the collective experience and wisdom of both her own medical practice and that of the team, to her books and online programs, thus providing a strong foundation of expertise which explains why her programs are so successful.

In her first best-selling book, The Immune System Recovery Plan, (April 2013) Dr. Blum offers her proven four-step program, which she has used to help thousands of patients reverse their symptoms and prevent future illness. Including 40 recipes and a workbook style approach to help readers design their own personal treatment plans based on their symptoms and individual lifestyle choices, The Immune System Recovery Plan is a groundbreaking, revolutionary program that shows how anyone can cure the causes of autoimmune disease, strengthen their immune systems, and bolster their overall health.

In 2013, Dr. Blum created one of the first comprehensive medical online programs as a companion for the Immune System Recovery Plan. Her online Healing the Gut program was a huge success and in 2017, with the creation of her new digital platform, blumhealthmd.com, she took what she learned and relaunched the HealMyGut program to be better than ever with additional support from individual and group coaching. Always gifted at bringing healing to her patients in person and through her books, through blumhealthmd.com, she created an effective online program that now provides support and insures success to even more people.
Next up? Dr. Blum's next book, Healing Arthritis, is due to be released in November 2017. Stay tuned!

Dr. Blum completed her Internal Medicine training at St-Luke's Roosevelt Hospital, her residency in Preventive Medicine at Icahn School of Medicine at Mount Sinai in New York City, and is Board Certified in Preventive Medicine and Integrative and Holistic Medicine. She received her Masters in Public Health at Columbia University, and her Certification in Functional Medicine from The Institute for Functional Medicine, in Gig Harbor, Washington.

In addition to her role as Founder of Blum Center for Health, Dr. Blum is on staff at Greenwich Hospital as an Integrative Medicine Specialist in the Medicine Department. She is also a member of the Senior Teaching Faculty at the Center for Mind-Body Medicine in Washington, D.C. and teaches throughout

the world in their training programs. She is also on the Board of Directors for the American College of Lifestyle Medicine's True Health Initiative.

Dr. Blum practices what she preaches. More than a decade ago, she was diagnosed with Hashimotos Thyroiditis, an autoimmune disease where the body attacks the thyroid as if it were a foreign tissue. By following the same Functional Medicine and lifestyle principles she prescribes to her patients, Dr. Blum cured herself of this serious condition.

Dr. Blum approaches medicine—and her life—from a whole body perspective, incorporating all facets of wellness into every breath. She lives in Armonk, NY with her husband, and loves to begin her day with a 20-minute meditation and a green smoothie made with love from the contents of her garden. Dr. Blum also plans family meals in the summer based on the same homegrown vegetables. She loves experimenting in her kitchen with new recipes and with the power of herbs for their medicinal properties. She completes her morning ritual with a hike in the preserve or a morning walk with her dog, Trixie, on her quiet country road. She's an expert skier, plays golf regularly with her husband, and is always planning active vacations for their three grown sons to join them. On most evenings, Dr. Blum can be found at home drawing inspiration and support from many of the books she reads on spirituality and self-realization.

LOREN MARKS
DC., DACBN

Methylation Defects, Mineral Imbalances & Their Effects on Adrenal Physiology and Mental Health

I have had a keen interest in Adrenal Physiology for many years. In order to test the stress response in my patients, I utilized the functional medicine model of salivary adrenal hormone profiles that were cross referenced with my own muscle response technique for proper indentification and therapeutic application. Over time, I felt I had gained sufficient knowledge to teach and share my experience with other practitioners who were interested in ***"Integrative Assessment technique" (IAT).*** This is a muscle testing technology that is vastly different from Applied Kinesiology. I learned about Applied Kinesiology from Dr. George Goodheart. He was a pioneer in chiropractic, who brought forth a new modality to find better answers to patient care, while living in the state of Michigan, where Chiropractors were limited to practice and use of diagnostics.

In 1990, I had met Dr. Dick Versendaal, a charismatic chiropractor, who was teaching a muscle testing procedure which was quite different from anything I had seen prior. He was truly an energetic healer that many have heard of but, not many have had the opportunity to see in person. He was avant-garde in his ideas and practice, but I was able to filter through some of his statements and find a process, that beneath it, would eventually lead me 17 years later, to create **IAT.**

How do you know you are right?

What sets **IAT** apart, is a founding principle that questioned the whole muscle testing process that started with "How do you know you are right"? Just because you achieve a change in a muscle response by contacting a reflex point located on the surface of the body-how do you know you are right. Thus my process began challenging what I had been taught. In order for this process to unfold, I knew I had to cross reference my findings with known diagnostic standards, such as Salivary Adrenal Hormone testing, followed by blood chemistries. The more I perused this process, the more I needed to know, and the more I knew, the better my results became.

So how does all of this tie in with **"Methylation Defects and Mineral Imbalances"** one might ask?

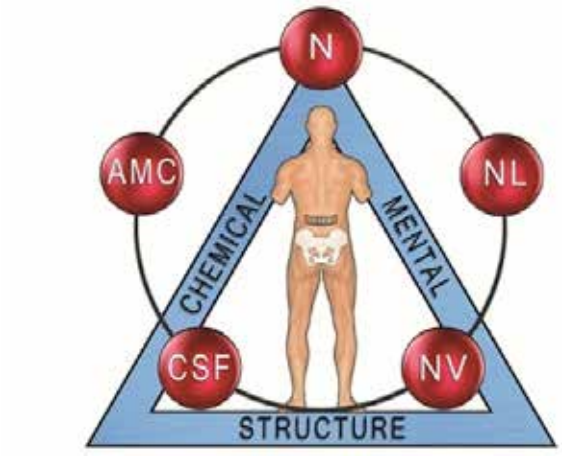


Figure.1

Well, in my process of seeking the truth, and performing all those Salivary Adrenal Hormone Profiles, it dawned on me that what I was reading in those tests was a patient's manifestation of their stress response over time. Despite that we could categorize what is known as their" level of adrenal exhaustion" into various phases, one might categorize this as end organ manifestation.

I then began to look at what I call Adrenal Perpetuators. What is driving these patients' maladaptive processes? So, I started looking at what others had to say. I found some doctors utilizing a variety of botanicals such as Adaptogens, others using DHEA, Pregnenolone, various adrenal supporting nutrients, and some stating that you must correct GI dysfunction, whether it is Dysbiosis, or a need for remediation and balance of the Microbiome.

It seemed wherever I turned, someone had a different perspective, and in reality they all were correct in some form or fashion. The reality is that one's adrenal physiology is designed to respond to all stressors, whether they are one of the many internal imbalances that we can manifest or a neuroendocrine response that comes from anxiety, depression and worry. The list can seem infinite. Actually, it's not, because we as humans can be defined into a variety of categories based upon a specific criteria and history followed by a prudent medical workup. This also means that we shouldn't be myopic and look for a single causation to a problem, because in today's world, most chronic illness is multifactorial. A more prudent statement might be to look for clinical adjacencies.

However when the body is under stress for a prolonged period of time, its adaptive capacity is challenged. Cortisol will always be elicited in response to a stressor, and DHEA, its counter regulatory hormone, will concomitantly shift as well. For some, this adaptive process makes us stronger. We find a way out and grow in the process. For others, their ship begins to sink after prolonged stress, and their HPA Axis begins to crash. What could be the common denominator that allows this to transpire?

Continuing on the path to find the holy grail of perpetuators, I began to define the various Neurotransmitter (NT) imbalances that seemed to be causing so much trouble in so many of these patients.

I formulated a way to examine most of the pertinent neurotransmitters with my IAT work, and to this day, I still marvel at its accuracy in how it reflects what patients are feeling without them telling you this in advance. I utilize natural medicines in my clinic, and to my surprise, NT synthesis and regulation are determined by a variety of nutrients such as; Magnesium, Vitamin B6, B12, Folates, TMG, Zinc, Copper, Amino Acids, and Essential Fatty Acids.

Figure.2

Methylation and its role in Mood, Behavior and Mental Health.

Through my research, I happened to come across the genius of Dr. William Walsh, PhD. His brilliant interpretation

of the science of genomics helped me bridge a better functional understanding of Methylation and its role in Mood, Behavior and Mental Health.

There has been quite a bit of interest in Methylation over that past few years, and for good reason.

Methylation or the regulation of CH3 in our cellular processes is responsible for a plethora of physiologic functions.

Impairment can result in RNA and DNA synthesis and repair problems which appear to be related to some cancers. Detoxification of heavy metals and estrogens and intracellular antioxidant regulation via Glutathione synthesis are dependent on normal methylation. Impaired Mitochondrial function can become altered and cardiovascular effects can manifest from elevated Homocysteine levels. Clotting alterations and Fragile X syndrome effect fetal development. Mood, Behavior and Mental Health manifestations can occur from impaired BH2 to BH4 production. BH2 is recycled into BH4 and is instrumental in the production of neurotransmitters, which regulates Serotonin, Dopamine, and Norepinephrine et al. While we are young in our understanding of the global effects that MTHFR and Methylation have on human health, great strides in genomic understanding and application are reported here, as a means to better understand etiologic mechanisms that cause human illness when impaired.

When Methylation comes up in professional conversations, the first thing discussed is the MTHFR enzyme (methylenetetrahydrofolate reductase). MTHFR is the largest molecular weight gene in the methylation cycle, and is responsible for the metabolism of Folic Acid and the basic conversion of the amino acid Methionine to Homocysteine.

Genes are responsible for one thing, and that is production of a protein that forms an enzyme necessary to complete a specific task.

The current understanding of gene dysregulation occurs when there is a SNP (Single Nucleotide Polymorphism) which is a mutation. When a gene mutates, it will usually do so in either one or two locations along its amino acid sequence. If one SNP occurs on a gene, it is termed Heterozygous and if two occur it is known as Homozygous. These SNP's reduce enzyme activity, but do not completely block their function. Interestingly, a mutation on the CBS enzyme is thought to upregulate, causing B6 to be used up at a greater rate in the formation of Glutathione synthesis.

Depending upon which gene and its responsibility, a certain percentage of its function is typically reduced. A heterozygous mutation produces less of an effect than a homozygous mutation in most instances; a compound heterozygous trait may impact enzyme function similar to a homozygous trait.

What's important to understand here, is that a mutation on a gene does not necessarily mean that the mutation will manifest or express.

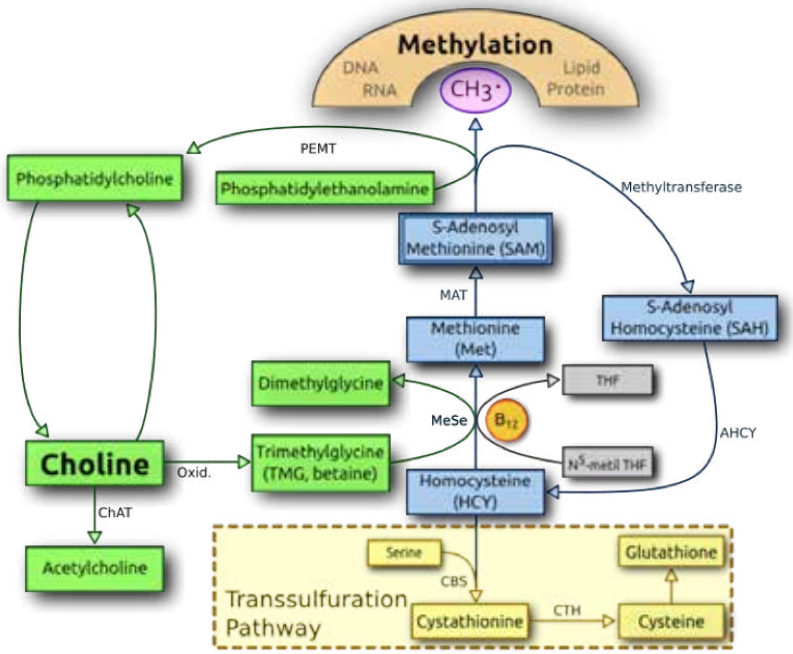
Ancestrally, we developed SNP's over a wide lineage of time. Keep in mind that the body has a remarkable adaptive capacity; some genes may upregulate while others downregulate, or perhaps certain SNP's have developed to counter certain mutations. We are still at a young stage in our understanding of these concepts.

What we do know, is that gene mutations may set the stage for a particular dysfunction to occur, but that does not mean they have manifested. Without biochemistry, we do not know their respective expression!

GENETICS MAY LOAD THE GUN, BUT IT'S LIFESTYLE THAT PULLS THE TRIGGER!

Epigenetics appears to be the deciding factors on gene expression, and can be summarized by this quote: GENETICS MAY LOAD THE GUN, BUT IT'S LIFESTYLE THAT PULLS THE TRIGGER!

This statement is particularly important when it comes to MTHFR. Too many doctors and nutritionists having a patients MTHFR results that show the presence of a C677T or A1298C SNP, are supplementing these patients with Vitamin B9 (Methyl Folate) on this basis alone. Given the understanding that they want to support the mutations expression, most would prescribe Methylfolate.



Methylation Cycle

Figure.3

Why might this be a problem?

First, let's look at some current associations. It is generally thought that SNP's involving C677T are strongly associated with alterations in Homocysteine. SNP's associated with A1298c appear to be tied to alterations in mental health. Despite these associations, I have seen some patients express a high homocysteine with, and others without a C677T SNP. This can occur because Homocysteine is regulated by many factors, one such factor is folates. Insufficient B12 or functionality of this nutrient can alter homocysteine levels. In addition, B6, its concentration or its ability to convert to Pyridoxine 5 Phosphate (P5P), sources of Trimethylglyceine (TMG) or betaine in our diet, Riboflavin (B2), and even age related changes, can alter its expression.

Secondly, and in my opinion, what if the patient has issues with Mood, Behavior and Mental health?

Nutrient Therapy has a profound effect on the expression of Neurotransmitter (NT) uptake.

What scientists have discovered, is that it is not the concentrations of NT's that have the most profound effects,

but the reuptake at the synapse and the rate at which this occurs. This is why the drug companies have largely moved away from the old classifications of antidepressants like Tricyclics and MAO inhibitors and moved to SSRI's and SNRI's.

Dr. William J. Walsh PhD, the successor of Abram Hoffer M.D. and others that studied the relationship of Ortho-molecular medicine on psychiatric ailments, used as its basis, nutrient therapy to optimize ones biochemistry. Dr. Walsh currently heads The Walsh Research Institute in Naperville, Illinois, a non-profit organization, dedicated to the advancement and treatment of brain based disorders.

The difference with Walsh is that he has been able to advance some of the earlier suspicions worked on by his predecessors. Genetic science and molecular biochemistry has helped pave the way for a better understanding of how nutrient therapy impacts neurotransmission. Electron and X-Ray Microscopy at Argonne National Laboratory is helping unfold some of the mysteries to how DNA attachments affect functionality.

The Key in methylation is to determine global methylation status, especially when treating any brain based illnesses. Whether you are addressing depression, anxiety, OCD, ADHD, PTSD, PD or AD, it is imperative to define global methylation status.

While MTHFR is the largest molecular weight enzyme in the methylome, and thus more susceptible to an alteration in its amino acid sequence, there are approximately 20 other genes that regulate the methylation process.

Walsh explains this as follows," Think of Methylation as a tug of war. Some genes are overmethylating, while others are undermethylating us. Who wins the war? The net effect of this process determines our global methylation status!"

How is this determined?

Walsh found that **Whole Blood Histamine (WBH),** which is diagnosed via blood chemistry (LabCorp only) or the SAMe to SAH ratio performed by Doctors Data, was the best way to establish these criteria.

Whole Blood Histamine must be 40-70ng/ml to express balanced methylation for mental health.

Histamine degrades methyl through one of the methyltransferases, such as HNMT, and the value is inverse to the process; meaning if one has a low WBH they are an Overmethylator. If one has a high WBH, they are an Undermethylator, based upon the above reference range.

If using the SAMe: SAH ratio, a low value is an Undermethylator, a high value is an Overmethylator.

Once global methylation has been determined, it's imperative to know that folates can worsen an Undermethylator. Yes you heard me correctly, despite the use of Methylfolate on depressed patients.

The studies did not differentiate between under and overmethation, just the effects on mood. Overmethylators can thrive on folates because they are actually low in folates.

Folates lower Serotonin in Undermethylators due to their effects on SERT as I will demonstrate.

Here's why- Methyl actually competes with Acetyl at the binding sites, but again it is not a concentration issue but an **Enzyme dependent process.**

Genetics- changing the way we think

Histones are structural proteins that are wrapped around by DNA . They are like a ball of yarn with a few threads sticking out (Chromatin). These threads are known as histone tails. Reactivity of neurotransmission at these tails is controlled by acetyl and methyl competition. Nutrient therapy can control reuptake of Serotonin, Dopamine and other NT's. This data is derived from some of the latest research according to Walsh:

- Competition between methyl and acetyl groups often determines whether a gene is expressed or silenced.
- Acetyl bookmarks promote expression
- Methyl bookmarks inhibit gene expression
- Nutrient therapy can impact the methyl-acetyl competition and alter expression of enzymes that control serotonin and Dopamine NT rates.
- In order for a gene to express, it must uncoil, it occurs electrostatically.
- Acetyl-Coenzyme A and SAMe are the donors of Acetyl and Methyl respectively, but their concentrations in brain cells are relatively unimportant.

It's not the amount of acetyl vs methyl that wins, but enzymes that dominate.

Acetylases, Deacetylases (put acetyl on or take it off) Methylases and Demethylases (put a methyl on or take one off) dominate attachment or removal of acetyl or methyl groups.

Epigenetic nutrient therapy for adjustment of serotonin or dopamine activity concentrates on the enzymes.

So the primary determinant of neurotransmitter activity at Serotonin, Dopamine and Norepinephrine receptors, are not concentrations, but enzyme competition at histone binding sites that promote or inhibit their expression. Transmembrane proteins that remove NT from the synapse via reuptake are the controlling factors. The amount present is controlled by the methyl- acetyl competition.

Nutrient Therapy

Niacin and Niacinamide act as Dopamine reuptake promoters (Lowers Dopamine activity especially in some schizophrenics via deacetylase activity) and are methyl sponges for Overmethylators. Think about the terminology, Overmethylation- too much methyl, which we need to reduce to create normalcy.

Methionine and SAMe are serotonin reuptake inhibitors (SSRI). They can work the same as meds, but take 1-2 months for clinical expression. Works best for Undermethylators, as they are the primary sources of methyl.

Folates reduce synaptic activity at serotonin, dopamine and norepinephrine receptors (promoters not inhibitors so you will worsen low serotonin depressives if you use this, despite its common use).

Zinc and glutathione increase glutamate activity at the NMDA receptors (OCD and certain schizophrenics benefit).

Many nutrients influence NT activity and brain function.

FOLATES REDUCE NT ACTIVITY

Folic Acid, Folinic acid and L-Methylfolate are effective methylating agents.
However folates also increase the expression of SERT transport proteins, resulting in reduced serotonin neurotransmission.
Most undermethylated depressives with low serotonin activity are intolerant to folates.
If you are an Undermethylator without a serotonin problem or need methylation support for homocysteine, folates and B12 work great and can be used freely.

Low Serotonin Activity Nutrient Therapy Approach

Enhance methylation and suppress acetylation of DNA and Histones
SAMe and Methionine act as SSRI's-reduced expression of SERT
Avoidance of Folate supplements
Augmenting nutrients- Zinc, Serine, Inositol, TMG, Cal/Mg, Vitamins A, B6, C, D and E.

Chemical Classification of Depression

The following values in percentage reflect Walsh's database from treating over 30,000 patients and compiling 1.5 million chemistries. This is the largest database on mental health utilizing chemistries currently known in the world.

Each biotype has its own characteristics. Keep in mind that some patients have more than one of these imbalances, such as an Overmethylator with Copper overload, which would cause extreme anxiety.

The biotypes represent completely different disorders, each with unique NT imbalances and symptoms. Separate treatment approaches are required for each biotype

A diagram of Walsh's Five Depressive Biotypes. He identified the 5 Bio Types of depression and their prevalence, and they are not all driven by serotonin!

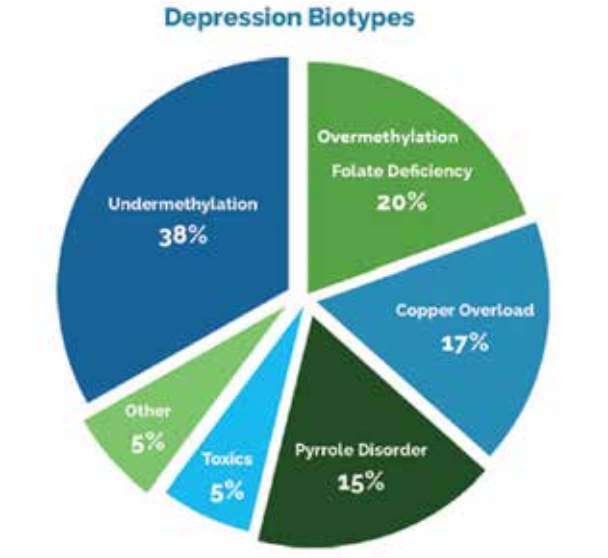


Figure.4

Zinc, Copper and their relationship to mental health

Copper and Zinc, two essential minerals responsible for a wide array of physiologic functions can easily be tested by running the following labs: **Serum Copper, Ceruloplasmin and Plasma Zinc.**

While the standard laboratory reference ranges are greater than those Walsh states here, keep in mind the contextual nature of this narrower range:

Zinc 90-135 ug/dl

Copper 70-110 ug/dl

Ceruloplasmin 16-45mg/dl

Zinc and Copper have an antagonistic relationship in the body, as they oppose one another. It is not just their individual values but ratios that are pertinent.

Many authors believe that the ratio of Zn to Cu needs to be at least 1:1. These findings not only relate to mental health, but to a risk analysis for Alzheimer's disease and oxidative loads.

In my clinic, I have tested well over 100 cases to date, and the propensity of my finding is that most patients are either low in Zinc, high in copper or present with both, especially in patients with mood disorders.

Ceruloplasmin is copper bound to protein as opposed to serum copper in the blood stream. 95% of copper should be bound to protein, and when it is not, free divalent copper acts as an oxidant.

Zinc on the other hand is an antioxidant, so it makes sense that if you have an elevated copper and a higher percent free; you are dealing with high oxidative loads.

Every mental health and brain based disorder has associated with it, a high oxidative load.

Inflammation in the brain is another emerging theory as an etiologic mechanism for depression.

When Copper is elevated above 110ug/dl it influences the relationship of Dopamine and Norepinephrine.

Dopamine in the presence of high copper, with the aid of the enzyme dopamine beta hydroxylase, converts to Norepinephrine. In healthy patients Dopamine can be considered a feel good hormone acting as an inhibitory NT. In the presence of high copper, we shunt this reaction and Norepinephrine becomes dominant, driving excitation and anxiety.

When we look at a laboratory report and see, a low Zinc and an elevated copper, other than the obvious decision to replete with zinc, we must always ask why this is occurring.

Chronic adrenal exhaustion may also be driven by high copper levels that are not properly opposed by zinc. Overstimulation from high norepinephrine as a result of elevated copper should be part of a clinician's workup when seeking allosteric remediation.

Pyrrole Disorders

A pyrrole disorder is a condition that occurs via an inherited trait. Also known as Kryptopyrroles or Hemopyrrolin-2-One or Mauve factor, are metabolic end products from the metabolism of hemoglobin. We all manufacture pyrroles and excrete them in the urine, but some patients produce high levels and when tested properly, we can state they have Pyrroleuria. Levels above 16mcg/dl are elevated and considered positive for the condition. Pyrroles have a high affinity for vitamin B6 and Zinc, carrying them out of the body continuously, driving depressed levels.

This may be one of the key reasons, some patients biochemistry will reflect low zinc, and a higher copper, but by no means is an exclusive cause.

Dietary intake and absorption, drug induced nutrient depletion, improper supplementation and detoxification of metals may also create these imbalances.

What about B6?

Of all the nutrients that have an effect on mental health, Vitamin B6 stands at the forefront. The final step in the activation of Serotonin, Dopamine and GABA is vitamin B6.

5HTP needs B6 to convert to Serotonin

Glutamate needs B6 to convert to GABA

L-Dopa needs B6 to convert to Dopamine

Below is a list of symptoms associated with Pyroluria. If a patient experiences 15 or more of these, it is likely that they have Pyroluria.

1. Little or no dream recall (B6)
2. White spots on finger nails (Zinc)
3. Poor morning appetite +/- tendency to skip breakfast (Zinc)
4. Morning nausea (B6)
5. Pale skin +/- poor tanning +/- burn easy in sun
6. Sensitivity to bright light (Zinc)
7. Hypersensitive to loud noises (Zinc)
8. Sensitivity to smells (Zinc)
9. Poor ability to cope with stress (Zinc and B6)
10. Mood swings or temper outbursts (Zinc)
11. Histrionic (dramatic, emotional) tendency (Zinc)
12. Argumentative/enjoy argument (Zinc)
13. New situations or changes in routine are particularly stressful (B6)
14. Much higher capability and alertness in the evening, compared to mornings (Zinc) | 15. Poor memory (Zinc and B6)
16. Obesity or Abnormal body fat distribution (Zinc)
17. Belong to a family with a lot of look-alike sisters

18. Dry skin (B6)
19. Anxiousness or nervousness, fearful, lifelong inner tension (B6)
20. Reaching puberty later than normal – growth after the age of 16 (Zinc)
21. Difficulty digesting, a dislike of protein or a history of vegetarianism (Zinc)
22. Tendency toward being a loner and/or avoiding larger groups of people
23. Stretch marks on skin (Zinc)
24. Poor sense of smell or taste; preference for spicy foods (Zinc)
25. Feel very uncomfortable with strangers
26. Frequently experience fatigue or exhaustion (Zinc)
27. A tendency to overreact to tranquilizers, barbiturates, alcohol or other drugs (in other words, a little produces a powerful response)
28. A tendency toward anemia
29. History of mental illness or alcoholism in family (Zinc and B6)
30. Easily upset by criticism, offended easily
31. Bad breath or body odor when ill or stressed (Zinc)
32. Prone to acne, eczema or psoriasis (Zinc)
33. Thin skin
34. Hyper-pigmentation of the skin
35. Bouts of depression or nervous exhaustion (B6)
36. Prone to frequent colds or infections (Zinc)
37. Abdominal pain; constipation, irritable bowel syndrome (Zinc)
38. Hair loss (lack of hair on head, eyebrows and/or eyelashes) (Zinc)
39. Irregular menstrual cycles, PMS (B6)
40. Low libido
41. Allergies (Zinc)
42. Tingling in arms and legs (neuropathy) (B6)
43. Migraines (B6)
44. Muscle pain (achey, flu-like tenderness) (B6)
45. Frequent yeast infections/yeast overgrowth (Zinc)
46. Reading difficulties (e.g. dyslexia)
47. Get motion sickness (B6)
48. Cold hands and feet (Zinc)
49. Codependency
50. Substance abuse/addiction (B6)
51. Creaking joints, joint pain, knee pain (B6)
52. Overcrowding of teeth in upper jaw (Zinc)
53. Poor looking tooth enamel; tendency for cavities (Zinc)
54. Delusions, hallucinations, paranoia (Zinc)
55. Emotionally unstable (Zinc)
56. Pessimism (Zinc)
57. Early greying of hair (Zinc)
58. Insomnia (Zinc and B6)
59. Prone to stitch in side when running (Zinc)

60. Hyperactivity (Zinc and B6)
61. Fluid retention (B6)
62. Obsessive Compulsive Disorder, which includes collecting/hoarding (B6)
63. Seizures (B6)
64. Hypoglycemia (Zinc)
65. Frequent ear infections as a child (Zinc)
66. Suicidal tendencies (Zinc)
67. Gluten intolerance (Zinc)
68. Prone to ovarian cysts (Zinc and B6)
69. Craving for sweets/carbs (Zinc and B6)
70. Tremors (B6)
71. Age related Macular Degeneration (Zinc)
72. Low Progesterone = miscarriage in first 7 weeks or early menopause (B6)

If a patient has a pyrrole disorder and their B6 and Zinc are depleted, it should now be quite apparent that this may be a causative mechanism in the etiology of their mood, behavior and mental health issues.

Once you begin testing patients and correlating this data, you will find some striking evidence to Walsh's claims.

Heavy metals

Heavy metal accumulation primarily occurs from environmental exposure over time, whether its source is water, food or inhalation. Heavy metal accumulation in wheat plants irrigated by waste water is a subject of great concern. Industrial production into our water supply directly or indirectly via the vaporization into the atmosphere, which accumulates in clouds and brought back to earth and sea are an ever present danger to all living plants and animals.

Lead, Arsenic, Cadmium and Mercury seem to be the most deleterious, but others are present as well.

By and large, allopathic medicine teaches doctors to evaluate heavy metals in the blood stream for acute exposure. Functional medicine is equally concerned; however chronic lower levels that accumulate in tissue overtime can be etiologic in the development of many disease processes. Neurologic tissue is very sensitive to heavy metal deposition, thus brain based disorders need to be investigated through proper screening methodologies in addition to current assessment criteria.

Challenging tissues stores, with and without provocation, is one such methodology. The urinary output of heavy metals has been studied over time, to reflect excretion from tissue stores after provocation. DMSA and EDTA are effective chelating agents for provocation, both as a diagnostic and therapeutic agent. Various functional medicine laboratories provide this service.

Since our genome is susceptible to altered expression from epigenetic insults, this is one such area that deserves greater attention, given the environment in which we now are forced to live.

If heavy metals are a source of toxin exposure altering the oxidative load or neurotransmission of a patient's mental or behavioral health, we owe it to our patients to do our due diligence and investigate their presence or absence.

I have discussed the role of methylation and specific mineral imbalances as they relate to mood, behavior and mental health and as a driver of chronic adrenal exhaustion. There is an exhaustive amount of data in the literature that can expound on many of these issues. My goal was to

provide more of a supported clinicians approach, rather than an academic discourse whenever possible.

What's exciting to me is how many doctors are willing to look into the role of nutrient therapy for the application and improvement of human health. The science is emerging to support this process in ways that we never thought possible. Nutrigenomics and the various other omics are showing us the role systems biology plays in our understanding of how we tick, and the best way to achieve optimization of our health. After 33 years of practice, I can't wait to see what's ahead.

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Dr. Loren Marks is a 1984 graduate of New York Chiropractic College and received his Diplomate in nutrition in 2003 from the American Clinical Board of Nutrition.

He has been in practice in NYC for 33 years, and has taught Clinical Nutrition for the past 27 years across the United States.

He is a post graduate instructor for Logan University, a noted speaker and frequent lecturer for his profession.

Dr. Marks is the founder of Integrative Assessment Technique (IAT). An assessment methodology embracing, nutritional biochemistry, emotional health and structural neurology.

Dr. Marks is coauthor of a chapter in Dr. Andrew Weil's series of texts on Integrative Gastroenterology, written by Dr. Gerrard Mullin, and he coauthored a chapter in "Arachnoiditis, the Evidence Revealed" with Dr. Mullin as well, by Dr. Antonio Aldrete.

He has written the forward for a recently published children's book titled "Free to be Gluten-Free!" by Heather Spergel, M.S. and is currently writing a chapter for an e book titled Optimal Health: Using Principles of Functional Medicine & Nutritional Genomics. His contribution will be on "Methylation Defects, Mineral Imbalances & Their Effects on Adrenal Physiology and Mental Health".

FELICE L. GERSH
MD

WOMEN, HEARTS, AND HORMONES:
The menopausal journey all women must take

Menopause Overview:
Not a Nice Story for Women

1. Hypertension and a decline in NO and other vaso-moderating molecules
2. Dyslipidemia (a rise in LDL, oxidized LDL, and a decline in HDL)
3. Increased oxidative stress
4. Development of atherosclerosis
5. Direct effects on the myocardium and adipose tissue functions

Chakrabarti S, Lekontseva O, Davidge S. IUBMB Life. June 2008; 60(6): 376-382
Saitoh, K and Akiwaki M. Hormones.

INTRODUCTION:

Menopause is a female condition which has been in existence since the beginning of human life itself; the progression of perimenopause into the state of menopause is a journey all women must take. And each woman must then face the huge consequences which ensue from the loss of the ovarian production of estrogen and progesterone. Going through menopause is, quite simply, not an optional event for women and filled with significance of a level often under recognized.

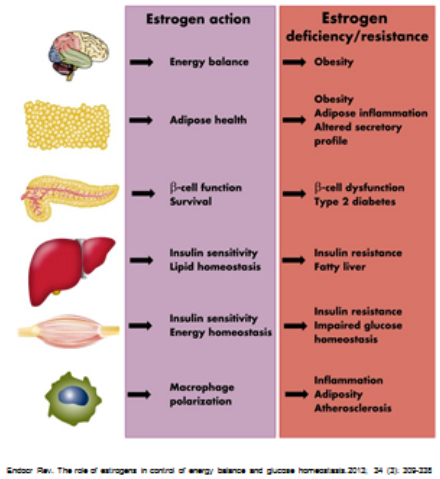
The designated name for this occurrence, "menopause," is a poor label for this monumental feminine event, manifesting sometime within the decade of the 40's and 50's, and then continuing on for life's duration. "Meno" is from the Greek language for moon and "pause," of course, refers to the cessation of the menses. Many women and physicians alike view menopause as nothing more significant than the end of female fertility, as manifested by the loss of ovulation and its accompanying cycle of period bleeding. The focus of treatment has been just on symptomatic hot flashes and night sweats, along with vaginal dryness and painful intercourse. The loss of the menstrual cycle is an obvious event, but what is occurring, silently and deeply within the female being, though not widely recognized, is of great significance, extending its reach far beyond the loss of reproductive function and the unpleasant hot flashes and vaginal dryness. For estrogen is the hormone of life itself, the giver of new life, and the true master of metabolic homeostasis.

In order to fully grasp the significance of menopause, and the inevitable loss of the peripheral production of estrogen, one must first understand some of the foundational issues involving estrogen and the female body. Estrogen was the first of all steroid hormones to make an appearance, as demonstrated by the finding of ancestral estrogen receptors in primitive creatures, such as mollusks, creatures which do not reproduce in the manner of mammals. Why did estrogen exist in such primitive creatures and what was its role? Essentially, estrogen existed for the purpose of ensuring survival! Estrogen is the master of virtually all genes involved in the regulation of energy production and metabolism, immune regulation, cognitive and digestive functions, and of course – in more "advanced life forms" like ours – estrogen manages the details of reproduction itself. And when thought about in greater depth than is often given to this topic, it becomes obvious why such should be the case. Would it make sense for a creature which is not metabolically healthy and viable to reproduce? In mammals, as in the more

primitive organisms, estrogen regulates such things as appetite, sleep, energy production and storage, fighting infections and integrating immune functions, and virtually all the aspects a functional, living creature needs to sustain life itself.

As the prime directive of all life is the creation of new life, along with the nurturing and caring for the "replacement being" to viability and independence, it is clear that there would need to be a master hormone, a key hormone to oversee and coordinate all critical life functions, and that hormone is estrogen! A hormone's purpose within the body is to deliver vital information to cells, so that they can perform the vital functions needed to maintain optimal health. Estrogen is the prime hormone of the female body performing that task.

Foundational to survival is a healthy circulatory system. Without a strong and properly beating heart, working with vibrant and compliant arteries and functional capillaries, the health of every cell in the body would be negatively impacted, and no organ would be able to operate in an optimal state. This chapter will serve as your introduction to the amazing and beautiful story of women, hearts, and hormones, a story of a beautiful synergy. There is no better place than with the heart, the foundation of the cardiovascular system, to begin our journey into the true meaning of menopause for each and every woman. Within every female there is a heart – the beating organ which sustains the flow of nutrients and oxygen to all of the cells of body – maintaining the existence of life.



The detrimental effects of estrogen deficiency on metabolism ... and on cardiovascular health ... are many

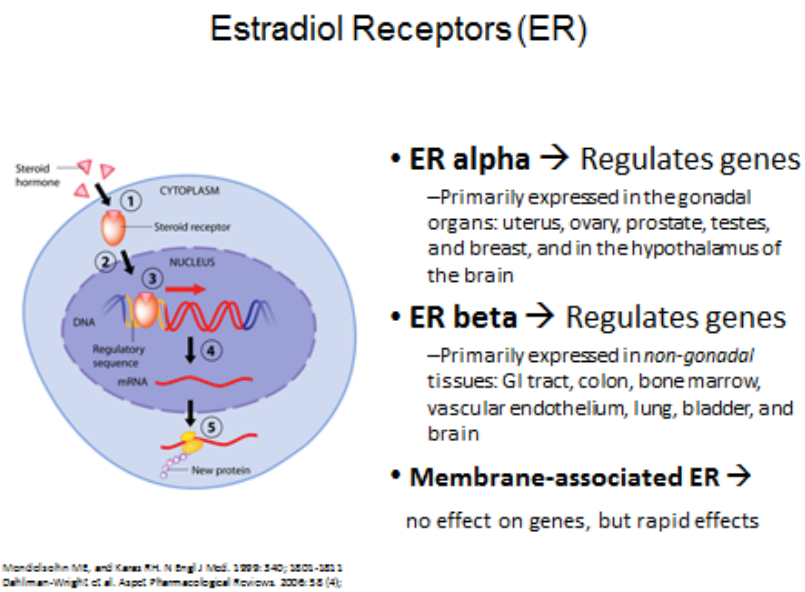
Endocr Rev. The role of estrogens in control of energy balance and glucose homeostasis.2013; 34 (3): 309-338

PART ONE: ESTROGEN BASICS

To begin our journey into the essential facts surrounding women, hearts, and hormones, we will start with a review of what estrogen is and its basic functions in the female body relevant to the cardiovascular system. It is now known that estrogen comes in three forms, estradiol, estrone, and estriol. The predominant type produced in large quantities from the ovaries during the reproductive years is estradiol. The prevalent form found in menopausal women, produced mainly in adipose tissue from circulating androgens via peripheral aromatization is estrone. And lastly, the dominant type found during pregnancy, made in the placenta, is estriol. We also now know that estrogen acts on nearly all cells of the body through three types of estrogen receptors (ER), known as ER alpha, ER beta, and cell membrane receptors. The alpha and beta receptors are classically known as nuclear receptors, meaning that they work through ligand receptors in the cell nucleus, attaching to the appropriate gene on the chromosome and ultimately resulting in the transcription of a protein, typically an enzyme. This process can take many hours or longer. On the other hand, estrogen works through membrane receptors by attaching to the receptors within the membranes and creating extremely rapid responses through the production

of cell signaling agents, known as kinases. The true complexity of the function of the estrogen receptors is much more complicated than what was just presented, as nuclear receptors ER alpha and beta can also function as membrane receptors, can up and down regulate each other, and can work simultaneously in both capacities.

There are both similarities and differences in the locations and functions of the different estrogen receptors. ER alpha receptors are located in the hypothalamus of the brain and regulate much that relates to metabolism and reproduction, while ER beta receptors are found predominantly in other areas of the brain such as the cerebral cortex, and deal more with emotions, sexuality, and cognition, and are also largely in the lining cells of the intestinal track and the endothelial lining cells of arteries and capillaries. That said, there are always mixtures of the different receptors and their interactions are still in the process of being deciphered. It is now known that estrogen receptors are present in the heart muscle cells and also play a large role in regulating the autonomic nervous system. The parasympathetic nervous system involves the vagus nerve, which regulates the parasympathetic nervous system and heart rate variability, very important to cardiac and overall health and wellbeing. The parasympathetic nervous system can be thought of as the instigator of the calming effect, slowing heart rate and dilating blood vessels, whereas the sympathetic nervous system is associated with a stress response with constricting of vessels and increasing heart rate. With the loss of peripheral estrogen production from the ovaries after menopause, the sympathetic nervous system becomes upregulated, relative to the parasympathetic, and women experience more palpitations and tachyarrythmias, along with higher sensations of stress and anxiety, all negative for the health of the cardiovascular system and of the "whole woman."



In addition to the estrogen receptors alpha, beta, and membrane, there is a newly discovered type of receptor, the Estrogen-Related Receptors (ERR), of which the ERR alpha is the most well understood. These receptors don't bind to estrogen itself, but require the presence of estrogen in order to work, and are located in tissues with high metabolic needs. The ERR's increase the production of energy, through increased fatty acid oxidation, induce increased mitochondrial replication, attenuate the production of reactive oxygen species (ROS), induce the expression of many antioxidant genes which normalize ROS formation, and modulates vessel tension by regulation of endothelial Nitric Oxide Synthase (eNOS) expression, a subject I'll cover in later on in this chapter. You are now beginning to realize the incredible power which estrogen has upon the cardiovascular system of the female body.

17β-Estradiol induced Estrogen-related Receptor

Increase fatty acid uptake/oxidation with increased mitochondrial replication, ATP generation and attenuated reactive oxygen species	E2 induced ERR-alpha expression modulates fatty acid metabolism and reduces the circulating lipids through	E2 induced ERR-alpha expression in endothelium – important role for E2 induced vasculo-protective effect - modulates vessel tension by regulation of eNOS expression

Estrogen receptors exist throughout the body, found in tissues most patients and clinicians are unaware have an estrogen relationship. These include the brain, lungs, bladder, vagina, arteries, mitochondria, muscles, heart, arteries, bones, joints, skin, and all aspects of the gastrointestinal tract, liver, and all cells of the immune system. Indeed, the newly discovered relationship interlinking the health of the gut microbiome, the immune system, the brain, the cardiovascular system, the skin, and more - is one of the biggest medical revelations in decades.

Another critical area in which estrogen impacts greatly on health, including the health of the cardiovascular system involves its role as the master of the Master Clock, managing the coordinated rhythm which is essential for the body to function correctly. There is a beautiful Circadian Rhythm of the female body, aligning all functions with the 24 hour rotation of our Earth on its axis. The master of this rhythm is the Master Clock, located in the brain, sitting atop the optic nerve at a site called the Superchiasmatic Nucleus. All organ functions must be in complete alignment with the Circadian Rhythm, working together in perfect unison. And it is estrogen with facilitates keeping this alignment via the Master Clock. Estrogen should be viewed as working at both a local and global level, helping to manage all organs with their day to day functions, while also managing the unified function of the organ systems. It turns out that having the various organs work in a beautiful synchrony is essential for optimal health. Estrogen helps to keep the beat – keeping the various organ systems working in a harmonious way. I view it with this analogy: estrogen is the conductor of the largest and most talented orchestra in the world. And this orchestra is tasked to play the most complex symphony ever created. This symphony has each section of instruments playing completely divergent and unique pieces of music, with very different beats and timing. Yet somehow, when all the sections of the orchestra play in perfect unison, the music created is unworldly in its beauty. Such is the music created when estrogen conducts the orchestra of the female body. All the seemingly disparate pieces (organs) somehow join together to create an amazing blend, in perfect harmony, known as optimal health and function. Once estrogen is in decline, with the advent of the perimenopause, all the various sections of the orchestra, our organs, begin to drift from the proper beat and rhythm, and the beautiful music begins to transform more and more towards noise and discord. At first the various sections of the body can continue their proper beat, but soon chaos develops, and disease and disorders develop, including cardiovascular disease.

With the onset of the perimenopause, progressing into menopause, and thereafter, a host of maladies typically befalls women. The rapidity, the degree, and variety of disorders each woman experiences are unique to her and depend on her early state of health, her genetics, and her lifestyle choices. Some of the conditions common to menopausal women are obesity, diabetes, osteoarthritis, osteoporosis, non-alcoholic fatty liver, sleep disturbances, sleep apnea, and insomnia, metabolic syndrome, cancers, autoimmune diseases, atherosclerosis, hypertension, sexual dysfunction, intestinal problems such as inflammatory bowel disease, gastroesophageal

reflux, and colon cancer, Alzheimer's disease and vascular dementia, depression, and aging skin. Now that is quite a horrendous list of conditions, and if you think about it, they represent the gamut of what we call AGING! In each case, these disorders match those seen with estrogen deficiency. So what then is aging? In my opinion, aging in women is a reflection of loss of estrogen! Indeed, with the decline in systemic estrogen, there is a comparable reduction in the loss of estrogen production in the organs which can produce estrogen locally, in a paracrine manner. It has been shown that estrogen production in the brain declines in a sad unison with the decline in ovarian production. And as well, with the decline in estrogen production from the ovaries one sees the degradation of the health of the gut lining cells, the enterocytes, foretelling of the increasing risk with the progression of menopause not only of the increase in the incidence of colon cancer, but of the body-wide impact of a dysbiotic, leaky gut!

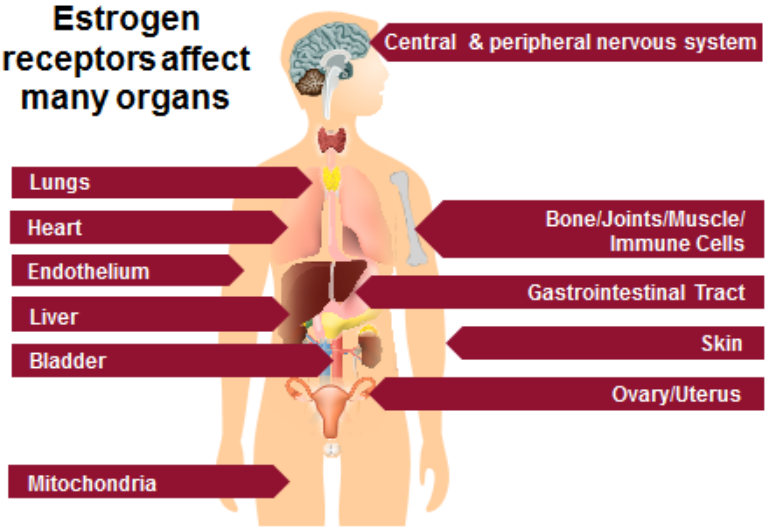
For there are estrogen receptors throughout the gut, from the mouth to the anus, including the amazing enteric nervous system, the gut parallel to the brain. With the decline in estrogen, the health of the GI tract falters and this can result in a high incidence of impaired gut barrier permeability, the famous so-called "leaky gut," which opens the door to the great array of ills associated with that condition, including autoimmune diseases, mood and cognitive disorders, AND cardiovascular complications. As well, it is now recognized that with the loss of estrogen, the makeup of the critical gut microbiome is altered, and this in turn leads to changes in the production of microbiome metabolites, such as acetate, proprionate, and butyrate – the short chain fatty acids. The short chain fatty acids (SCFAs) have immense impact on the barrier function of the gut itself, the blood brain barrier, and of the arteries. SCFAs are involved in signaling between the gut immune system, the enteric (gut) nervous system, the liver, the pancreas, and the brain. Loss of proper production of SCFAs results in a huge array of problems, including impaired gut barrier function, systemic inflammation, insulin resistance, and fatty liver. Needless to say, all have a huge impact on the health and function of the cardiovascular system. With the loss of ovarian estrogen production, a domino effect of health related problems develops.

In concordance with the impact of estrogen on the gut, resulting in great metabolic effects, some additional examples of the metabolic alterations which come from declining estrogen levels include altered brain function with changes in sleep quality and increased incidence of sleep apnea, which increases cardiovascular ills such as arrhythmia and hypertension; the dysregulation of adipose tissue production of adipokines (adipose tissue related hormones), resulting in more central and visceral obesity and ensuing systemic inflammation; the dysregulation of pancreatic beta cells and increase in type 2 diabetes; impaired glucose regulation and uptake in muscle, increasing insulin resistance and further facilitating the development of fatty liver, and altered function of immune cells leading to more production of inflammatory cytokines, resulting in the progression of inflammation, adiposity, and atherosclerosis.

As you can see, the loss of estrogen production from the ovaries, which occurs in all women, has an incredible array of diverse and negative results, encompassing virtually every organ and every system of the body. As we in functional medicine well know, all is related to everything within the body. When something impacts the gut, the kidneys, the brain, the muscle, the gut, adipose tissue, the immune system, and more, there will be an inevitable impact upon each and every other body system. And so, of course, that holds true for the impact upon the cardiovascular system. To truly comprehend the immense impact which menopause has on the cardiovascular system, one must first completely understand the global the impact of estrogen upon the female body as a whole.

Now that you have received a taste of all that estrogen does in the female body, and of the great impact upon all systems once ovarian estrogen production is lost, we can now focus more specifically upon the cardiovascular

system. And at the conclusion of this chapter, with your basic knowledge aasured, I will offer some useful recommendations to immediately implement, to assist your patients in maintaining cardiovascular health, and with that, the health and happiness they wish and deserve to have, for the duration of their lives.



PART 2: AN OVERVIEW OF THE IMPACT OF MENOPAUSE ON THE CARDIOVASCULAR SYSTEM

Menopause Overview

- A decline in estrogen is associated with:

1. Hypertension and a decline in NO and other vaso-moderating molecules
2. Dyslipidemia (a rise in LDL, oxidized LDL, and a decline in HDL)
3. Increased oxidative stress
4. Development of atherosclerosis
5. Direct effects on the myocardium and adipose tissue functions

- Menopause exacerbates these cardiovascular risk factors
- Evidence shows that women who go through menopause earlier are at increased risk of cardiovascular complications

Chakrabarti S, Lekontseva O, Davidge S. IUBMB Life. June 2008; 606(6): 376-382
Saltiki, K and Alevizaki M. Hormones. 2007; 6(1): 9-24

Coronary heart disease is the number one killer of women in the world. It kills more women than does all forms of cancer, diabetes, Alzheimer's Disease, and pneumonia. Yet it is underappreciated as a killer of women, and women remain underrepresented in cardiovascular research. In fact, most women still consider coronary artery disease to be a "man's disease." Sadly, when women are diagnosed, outcomes are generally far worse than they are for men, yet women are typically treated more conservatively and are often treated later in the course of their disease processes. Prior to menopause, most women are greatly aided in their cardiovascular state by the presence of estrogen, but with the onset of perimenopause, this benefit is quickly lost. In fact, during the perimenopause years, women are already developing atherosclerosis. Recall what I said earlier, that the word menopause is a poor label for the process of loss of estrogen production from the ovaries. This is a process of ovarian senescence, marked by the cessation of menstrual cycles near the end of this aging process, not at the

beginning. We must stop thinking of menopause as a finite time, and begin thinking of it as a process over time, a process bringing with it the onset and evolution of cardiovascular problems for women. These problems progress silently throughout this process, and often cost women their lives far earlier than should be the case.

According to the American Heart Association statistics, an overall increase in heart attacks among women is seen about 10 years after menopause occurs. For most women, that would be about age 60. To bring home that point, they emphasize those 400,000 women in the US die of heart disease each year – for an estimate of one death every minute.

The incidence of hypertension is incredibly high. Overall, worldwide, 25% of women have hypertension, of which 60% is uncontrolled. In the US, among women over age 60, more than 75% are hypertensive, and by age 75, a shocking 85% of women have high blood pressure. Data is clear that the earlier a woman goes through menopause, the more significant her cardiovascular problems, including the onset of heart failure.

Another enormous facet of estrogen function impacting the cardiovascular system is the loss of the proper functioning of the autonomic nervous system – the parasympathetic and sympathetic nervous systems which were already touched upon. The autonomic nervous system is controlled by estrogen, and linked to the Master Circadian Clock. After menopause, the autonomic nervous system becomes dominated by the sympathetic component, which creates more anxiety, a faster heart rate, more sleep disturbance, and appetite dysregulation. Accompanying the increase in sympathetic tone is an increase in cortisol production. In fact, the Circadian Rhythm with cortisol is often flipped, with the highest cortisol levels occurring at night, and the lowest in the morning. Along with this, many women become "non-dippers," meaning that their temperature and blood pressure doesn't drop during the night as it should. This also impacts sleep and increases the risk for early morning strokes and heart attacks. Sleep is impacted and melatonin production and its proper rhythm is altered, which adds to all the risks. Melatonin is a potent antioxidant and acts in the gut to maintain its proper function and its dysregulation has great cardiovascular implications.

Regarding the issue of the "flipped" Circadian Rhythm, a study was performed in which the subjects had the day and night completely flipped, living as though high noon was midnight. And what was found after just eight days of this "flipped" rhythm was a huge impact on many measures of cardiovascular and metabolic health. There were significant and harmful changes in levels of inflammatory markers, leptin, lipids, and insulin. With the loss of estrogen comes loss of Circadian Rhythm control, and its great impact upon the cardiovascular system unbalancing the beautiful matrix of life systems.

Impact of 8 Days of "Flipped" Circadian Disruption

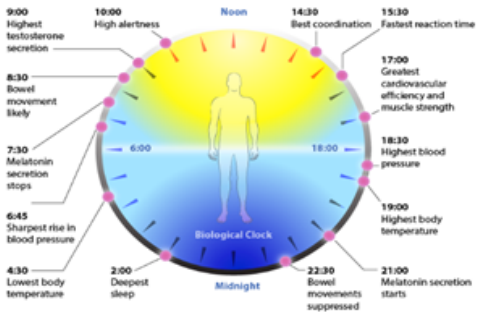
- Decreased leptin (-17%)
- Increased glucose (+6%)
- Increased insulin (+22%)
- "Flipped" daily cortisol rhythm
- Increased mean arterial pressure (+3%)
- Reduced sleep efficiency (-20%)

Impacting the cardiovascular system!

Scheer et al., *PNAS* 2009;106(11):4453-8.

The Circle of Life: The Rhythm

These daily fluctuations, or *circadian rhythms* (from Latin: "about one day"), are fundamental to all organisms, from bacteria to human beings. Circadian rhythms help coordinate and synchronize our internal body functions, as well as our interactions with the external world.



http://dyingandgrief.com/tag/melatonin-sundowning-syndrome-supplement

PART 3: THE CRITICAL IMPORTANCE OF ARTERIAL ENDOTHELIAL HEALTH

The vasculature is the critical delivery system of the body, funneling oxygen and nutrients to all cells, in all parts of the body. But the arteries and capillaries themselves are not just tubes of varying diameters; rather they are very dynamic structures which have a lining, called the endothelium, which is a very active entity. Classically thought to be an inert membrane, the endothelium is now known to play an integral role in metabolic, immunologic and cardiovascular health. It needs to be capable of withstanding the impact of mechanical stressors, such as stretch, shear stress, and pressure, from the turbulence of the blood surging within it, particularly at bifurcations. The arterial endothelium contains cells which have the capability of performing a variety of incredibly important functions, acting as the interface between the circulating blood and the vascular wall. The endothelium maintains vascular homeostasis by its synthesis and release of a wide range of molecules, in response to physiologic and chemical stimuli, including the production of the incredibly important gas, nitric oxide. The endothelium makes or reacts to other humoral agents involved in vascular tone, clotting, and fluid regulation, such as angiotensin II, endothelin 1, aldosterone, bradykinin, and thromboxane. Other chemical factors can impact endothelial function, such as glucose, homocysteine, and Reactive Oxygen Species (ROS). And not surprising to those who have read all the previous material in this chapter, all of these diverse processes and functions are related in various ways to estrogen. Indeed, estrogen regulates the genes involved in the production of the enzymes involved in the evolution of hypertension, which is why loss of estrogen is so catastrophic.

PART 4: THE NECESSITY OF NITRIC OXIDE FOR VASCULAR WELLBEING

Shared illnesses associated with a decline in estrogen or nitric oxide

Decline in estrogen	Decline in nitric oxide
• Atherosclerosis • Inflammation & Immune Dysregulation • Alzheimer's Disease • Cancers (Breast, Colon, Hepatocellular)	• Atherosclerosis • Inflammation & Immune Dysfunction • Alzheimer's Disease and Vascular Dementia • Cancer via uncontrolled cell proliferation • Hypertension • Thrombosis
• Metabolic Syndrome, Diabetes • Obesity • Osteoarthritis/Osteoporosis • Neuro-Inflammatory Diseases • NAFLD • Sleep Disturbance/Insomnia	• Peripheral Artery Disease • Sexual Dysfunction –male and female

Nitric oxide is a critically important gas, produced in a multitude of sites, including the gastrointestinal system, and within arteries themselves. It is known as a Redox signaling agent, meaning that it is involved in reduction and oxidation reactions. The focus here will be on the arterial endothelial production of nitric oxide, through the stimulus of the enzyme endothelial Nitric Oxide Synthase (eNOS), produced by the endothelial cells under the influence of our beloved and amazing hormone, estrogen. Nitric oxide (NO) is a potent anti-oxidant involved in facilitating dilation of blood vessels, reducing blood clotting, reducing inflammation in arterial walls, reducing LDL oxidation, reducing arterial wall thickening, and reducing free radical formation. In an interesting study of mice lacking the gene to make NO, the mice developed a metabolic syndrome-like phenotype, developing hypertension, elevated levels of cholesterol, triglycerides, free fatty acids, and abnormal leptin levels. This manifested as an increase in visceral fat accumulation of 30-40%. Loss of estrogen production from the ovaries has a dramatic impact on all arteries, from the largest to the smallest capillary. The loss of estrogen results in the rising incidence of hypertension and renal dysfunction, damage to the endothelial integrity of arteries, resulting in widespread "leaky" arteries, a damaged blood brain barrier and increased extracellular fluid accumulation.

PART 5: ESTROGEN AS THE REGULATOR OF CRITICAL ENZYMES RELATED TO METABOLIC AND CARDIOVASCULAR HEALTH

Estrogen-Regulated Cardiovascular-related Genes

Vasodilation and vasocontriction
- Prostacyclin cyclooxygenase
- Prostacyclin synthase
- Endothelial NO synthase
- Renin and angiotensin
- Endothelin-1

Lipid Metabolism
- Lipoprotein lipase
- Apolipoproteins
- Leptin

Immune activity
- Vascular-cell adhesion molecule
- Cytokines (IL1, IL6, TNFα)
- Cytokine receptors

Coagulation
- Fibrinogen
- Coagulation factors
- Protein S

Angiogenesis
- Matrix metalloproteinase
- Vascular endothelial growth factor

Non-Genomic Effects
- Fast-acting actions such as NO facilitated vasodilation

Saltiki, K and Alevizaki M.. Hormones. 2007; 6(1): 9-24

As you can see from the list of enzymes on the above chart, estrogen is involved in a great array of enzymatic functions involved with metabolic and cardiovascular health, and this list is not at all exhaustive. Among the listed enzymes which I would like to touch on is Prostacyclin cyclooxygenase (COX 1 and 2), Matrix Metalloproteinase, Renin and angiotensin, Endothelin 1, and the cytokines.

I wanted to briefly touch on these particular enzymes as key ones involved with the induction of hypertension and overall systemic inflammation. The important point I want to give to you is that estrogen dampens down the process of inflammation! There is a delicate and dynamic balance always in place within the human body. Clearly those involved with Chinese Medicine, with their understanding of the balance of Yin and Yang, and within the

teachings of Ayurveda, with the balance of the Doshas, it was long ago recognized that forces are always at play within the body and that optimal health requires a balance of these forces.

The essential take away is that estrogen is pivotal to maintaining the balance of these forces. Inflammation is critical to life, for without the ability of the body to mount an inflammatory response, there would be no defensive structure to the body, and any invading bacteria or virus would take hold and destroy us. The human body has an absolutely amazing system designed to maintain immune cell balance and control of inflammation. Without estrogen, there can be no proper control of these processes. All of the enzymes I mentioned, the COX 1 and 2, angiotensin and renin, endothelin 1, the inflammatory cytokines, and matrix metalloproteinases, as well as NADPH oxidase, are key players in the inflammatory response. Without the "supervision" of estrogen, they can create havoc, leading to hypertension, kidney disease, dangerous cardiac remodeling increasing valvular disease and heart failure, and of vascular dementia.

Another enzymes controlled by estrogen is Paroxanase 1 (PON 1), which is an essential enzyme in maintaining the proper state of LDL cholesterol. PON 1 prevents the oxidation of LDL cholesterol, an essential step in the development of atherosclerosis. The production of glutathione, the master antioxidant and detoxifier of the body also falls under the control of estrogen, including Glutamyl Cysteine Ligase and Glutathione Peroxidase. Superoxide Dismutase (SOD) is another critically important enzyme under the control of estrogen. Superoxide is an obligate byproduct of oxidative phosphorylation – the production of energy from fat in the mitochondria. It is an extremely toxic substance and if it accumulates within the mitochondria, they will die. Superoxide Dismutase is the enzyme is necessary for the reduction of toxic superoxide to hydrogen peroxide, which can then cross out and undergo alteration to harmless water. After menopause, with the loss of estrogen production from the ovaries, there is damage to mitochondria from the accumulation of superoxide within them. The mitochondria are the powerhouses of the cells and are present in great numbers within the cells of the heart. Damaged mitochondria within the heart have grave implications for the health and function of the heart, including the increased incidence of heart failure.

As was mentioned, after menopause there are changes in the lipid profile of women. PON 1 and its key role in preventing the oxidation of LDL cholesterol is a huge issue. The small chart below shows some of the additional ways in which estrogen imparts its influence on maintaining the benefits of a healthy lipid and cholesterol environment within the body. This includes decreases in the activity of enzymes as such as lipoprotein lipase and HMG COA Reductase. It is through the activity of estrogen that women in the reproductive years have lower LDL levels and higher HDL levels than men.

Lipid Metabolism: Cholesterol

- Compared to men, during reproductive years, women have:
  - Lower LDL levels
  - Higher HDL levels
  - Lower total lipid levels
- Estrogen upregulates the expression of:
  - Apo-proteins
  - LDL receptors – responsible for the uptake of lipoprotein
- Estrogen decreases:
  - Lipoprotein lipase
  - HMG-CoA Reductase activity

Saltiki, K and Alevizaki M. Hormones. 2007; 6(1): 9-24

PART 6: SOME ACTIONS TO TAKE TO AMELIORATE THE NEGATIVE IMPACT OF ESTROGEN LOSS:

MY THERAPEUTIC PLAN

Faced with the disturbing array of scientific data on the negative effects of menopause upon the female cardiovascular system, it's now important that I share with you some practical strategies to reduce the damaging effects throughout the cardiovascular system.

My strategy is straightforward and relatively easy to implement. It starts with the obvious question – what can we do? It turns out that though we obviously cannot prevent the development of menopause, we can certainly reduce the unfortunate and damaging sequelae which menopause creates for all organ systems of the body, and most particularly for the cardiovascular system.

A Therapeutic Plan

- Lab testing, Imaging, Echocardiogram
- Hormones
- Detox and Diet
- Exercise
- Stress control
- Sleep
- Supplements

I always begin with imaging studies and lab testing as I believe that you cannot properly monitor what you do not measure. I check on the current levels of systemic inflammation within the woman's body, her hormonal state, select genetic tests, the status of the arterial endothelium and the heart, and often look at her level of heavy metals, micronutrient status, and her gut microbiome.

Imaging:
CIMT, Echocardiogram

Lab Testing

- Inflammatory markers
- Advanced and routine lipid panels
- Oxidized LDL
- Uric acid and ferritin
- Apo E
- MTHFR
- ADMA
- TMAO
- Micronutrients
- Gut microbiome
- Microalbumin
- Heavy metals
- Hormones

I like to begin by looking at the function and structure of the heart by reviewing an echocardiogram. What I look to see is whether or not there are signs of poor energy production within the heart, which is manifested as mild diastolic dysfunction. Sadly, this vital sign of heart health is typically completely overlooked by most cardiologists. I have seen many patients who have brought in their echocardiogram reports which show mild diastolic dysfunction and their cardiologists have never even mentioned the finding. Mild diastolic dysfunction is a significant finding which indicates a reduced level of energy production by the myocardial myocyte mitochondria as evidenced by an altered filling stage of cardiac function. You are now aware that estrogen is critical to the maintenance of mitochondrial health via the enzyme superoxide dismutase and the production of proper glutathione levels via glutamate cysteine ligase and glutathione synthetase. The loss of estrogen can manifest with an abnormal echocardiogram. As well, cardiac valves may be damaged by chronic hypertension, resulting in a state of valvular insufficiency and regurgitation. Lastly, loss of estrogen can result in the abnormal functioning of matrix metalloproteinases, causing inappropriate tissue remodeling and subsequent cardiac dysfunction.

In the presence of hypertension or an arrhythmia, I also order a sleep study to evaluate the presence of obstructive sleep apnea and other sleep disorders. As you are now aware, loss of estrogen impacts on the autonomic nervous system through both the dysregulation of the Master Clock and the Circadian Rhythm, upregulating the sympathetic nervous system at the expense of the parasympathetic, and through the alterations to the gut microbiome which can impact on the production of short chain fatty acids and other metabolites, further impacting on the function of the vagus nerve.

As I mentioned, I also order an array of laboratory tests to evaluate the state of inflammation. I order a myeloperoxidase (MPO), indicative of injury and damage to the endothelium through the measurement of this inflammatory enzyme produced by macrophages. Additionally, I look at the following: the PLAC test which provides an assessment of inflammation and possible atherosclerosis within the artery wall, microalbumin, which reveals "leaky arteries," due to endothelial dysfunction, F2 Isoprostanes which is reflection of oxidative stress due to poor lifestyle choices, and an hs CRP which is a reactive marker of systemic levels of inflammatory cytokines. Thyroid function tests, Vitamin B12 and D levels are also ordered.

The maintenance of a healthy gut microbiome and a properly functioning enteric nervous system is essential to a healthy cardiovascular system. Emphasizing the consumption of an anti-inflammatory diet is essential. For women who are menopausal or peri-menopausal, but are healthy, I propose a modified Mediterranean Diet, high in the consumption of polyphenol containing vegetables and fruits, along with whole grains, but excluding all conventional wheat products. Sadly, wheat grown in the USA is covered with toxic herbicides prior to harvesting, for their function as desiccants, resulting in a wheat product which is extremely toxic to the gut microbiota. Of course I recommend that all food eaten is organic. Avoiding all processed foods and incorporating only whole foods in their natural state is imperative. Whole, organic foods have significant quantities of nutrients of all sorts, and of both soluble and insoluble fiber. Fiber is essential as food to nourish the microbiota of our gut, and in fact, resistant starch, which has been shown to be of great benefit for metabolic dysfunction, is not digestible by our human digestive enzymes, and can only be broken down, fermented, by the gut microbiota. Foods high in insoluble fiber include whole grains, beans and legumes, vegetables such as parsnips, okra, potatoes, asparagus, beets, artichokes, green bananas and plantain, sweet potatoes, broccoli, Brussel sprouts, kale, green beans, carrots, and flax seeds. Fruits, particularly those with skins, nuts, and seeds are also good sources, and in general, all vegetables will have a nice amount of fiber.

As for animal proteins, I recommend only organic, free range, grass fed, or wild animals be eaten, with the ex-

ception of sustainably raised farmed fish, if such can be located. Being aware that larger fish can contain high levels of mercury is important, and such fish should be only minimally consumed, if at all. Regarding dairy, I recommend primarily fermented whole and organic products, preferably from raw sources, if such can be found and authenticated as safe.

I also now recommend eating foods considered to be phytoestrogens, including flax seeds (ground) and whole organic soy foods. New data show that such foods can bind to gut receptors for estrogen, improving the composition of the gut microbiome and facilitating the production of neurotransmitters, particularly of serotonin. Additionally, such foods help to maintain the integrity of the gut barrier, reducing the incidence of "leaky gut," lowering systemic inflammation and all of the negative consequences inflammation creates. Be sure only whole and organic soy products are consumed, avoiding processed soy and soy derivatives. I recommend such soy foods as the whole beans, miso, and tofu.

Diet: The Modified Mediterranean Diet

- Initially, if any abnormalities, start with a modified vegan diet
- As health improves, progress to a modified Mediterranean diet
- Mediterranean diet was found to improve lipid levels (raise HDL and lower TG) in postmenopausal women

Bihuniak, J. D., Ramos, A., Huedo-Medina, T. et al.. J Acadam Nutri & Diet. 2016. 116(11), 1767-1775.

For my peri and menopausal women patients who already are metabolically ill, with such conditions as hypertension, obesity, dyslipidemia, prediabetes and early diabetes, I recommend a much more restrictive diet – a modified vegan diet. It has been shown that when the gut microbiome is already dysbiotic, with a bad array of bacteria growing and leaky gut likely already established, the consumption of animal products can result in the production of toxic products to the cardiovascular system such as TMAO and nitrosamines. It is beyond the scope of this simple chapter to delve deeply into these matters, but it is clear that it is best to re-establish a healthy gut barrier and a healthy microbiome in the gut prior to placing animal products into the gut.

The best approach to re-establishing a healthy gut and gut barrier is to feed the bacteria with fiber, and to follow the functional medicine principles of the 5 R's for the restoration of gut health. And again, definitely include phytonutrients!

Best Microbiome Nurturing Diet- Modified Vegan Diet

- Healthy fats-Omega 3 supplementation, Omega 6 and 9 from plants, olive oil and olives, "saturated fat" from coconut oil
- Low protein (approximately 12%)
- High complex carbohydrates (70%)
- No animal protein-including no dairy or eggs initially
- No added sugars or processed foods, chemical free
- Rich in complex carbohydrates: whole-grains, all varieties of vegetables, beans, legumes
- Loaded with green leafy vegetables and root vegetables
- Rich in natural fiber and prebiotic and probiotic products

Studies have shown that in just one month of following a high fiber vegan diet that dramatic improvements can be seen in virtually all measures of inflammation and insulin function. This approach as well is excellent for reversing fatty liver, commonly seen in menopausal women and greatly linked with metabolic and cardiovascular dysfunction.

Eating a large array of varying vegetables and fruits is essential. There are amazing effects of phytonutrients and the hormedic effects of polyphenols are great. We should consider food to be medicine and in fact can function as hormones, as polyphenols can circulate and actually attach to hormonal receptors, producing beneficial effects. The expression of "eat the colors of the rainbow" applies to the maintenance of cardiovascular health in menopausal women.

General Recommendations

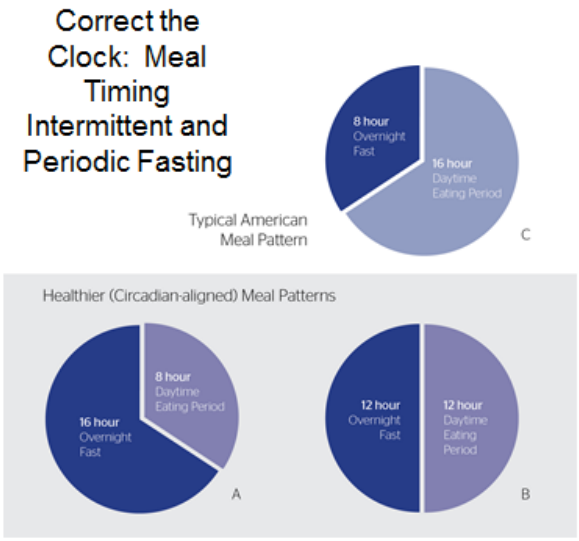
Include

- Potassium and nitrate rich fruits and vegetables, esp. cruciferous vegetables, beets, green leafy vegetables
- High fiber, whole grains (no wheat or gluten), beans and legumes
- Omega-3 rich nuts and seeds
- Unrefined oils and vinegars
- Unadulterated herbs and spices
- Probiotic rich foods

Limit – none is best!

- Limit animal protein (none at first)
- No refined carbohydrates (no wheat or gluten) and fats
- Alcohol
- Artificial colors, flavors and sweeteners
- Allergens and intolerances

I approach dealing with the altered Circadian Rhythm by promoting timed and regular eating, with long periods of fasting on a daily basis. Typical Americans often eat around the clock, and late into the night. The best way to entrain the clocks of the gut microbiota, and subsequently of the liver and the rest of the body, particularly when the Master Clock is not working as well as in premenopausal days, is by eating no more than 3 meals a day, and preferably just 2 with a small snack of primarily fat, and to consume all food within a time frame such that a minimum of 12 hours lapses between dinner and breakfast. Timed eating and periods of fasting each 24 hours entrains the peripheral clocks and can significantly help maintain metabolic homeostasis, and thereby cardiovascular health.



I also greatly advocate for the inclusion of periodic fasting, which has been shown in published studies to lower systemic markers of inflammation, improve insulin sensitivity and lipid profiles, increase brain derived neurotrophic factor, cause apoptosis (programmed cell death) of unhealthy cells, and promote the rejuvenation of organs through autophagy (self- repair) and through the stimulation of stem cells. These benefits can be obtained through the implementation of a 4 day water fast or more safely. Alternatively, the same or better results, can be gained, and easily accomplished, through the use of the 5 day fasting mimicking diet developed at the Longevity Institute at USC. In full disclosure, at the time of this writing, I have done the diet 7 times myself and I am now a paid advisor with the company which grew out of this research.

Not surprisingly, I heavily promote exercise, for which there is an abundance of data to support its use in cardiac health maintenance and restoration. Research supports that women who exercise lower their blood pressure, fasting blood sugar levels, improve lipid profiles, and lower weight, but can also improve the composition of the gut microbiome and the health of the gut.

The best time to exercise is in the mid-morning, in keeping with the dictates of the Circadian Rhythm. If that is not feasible, encourage your patients to exercise in the morning and take a walk outside in the midday, as the weather permits. I also recommend touching the earth with one's feet – on grass or dirt or sand. This process of grounding, sometimes also called earthing, is amazingly beneficial and helps with many issues, including helping reset the Circadian Master Clock.

Also key to helping with the Circadian Rhythm is the consistency of bedtime. Going to sleep by around 10:30 PM is important, as melatonin release is also programmed by clock genes. Getting enough sleep is essential for cardiovascular wellbeing.

Exercise

- Lack of exercise is as much of a risk factor as smoking!
- Research has shown that women who regularly exercise have:
  - Lower blood pressure
  - Blood glucose levels
  - Improved lipid profiles
  - Reduced weight

Lee V and Foody J. Current Atheroscleorosis Reports. 2008; 10:295-302.

Dealing with life's stressors is another key matter, essential to heart health. Many options exist, including the many forms of meditation, guided imagery, progressive relaxation, and hypnosis. Mood issues greatly affect heart health. Women are especially prone to the effects of emotions on the heart, increased following the onset of menopause.

My integrative approach to heart health involves supplementation. I truly believe supplements should be just that – an addition to all of the other things needed for health, which is why I am dealing with this issue last.

There are many supplements helpful for the cardiovascular system, and I'll mention just a few favorites. For heart energy, I suggest COQ10, D Ribose, and Acetyl L Carnitine. I am not a fan of statins, but should someone be on one, be sure to supplement with COQ10. Many pharmaceuticals deplete the body of nutrients and it is important to replete what is lost.

Some of the other supplements I like are Berberine, Bergamot, N Acetyl Cysteine, Resveratrol, grape seed, Quercetin, polyphenols such as pomegranate or Pycnogenol, and plant sterols. Some basic information is included below on a few select items, but it is beyond the scope of this chapter to delve into a discourse on all of these supplements. Of course, all who are low need Vitamin D, a B complex (usually methylated), and a probiotic. Where fatty liver occurs, a detox is needed, along with Vitamin E as mixed tocotrienols and tocopherols, milk thistle or a derivation, and selenium. Gut healing is needed, involving fiber prebiotics, glutamine, zinc carnosine, and some Vitamin A. Small doses of melatonin can be helpful. I suggest .5-1 mg 4-6 hours before expected bedtime, to support the resetting of the clock. Recommend the bedroom be very dark and cool and quiet.

Another supplement I commonly use for the treatment hypertension is a precursor product for nitric oxide. Nitric oxide is often present in reduced amounts in the arteries of menopausal women, resulting in more oxidative stress. I avoid arginine and prefer a product with citrulline, which has been shown to be more advantageous.

Berberine Clinical Trials

- Randomized, double-blind, placebo-controlled clinical trial on 24 patients diagnosed with metabolic syndrome. Over a 3 month period, berberine significantly reduced waist circumference (in women), moderated triglycerides and supported insulin sensitivity.*

- Double-blind, placebo-controlled, cross-over trial of 144 subjects. After 3 months, berberine administration significantly decreased body weight, BMI while supporting healthy lipid profiles compared to placebo.*

Pérez-Rubio KG, González-Ortiz M, Martínez-Abundis E. Metab Syndr Relat Disord. 2013 Oct;11(5):366-9.
Derosa G, D'Angelo A, Bonaventura A, et al. Expert Opin Biol Ther. 2013 Apr;13(4):475-82.

N-acetyl-l-cysteine

- Derivative of the amino acid l-cysteine, which is a precursor for glutathione
- Supports tissue levels of glutathione and helps chelate heavy metals

- In animal models, NAC supported
- Healthy lipoprotein function
- Immune mediator activity in the arterial wall
- Glucose homeostasis
- Antioxidant status
- Glutathione status

Meng XP, Yin CS, Li ZX, et al. Zhonghua yi xue za zhi. 2009; 89(26):1850-1853]
Souza GA, Ebaid GX, Seiva FR, et al. Evid Based Complement Alternat Med. 2011;2011:643269.

Phytosterols

1. Compete with cholesterol for absorption into the body
2. Promote excretion of cholesterol via bile acids

- Randomized, clinical trial in adult subjects:
- Plant sterol moderated LDL-cholesterol concentrations from baseline in by between 15.1% and 26.8%.

- Meta-analyses of over 40 clinical trials suggest that phytosterols provide significant support for healthy lipid profiles.

Lau VW, Journoud M, Jones PJ. *Am J Clin Nutr.* 2005 Jun;81(6):1351-8.
Chen JT, Wesley R, Shamburek RD, et al. *Pharmacotherapy.* 2005 Feb;25(2):171-83.

Supporting Nitric Oxide: Why Citrulline?

•Arginase – degrades orally administered L-arginine

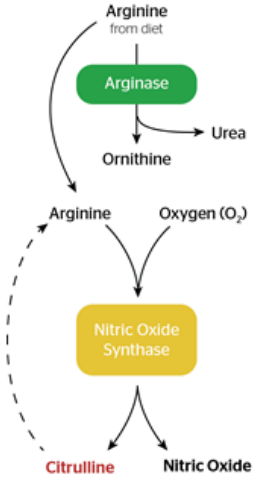
- Restricts arginine absorption by 38% - 70%

Citrulline – Avoids arginase; better absorbed and utilized than arginine

Double-blind, randomized, placebo-controlled crossover study of 20 healthy volunteers

L-citrulline increased AUC and C_{max} of plasma L-arginine more effectively than L-arginine*

Schwedhelm et al. *Br J Clin Pharmacol.* 2008 January; 65(1): 51–59.



Hormonal Supplementation

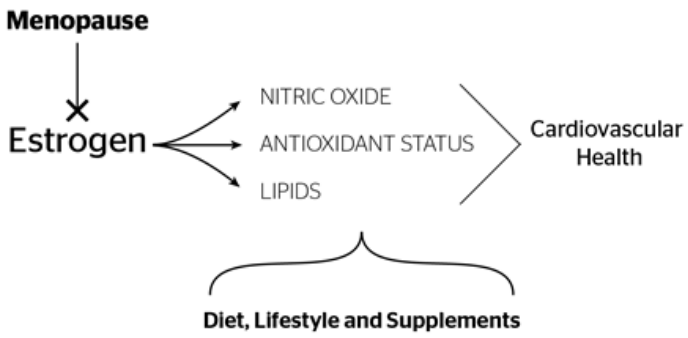
Lastly, I will only briefly touch on the topic of hormones, but strongly believe that hormonal therapy has a great deal of merit. After years of instilling fear in the hearts and minds of health care practitioners concerning the use of hormones in menopause, there is now beginning to be a return to rational thought. The Women's Health Initiative did not utilize human hormones and had an oral delivery system for the estrogen component. We now know that the first pass of hormones through the liver increasing thrombophilic tendencies and that is likely the mechanism for the elevated incidence of stroke ween with the use of conjugated equine estrogens. Later studies with the use of topical estradiol have not shown such risks and observational studies have shown reduced cardiovascular risk and ongoing studies are also very reassuring. In fact, the American Heart Association has recently placed on its website information of a very reassuring nature concerning the use of hormones by menopausal women, near to the time of onset of the menopause.

Concerning the use of hormones, I want to emphasize that only human bioidentical hormones should be used, and estradiol should always be given in a topical form. As well, avoid the use of estriol, due to concerns of hormone-hormone receptor issues. Estriol only binds with the ER beta and as our understanding of estrogen receptors has grown, it is becoming clearer than it is best to provide just estradiol and allow the body to convert some to estriol as it deems appropriate. ER receptors interact with each other and excessive stimulation of ER beta could result in an unwanted downregulation of ER alpha, with negative consequences.

The last comment on hormone therapy is that at least we as a functional medical community should consider the idea that the best way to deliver hormones would be in a physiologic manner. The use of static low dose hormones was begun at a time when little about estrogen receptors was known and the myriad effects of estrogen throughout the body were unrecognized. Systemic estrogen was given solely for the relief of hot flashes. Progesterone was deemed unneeded and downright unnecessary, and possibly dangerous. New understandings of how these hormones affect a great number of bodily functions, along with the recent recognition that hormones are delivered with a rhythmic Circadian and lunar rhythm, has changed the paradigm of how we should view hormones. The complex interaction of hormones and their receptors is becoming more recognized, and so the paradigm of delivering hormones to women in a static and non-physiologic manner may soon change, opening up new therapeutic vistas for menopausal women.

Ultimately, the approach to women in menopause, to maintain cardiovascular health, will incorporate the entire functional medical matrix as we now understand it, with extra emphasis on timed eating and periodic fasting, along with new approaches to hormonal supplementation.

Summary



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Felice L. Gersh, M.D. is a rare combination of a Board Certified OB/GYN who is also fellowship trained in Integrative Medicine at the University of Arizona School of Medicine. She received her undergraduate degree in history from Princeton University and her medical degree from the University of Southern California School of Medicine, which was followed by a four year internship and residency in OB/GYN at the prestigious Kaiser Hospital in Los Angeles.

She combines her talents as an Integrative Physician, specializing in all aspects of female health. She is especially renowned for her expertise in hormonal management of women, and has a unique specialization in the unique complex medical problems faced by reproductive women.

In addition to being a sought-after international speaker and published writer, she works full time as the Medical Director of one of the most successful private practices in Orange County, California: The Integrative Medical Group of Irvine. Her long and distinguished career has also included many years serving as an Assistant Clinical Professor of OB/GYN at the Keck/USC School of Medicine, appearing as a frequent guest lecturer to MD/MBA students at the UCI Paul Merage School of Business, and working as a highly respected forensic medical expert in gynecological matters. She continues a close affiliation with the Fellowship in Integrative Medicine at the University of Arizona School of Medicine, lecturing to the fellowship students and helping the Fellowship candidates with their comprehensive examinations.

Dr. Gersh has been the recipient of numerous awards, including the being initiated into the Alpha Omega Alpha medical honor society, recognizing the top 5 percent of medical students, named the outstanding volunteer faculty for the OB/GYN Department at USC-Keck School of Medicine, awarded the status as a Physician of Excellence for Orange County 13 years in a row, a named SuperDoctor of Southern California for the past few years, and recognized as a TopDoc, as well as others.

Dr. Gersh has been heard around the world on numerous podcasts and webinars and is an international lecturer, most recently speaking in Australia, New Zealand, and Dubai. Dr. Gersh is currently authoring a book on her unique approach to the care of women.

KARLA DUMAS
RDN, LDN

LAUREN PITTS
MA RD LD

Plant-Based Diets in a Nutshell: Understanding the latest research and recommendations

Medical professionals everywhere have something to celebrate: Plant-based eating is on the rise. Americans consumed 19 percent less beef from 2005-2014 according to the Natural Resources Defense Council. It's not just the sustainability set making these claims. In 2016, Meatingplace, a meat industry trade publication, reported that according to its polling, "70 percent of meat eaters are substituting a non-meat protein in a meal at least once a week and 22 percent said they are doing it more often than a year ago." A major shift towards a plant-based diet is afoot because many people, including medical professionals, recognize our dietary scales are currently imbalanced.

American's diets are currently too heavily reliant on animal products, while rarely meeting the requirements for fruit and vegetable consumption. A study conducted by The Medscape Journal of Medicine, found that "few American adolescents or adults reported consuming the recommended amounts of fruits and vegetables." The researchers noted increasing Americans' fruit and vegetable consumption is an important public health strategy for weight management and reduction of risk for chronic disease.

There's strong scientific support for the many health benefits of a plant-based diet. Consuming an entirely or mostly plant-based diet has been shown to reduce the risk for some of the nation's top killers, such as heart disease, cancer, type 2 diabetes and obesity. A plant-based diet consisting of fruits, vegetables, whole grains, beans, legumes, nuts and seeds can and should be used in the prevention and treatment of certain diet related chronic diseases.

Fortunately, times are changing and there's push underway to move vegetables to the center of the plate. It's coming from the medical community and the food industry, unlikely allies. From 2015-2017, food industry analysts perennially named vegan eating, plant-based food, and vegetarian food top trends. In its 2017 food predictions, Forbes forecasted "vegetables will continue its rise on the dinner plate, as animal proteins and heavy side dishes make way for more vegetarian options." Here's how advocating for a more plant-centered diet can help improve public health.

Heart Disease

Every hour in the United States, 90 people die from heart disease, stroke and other cardiovascular diseases. That's one person every 40 seconds. Studies have shown an improvement in abdominal obesity, blood pressure, and serum lipid profile and blood glucose in people on a vegetarian diet. Researchers have found an even greater reduction in heart disease risk factors among vegans compared with omnivores and other vegetarians. Vegans—those who abstain from meat, poultry, eggs, and dairy—consumed the least total and saturated fat, consumed the most fiber, had the healthiest cholesterol levels and healthiest body weights, according to the EPIC-Oxford study. Vegetarian groups had a 32 percent lower risk of ischemic heart disease compared to non-vegetarians, even after adjusting for BMI. A decrease in markers of inflammation, such as C-reactive protein and oxidative stress were seen with a vegetarian diet as well as a greater protection against plaque buildup in the artery walls, known as atherosclerosis. The Adventist Health Study-2 showed a decreased risk for heart disease amongst vegetarians as well. Vegetarians had a 13 percent & 19 percent decreased risk for developing CVD and ischemic heart disease among 73,308 Seventh-Day Adventists researched. Vegetarians have a lower risk for heart disease by regularly consuming a variety of whole fruits, vegetables, whole grains, legumes, nuts and seeds.

Vegetarians have a lower prevalence of hypertension compared to non-vegetarians. When comparing veg-

ans, vegetarians, fish eaters and meat eaters, vegans had the lowest systolic and diastolic blood pressure levels and lowest rate of hypertension of all diet groups according to the EPIC-Oxford study. This was reaffirmed by the Adventist Health Study-2, which found vegans have the least hypertension and lowest blood pressure levels among all vegetarians and omnivores. The American Heart Association (AHA) agrees that "a pro-vegetarian diet emphasizing higher proportions of plant-based foods compared to animal based foods may help lower the risks of dying from heart disease and stroke by up to 20 percent." The AHA goes on to say "researchers suggest that substituting some of the meat in your diet with vegetables may be a simple way to lower the risk of heart-related death."

Focusing on plant foods is not only important for adults, but for children as well. The AHA examined cholesterol levels and atherosclerosis in children and stated "there is compelling evidence that atherosclerosis and its precursors begins in childhood and progresses slowly into adulthood." It's typical to see the fatty streaks by the age of 10. Children aged 2 years and older are encouraged to eat at least five servings of fruits and vegetables daily as well as other foods low in saturated fat and cholesterol. Plant-based foods including plant proteins (beans, legumes, nuts and seeds) are naturally cholesterol free and low in saturated fat.

Cancer

Approximately 39.6 percent of men and women will be diagnosed with cancer at some point during their lifetimes, roughly 124 million people. Consuming a plant-based diet full of whole fruits, vegetables, beans, legumes, whole grains, nuts and seeds can lower the risk of certain types of cancers. In a meta-analysis published in the Annals of Nutrition and Metabolism, overall cancer incidence rates were significantly lower in vegetarians than non-vegetarians with seven studies reporting vegetarians had an 18 percent lower overall cancer incidence and a 29 percent lower ischemic heart disease mortality. Vegan diets appear to offer an even greater protection against overall cancer incidence compared to omnivorous and vegetarian diets. A study published in the American Association for Cancer Research concluded that vegan diets may be associated with a decrease in the incidence of all cancers combined and specifically the risk of female-specific cancers when compared with non-vegetarians. Vegetarians (mainly lacto-ovo-vegetarians) as a combined group have lower risk of all cancers in particular gastrointestinal cancers than meat eaters.

Another study published in the American Journal of Clinical Nutrition found that vegan diets showed a statistically significant protective association with prostate cancer risk with a 35 percent lower risk compared to non-vegetarians. On the other hand, a significant and positive association was observed between processed red meat intake and colorectal cancer. Consumption of processed red meat was also shown to increase the risk of dying from cancer as well as from cardiovascular diseases and "other causes of death." A link has been suggested between specific plant foods such as fruits and vegetables, plant constituents such as fiber, antioxidants, and other phytochemicals for maintaining a healthy weight and a lower incidence of cancer.

The American Institute for Cancer Research, which reviews thousands of studies, stated "When it comes to American health, the research shows one thing very clearly: We all need to eat more plants and less meat." Plant-based diets may be an effective way to help prevent, treat, slow or even reverse cancer progression. Populations that have the lowest rates of cancer generally have diets centered on whole plant-based foods.

Type 2 Diabetes

29.1 million Americans have diabetes and 8.1 million are undiagnosed according to the Centers for Disease Control and prevention. A diet that concentrates on high fiber, whole plant-based foods lowers the risk of type 2 diabetes and serves as an effective therapeutic tool in the management and potential reversal of type 2 diabetes. In The American Diabetes Association (ADA)'s 2017 Standards of Medical Care in Diabetes, plant-based diets were named as acceptable diets for the management of type 2 diabetes and prediabetes.

Research supports the use of a plant-based diet for prevention and treatment of type 2 diabetes. The Adventist Health Study-2 reported vegans and lacto-ovo vegetarians had a one-half reduction in risk of type 2 diabetes compared with meat eaters, even after adjusting for socioeconomic and lifestyle factors, as well as BMI. The Adventist Health study also found that the odds of developing diabetes among non-diabetics were reduced by 77 percent for vegans and by 54 percent for lacto-ovo-vegetarians.

On the other hand, red and processed meats are strongly associated with increased diabetes risk. Research from the Harvard T.H. Chan School of Public Health showed that a daily 100-gram serving of unprocessed red meat (about the size of a deck of cards) was associated with a 19 percent increased risk for type 2 diabetes. One daily serving of 50-grams of processed red meat (half the size- one hot dog or two slices of bacon) was associated with a 51 percent increased risk. In a randomized clinical trial, a low fat vegan diet was compared to the ADA Guidelines and 43 percent of the vegan group and 26 percent of the ADA group participants reduced diabetes medications. The medication-stable participants had significantly greater changes in A1C, weight, BMI, waist circumference, total cholesterol and LDL cholesterol in the vegan group compared to the ADA guidelines.

Vegetarian and vegan diets are rich in vegetables and fruits, foods that can reduce chronic inflammation. Studies have shown that vegetarian and vegans consume more of these foods compared to non-vegetarians. Vegetarian and vegan diets contain substantially lower amounts of saturated fat compared to non-vegetarian diets and typically include foods that have a low glycemic index, such as beans, legumes and nuts.

Obesity

Nearly two thirds of adults are considered overweight or obese and that number continues to increase.

Plant-based dietary patterns are associated with a lower body mass index. As researchers at Johns Hopkins Bloomberg School of Public Health reported, diets high in meat consumption are associated with obesity, showing a consistent positive association between meat consumption and BMI, waist circumference, obesity and central obesity. The Adventist Health Study-2 found mean BMI was lowest among vegans (23.6) and incrementally higher among lacto-ovo vegetarians (25.7), pesco-vegetarians (26.3), semi-vegetarians (27.3) and highest among meat eaters (28.8). Research published in the American Journal of Clinical Nutrition, found the prevalence of overweight or obesity was 40 percent among omnivores and 25 percent among lacto-ovo vegetarians. The Journal of the American Medical Association published a study looking at the association of animal and plant protein intake with all-cause and cause-specific mortality. Researchers found that "substitution of plant protein for animal protein especially that from processed red meat, was associated with lower mortality suggesting the importance of protein source."

Environment

Eating less meat and more plant-based foods is not only good for public health, but the health of the planet. Animal agribusiness is very resource intensive. It takes massive amounts of resources to produce animal products, such as land, water, fertilizer, and oil, significantly more than it does to grow other types of foods like fruits, vegetables, whole grains, beans and legumes.

When focusing on water usage from animal agriculture alone, the numbers are staggering. The Environmental Protection Agency compared the production of wheat, soy and beef and estimated it requires about 25 gallons of water to produce one pound of wheat, 250 gallons of water to produce one pound of soy, and 2,646 gallons of water to produce one pound of beef. The amount of water used to produce livestock is significantly more than used to produce plants.

In addition, meat production has been implicated as a leading contributor to climate change. A study from the Food and Agriculture Organization of the United Nations has identified that global farm animal production accounts for 14.5 percent of all human-caused greenhouse gases (GHG). Based on expected demand and global population increase, farm animal production alone is projected to emit over two-thirds the amount of GHG considered sustainable by 2050.

Substituting beans, legumes and other plant-based proteins for animal products in the diet would significantly reduce our eco-footprint. According to research featured in Public Health Nutrition, producing 1 kilogram of protein from kidney beans instead of beef utilizes 18 times less land, 10 times less water, 9 times less fuel, 12 times less fertilizer, and 10 times less pesticides. In addition, beans are a lot healthier than beef providing protein without the added cholesterol and saturated fat found in beef. As an added bonus, beans are also a great source of fiber, which is important because most Americans don't consume nearly enough fiber.

Beans and legumes also contain phytochemicals, which are plant chemicals that may reduce the risk for certain diseases, like cancer.

Summary

The research on plant-based diets continues to evolve. Current evidence shows there are many health benefits of vegetarian and vegan diets, especially compared to a typical omnivorous diet. The Academy of Nutrition and Dietetics released its updated position statement on vegetarian diets in December 2016. In summary, it states, "It is the position of the Academy of Nutrition and Dietetics that appropriately planned vegetarian, including vegan, diets are healthful, nutritionally adequate, and may provide health benefits in the prevention and treatment of certain diseases. These diets are appropriate for all stages of the life cycle, including pregnancy, lactation, infancy, childhood, adolescence, older adulthood, and for athletes."

In a time where half of American adults have one or more chronic preventable diseases and the medical costs associated with obesity are estimated to be at minimum, $147 billion per year, health professionals must continue to emphasize nutrition as the leading intervention for preventing and reversing disease state.

The Dietary Guidelines for Americans notes most Americans today aren't getting enough potassium, dietary fiber, choline, magnesium, calcium, and vitamins A, D, E, and C. The majority of those nutrient requirements can be easily met when consuming a diet high in plant foods. Much like any dietary pattern, particular considerations

must be taken to ensure all essential nutrient needs are met. Let's take a closer look at some of the more common nutrients of concern.

Plant-Based Protein Consumption

Adequate protein consumption is one of the leading concerns of individuals considering a plant-based diet. When appropriate calories are consumed, a protein deficiency is rare. People following vegetarian and vegan dietary patterns routinely meet and even exceed protein recommendations. The proper protein recommendation for all adults is 0.8-0.9 grams of protein per kilogram of ideal body weight per day.

In actuality, most Americans are more likely to suffer from protein excess. The adverse effects associated with long-term high protein diets may include disorders of bone and calcium balance, disorders of kidney function, increased cancer risk, disorders of the liver, and worsening of coronary artery disease. Therefore, there is currently no reasonable scientific basis to recommend protein consumption above the current recommended daily allowance, due to its potential disease risks.

There is also no longer evidence to support the need to combine protein foods in order to create complete proteins. Consuming a variety of plant foods will provide enough of the essential amino acids one requires each day to meet protein needs. Encouraging the regular consumption of a variety of beans and legumes and other protein-rich plant foods, like soy products, will ensure adequate protein for those following a plant-based diet. A study in the Asia Pacific Journal of Clinical Nutrition identified beans as the strongest dietary predictor of survival in older populations, with an 8 percent reduction in risk for every 20 grams consumed daily. Regular consumption of legumes and soy products will also benefit populations that may require increased protein needs, like older adults, pregnant women and athletes.

Iron

Iron is the most common nutrient deficiency internationally, which is why everyone, independent of dietary patterns, should be ensuring adequate daily intake. Current research has found those following a plant-based diet consume at minimum, the same amount of iron, as omnivores. The iron stores of those following a plant-based diet are found to generally be lower. While one may identify this as a concern, the latest evidence has associated elevated serum ferritin levels, or stored iron, with increased risk of type 2 diabetes, coronary heart disease and certain cancers.

Non-heme iron is found in abundance in plant foods. Iron-rich plant foods are legumes, nuts, seeds, tempeh, tofu, whole grains, vegetables and dried fruit. The absorption rate is dependent upon one's personal need, current stores and other compounds like phytates, polyphenols, tannins and calcium supplements. Phytates play a major role in the absorption of iron and other minerals, like zinc and calcium. Phytates are commonly found in legumes, nuts and seeds and whole grains. Choosing to soak, ferment, sprout, or leaven with yeast when eating grains, beans, peas and lentils can help break down phytate compounds and increase the absorption of iron. Avoiding coffee, tea, and wine and choosing vitamin C-rich foods while eating iron-rich foods can also help with absorption. It has also been recommended to sauté onions and garlic with bean and grain dishes to increase availability of the iron.

Evidence suggests one's body will more readily absorb non-heme iron when stores are low. This is partly because the effect of the inhibitors and enhancers can diminish over time. This information is testament to how amazing

our bodies are in adapting based on need. Women, teenagers and athletes may require increased iron recommendations.

Zinc

Zinc is a mineral necessary for healthy immune function, growth, wound healing, nerve development and mental alertness. Dietary intake of zinc among those following a plant-based diet is similar to those following omnivorous diets. Much like that of iron stores, zinc stores are found to be lower, but within the normal range. The best plant sources of zinc include: nuts and seeds, (especially pumpkin seeds), soy products, legumes, grains, and fortified cereals. As with iron, the phytate compounds in whole grains and legumes can decrease the absorption of zinc. Choosing to soak, ferment, sprout or leaven with yeast can increase the absorption. Avoid taking calcium and iron supplements too close to meals with zinc-containing foods, as this can also decrease absorption. Vitamin C containing foods have also been shown to increase absorption. Evidence suggests one's body will more readily absorb zinc when stores are low. The populations that must be most aware of zinc intake are pregnant and lactating women, infancy through adolescence and older adults.

Iodine

While the recommended amount of iodine is very small, it is still a vital mineral. Iodine plays an important role in most organ systems, especially the thyroid. Plant-based diets have been shown to be low in consumption of iodine. Iodine content in plant sources can vary widely. Consuming adequate amounts of sea vegetables and using iodized salt are two ways to consume sufficient iodine. The daily recommendation is 150 mcg of iodine, which can be consumed in greater quantities over several days throughout the week. One half of a teaspoon of iodized salt or 1½ sheets of nori (a sea vegetable) can provide the daily recommended intake of iodine. Iodine deficiency in pregnancy can lead to serious health implications, which is why pregnant and lactating women following a plant-based diet are encouraged to take an iodine supplement.

As noted, iodine is associated with proper thyroid function. Many foods commonly found in large quantities in a plant-based diet contain goitrogens. Some examples of goitrogen containing foods are: soy foods, spinach, broccoli, sweet potatoes, peanuts, strawberries, pears, peaches and pine nuts. If a person has an iodine deficiency, these foods can potentially interfere with thyroid metabolism and lead to the development of a goiter. It's important to reiterate this can only happen if there is an existing iodine deficiency. If one's iodine levels are within the normal range, these nutrient-dense plant foods are absolutely acceptable to consume.

Calcium

Calcium is an important mineral for healthy bones and teeth. Humans in many parts of the world consume little or no dairy and are able to consume adequate amounts of calcium. Calcium intake can vary among those following plant-based diets; however, one can certainly meet daily calcium recommendations with plant foods.

When considering plant foods high in calcium, the bioavailability can be largely dependent upon the oxalate content. Fiber and phytates appear to be less important inhibitors. Oxalic acid, a naturally occurring plant compound, can combine with iron to reduce the absorption during digestion. High-oxalate vegetables like spinach, beet greens, Swiss chard, chives, parsley and amaranth, may only offer an absorption rate of around five percent. Low-oxalate vegetables, like broccoli, kale, bok choy, Napa cabbage, watercress, collard, turnip or mus-

tard greens offer an absorption rate of at least fifty percent. In comparison, the absorption rate of milk is around thirty percent, which is also the same rate as fortified plant milks and calcium-set tofu. Foods like figs, tahini, black strap molasses, edamame, tempeh, white and pinto beans, almonds, dried fruit, calcium-fortified juices and oranges are also good food options when considering calcium intake. For those with increased needs or unlikely to consume enough plant foods high in calcium, a supplement should be recommended. The recommended intake is as follows: 1000 mg/day for individuals ages 19 to 50 years and 1200 mg/day for those over the age of 50.

Omega-3 Fatty Acids

When it comes to essential fatty acids, those following plant-based dietary patterns generally don't consume dietary sources of eicosapntaenoic acid (EPA) or docosahexaenoic acid (DHA), the long-chain omega-3 fatty acids. However, the dietary consumption of alpha-linolenic acid (ALA) is similar to those following omnivorous diets. ALA can be converted to EPA and DHA, which is critical for vegetarians and vegans to obtain adequate omega-3 fatty acid levels. Long chain omega-3 fatty acids play important roles in reducing inflammation and reducing the risk of certain chronic diseases, like heart disease, and play a role in cognitive and behavioral function. Ensuring adequate consumption of omega-3 fatty acids is especially important for pregnant and lactating women, as these fatty acids play an important role in development and growth. As various studies have indicated and identified in the Academy's position paper, "vegetarian and vegan children do not appear to experience impairment in visual or mental development, and adults are found to experience a reduced risk for cardiovascular disease."

The first step in ensuring optimal conversion of ALA to EPA and DHA is to follow a balanced plant-based diet with a variety of foods. Consuming enough calories, vitamins and minerals sets the body up for success. Another consideration is to not overconsume foods high in linoleic acid (LA), because too much omega-6 fatty acids can reduce the conversion of omega-3 fatty acids. The ratio of LA to ALA should not exceed 4:1. In general terms, omega-6 daily intake should be 9 to 13 grams and omega-3 intake should be 2-3 grams.

The best sources of ALA are flax, chia, canola, and hemp seeds, walnuts and their corresponding oils, along with green leafy land and sea vegetables. Adding this amount to one's diet can be very simple. For example, 1 ounce of walnuts contains 2.6 grams of ALA and two tablespoons of flaxseeds contains 3.2 grams of ALA. For those with increased needs, supplementing with a low-dose microalgae-based DHA supplement can also ensure adequate levels of omega-3 fatty acids.

In summary, the Academy states "omega-3 fatty acid needs of healthy individuals can be met with ALA alone, and that endogenous synthesis of EPA and DHA from ALA is sufficient to keep levels stable over many years."

Vitamin B-12

Because vitamin B-12 is not found naturally in a plant-based diet, one must supplement or consume reliable fortified food options, like fortified nutritional yeast, in order to avoid becoming deficient. Over time, vitamin B-12 deficiency can lead to serious health concerns and even death. Adults over the age of fifty often experience decreased absorption of vitamin B-12 due to atrophic gastritis, no matter one's dietary patterns, and supplementation is recommended. The current recommendations for supplementation include: 25-100 mcg cyanocobalamin, sublingual daily or 1,000 mcg cyanocobalamin, sublingual, two to three times per week. Vegetarian and vegan infants and children should also be monitored for adequate vitamin B-12 status.

Vitamin D

To ensure adequate intake of vitamin D among most of the population, one should obtain adequate sun exposure, choose a vitamin D supplement or consume vitamin D fortified foods. Subcutaneous exposure is dependent upon many factors. When it comes to foods within a plant-based diet, fortified juices, cereals and nondairy milks can meet daily requirements. Additionally, mushrooms treated with ultraviolet light can provide a significant source of dietary vitamin D. Sun Bella and Dole are two examples of brands offering ultraviolet light treated mushrooms. As we age, our bodies synthesize vitamin D less efficiently, which is why older adults are encouraged to increase sun exposure or take a supplement.

Nutrition Considerations Among Life Stages

A Plant-Based Pregnancy

The Center for Disease Control and Prevention reports one in five women are obese when they conceive. Obesity can increase the risk for many complications to the mother like gestational diabetes, preeclampsia, cesarean deliveries and stillborn births. Not to mention the risks to the infant, such as abnormal intrauterine growth and childhood obesity. Plant-based diets are associated with lower body mass index, with the lowest BMI associated with those following a vegan dietary pattern

A well-balanced, plant-based diet throughout pregnancy is not only safe, but as the Academy of Nutrition and Dietetics points out, "can give your baby the best possible start." The evidence continues to suggest pregnancy outcomes for vegetarian and vegan women are similar to pregnancies from omnivorous women. In fact, women following a plant-based diet are found to have lower incidences of gestational diabetes, excessive weight gain and preeclampsia. As with any pregnancy, getting enough calories from a variety of plant-based foods is necessary. Increased calorie and protein needs can be met in the second and third trimesters with energy- and nutrient-rich foods like hummus or bean dishes, avocados, whole grains, nuts and nut butters.

Plant-based meals are packed full of vitamins and minerals, offering an easy way to meet the increased needs associated with pregnancy and lactation. Increased iron needs can be met with foods like beans, tofu, pumpkin and squash seeds and grains. Encourage expectant mothers to eat non-heme rich iron sources or supplement with a low dose iron supplement. For maximum benefits, including a vitamin C source like dark green vegetables or citrus fruit will maximize absorption. As an added benefit, non-heme iron has been linked to better birth weight.

Choosing foods high in ALA omega-3 fatty acids, like walnuts or flax, chia, canola and hemp seeds and their oils will ensure EPA and DHA levels are met. This is important for the development of the brain and retina. Expectant mothers, along with all people following a vegan diet, must be taking a vitamin B12 supplement or consuming foods fortified with vitamin B12.

Lactation, Infancy and Toddlers

As with all births, breast feeding for at least the first six months, is recommended by the American Academy of Pediatrics as well as the World Health Organization. Lower levels of environmental toxins have been identified in breast milk from women following plant-based dietary patterns.

If breastfeeding is not an option, only commercial iron-fortified soy formulas should be given. Cow's milk or other

plant-based milk substitutes should never replace breast milk, as these do not have the appropriate amounts of protein, fat, carbohydrates and other essential nutrients and can be detrimental to the baby's health.

Once infants begin consuming solid foods after four to six months, begin with infant cereals and pureed vegetables and fruits. At seven to eight months it's appropriate to include foods high in calories, protein, iron, vitamin D and zinc. Recommendations may include hummus, tofu, soy yogurt, well-cooked legumes, and mashed avocado and cooked dried fruit.

Continue including higher calorie and nutrient-packed options like avocado, nuts and seeds, nut and seed butters, dried fruits, fresh vegetables and fruits, full-fat and calcium-fortified soy products, meat analogs, and bean spreads. It would be recommended to ensure vitamin B-12 supplements and fortified foods, such as fortified nutritional yeast are consumed.

Adolescents and Teens

As noted in The Academy's position paper on vegetarian diets, vegetarian children and teens are at lower risk than their non-vegetarian peers for overweight and obesity during childhood and adulthood. Studies have found children following a plant-based dietary pattern consume greater amounts of fruits, vegetables, fiber and less fat and cholesterol overall. Due to increased calorie needs for the age group, adding nutrient-dense snacks throughout the day is a great way to help rapidly growing children. Nuts, seeds, nut butters, avocado, soy products and beans are all good choices. As with all age groups, be sure children and teens are consuming a variety of foods rich in calcium, iron, zinc, vitamin D and vitamin B12.

Considerations for the Aging Population

As noted in The Academy's position paper on vegetarian diets, "Nutrient intakes of older vegetarians are similar to or better than older non-vegetarians." Further evidence has found proper nutrition throughout life can improve quality of life and even extend the lifespan. As noted earlier, people following vegetarian and vegan dietary patterns are less likely to have common chronic diseases like obesity, heart disease, type 2 diabetes, hypertension, and certain cancers.

Older adults have been shown to require and consume fewer overall calories, while some nutrient needs increase with age. This may be in part because our body's ability to efficiently absorb and use these nutrients decreases with age. Because of this, older adults may need greater amounts of protein, vitamin D and vitamins B12 and B6. Vitamin B6 can easily be increased in the diet by consuming foods such as avocados, legumes, nutritional yeast, nuts and seeds, spinach, whole grains and fortified breakfast cereals. As with all populations, consuming adequate amounts of plant foods high in iron, zinc and calcium should be advised. To avoid constipation, be sure enough fluids are consumed while eating a high fiber diet. If individuals are finding it difficult to consume adequate fluids, encouraging high intake of fresh fruits and vegetables is a great recommendation, since these foods generally have a higher water content.

In summary, properly planned vegetarian and vegan diets provide adequate nutrient intakes for all stage of the lifecycle and are useful in the therapeutic management of many chronic diseases.

Resources for Groups and Dining Operations

As more Americans and people worldwide consider following a vegetarian or vegan diet or consuming more plant-based meals, the resources and support continue to grow. This support makes the transition process even easier for individuals, families and groups.

The Dietary Guidelines for Americans 2015 edition recommend vegetarian diets as one of three healthful dietary patterns. Nonprofit organizations such as the Physicians Committee for Responsible Medicine, Nutritionfacts.org, The Vegetarian Resource Group, The Humane Society of the United States, Oldways Vegetarian Network and the Vegetarian Nutrition Dietetic Practice Group of The Academy of Nutrition and Dietetics offer resources for individuals and professionals on plant-based dietary patterns. For physicians and other health professionals, organizations like Kaiser Permanente, The American College of Lifestyle Medicine, and the Plant-Based Prevention of Disease, offer a variety of research and guidance on plant-based diets.

Online Resources

www.vndpg.org
www.vegetariannutrition.net
www.vrg.org
www.PCRM.org
www.veganhealth.org
www.nutritionfacts.org
www.vegweb.com
www.vegetarian-nutrition.info
www.forwardfood.org

With plant-based eating gaining momentum across the country more and more institutions are looking for ways to market and offer delicious plant-based meals. The Humane Society of the United States hosts free Forward Food seminars and culinary workshops, offering institutions the opportunity to learn about plant forward initiatives. Forward Food equips attendees with the necessary tools to implement these programs at their organizations.

Forward Food offers food service directors, chefs, dietitians and other food service and medical professionals sample menus, recipes, cooking skills, and marketing and promotional tools to allow them to determine what will be most successful for their institutions. Forward Food empowers attendees to positively impact their customers and the environment by celebrating plant-based meals. The Humane Society of the United States hosts Forward Food training all over the country on an ongoing basis. Attendees have the opportunity to receive continuing education credits at no cost.

In summary, encouraging a plant-based diet can be a therapeutic tool in the prevention and treatment of diet related chronic diseases, such as heart disease, stroke, certain types of cancer, type 2 diabetes, and obesity. Plant-based diets can be healthful for all stages of life. As Hippocrates said, "Let food be thy medicine and medicine be thy food." Those words remain as apt today as ever.

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Karla Dumas is a registered and licensed dietitian nutritionist with The Humane Society of the United States. With over ten years of experience in the field of child nutrition and school food service management, she has partnered with foodservice programs throughout the country, like Miami-Dade Public Schools and Hillsborough County Public Schools to implement plant-strong initiatives. By developing resources like menu cycles and kid-tested, school-approved meatless recipes that meet federal guidelines along with offering culinary workshops for school food service professionals, she continues to support school districts and other institutions with more plant-based meal options. Dumas received her plant-based culinary certification through Rouxbe cooking school. She currently serves as the secretary for the Vegetarian Nutrition Dietetic Practice Group with the Academy of Nutrition & Dietetics. Karla's work in nutrition has been featured in numerous media outlets, such as Tampa Tribune, Today's Dietitian, and the Miami Herald. Karla lives in Florida with her husband, stepdaughter and eight dogs. In her free time, she enjoys camping, gardening and running Ragnar Relay races.

Lauren Pitts is a registered dietitian for The Humane Society of the United States. She has successfully worked with several schools, hospitals, universities, and other institutions to implement healthier, more sustainable plant based meals. In these mutually-beneficial partnerships, Lauren introduces these institutions to plant-based foods through recipe planning, chef trainings, and marketing support. Prior to working with HSUS, Lauren focused on individual nutrition counseling and corporate wellness. Lauren is the Congressional Ambassador Coordinator for the Public Policy Council of the California Academy of Nutrition and Dietetics and the webinar chair for the Vegetarian Nutrition Dietetics Practice Group. Lauren lives in Los Angeles and enjoys hiking, traveling, cooking and time spent with family and friends.

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Q. How many doctors does it take to treat a migraine?
A. That would depend on how you define "treat"…

That intro may be a cute play on the old joke that goes something like "How many women/men/lawyers/psychiatrists does it take to screw in a lightbulb," but if you think about the question truly, it's not funny.

To the unsuffering, the migraine experience can't be fully understood, and even most patients can't understand how their body is capable of generating such pain. Getting to the bottom of a patient's misery shouldn't be like an episode of "House"—throwing possibilities on the whiteboard and seeing what sticks—only to be saved by Dr. House after excruciating trial and error.

As physicians, we owe our migraine patients commitment, compassion, and courage to dig deep for answers, to use what has worked well for others or keep turning over those stones to find a remedy—or a combination thereof—that can lead to a pain-free existence. In other words, there must be a better way to treat migraine

In the realm of today's traditional and alternative treatment paradigms, patients can choose from many options when it comes to getting relief for their migraines. There are those who start with the Western medicine approach, presenting to their GP or internist with headache pain and then expecting to receive medication to stop it. Pressed for time in the current healthcare environment of having 10- to 15-minute appointments, the necessary intake needed to try to get to the root of a patient's migraine episodes gets squandered for the reach for the script pad. And there are excellent preventive and rescue meds on the market that abate or shut down a migraine if taken properly. But we should understand why the migraines come in the first place, and that involves more time and investigation than many doctors are given in today's climate. All providers are given tools to work with. Now it is up to the patient to request the use of more tools to improve their pain condition.

Functional Medicine Offers a New Toolbox

The conventions of Western medicine involve identifying disease or disorder and treating it typically with pharmaceuticals. Those physicians who subscribe to the philosophy of looking at the relationship of genetic, environmental, and lifestyle influences that typically explain disease or ailments are practitioners of functional medicine, which has been gaining traction within the healthcare community.

The first time I heard the term "functional medicine" was during a casual conversation in the hallway of my new headache clinic. At the time, I was co-

directing a wellness center with a chiropractor and he suggested I learn more about it. I had no idea what the term "functional" meant in relation to medicine, but the concept stayed with me. As I was to later learn, functional medicine focuses on the total health and well-being of the patient. It uses a systems-oriented approach in which the doctor focuses on the whole patient, rather than just the symptoms.

Integrative medicine combines both Western (traditional) medicine with Eastern (alternative) medicine. Functional medicine goes a step further. This approach involves looking at the "functioning" of the system to see where the body is not functioning optimally. For example, a patient may complain to their physician about low thyroid symptoms, the levels will be checked, but then the thyroid labs appear normal. A functional practitioner will look at the labs and may find that some of the tests may appear "low normal" in the testing range. This practitioner may even check further labs which are not routine or have the patient submit urine or saliva samples to obtain a measure of hormones from a different perspective. Combining this with the clinical symptoms may lead that practitioner to offer a supplement, change in diet, or even a medication to improve the symptoms and bring the labs to a more optimal range.

Soon after my chat with the chiropractor, I learned about a 3-day functional medicine conference. I had the chance to attend and during the very first conference session, I learned that in order to have vibrant health, all of the body's systems (such as the digestive, nervous, respiratory, and circulatory) need to efficiently operate in concert. I felt as if I had just been handed the key to understanding how the human body truly functioned. It suddenly became clear to me that a migraine—which was once strictly considered a neurologic condition—could now be traced to any number of conditions, such as digestive imbalances, food allergies, or thyroid dysfunction.

The more I continued my study of migraine and other neurological symptoms based on this new paradigm, the more I realized how complicated it was for the body's nervous system to independently generate an attack of pain or symptomatology. During a migraine attack, even though an excitable brain and an activated brainstem lead to changes in serotonin activity, this excitability occurs when the system is provoked. The truth is that this activity—along with inflammation of the nerve endings, dilation of cranial blood vessels, and the entire activation of the nervous system—is closely connected to the entire physiology of the body.

The intricate links between the body's organ systems soon became even clearer. I began to understand how dysfunction in the digestive tract—poor digestion due to food intolerance, pesticide residue from food or other toxins—impaired the liver and compromised its ability to detoxify. Those accumulated toxins in the liver and the fatty tissues of the brain caused fatigue, mood changes, and headaches. I soon concluded that the migraine was actually a symptom related to the digestive system and possibly other organ systems, rather than a symptom caused by dysfunction of the brain.

To substantiate my new conclusion, I began scouring my patients' lab tests in search of links to digestive imbalances. The subsequent recommendations I made included dietary changes, exercise, stress reduction, yoga, B vitamin and/or magnesium supplements, or herbal remedies. These powerful and effective interventions could be used in conjunction with conventional care and medications. My goal was to help my patients build a foundation of health that could potentially reduce the need or reliance on pharmaceutical drugs.

The Hippocratic Oath is a code of ethics to which all physicians swear to adhere. It requires that doctors keep their patients from harm, and it is a basic tenet of functional medicine's approach to health. Because many pharmaceutical drugs potentially cause a cascade of secondary issues, the goal in functional medicine is to first rebalance the body naturally, *without* using medications. It is a look further into cause and effect since we know that one of the main causes of imbalance and disease is the inability to manage chronic stress on a physical and emotional level. Eating inflammatory foods, suppressing feelings, living a sedentary lifestyle, and grappling with intense work, school, or family situations can all take their toll. Years of imbalance can lead to internal damage and disharmony, causing the mind and body to react with many disease processes, including chronic migraines, ADHD, and mood disorders, to name just a few.

Expanding the Toolbox with Ancient Medicine

I have been trained as medical doctor under Western medicine, yet my natural curiosity has led me to look beyond what is in front of me, beyond what a patient presents. As a board-certified neurologist specializing in headache pain and neuropsychiatric disorders, I use an integrative medical approach in my practice that bridges modern science with an ancient medical practice known as Ayurveda—pronounced *eye-yur-VAY-duh.* As a result, I have helped thousands of patients to overcome debilitating and crippling headache pain and other complex neurological symptoms.

Ayurvedic medicine is a system of healing that originated 5,000 years ago in India. The goal of Ayurveda, which means "science of life," is to guide people to make healthy choices based on the specific needs of their body and mind. Further, it encompasses a broad spectrum of diagnostic tools that make it possible to recognize and correct imbalances in their earliest stages. Conventional medicine provides pain relief, while Ayurvedic assessments help to reconnect to the body's unique needs and ideal state of balance.

Since my neurological perspective is layered in Eastern medicine, I decided to add Ayurveda to my existing traditional-care model to offer patients a more profound understanding of why they were suffering and what they could do to proactively improve their condition. My journey began with seeking more than prescribing narcotics, steroids, and injectables for my patients. And interestingly, an early stop on that journey began with needing to treat my own children who struggled with digestive issues and headaches. For them, I followed the functional medicine protocol of food elimination and nutrient/gut

replenishment, which allows one to delve into systems-based healing by supporting the digestive system, liver functioning, nutrient deficiencies, and such. Yet I then shifted to Ayurveda searching for more.

With the Ayurveda model, I learned the concept of dosha typing and understanding one's unique nature. From here, I learned that I could delve further into using foods to balance the nature. In addition, this model would allow me to truly assess the mind-spirit behind healing the physical body.

The success I've experienced in treating many forms of pain is based on the premise that all symptoms are potentially a manifestation of multiple systems gone awry, rather than a single system experiencing dysfunction. Combining conventional and Ayurvedic principles helps individuals to understand the underlying causes, rather than just treating the symptoms. No matter how long the problem has been manifesting, based on the principles of Ayurvedic medicine the root cause is always the same: imbalance. This imbalance can manifest in a patient's structure, physiology, psychology, or all 3. As physicians, we must determine the cause of the systemic imbalance so that it can be corrected. We must be willing to change the rules as you will be surprised to learn that many of your beliefs may have not been in alignment with your individual needs.

Ayurvedic philosophy teaches that balance is fostered when the body, mind, and spirit are in harmony with nature. This harmony can be achieved by doing something as simple as creating a regular routine for going to bed and awakening, eating foods that nourish the body, or exercising in a way that is best for one's unique type. As the sun rises, we should awaken. As the sun sets, we should go to sleep. When the body signals hunger, we should eat. If stressed, we should take steps to relax.

Ayurveda encompasses a broad spectrum of diagnostic tools that makes it possible to recognize and correct this imbalance in its earliest stages. The first step is the determination of a patient's constitutional, or dosha, type: Vata, Pitta, or Kapha. The determination of dosha is based on an assessment that includes such factors as complexion and quality of the skin, prominence and shape of joints, body structure, shape of the eyes, manner of walking and talking, weather preferences, and sleeping habits. This assessment, in conjunction with checking radial (wrist) pulses and the condition of the tongue, provides information about the state of the body and mind long before the disease process registers as "positive" on conventional diagnostic tests.

Conventional medicine looks at the structure of the body, while Ayurvedic medicine takes into account the energy behind the physical structure. According to Ayurvedic principles, there are 3 different types of energy—the above-mentioned doshas—that govern the functions in the mind and body. These doshas represent the physical and mental characteristics inherent in all people:

- Vata (a combination of air and space elements, thin in physical stature)

- Pitta (a combination of fire and water elements, muscular in physical stature)
- Kapha (a combination of water and earth elements, large in physical stature)

The Six Stages of Disease

Ayurvedic medicine is based on the principle that there are 6 stages of the disease process.

Stage 1: Accumulation begins in an organ of 1 of the 3 main dosha sites when excessive lifestyle choices, such as too much stress or too much fast food, lead to an internal blockage. Minor symptoms are noted at this step, such as gas (Vata), heartburn (Pitta), or bloating (Kapha).
Stage 2: Aggravation occurs when accumulation continues without treatment. The symptoms become more bothersome, last longer, and occur more frequently.
Stage 3: Dissemination results when the imbalance in the original organ of the aggravated dosha increases beyond capacity. Symptoms become more pronounced.
Stage 4: Localization occurs when the aggravation spreads to weaker organs of the dosha (ie, inflammation in the digestive system leads to an inflamed right knee, without symptoms of pain).
Stage 5: Manifestation is the first stage in which conventional or Western medical tests can discern a sign of disease. The disorder is now fully developed with clinical features (ie, right knee is now painful).
Stage 6: Disruption is the chronic stage. It occurs when a person ignores the previous symptoms. Now the illness shows signs that help identify its dosha origin, and there may be complications as well. Healing from chronic illness is possible, but it takes the longest to achieve (ie, right knee pain and right side of the head are now painful).

During Stages 1 and 2, making dietary shifts and lifestyle adjustments can reverse the imbalance in most cases. In Stages 3 and 4, the Ayurvedic protocol often includes herbal therapies and cleansing procedures. In Stages 5 and 6, multiple approaches are needed to address the physical and mental imbalances.

No matter what the symptoms or disease, the great news is that with Ayurveda, patients have the chance to reverse the process. It's never too late to create conditions for the body to heal. It may require a longer period of time or take more work, but healing can occur. It is during this time that an action plan and realistic goals are needed. All change begins in the mind—making one's mind up that they're ready to change is the first and, most often, hardest step.

Treat the Person, Not the Disease

One of the primary principles of Ayurveda is that everyone is born with a specific doshic composition. As mentioned earlier, dosha is each person's

unique constitution, composed of some combination of the 5 elements of air, space, fire, earth, and water. Knowing a patient's specific dosha type—Vata, Pitta, and Kapha—is helpful in order to understand their specific mind-body type and relieve nagging headache symptoms and any others they are experiencing. Remember that it's a system, not a symptom, that we will be treating. Improving one symptom will likely lead to an improvement of another, seemingly unrelated symptom.

From an Ayurvedic perspective, headache is defined based on dosha involvement, and its subsequent imbalance. Once a patient's headache is categorized, the cause of the pain arising from nervous tissue or bone structures will help dictate the treatment. Depending on which dosha is being influenced, different headache types will manifest.

Vata-type headaches, known in Western medicine as tension-type headaches, are often located in the cervical/occipital regions and have a throbbing component that feels like a 'tight band' around their heads. These headaches are generally not as severe in intensity and often do not have any associated features such as light sensitivity, smell sensitivity, nausea, or vomiting associated with them. Sound sensitivity may be present, as it reflects an excitable nervous system. These headaches are most often induced by stress, especially when the daily routine of sleeping and eating are not followed in a regular fashion. Regular schedule is key to improving this type of pain.

Vata individuals are mainly created with air and space elements and tend to have a need to stay active. This personality is enthusiastic and vivacious but also tends to be very excitable. These individuals do not like routine and often find themselves shifting from one activity to the next. Because of all this imbalance, a Vata will need harmony for the day to seek relief from headache, and should find benefit in slowing down and doing calming activities such as restorative yoga. There are specific poses that Vatas may benefit from, and they respond to yoga that focuses on hip opening and improving digestive function. Suitable breath work and meditation are recommended to balance this mind-body type with an often-anxious mind.[2] Foods that are beneficial are warm, cooked options, as Vata types tends to become dry and cold very easily.

Pitta-type headaches, referred to as migraine in Western medicine, are often located in the retro-orbital/temple regions and have a sharp, intense component to them. These headaches are often moderate to severe in intensity and associated with nausea, vomiting, and light sensitivity. Pitta, the fire state, is often linked to the development of inflammation. Thus, the use of anti-inflammatory medications, herbals, or injections is understood as helping this type of headache.

Pitta individuals are composed of fire and water elements and tend to be perfectionistic, organized, and determined. These personalities have a tendency to become angry and irritable if they become stressed. A Pitta would benefit from adding relaxation to their daily routine, particularly yoga techniques that involve twisting the spine.[2] Foods best for Pittas should be sweet and cool.

Kapha-type headaches, which are often similar to the Western term of "sinus headache," are often located in the frontal areas. This headache is often associated with congestion and allergies and can worsen with changes in season, especially in springtime.[1]

Kapha individuals are composed of earth and water elements and tend to be compassionate, calm, and relaxed. These personalities are the ones least affected by stress. However, Kaphas can become heavy and congested easily, so for them, adding movement to their day is essential. Exercise that involves standing and moving is very important.[2] Foods that are light and dry best keep this state in balance.

People with headache may present with combinations of doshic imbalances. For example, one may have a Pitta-Vata headache or a Vata-Kapha headache. These headaches need to be treated by balancing out both imbalanced states.

Migraine definition in Western Medicine

Conventional medicine developed its own classification system of migraine headaches, which include the following characteristics:

- Moderate to severe in intensity
- Lasting a few hours to a few days
- Association with nausea and/or vomiting
- Light and sound sensitivity
- Pulsating in nature
- Usually occurring on one side
- Aggravated by routine physical activity
- Triggers aren't always consistent and clear, but involve exposure to fluctuations in hormones, weather, stress, and certain foods
- About 20%-30% of patients may have an "aura," which is a visual and/or sensory phenomenon that can precede an attack of pain
- Women are impacted 3 times more often than men

Reach for the Script Pad, the Apothecary Shelf, or Both

To treat migraine in the conventional fashion, not surprisingly, pharmaceuticals are the order of the day. This is the traditional western medicine approach and, for some, crucial to surviving through a day of pain. Abortive medications are those used to "abort" or stop attacks of pain. There are 2 types specific and nonspecific for migraines. Any medication that works on the serotonin nervous system is considered to be "specific." Serotonin is one of the most calming neurotransmitters of the brain. For some people, during a migraine the nerves become excitable. The brainstem along with the trigeminal nerve, which is responsible for sensation in the face and meninges, can create the pain signals. Serotonin binds to certain receptors and quiets the signals.

The main "specific" groups are known as the triptans. These include sumatriptan (Imitrex®), frovatriptan (Frova®), zolmitriptan (Zomig®), and rizatriptan

(Maxalt®). Triptan medications have been the holy grail of migraine treatment, and most of them are effective and reliable. If triptans weren't available, I'm not quite sure how I would've been able to help my patients. I recommend trying at least 2 or 3 different categories of triptans in different forms (eg, nasal spray, nasal delivery, oral, injectable) before determining the class is a failure. Compounded topical options are even available to try. It's when a triptan fails that I feel most perplexed about how to help manage acute pain. The other, non-triptan, options may lead to further digestive distress or rebound and habituation over time with excessive use.

Continued advances in the field of pharmacology have led to an increase in understanding which medications are most effective when migraines impact any of the 7 serotonin subtypes, 5-HT. I try to avoid prescribing narcotics and/or barbiturates due to the risk of dependency or addiction. In addition, research has found that these medications can potentially *increase* pain due to the impact they have on some of the body's serotonin receptors.[3]

Other medications that work on specific serotonin receptors (along with neurotransmitter receptors such as dopamine) are ergots, such as Migranal ® or DHE ®(dihydroergotamine). These have been available longer than the triptans. I prescribe Migranal® to help break long cycles of migraines. It is beneficial because it doesn't lead to rebound.

There are also nonspecific, abortive medications that don't seem to work directly on the "migraine center." These include muscle relaxants (Flexeril®), anti-inflammatories (Aleve®), narcotics (Vicodin®), and steroids (Prednisone®).

If the headache is milder, anti-inflammatories do seem to work well. One anti-inflammatory, diclofenac, is approved as an abortive for migraine. In more severe attacks, steroids or DHE® seem to be very effective. We need to remember that these may impair digestive function over time.

Preventive medications can mean the difference of seeing vastly reduced migraines or perhaps none at all. There are 3 broad categories of preventive medications and many smaller categories.

BLOOD VESSEL REGULATORS – I use this name euphemistically so that patients don't think they have blood pressure issues. However, the truth is that these medications were first approved by the FDA to control hypertension. Later, they were found to be helpful for other conditions.

Beta-blockers is a category of medication in this group approved for treatment of migraines. The FDA-approved choices are propranolol and timolol, which, interestingly enough, seem to have an effect on serotonin activity. These medications are helpful but can lead to side effects such as fatigue and exercise intolerance.

Verapamil ®and candesartan are other medications also approved for hypertension but have generally been found to be helpful for certain

headache conditions. Interestingly, verapamil ®, which is a calcium channel blocker, seems to be most effective for patients who have a magnesium deficiency. When magnesium stores are replenished, verapamil ® is usually no longer needed, meaning that it may be beneficial for migraine patients to balance their magnesium levels first. For more information on this issue, read *The Magnesium Solution for Migraine Headaches* by Jay S. Cohen, MD. I generally recommend a compounded magnesium nutrient blend if someone responds to Verapamil.

NEUROMODULATORS – These medications, which were approved to manage seizures, seem to have a quieting and calming effect on the nervous system. The most popular and FDA-approved medication in this category is topiramate (Topamax®). This drug has gained popularity not only because of its effectiveness, but also because it may assist with weight loss in some individuals. It's one of the few preventives that have this beneficial side effect.

Divalproex (Depakote®) is also approved for migraine, but it comes with the potential side effects of weight gain, hair loss, and elevation of liver enzymes. That's a high price to pay for improvement in migraines or moods. However, some patients have taken it because natural agents haven't been enough for their genetics or dosha type. It's important to always consider the risks and benefits of a medication versus a natural supplement.

Other neuromodulators are gabapentin (Neurontin®), levetiracetam (Keppra®), pregabalin (Lyrica®), and oxcarbazepine (Trileptal®). Although these drugs have not been well studied, they can be found to help alleviate pain in certain cases.

OTHER MEDICATIONS – The third category of medications consists of FDA-approved drugs that have impact but are not designated for the treatment of migraines.

Neurotransmitter Balancers
We have been trained to utilize the classification the FDA has given for these medications: antidepressants, antipsychotics, or anxiolytics. These labels often create a stigma for the patient since they are often not being prescribed for that purpose. If I do prescribe one of these medications, it's due to low serotonin/norepinephrine levels (either genetics, fatigued adrenals, or poor production by the digestive system) or hormonal imbalance (caused by estrogen dominance).

While none of these medications have been designated by the FDA for treatment of migraines, they can be very effective in low doses when natural agents provide no relief. There are side effects, however: weight gain, loss of libido, and flattening of mood. I have even seen a depletion of nutrients, which also needs to be taken into account. For example, according to researchers, SSRIs (such as Prozac®) can lead to low B vitamin levels.[4]

Botox®

You may be surprised to learn that despite my desire to make integrative medicine the foundation of my practice, there are many times when I have recommended Botox® for my patients. Why? Botox® is an agent that I studied during my residency because I felt it offered a unique approach to treating patients suffering with pain.[5] Botox® (onabotulinumtoxinA) has been approved by the FDA for use in treating chronic migraine since October 2010.

Botox® can lead to the reduction of migraines for 3 months after the injections are administered, due to its activity at the nerve ending.[6] It is believed to decrease the amount of CGRP (calcitonin gene-related peptide) released from the nerve ending. This peptide is considered a neuroinflammatory peptide responsible for inducing pain. With less neuroinflammatory peptide release, the adrenals can reduce their release of cortisol and rest. I believe this is one of the best approaches available to not only arrest migraine pain but also provide a break for overstressed adrenals.

I use Botox® to provide relief from chronic headaches. It serves as a bridge as patients begin utilizing integrative approaches such as supplements, nutrients, and changing their diets. This also limits the need for abortive medications. I think it's a win-win for many of my patients, especially now that most insurance coverage has expanded to cover its use for those with chronic migraines.

New Class of Medications on the Horizon

With the understanding of the importance of CGRP in the role of efficacy of Botox® injections, pharmaceutical companies are now studying the possibility of using CGRP receptor antagonists as a potential new tool to prevent chronic migraines.

Ancient Herbals to Balance the Mind and Body

I am constantly amazed by the power of Ayurvedic herbals. Many of these herbs have been utilized for thousands of years to balance the body and the mind. Wonderful shifts in the system occur when these herbs are used in synergy and in optimal doses. Ayurvedic herbals provide a deeper level of treatment beyond replenishing nutrients and enzymes. They are often dosha specific, so they address the root of the imbalance based on a patient's individual needs.

Below are just a few of my favorites that I've seen work beautifully on some truly tough-to-treat patients:

Ashwagandha (Withania somnifera)
Ashwagandha is an adaptogenic, and it is considered to be the best rejuvenating and restorative herb. It helps to reduce the symptoms of overwork and promotes rest without drowsiness. It also clarifies and calms the mind and may balance hormones due to its adaptogenic effects on the adrenals, thus improving progesterone levels. It may also improve libido.[7,8]

Triphala

Triphala is most effective for the digestive system. It is composed of 3 powerful herbs that have an important role in cleansing the blood and balancing the system. It is one of the most respected herbal combinations and has been used in India for more than 5,000 years.

Amalaki, which is very Pitta-pacifying, has very high vitamin C content and can help the immune system. It works as a strong antioxidant and can improve digestion.[7]

Bibhitaki has a laxative effect, and it improves the workings of the digestive system. It also cleanses the respiratory tract. Further, Bibhitaki has an antibacterial effect and can decrease congestion and cough. In addition, it has an adaptogenic effect that allows it to improve the immune system.[9]

Haritaki can improve nutrient absorption and digestion and help prevent gallstones. This herb helps to remove toxins and can help with weight loss. It pacifies all 3 doshas.[10,11]

Turmeric (Curcuma longa)

Turmeric is yellow in color and is a strong anti-inflammatory, antioxidant, and natural antibiotic.[12] It improves intestinal flora and may have a positive effect on healing ulcers and reducing the symptoms of indigestion.[13] It supports the liver and may improve the patient's cholesterol profile.[14]

Replenishing Nutrients When Depleted

This chapter wouldn't be complete without mention of a few nutritional supplements that can play significant roles in a patient's neurological health. I will highlight 3 standouts below.

Magnesium Glycinate and Citrate Chelate

Magnesium is one of the most beneficial and essential nutrients for the body's functional needs. It's a cofactor, involved in the activation of more than 300 enzymes in the body. Benefits of magnesium supplementation include improved sleep, decreased anxiety, relaxation of muscles, improved glucose uptake, improved bone health, and decrease of blood vessel constriction. Studies have documented the benefits of magnesium in migraine, especially menstrual cycle-related migraines.[15] The magnesium formula I recommend is combined with both citrate and glycinate. It is chelated, which makes it easier to digest, and is more tolerable, with very few side effects.

Vitamin B1 (thiamine)

Vitamin B1 helps the body adapt to stress and avoid adrenal burnout. It's necessary for energy production, carbohydrate breakdown, and thyroid hormone metabolism, and is needed for proper nerve function. One caveat: This vitamin can be depleted with the use of oral contraceptives.

Vitamin B2 or Riboflavin/Riboflavin 5 Phosphate

Vitamin B2, or riboflavin, is associated with most of the body's energy pathways. It's an essential vitamin for mitochondrial health, which is often found to be involved in migraine.[16]

Vitamin B3 (niacin)
Vitamin B3, or niacin, is used in at least 40 chemical reactions in the body. This vitamin is well known for its potential cholesterol-lowering properties (it converts cholesterol to pregnenolone, a hormone that helps memory, amongst other things) and its role in mitochondrial energy production, which is often impaired in people with migraines.

Vitamin B6 (pyridoxine)
Vitamin B6 is essential for detoxifying chemicals and is paired with more than 100 different enzymes. It's key to synthesizing several neurotransmitters, such as serotonin, which are linked to both insomnia and migraine.[17]

Vitamin B9 (folic acid)
Vitamin B9, or folic acid, is best known for its role in energy production. This vitamin detoxifies hormones such as estrogen, along with heavy metals, and is needed for the conversion of dopamine. Studies have shown folic acid to be helpful in the treatment of migraine, especially if associated with elevated homocysteine levels.[18]

Methylated Vitamin B12 (methylcobalamin)
This vitamin is synthesized by bacteria and may be found to be low in vegetarians, vegans, or people with digestive issues. Methylcobalamin is the active form of B12 and is useful in decreasing homocysteine levels, synthesizing SAM-e (which can be very helpful for mood disorders), and supporting adrenal health.

CoQ10 (as ubiquinol)
This fat-soluble nutrient is responsible for producing energy for cells but must be used in the ubiquinol form, the reduced, active, antioxidant form of CoQ10. Age makes it harder to convert CoQ10 to ubiquinol. This is one of the strongest antioxidants available, protecting cells from free radical damage. Remember that this nutrient can become depleted if one is taking a statin drug (cholesterol-lowering medication), certain blood pressure drugs, and antidepressant medications. CoQ10 has been well studied for its benefits in reducing migraine headaches.[19]

Please visit **www.truptigokanimd.com** to learn more about the rewarding benefits of weaving ancient medical treatments into your life and practice. My first book, *The Mysterious Mind: How to Use Ancient Wisdom and Modern Science to Heal Your Headaches and Reclaim Your Health*, covers this topic and is now available from Amazon. For those who purchase the book, enjoy the free 50-page download to her cookbook, *Lose Weight and Feel Great: the Ayurvedic Way.*

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in seeking it because of anything you read in this chapter. Any questions that you may have regarding the diagnosis or treatment of a medical condition or any product or supplement described in this chapter should be directed to a qualified healthcare professional.

All matters concerning your health require ongoing medical supervision. If you have a known or suspected medical, psychiatric, or psychological condition, or are taking medications or supplements of any kind, you should consult a qualified healthcare professional before following any of the suggestions described in this chapter. Any dosages described in this chapter are intended only as guidelines. You need to consult with your healthcare professional before you use any suggestions found in this chapter.

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TRUPTI GOKANI, MD

An award-winning, board-certified neurologist, Trupti Gokani, MD has dedicated her life to developing a unique blend of modern medicine and ancient philosophy. By melding these approaches. she's become a highly sought after speaker and health coach sharing holistic wellness strategies with larger-than-life media personalities like Dr. Oz, global pharmaceutical giants like Pfizer, and individuals with a wide range of symptoms, from debilitating migraines to chronic fatigue.

She's best known by those in Chicago's North Shore for her revolutionary integrative approach to treating headache pain. The Zira Mind & Body Clinic's patients swear by her unique methodology focused on healing the head by identifying the disconnect between the mind and the body. When not in the clinic, Dr. Gokani dedicates her insights to speaking and media engagements aiming to help Americans understand the "purpose" of their pain and how to heal themselves through a deeper appreciation of the mind-body-spirit connection.

QUALIFICATIONS & BACKGROUND

Dr. Gokani earned her medical degree from the University of Illinois at Chicago, where she also completed her training in neurology, was Chief Resident, and pursued additional post-doctoral training and certification as a Master Clinical Psychopharmacologist. She has continued to educate herself for the benefit of her patients, gaining experience and credentials in Ayurvedic medicine, clinical psychopharmacology and transcendental meditation. She has also pursued training in Functional Medicine. She is certified by the American Board of Neurology & Psychiatry, and is licensed to practice in Illinois and California.

She has also lectured extensively in the fields of neurology and psychiatry, specifically regarding headaches, mood disorders, insomnia, adrenal fatigue, hormonal issues and adult attention deficit disorder (ADD). She has spoken at the American Headache Society, the Midwest Pain Society, the American Academy of Neurology, and the American Psychiatric Society. Her work — on topics ranging from Botox efficacy and safety, to the prevalence of bipolar disorder in cluster headache patients — has been published in esteemed journals such as the American Journal of Pain Management. She has also published abstracts pertaining to food allergies and headaches, along with the Ayurvedic approach to migraine, in the well-regarded Journal of Headache. She studied the prevalence of adrenal fatigue in her practice and presented her work at the Academy of Pain Annual Symposium.

Dr. Gokani recently published her first book, The Mysterious Mind, and is currently contributing to a health documentary on Ayurveda. She is available for speaking engagements and media appearances in addition to her ongoing work at the Zira Mind & Body Clinic and private coaching intensives. For more information, visit Dr. Gokani at https://truptigokanimd.com/.

SHILPA JOSHI
RD

PROF SHASHANK R JOSHI
MD, DM, FRCP, FACE, FACP, FICP

Medical Nutrition Therapy (MNT) In Type 1 Diabetes : Indian Prespective

Shilpa Joshi MSRD, Mumbai Health and Diet Centre
Shashank R Joshi MD, DM, Consultant Endocrinologist, Lilavati Hospital, Mumbai

Diet forms a cornerstone of diabetes management. It is especially true if diabetes is managed with help of insulin. Insulin therapy calls for very strict diet regimen, so as to prevent hypoglycemia and sometimes very high blood glucoses. Strict dietary protocols show least compliance among patients. Hence a approach to dietary management in diabetes is called as "carbohydrate counting". It has been seen that patients are better able to manage sugars when they are given diets with liberal choices which helps them to select foods when they are eating at home or outside.

Carbohydrate counting has two distinct methods: Basic Carbohydrate counting, a simpler but more rigid approach, and Advanced carbohydrate counting, a complex one but more flexible. Basic Carbohydrate Counting is appropriate for people with consistent meal plan, regular physical activity and no or premix insulin regimen. Premix insulins are very commonly prescribed in India. Advanced Carbohydrate Counting is for one with flexible eating plan and insulin regimen like multiple daily injections or on insulin pump. It builds on the skills and concepts taught in the basic carbohydrate counting meal planning.

The principle of carbohydrate counting is "carb is a carb", which means that all kinds of carbohydrates causes blood glucose to rise .This happens whether carbohydrate is simple like sugar or jaggery, or complex like wheat, jowar etc. Hence all carbohydrates are counted in a similar manner. Also carbohydrate is the nutrient which elicits highest amount of glucose response and therefore focus of carbohydrate counting should be on total carbohydrate.

Other macronutrients in the diet, i.e., fat and protein, can influence the postprandial blood glucose level, however. For example, dietary fat slows glucose absorption, delaying the peak glycemic response to the ingestion of a food that contains glucose(1–3).In addition, although glucose is the primary stimulus for insulin release, protein/amino acids augment insulin release when ingested with carbohydrate, thereby increasing the clearance of glucose from the blood (4-6).

Record keeping and SMBG are very important for carbohydrate counting. This helps both the clinician and the person with diabetes to understand patterns and also decide /understand what is going wrong with the blood sugar management. More sugar readings we have, patterns are better understood and hence make the proactive changes needed. Patterns also help the person with diabetes to make better food choices in absence of nutritional labels. This is necessary as most of the food available in India in restaurants, food courts, small eating joints are not labeled and it is difficult to calculate carbohydrates in these foods. So when patients consume these foods they can rely on these patterns to decide their dose of insulin using carbohydrate counting.

In this method carbohydrates in foods are measured in grams and each food item containing 15 gram carbohydrate is called one carbohydrate exchange. With this principle in mind all foods are converted in carb. exchanges in raw and cooked form and an exchange list is prepared and given to the patient.

Bolus dose adjustment:

Calculate patient's total daily dose of insulin (TDD), which includes both basal and bolus dose. For e.g. if a patient was taking 20 units of basal insulin and 10-10-10 u of bolus insulin with all three meals then, the TDD for

that patient is 50units.

Now divide 500 by the TDD i.e. 500/TDD= 500/50=10

This is called the insulin to carbohydrate ratio (ICR). An insulin-to-carbohydrate ratio is a personalized ratio used to help calculate the amount of insulin needed to "cover or match" the carbohydrate consumed at the meal. So in this example: for every 10 grams of carbohydrate consumed, 1 unit of bolus insulin is required. ICR will vary from person to person depending on person's insulin needs and sensitivities. With this data patient can plan/ alter his/ her diet and adjust the insulin dose as per food intake.

So, if the patient is consuming

Onion poha (2 vati) = 40 grams of carbs
Milk (200ml) = 10 grams of carbs
Fruit (1 apple) = 10 grams of carbs
Total carbs = 60 grams
Insulin to carb ratio (ICR) =1:10
Therefore 60/10 = 6 u

So with such a meal, patient needs 6u instead of 10units insulin. This dose will prevent the patient from eating way too much just to prevent a feeling of low sugars. Also if the patient chooses to eat more than this he can increase insulin dose by adding the amount of carbohydrate he has eaten more. This also helps patient to choose food he wishes to eat like may be jam bread, eggs or even chappati bhaji.

Insulin sensitivity factor:

Insulin sensitivity factor (ISF), correction factor (CF) or supplemental factor is required to calculate amount of insulin needed to bring back blood glucose to within prescribed pre-prandial target goal.

To calculate insulin sensitivity factor we use a rule of 1500 or rule of 1800. The choice of this rule depends on the kind of insulin used and sensitivities, if regular insulin is used or one is insulin resistant then we use rule of 1500 and if analogue insulin is used or are insulin sensitive then, rule of 1800 is used.

To find our ISF we again need to calculate the TDD. Divide the constant depending on kind of insulin used or sensitivity by TDD.

For e.g. if the patient is using regular insulin/ insulin resistant, 1500/TDD= 1500/50 =30

Or if the patient is using short-acting analogue/ insulin sensitive then, 1800/50= 36

Therefore 1 unit of insulin gets blood sugar down by 30mg/dl if regular insulin/ insulin resistant and 36 mg/dl if analogue is used/insulin sensitive. This factor will enable the patient to add or deduct the amount of insulin needed to return to target blood range.

If the correction bolus doses are more than 8% of persons TDD then it's time to review our basal and bolus doses. (7) That is, if we are adding/deducting numerous correction doses it indicates poor glycemic control and time to visit our clinician.

We also need to consider the amount of active insulin still present in the body from the most recent bolus dose while reviewing the factors affecting our blood glucose levels.

Advantages:

Carb counting has many advantages. It gives patient a near normal eating pattern whereby patient is never lost out on food choices. It helps patient to maintain near normal blood sugars and better their HbA1c. Despite of food choices healthy eating habits can be taught to patients.

Disadvantages:

Weight gain is biggest challenge faced by patient doing carb. counting. Weight gain is due to many food choices available and also maintaining near normal blood glucose causes weight gain. Patient may land up with eating more carbs. because he can inject more insulin matching with carb. intake and eventually eat more calories.

Precautions:

Though carbohydrate counting liberalizes the food choices and gives patients many options, it is important to educate patient about the right portion size and healthy choices. Avoiding or limiting healthy sources of carbohydrate to achieve good glycemic control is also not the right approach as it can compromise nutritiona status. Right eating principles should be emphasized upon and over doing of any single nutrient should be forbidden on regular basis.

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Shilpa Joshi is a post-graduate in Microbiology who has subsequently done PG Diploma of Dietetics form SNDT Women's University at Mumbai. She has subsequently completed her training from B.Y.L Nair Hospital and T.N Medical College and qualified as an RD-Registered Dietician with the Indian Dietetic Association. She is National

Executive committee of Indian Dietetic Association. She is also Honorary Secretary of All India Association For Advancing Research in Obesity. She is currently the Consultant Dietician and Educator at Mumbai. She has about 12 publications in peer reviewed journals and has presented nationally and internationally in meetings. She has authored several Textbook chapters. She is also master trainer "Diabetes Conversation Maps", International Diabetes Federations' initiative for diabetes education. She has presented at various international meetings including at the American Diabetes Association, International Diabetes Federation and International Confederation of Dietitians. She is runners up recipient of Wimpfheimer Guggenheim's International Essay award (2017) of the Academy of Nutrition and Dietetic Foundation on Malnutrition. She is also a certified Insulin Pump Trainer. She is a visiting faculty to Nirmala Niketan college(Mumbai University) and SVT College of Home Science (SNDT Women's University) where she teaches clinical nutrition and Dietetics.

Prof Shashank R Joshi MD,DM,FRCP,FACE,FACP,FICP

Prof Shashank Joshi is the President of Indian Academy of Diabetes, President of Hypertension Society of India , Immediate Past, President of Endocrine Society of India, Immediate Past President, API (Association of Physicians of India) (2014-15) and Past President of RSSDI (Research Society for Study of Diabetes in India).

Consultant Endocrinologist at Lilavati and Bhatia Hospitals & Joshi Clinic.

He is a faculty at Grant Medical College in Endocrinology. Dr.Shashank R. Joshi is practicing Endocrinologist and Diabetologist who has topped all years of MBBS, MD, and DM with Gold Medals. He is a Fellow of the American College of Endocrinology (USA), American College of Physicians (USA) and the Fellow of the Royal College of Physicians (Glasgow and Edinburgh). He has more than 600 research publications to his credit. He is the Hon. Emeritus Editor of JAPI (Journal of The Association of Physicians of India), Ex Editor of Indian Journal of Obesity, Indian Journal of Endocrinology and Metabolism and Indian Journal of Clinical Pharmacology and Therapeutics and several other leading medical journals. He is affiliated to several leading hospitals of the city including Lilavati & Bhatia Hospitals. He is the Past President, AIAARO (All India Association of Advancement for Research in Obesity, IASO Affiliate), Chapter Chair (India), American Association of Clinical Endocrinology (AACE). He is visiting faculty to several Indian and International Universities. He is actively involved with evidence based work in Endocrinology including Diabetes, Obesity, Thyroid, Osteoporosis and Growth. He was awarded "International Clinician of the year 2012" by the American College of Endocrinology. He has been conferred in 2014 "Padma Shri" by Government of India.

REGINA DRUZ

MD, FACC, FASNC, AFMCP

Fit in Your GENES: A Contemporary Holistic Cardiology Program for Prevention and Treatment of Cardiovascular Diseases

Introduction

Cardiovascular disease, encompassing vascular and structural types, continues to be the most common chronic disease. For the past 50 years, cardiac disease consistently remained a number one cause of death in both men and women. Despite ongoing successful efforts in reducing mortality from cardiovascular disease, current preventive and treatment strategies failed to stem the rise in its prevalence. Fueled by the obesity and diabetes epidemic, compounded by the exposure to environmental toxins, and disruption in our responses to stress, cardiac disease continues to grow in numbers. From the economic perspective, cardiovascular disease outpaces all other chromic diseases. It also exerts a substantial emotional and financial toll by impacting many patients during their most productive years.

Traditional risk factors for heart disease, defined through Framingham Heart Study, identified age, gender, hypertension, dyslipidemia, smoking, diabetes and family history as contributors. However, these factors combined account for approximately 50-70% of cases of heart disease. Up to 50% of patients with first myocardial infarction do not have any of the traditional risk factors.

It is well known that lifestyle intervention is highly effective in preventing, and treating chronic cardiac disease. Up to 80% of heart disease events, including heart attacks and strokes, may be prevented through a lifestyle approach. This approach emphasizes whole and natural foods, plant-based diet, healthy oils, stress management and physical activity. Exemplified by Dr. Dean Ornish program, this approach emphasizes prevention over medication and procedures.

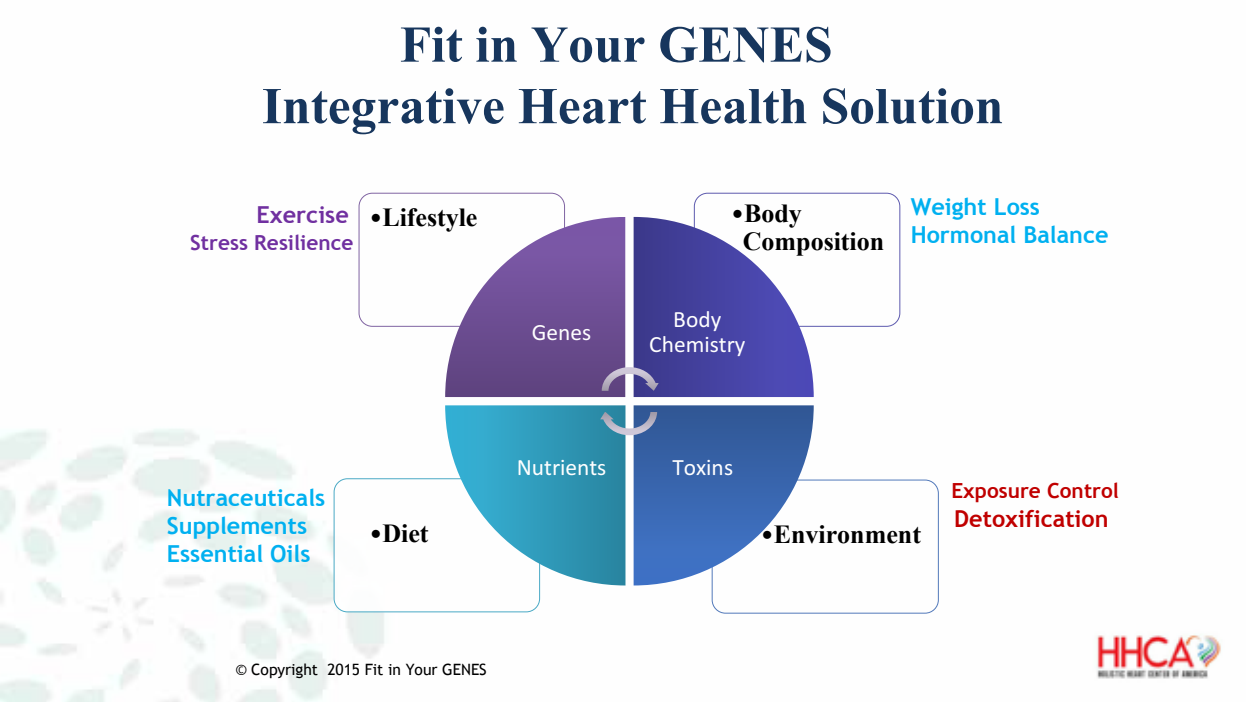
Functional and Integrative Therapies Based on Genome, Environment, Nutrition, Exercise and Supplements

Rapid advances in vascular biology identified endothelium, a one cell thick inner lining of the blood vessels, as critical interface that plays a pivotal role in formation and progression of vascular plaques. The molecular mechanisms shaping endothelial function include inflammation, oxidative stress and autoimmunity. Subsequent clinical research highlighted the impact of inflammation by demonstrating an increased cardiovascular risk in patients with systemic inflammatory conditions, such as lupus and rheumatoid arthritis, chronic infections such as human immunodeficiency virus, and those with disrupted metabolism, such as seen in metabolic syndrome, diabetes and obesity.

At the same time, ongoing efforts in sequencing of the human genome, and refinement of the sequencing techniques, made it possible for patients to inexpensively obtain access to their single nucleotide polymorphism (SNPs) for genes guiding energy utilization and toxic substance removal, and even some disease-specific genes. These genes, involved in methylation, folate, trans-sulfuration, nitric oxide and gluthatione production cycles, are closely involved in regulating levels of vascular inflammation, thus impacting our endothelial and metabolic health.

These developments created a remarkable opportunity. For the first time, we may be able to deeply personalize lifestyle interventions to help patients across a spectrum of vascular diseases by focusing on how their genome is interacting with multiple factors, all contributing to inflammation, oxidative stress and autoimmunity that affect endothelial lining, a pivotal interface in initiation and progression of vascular diseases.

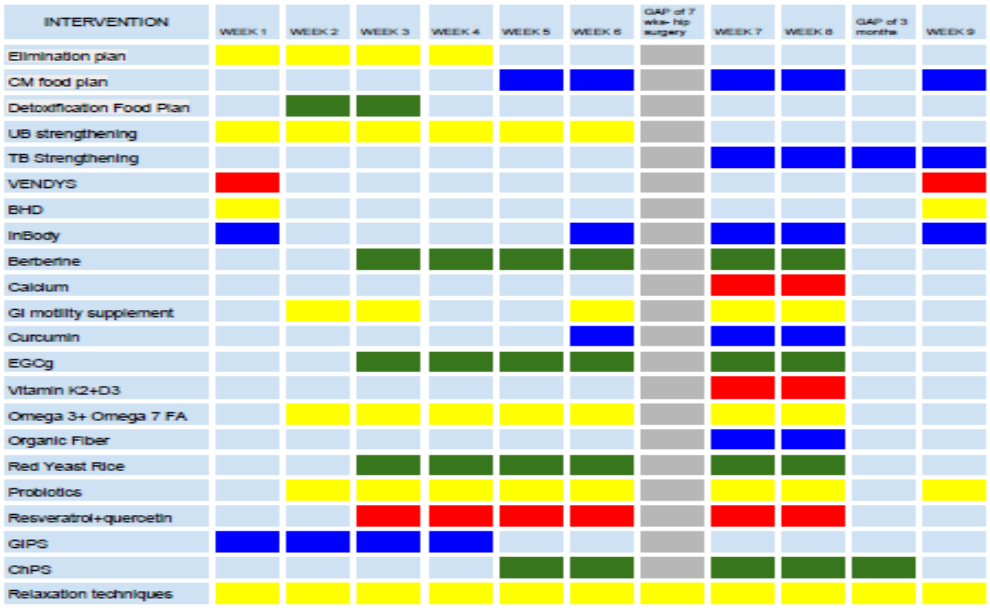
Functional and Integrative Therapeutics based on Genome, Environment, Nutrition, Exercise and Supplements (Fit in Your GENES) program provides a personalized lifestyle intervention plan for any patient at risk for or suffering from cardiovascular diseases. The program is based on identifying SNPs that underlie each patient metabolic imbalances, and applying foundational and condition-specific lifestyle interventions to minimize their influences thereby pushing down on inflammation, oxidative stress and autoimmunity affecting vascular lining. The pillars of the program are seen in the diagram below:



Case Presentation

A 57 y/o woman presents seeking treatment for early carotid artery disease and elevated cholesterol. She experienced menopause early, in her late 40s. Despite being physically active, and eating organic food, she has a self-described "sweet tooth". Her job as a school teacher is stressful at times. Her spouse is supportive. She suffers from bouts of anxiety and gastrointestinal distress. She is not overweight, and her body composition parameters are all within normal range for age and gender: weight 120.6 lbs, height 5'5", BMI 26.9, percent body fat at 22.2%, and visceral fat at 5%. Her initial blood work was notable for elevated total cholesterol (263 mg/dl), with elevations in direct LDL (169 mg/dl), elevated Lp(a) (at 117 mg/dl), and elevated markers of inflammation with hs-CRP at 1.4 and fibrinogen at 389 mg/dl. Based on her clinical parameters, the ACC/AHA Lipid Guidelines estimated risk of atherosclerotic coronary vascular disease was calculated as <5% over 10 years, placing her not in statin benefit group. Her Reynolds Risk calculator, accounting for the hsCRP, places her in low risk group as well. However, projecting 10 years forward, to the age of 67 years old, her risk of cardiac events rises 300% if she were to continue with the current levels of risk factors. She suffers from osteoarthritis, and during her pre-operative assessment, she underwent a carotid Doppler evaluation that disclosed early atherosclerosis in both carotid arteries.

Patient was interested in preventing further progression in her early vascular disease, in addition to addressing her fatigue, anxiety, and gastrointestinal discomfort. She underwent a 6 month Fit in Your GENES Program with all phases summarized below:



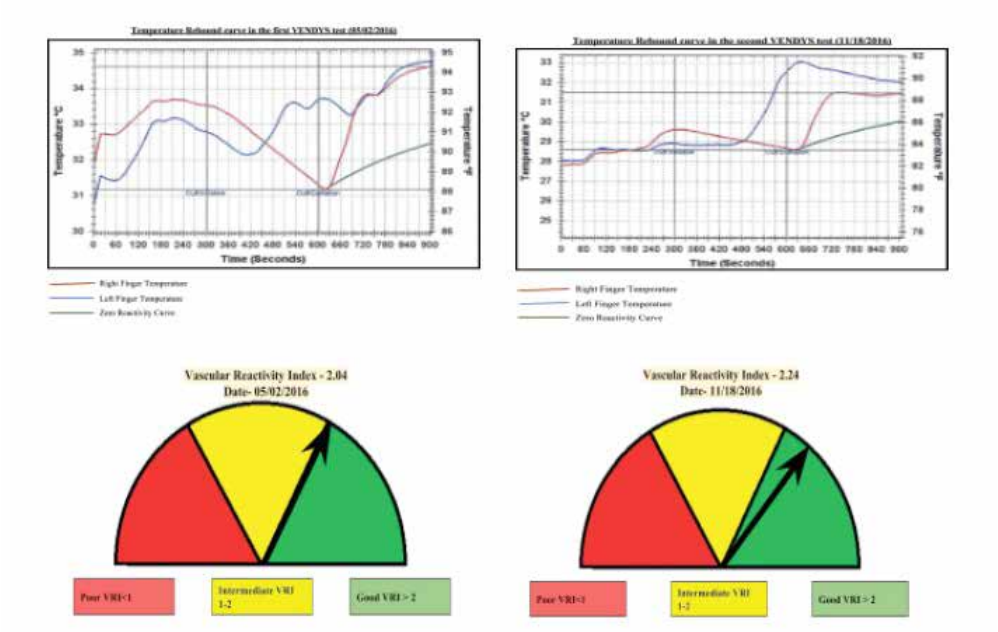
At 6 month follow up, her metabolic parameters have improved significantly as seen in the table below:

Table 2

Index	Initial (05/05/2016)	Final (11/25/2016)	Optimal
Total Cholesterol	263	227	<200
Direct LDL-C	169	129	<70
HDL-C	81	95	>60
Triglycerides	93	41	<150
ApoB	127	104	<80
Lp(a)	117	80	<30
Fibrinogen	389	333	<370
hs-CRP	1.4	0.6	<1.0
Homocysteine	9.4	11	<10
Monounsaturated FA Index	23.4	18.3	>22
Vitamin-D, 25-OH	46	79	30-100
BUN/Creatinine Ratio	22.9	23.7	<=23

Her Reynolds Risk score also showed a 3-fold drop in 10 year risk if she were to maintain her current level of metabolic improvement. Even more importantly, her vascular function, measured as endothelial reactivity in the brachial artery (Endothelix, Inc) improved

dramatically as seen in the diagram below, with vascular reactivity index moving well into the optimal (green) region:



Conclusion

Fit in Your GENES Program is a multi-faceted approach based on functional medicine that allows effective personalized lifestyle intervention for patients with cardiovascular risk factors and diseases. At the Holistic Heart Centers of America, we provide patient care, professional education, and access to our proprietary programs and practitioner network to create a vibrant community of patients and practitioners achieving optimal wellness.

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Dr. Druz is a board-certified cardiologist, nationally recognized for her expertise in heart health, cardiac imaging and clinical research. A graduate of the Cornell University Medical College, Dr. Druz completed her residency in internal medicine and cardiovascular fellowship at the Weill Cornell Medical Center-New York Presbyterian Hospital, a preeminent national institution recognized for its long-standing tradition of excellence. Seeking to prevent and reverse heart disease, and not just merely treat the end-stages of it, Dr. Druz immersed herself in the practice of integrative and functional medicine. She has developed Fit in Your GENES™ functional medicine program that uses personalized genomics to reverse cardiac disease risk factors, such as inflammation and oxidative stress, and halt progression of endovascular damage through targeted lifestyle interventions. Dr. Druz is also a healthcare innovator, developing digital and mobile health solutions. She is currently combining her interests in functional medicine and technology by creating a telemedicine platform for holistic heart health. Currently, Dr. Druz is serving as a Chief of Cardiology in a community hospital in Far Rockaway, New York. She maintains a private practice in integrative cardiology in Long Island, New York. She is a board member of the American Society of Nuclear Cardiology, and is an inaugural chairwoman of the American College of Cardiology Innovation Section. Dr. Druz has authored numerous peer-reviewed research publications, and is actively involved in the National Institutes of Health Trial to Access Chelation Therapy (TACT-2). She is Clinical Professor of Medicine at SUNY Downstate School of Medicine. A nationally recognized speaker, Dr. Druz frequently lectures at the American College of Cardiology, Integrative Health Symposium, American Academy of Restorative Medicine. She is often interviewed as a medical expert by media channels. Dr. Druz aspires to create a sustainable, contemporary cardiology practice paradigm, based on functional medicine and holistic, patient-centric approach.

DAVID BRADY
ND, DC, CCN, DACBN

MICHAEL J. SCHNEIDER
DC, PhD

Fibromyalgia-Proper Diagnosis is Half the Cure!

David M. Brady, ND, DC, CCN, DACBN the author of The Fibro-Fix with Michael J. Schneider, DC, PhD

Your patient tells you they have fibromyalgia, now what?

So your patient says they have fibromyalgia (FM) and they were told that there is no known cause or cure. The best their family physician can do is suggest they take some prescription medications and learn to live with the pain. Should they, and you, accept this diagnosis and prognosis?

Before we answer that question, read a few real-life stories from these patients below:

- I was diagnosed with fibromyalgia and suffered with widespread pain, fatigue, and inability to lose weight. After two years of unsuccessfully trying different pain and anti-depressant medications, I finally got a second opinion and was diagnosed with a previously undetected thyroid problem. My fibromyalgia pain went away completely after I was put on thyroid hormone replacement.

- I suffered with terrible fatigue and achiness throughout my body, but especially in my legs. My doctor told me I had fibromyalgia and gave me an antidepressant. At the same time, one of my best friends told me she had the same symptoms, but that her pain turned out to be related to her cholesterol medication. I asked my doctor about this and he took me off Lipitor™; and within 2 months my fibromyalgia pain went away.

- I suffered with pain in multiple joints and my doctor checked for rheumatoid arthritis, which was negative. I was told I had fibromyalgia and was put on pain medications. After a few months I went to a rheumatologist who did new blood tests and found I had inflammation somewhere in my body. More blood tests confirmed that I had Lyme disease. I was put on an antibiotics protocol and my fibromyalgia pain went away completely.

- I was diagnosed with fibromyalgia after my doctor ran numerous blood tests and could not find any medical problem that could explain my severe fatigue and widespread pain. I did notice that my symptoms got much worse around the time that my husband was diagnosed with prostate cancer. I was not sleeping through the night and started to develop panic attacks. My doctor recommended that I take a muscle relaxant before bedtime to improve my sleep and a low dose anti-depressant to help reduce my anxiety. In addition, I decided to take some yoga classes and cut back on the amount of coffee that I was drinking, both of which seemed to help reduce my stress levels. Now my fibromyalgia pain is greatly reduced and I am starting to feel normal again.

Each of these stories had a happy ending. Why? Because the doctor eventually figured out what was causing symptoms that were labeled, correctly or incorrectly, as fibromyalgia. Proper diagnosis is half the cure. If the diagnosis is not correct, how can the treatment be correct?

Proper Diagnosis is Half the Cure!

So, was the diagnosis of fibromyalgia correct in all these cases? If all of the patients suffered from the same condition, why did they require such different treatments? In the first 3 cases, the patient was incorrectly given a diagnosis of FM when another medical condition was eventually found that accounted for the symptoms of widespread pain and fatigue. The pain and fatigue went away in each of these cases, because proper diagnosis led the doctor to prescribe the proper treatment and medication.

FM is the correct diagnosis only when truly global pain and persistent fatigue are present, along with other centrally-mediated problems such as anxiety, depression, irritable bowel-like symptoms, and unrefreshed sleep are

present and other medical conditions that may explain the symptoms have been ruled out. As we can see in the first 3 cases above, the doctor gave the diagnosis of FM prematurely….before exploring all other possible causes for the pain and fatigue. Only in the last case was the patient correctly given a diagnosis of FM; after all other medical conditions were excluded and eliminated.

This last patient fits the classic profile of a FM patient as first described by the American College of Rheumatology in 19901, when the criteria for making a diagnosis of FM was first published. This diagnostic criteria was revised in 2010 and again modified in 20112. We have decided to use the term "classic FM" to describe this type of patient who has undergone extensive medical testing to rule out all possible medical diseases, as well as functional and metabolic issues, that could be causing the symptoms of widespread pain and fatigue. This is a very important and critical point; that the diagnosis of classic FM can only be made when there is no other disease(s) or disorder(s) present that could account for the symptoms.

In our previous examples, the patients clearly had other medical problems that were causing their symptoms of widespread pain and fatigue. The first patient had an underactive thyroid condition, and was not suffering from classic FM. The second patient was experiencing a reaction to cholesterol lowering medications, and was not suffering from classic FM. The third patient had Lyme disease, and was not suffering from classic FM. Essentially those 3 patients were misdiagnosed with FM when in fact they had other medical problems that accounted for their symptoms of widespread pain and fatigue.

So why do we have a dilemma? Doctors often use the single word fibromyalgia to diagnose a complex of symptoms that can have multiple causes. Worse yet, doctors often prescribe the same treatment package to all the patients they label with the term fibromyalgia. It is like using the term back pain and prescribing muscle relaxers to all patients with back pain. Some may have strained muscles, some may have arthritis, some may have herniated discs, and a few may even have a hidden fracture or dislocation. Sometimes the one-size-fits-all prescription may help patients get better, but not usually.

As a standard course of treating classic FM, most doctors will prescribe a combination of the following 3 treatments: (1) medications for sleep, pain, anxiety, and/or depression; (2) mild exercise for relaxing the muscles and to promote better blood flow; and (3) psychological counseling or relaxation techniques for reducing the emotional distress associated with fibromyalgia.3

In fact, these 3 treatments can be very helpful for a patient who is truly suffering from classic FM. We'll talk a lot more about classic FM in the next page or two, but for right now it is important to know that only a small number of patients diagnosed with FM actually suffer from this classic variety of the syndrome. Most people who are told they have FM are really suffering from another problem. A study by Fitzcharles et al revealed that of patients diagnosed with FM by primary care physicians and rheumatologists ended up with an incorrect diagnosis a staggering 66% of the time when evaluated subsequently by a panel of FM experts.4 There are 3 broad categories of these conditions - other than classic FM - that are most often the cause of widespread pain and fatigue:5

(1) Medical problems that may cause widespread pain and fatigue: examples are thyroid disease, diabetes, Lyme disease, cancer, and other medical diseases;

(2) Musculoskeletal problems that may cause widespread pain and fatigue: examples are trigger points or "muscle knots", spinal joint problems such disc degeneration and pinched nerves.

(3) Functional/Metabolic problems that may cause widespread pain and fatigue: examples are subtle functional hypothyroidism, inefficiency of energy production in the cells of the body due to mitochondrial dysfunction, nutritional deficiencies (including vitamin D, CoQ10, carnitine, B vitamins, magnesium, etc.), chemical and food sensitivities, reactions to medications, and other problems with body metabolism and biochemistry.

Unfortunately, the standard treatment approach for classic FM will not help patients with pain and fatigue caused by conditions within any of these 3 categories.6 So what's the solution to this dilemma? Actually the answer is simple. The doctor needs to find the cause of the widespread pain and fatigue, and prescribe treatments that eliminate the cause. It doesn't help to have a doctor tell the patient they have fibromyalgia without first ruling out a condition in one of these other 3 categories of medical problems. However, if the doctor has performed an extensive medical history and laboratory tests, and still cannot find a cause for your symptoms of widespread pain and fatigue – the patient may indeed be suffering from classic FM. We will now provide a brief explanation of classic FM.

Classic Fibromyalgia:

The actual cause of classic FM is unknown, but is theorized to be an unusually strong response by the nervous system to physical and/or emotional trauma. Some people develop classic FM after a very severe car accident, work related injury, serious surgical procedures, physical or emotional abuse, or witnessing a horrific event. These traumatic events may lead to a heightened and prolonged pain response to many sorts of stimuli that would not normally be perceived as painful, such as: bright lights, sounds, changes in temperature, moderate pressure on the skin or muscles, household chemicals, etc. Many researchers now believe there is a strong genetic predisposition to the development of classic FM because it tends to run in families, but clearly the right constellation of environmental factors also have to be present.8

In addition to living with chronic pain and fatigue, many classic FM patients have extraordinary amounts of stress in their life or may have experienced intensely emotional events that have caused their nervous systems to have heightened responses to pain (similar to people who experience post traumatic stress syndrome). It is important to realize that these patients are not suffering from some sort of psychological defect; classic FM patients are not "imagining" their pain. The pain is quite real and researchers can see abnormal changes in pain processing in the brains of classic FM patients with a special type of MRI scanning known as functional MRI (fMRI).9

For some unknown reason, the brains of classic FM patients do not process pain in the same way as healthy patients without FM. Research has also shown that there is a lower amount of certain chemicals in the brain fluids of classic FM patients, which could explain the heightened pain responses and lead to failure of the descending anti-nociceptive system (DANS).7 (See Figure 1) This is why certain prescription medications and nutraceuticals can help to reduce these chemical imbalances and thereby relieve the chronic pain of FM.3 Because the underlying cause of classic FM seems to be related to emotional stress or previous traumatic experiences, the most effective treatment is a combination approach that incorporates medication/supplementation, exercise, and relaxation techniques.10

Figure 1: Descending Antinociceptive System (DANS)

Here's a checklist of symptoms that are found most commonly in patients with classic FM:

- Unrefreshing sleep
- Difficulty with concentration
- Extreme fatigue/low energy
- Inability to tolerate exercise
- Irritable bowel syndrome
- History of depression/anxiety
- Extreme sensitivity to touch
- Widespread pain/tenderness
- Migraine headaches
- Grinding/clenching teeth
- Multiple chemical/food sensitivity
- Irritable bladder syndrome

If your patient has experienced widespread pain for more than 3 months and has at least 4 of the above symptoms, they may very well be suffering from classic FM and may be a candidate for the standard medical approach. Certain medications, or non-medication neurotransmitter precursors such as 5-hydroxytryptophan (5-HTP), can be helpful to reduce the level of pain, unrefreshing sleep, and emotional stress.11 However, other approaches can be helpful to 'retrain' the nervous system and the body's responses to pain. These include activities such as: mild aerobic exercise, yoga, tai chi, meditation, and self-relaxation techniques.12 Sometimes psychological counseling that uses a cognitive behavioral therapy approach is also quite beneficial to classic FM patients.

If your patient do NOT have at least 4 of the symptoms noted above, then you should look for some other cause of your patient's FM symptoms. It is likely that instead of having classic FM, they are suffering from some other medical problem that may mimic FM. The first thing is to make sure their symptoms of widespread pain and fatigue are not caused by some undiagnosed medical problem, which we will discuss in the next section.

Common Medical Problems That May Be Confused With Classic FM

In patients who complain about generalized pain and fatigue, it is imperative that the doctor rule-out the presence of any medical condition or disease that is known to cause many of the symptoms associated with classic FM. Hypothyroidism, anemia, rheumatoid arthritis, Lyme disease, rheumatic auto-immune disorders such as ankylosing spondylitis (AS) or scleroderma, multiple sclerosis, and cancer are some possible causes for symptoms of vague and diffuse musculoskeletal pain associated with pronounced fatigue.5 Most of the medical assessment appropriate in this type of situation comes in the form of laboratory testing, to include any or all of the following screening tests:

- Complete red and white blood cell count with white cell differential
- Thyroid function tests; (total and free T3 & T4, TSH, and thyroid antibodies)
- Standard blood chemistry
- C-reactive protein and/or erythrocyte sedimentation rate (ESR)
- Lyme Test, rheumatic/autoimmune profiles (as necessary)

As simple as these screening tests may be to perform, it is not uncommon for doctors to fail to have any laboratory tests performed on their patient, and still render a diagnosis of FM despite the fact that according to American College of Rheumatology (ACR) guidelines and criteria, a diagnosis of FM should not be rendered until all lab tests come back negative and fail to detect any obvious medical reason for the symptoms.2

The doctor should employ a simple, rational approach to laboratory assessment, which includes an initial complete blood count (CBC) as a screen for common forms of anemia (unhealthy or low levels of critical oxygen-carrying red blood cells), and an assessment of white cells to rule out infection or marrow disease.13 More specifically, obvious reasons for excessive fatigue, such as anemia, can be ruled out on the CBC by screening for low RBC count, altered hemoglobin and abnormal RBC indices such as MVC, MCH, and MCHC tests. An erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) test can help to confirm the presence or absence of inflammation or infection. Although the ESR and CRP tests are non-specific, extremely high values found on these tests may indicate the need for further laboratory testing for underlying autoimmune rheumatic diseases or possible undiagnosed serious illnesses, including malignancy (cancer).

Thyroid blood tests should be routinely performed in patients who present with the complaints of widespread pain and fatigue in order to rule out obvious hypothyroidism as the cause of these symptoms. While the classic signs and symptoms of low thyroid function, including fatigue, weakness, cold intolerance, low temperatures, weight changes (usually weight gain) and depression are routinely considered by doctors, common musculoskeletal signs and symptoms of hypothyroidism include muscle pain, stiffness, muscle cramping, muscle weakness, numbness and tingling, and joint pain are often not considered. The incidence of muscle and joint symptoms with hypothyroidism has been reported to be as high as 30-80%.14 These facts are extremely important since it is precisely these vague muscle and/or joint symptoms, which may drive the patient to you initially. Many patients suffering from these symptoms will likely be unaware that they have a thyroid condition, and if missed by the physician, their symptoms may inadvertently be misdiagnosed as FM. More information will be provided on thyroid conditions in the next section on functional metabolic disorders often misdiagnosed as FM.

The doctor should also order a standard blood chemistry panel, as it is very useful to evaluate the patient's overall general health who is experiencing widespread pain and fatigue. This panel should be done after an 8-10 hour fast and generally includes serum blood sugar, liver enzymes (liver function tests), cholesterol, blood lipids (fats), and kidney function tests. Of course these laboratory tests should be correlated with physical examination findings and other diagnostic tests. If the physical exam findings are suggestive to that the patient may be suffering from joint pain and/or obvious soft tissue inflammation, not simply increased pain perception in the soft tissues, additional laboratory studies such as a rheumatoid panel and Lyme disease, and co-infections, screening tests may be warranted.

It is highly important to note that if laboratory studies are positive for any of the above noted medical conditions or diseases, a diagnosis of "FM" may very well be inappropriate. In the author's clinical experiences, patients who have diseases that go undetected due to a shoddy examination and investigation are often misdiagnosed as having FM in an attempt to explain or justify their constellation of symptoms. As a general rule, no patient should ever be given a diagnosis of FM without a complete physical examination and basic screening laboratory testing to rule out the underlying medical conditions.

Muscle and Joint Conditions That May Be Confused With Classic FM

One of the most common reasons for a mistaken diagnosis of classic FM is pain that is actually arising from several muscles and joints of the body. Widespread pain is often caused by a few different painful conditions that all put together feel like just one big painful condition. For example, a patient might have injured the lower back in a work related accident 2 years ago, had a whiplash to the neck from a car accident, and also twisted the knee while walking down the stairs. When this patient makes an appointment, the doctor asks, "Where do you hurt?" The response might be "my lower back, neck, and knee…geez, doc….I just seem to hurt everywhere". The busy doctor may quickly make the diagnosis of classic FM and not take enough time to sort out the fact that this patient actually has 3 separate and distinct problems; a low back problem, a neck problem, and a knee problem. Sure the patient may be thought to have "widespread pain", but it is actually caused by 3 distinct muscle and joint problems and not classic FM.

This happens quite frequently with senior patients, who often have some degree of arthritis in several joints and come to their doctor with a complaint of widespread pain. Most primary care doctors simply don't have the time or training to perform a comprehensive physical examination of the muscles and joints, and may be quick to label a patient with classic FM. Many senior patients have an overlap of general widespread pain from arthritis, but also have one or two localized muscle or joint problems that could respond well to treatment by a physical therapist, chiropractor, or massage therapist.

It might seem simple, but there is a basic principle of diagnosis that can quickly determine if the pain is coming from a muscle or joint. Movement should reproduce the pain if the pain is coming from a musculoskeletal structure. For example, if the patient has pain between the shoulder blades coming from the neck or shoulders, movements of the neck or shoulders should cause the pain to get worse. If there is absolutely no movement or position that makes the pain worse, the pain may not be coming from a muscle or joint, and other sources of the pain should be considered.

A certain type of muscle pain is often mistaken for classic FM. In order to talk about this, we first need to clear up a very common mistake that is made in medical clinics. This is the mistaken belief that the tender points found in FM are the same as the trigger points found in another condition known as myofascial pain.15 Most doctors know about trigger points; they are the "knots", "lumps", or "taut bands" found in painful muscles after too much exercise or remaining in a poor posture for too long.

It is really important not to confuse the words "trigger point" and "tender point". These are NOT the same condition. The word tender point is used with the classic type of FM where the patient reports widespread pain and multiple areas that are extremely painful to even the lightest touch. In classic FM these tender points are painful but are generally not lumpy, hard, or nodular; they are simply "tender". However, the trigger points found in myofascial pain have a very distinctive texture; they feel hard and lumpy. Some people describe the way trigger points feel as "cords" or "guitar strings". All of these words are simply attempts to describe the observation by patients and doctors that trigger points have a distinctive texture to them, whereas tender points have no such distinctive texture.

As a patient, you can figure out for yourself whether or not your painful areas are tender points or trigger points. Gently rub the muscles over the areas of your pain. Close your eyes and let your fingers tell you what you feel. Does the area of painful muscle feel different from the same area on the opposite side of the body? If you roll across these painful "knots", does it reproduce your pain and cause a "twitch" in the muscle? If so, you may very well be suffering from trigger points and myofascial pain, not tender points and FM.

Of course, trigger points can be successfully treated with deep massage, ischemic compression techniques and stretching methods that are commonly used by chiropractors, physical therapists, physiatrist, and massage therapists. Acupuncture can also be used to treat trigger points. But remember that the tender points found with classic FM are generally not going to respond to manual massage or therapies, because the tender points are centrally mediated alterations in pain perception and not really areas of true muscle problems. They are just painful areas due to abnormal processing of pain signals by the brain and nervous system. That's why deep pressure massage techniques don't seem to work as well with classic FM patients.

It is also possible that your patient's pain is coming from joints that lie deep to the muscles. In this case, you will not feel any lumps, knots, or taut bands in the muscles because the painful joint is much deeper. However, you should still be able to provoke the pain with certain movements and positions. For example, if the patient has pain in the neck area that is coming from the joints of the cervical spine, the pain should get worse when rotating the neck fully to the right and left, looking up toward the ceiling and down toward the floor. If there is pain in the shoulder that is coming from the shoulder joint, the pain should worsen with full elevation of the arm toward the ceiling or reaching back behind the back.

Functional Problems with Metabolism That May Confused With Classic FM

More subtle "functional" disorders may represent various types of sub-clinical disease states and disorders involving dysfunction of internal organs and individual metabolism, rather than true pathology. These functional disorders are often not on the busy traditionally trained clinician's radar screen and range the gamut from simple vitamin and mineral insufficiencies, to more hidden functional disorders such as energy metabolism disorders (mitochondrial dysfunction), subtle endocrine imbalances (subclinical thyroid disorders, abnormalities is stress physiology, etc.), opportunistic intestinal infections (dysbiosis), blood sugar abnormalities (reactive dysglycemia), post-viral immune suppression, and other conditions that are not readily apparent on standard laboratory screening tests.

Energy Metabolism

Several nutritional deficiencies have been identified in patients with fatigue and widespread tenderness, including coenzyme Q-10 (CoQ10) and carnitine, both absolutely critical in the cellular production of energy, proper cognitive function and muscle function and metabolism.16-17 Studies also suggest that the use of supplements to include B-vitamins, magnesium and malic acid (malate) have shown positive results in FM patients.18-20 However, there is speculation that these interventions mainly aid in the biochemistry of energy production within the mitochondria of cells, including in muscles, which may alleviate the fatigue and muscle soreness often reported by patients diagnosed with FM, but they may not really be addressing issues specific to classic FM. In the author's experiences, in mild to moderate cases of fatigue and widespread achiness, supplementation with the above nutrients may have a significantly positive clinical effect. However, patients with severe fatigue usually do not respond adequately to these supplements alone, and require a more comprehensive functional approach. All of these functional disorders, and many more not mentioned, have the common denominator of potentially causing symptoms of low energy, fatigue, and widespread achiness, which are difficult to diagnose and often lead to an inappropriate diagnosis of FM.

The Importance of Optimal Thyroid Function

The thyroid gland is responsible for synthesizing several hormones that have vast effects on overall body metabolism. It is unique among endocrine glands in that large amounts of hormones are created and stored in the

thyroid and then released very slowly. Iodine ingested from food and water is concentrated by the thyroid gland and combined with the amino acid tyrosine in various chemical configurations to create the active thyroid hormones triiodothyronine (T3) and thyroxine (T4). The numbers 3 and 4 are used to identify the number of iodine units incorporated into the hormone's structure. All reactions necessary for the formation of T3 and T4 are influenced and controlled by thyroid stimulating hormone (TSH), produced in the pituitary gland in the brain (See Figure 2).

Figure 2: Thyroid hormone structures

As was stated previously, thyroid function laboratory tests should be routinely performed in patients who present with complaints of widespread pain and fatigue in order to rule out overt hypothyroidism as the cause of these symptoms, including thyroperoxidase and thyroglobulin antibody tests to screen for cases of autoimmune thyroid conditions such as Grave's disease and Hashimoto's thyroiditis. However, more subtle presentations of thyroid dysfunction should also be considered, even when standard lab values are within normal range. Many cases of hypothyroidism will respond well to the use of common hormone replacement medications, such as Synthroid™, Levothyroid™, or Levoxyl™. However, these medications only contain synthetic L-thyroxine (T4). Many patients suffer from and inability to efficiently convert the relatively inactive T4 hormone to the much more active T3 hormone, often instead producing more of the relatively inactive reverse T3 (rT3) (See Figure 3).

Figure 3: Thyroid hormone peripheral conversion

This condition sometimes referred to as euthyroid sick syndrome, low T3 syndrome, or thyroid peripheral conversion disorder. One possible reason for this can be elevations in the adrenal hormone cortisol due to acute or long-term stress. In these situations, patients often do not feel relief of their symptoms when placed on T4 thyroid hormone replacement therapy alone. The use of a combination of thyroxine (T4) and triiodothyronine (T3) therapy together (i.e., Armour Thyroid™, NatureThroid™, or combination therapy of Synthroid™ and Cytomel™) is very often required to adequately manage patients who do not adequately respond to T4 therapy alone. These patients may not have overt abnormalities on standard thyroid laboratory studies and they may have been told that their thyroid is fine. Doctors need to pay close attention to patient's clinical symptoms and temperature, and also utilize closer inspection of laboratory testing, and consider a trial of thyroid treatment for patients with clinical symptoms of hypothyroidism who have laboratory results in the lower part of the normal range for both total and free T3 and T4 and/or a TSH result in the upper part of the normal range. Since only the free (unbound) hormones can enter cells and bind to the thyroid hormone receptors on the cell nuclei, the free T3 and T4 hormones should be ordered and evaluated for comprehensive thyroid evaluation, something which is often not done by many conventional doctors, including endocrinologists. When these free hormones, particularly free T3, bind to the nuclear hormone receptor in a cell they regulate DNA (genetic) control of various biochemical processes, thereby altering metabolism throughout the entire body. Lowered function of the thyroid gland, regardless of the cause, can result in profound physiologic effects throughout virtually all systems of the body. General signs and symptoms include fatigue, weakness, cold intolerance, low temperatures, weight changes (usually weight gain) and depression. Generally speaking, lower levels of thyroid hormone entering cells will slow overall metabolism and energy, while higher levels will increase overall metabolism and energy.14

Here's a checklist of symptoms that may be found in patients with a hypothyroid condition:

- Extreme fatigue/low energy
- Weight Gain
- Difficulty with concentration
- Inability to tolerate exercise
- Cold all the time
- Constipation
- Chronic infections
- Frequent post nasal drip
- Swollen look to face
- Weakness
- Muscle cramps/aches
- Joint pain
- Numbness/tingling
- Hard time remembering things
- Carpal tunnel syndrome
- High blood sugar
- High blood fats (cholesterol)

It is the author's experience that undiagnosed subtle thyroid issues are one of the most prevalent reasons for complaints of fatigue, achiness and cognitive dysfunction and the eventual misdiagnosis of FM, particularly in women. To learn more about functional hypothyroid disorders please see the "media-articles" tab at DrDavid-Brady.com.

Stress and the Adrenal Glands

It is also important for doctors to evaluate how the body responds to stress in all patient's complaining of fatigue. This is often done by evaluating the status and functioning of the adrenal glands. This is necessary due to the fact that increases in adrenal catecholamines, the fight-or-flight stress hormones produced by the adrenal glands, and increases in the activity of the sympathetic nervous system have been implicated in FM. Evaluation of cortisol, another stress hormone produced by the adrenal glands, should also be assessed when screening for adrenal dysfunction. The pattern of low cortisol and elevated catecholamines are common in those diagnosed with FM and have also been associated with post-traumatic stress disorder (PTSD), which may explain the common emergence of FM diagnoses in people who have undergone significant stress, life-altering events and trauma.21 In patients with this classic pattern, psychological counseling and stress-reducing lifestyle modifications and cognitive behavioral therapy techniques are imperative.

In summary, there appears to be a certain sub-set of patients who may receive an inappropriate diagnosis of FM and do not display the entire spectrum of clinical elements indicative of classic FM, they do not show any positive laboratory findings indicative of overt organic medical pathology or disease, yet have significant functional deficits in their metabolism and certain organ systems. The functional medicine approach to the treatment of these patients is not based on any one infectious agent or treatment modality as the curative, or even palliative, solution. It is based on the principle that restoration of proper cellular biochemistry and metabolism, in a manner unique to the individual's needs, through balancing the endocrine system, correction of nutritional deficiencies, and the reduction of cumulative toxic load and oxidative stress will allow normalization of mitochondrial function, cellular energy production, and ultimately lead to a reduction in the signs and symptoms of low energy, fatigue, and widespread achiness.23 Many of these factors can be addressed with simple lifestyle changes by the

patient, including eating a varied and balanced fresh-food diet, consuming reasonable but targeted vitamin, mineral and herbal supplements, and engaging in stress management techniques such as regular light exercise, proper sleep, adequate recreation and relaxation, deep-breathing exercises, guided imagery, yoga, meditation, prayer, biofeedback and other forms of cognitive behavioral therapy.3

The old adage that "diagnosis is half the cure" is certainly true. Very targeted and individualized treatment intervention is also a key.

Basic General Supplementation Plan for Those Diagnosed with FM: (Can be helpful whether you actually have classic FM or not)

- Magnesium: 500-1,000 mg per day in divided dosages (glycinate or malate form preferred)
- B-Complex: 50-100 mg twice daily
- CoQ10 (oil-based soft-gel): 100 mg twice daily
- L-Carnitine: 500 mg 2-3 times daily
- 5-Hydroxytryptophan (5-HTP): 50-100 mg 2-3 times daily (only under supervision)
- Melatonin (sustained release preferred): 3-6 mg 30 minutes prior to bedtime if patient is experiencing insomnia or unrefreshed sleep.

Dietary Modifications:

1. Avoid food allergens and caffeine

2. The consumption of non-processed whole foods is critical in order to avoid chemical food additives as much as possible. Simple sugars should be limited as much as possible in the diet. A low allergy-sensitivity diet (avoid gluten, dairy, corn, etc.) should be followed for several weeks followed by reintroduction of foods one at a time in order to determine if any of these specific foods contribute to a worsening of symptoms. Variation in food consumption patterns should be strived for. Artificial sugar-substitutes and caffeine should be entirely eliminated.

Lifestyle Modifications:

- Keep predictable sleep patterns (in bed by 10 pm, don't over sleep in morning)
- Get moderate exercise, but do not over-exercise

Current Drug Therapies:

Treating all symptoms of central sensitization is the key focus of the three FDA-approved medications for FMS pain, inclusing pregabalin, duloxetine and milnacipran. In 2007 pregabalin (LyricaTM), an alpha-2-delta (α2δ) ligand, became the first medication to gain FDA approval for treatment of FMS pain. Although, as with each of the three approved FMS medications, the exact mechanism of pregabalin's pain-relieving action is not yet clear, it is currently believed to function via reducing nervous system hyper-excitability. Pain reduction may also result from decreased release of pro-pain neurotransmitters in the spinal cord and through modulating pain transmission in the spinal cord.3

New Emerging Therapies:

A recent Stanford University study using very low doses (3-4.5mg at bedtime) of the medication naltrexone, an opiate an opiate blocker, demonstrated a 30% reduction in pain for all 10 of the patients in this small study.23 Further research is called for, especially given the low cost and side-effects profile of this medication. Its mechanism of action is suspected to not be through its known opiate modulation capabilities, but instead may be through its pleomorphic anti-inflammatory and immune modulation capabilities and the possibility of it reducing the micro-glial inflammation deep in the brain now being reported in classic FM, though this still is yet to be clarified.24

Remember Proper Diagnosis is Half the Cure!

It is very important to know whether or not the patient is really are suffering from classic Fibromyalgia (FM). You should never issue a diagnosis of FM unless you have fully explored all other possible causes for your patient's widespread pain and fatigue. This includes careful consideration of all other medical conditions, musculoskeletal problems, and functional metabolic issues. These other causes of widespread pain and fatigue are actually more common than classic FM and must be excluded or eliminated.

Dr. Brady's new book, The Fibro Fix, provides a wealth of information on how to negotiate your way toward rendering the proper diagnosis and the proper treatment for symptoms of widespread pain and fatigue. Preview the book at FibroFix.com. Also, learn more about The Fibro-Fix Summit where Dr. Brady interviewed 30+ experts on FM and related disorders often misidentified as FM at FibroFixSummit.com.

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Dr. David M. Brady

Dr. David M. Brady has 25-years of experience as an integrative medicine practitioner and over 21 years in health sciences academia. He is a licensed naturopathic medical physician in Connecticut and Vermont, a board certified clinical nutritionist, and completed his initial clinical training as a doctor of chiropractic in 1991. He currently serves as the Vice President for Health Sciences, Director of the Human Nutrition Institute, and Associate Professor of Clinical Sciences at the University of Bridgeport in Connecticut. He maintains a private practice, Whole Body Medicine, in Fairfield, CT. Dr. Brady is also an expert consultant to the professional nutraceutical & nutritional supplement and clinical medical laboratory industries, serving as Chief Medical Officer for Designs for Health, Inc. and Diagnostic Solutions Labs, LLC. He is an internationally sought-after presenter on nutritional, functional and integrative medicine. He has appeared on the speaking panel of some of the largest and most prestigious conferences in the field including; IFM, ACAM, A4M, IHS, AANP and many more. Dr. Brady has published a multitude of peer-reviewed scientific papers and textbooks related to chronic pain, autoimmunity and functional gastroenterology and is a featured contributing author in the medical textbooks; Advancing Medicine with Food and Nutrients-2nd Ed. (edited by Kohlstadt I-Johns Hopkins Univ.), Integrative Gastroenterology (edited by Mullin G-Johns Hopkins Hospital) and Laboratory Evaluations for Integrative and Functional Medicine -2nd Ed. (edited by Bralley & Lord). His latest popular book, The Fibro-Fix, was published by Rodale and released July of 2016 and coincided with his hosting of the popular online Fibro-Fix Summit in June of 2016 with over 30,000 attendees. You can learn more at DrDavidBrady.com, FibroFix.com, and FibroFixSummit.com.

Michael Schneider, D.C., Ph.D.

Dr. Michael Schneider graduated from Palmer College of Chiropractic in 1982 and maintained a private chiropractic practice for over two decades that focused on myofascial and muscular disorders. He obtained a Ph.D. in Rehabilitation Science from the University of Pittsburgh in 2008, where he now works full-time as an Associate Professor in the School of Health and Rehabilitation Sciences, as well as the Clinical and Translational Science Institute at the University of Pittsburgh. Dr. Schneider has published a multitude of peer-reviewed papers on the topic of fibromyalgia, including a current systematic review of the literature for all complementary and alternative therapies used to manage FM. He has a unique understanding of FM from his dual experiences as a clinician treating patients with FM and as a researcher reviewing the scientific literature about FM.

SUSAN LINKE

MBA,MS RD LD CGP CLT

Irritable Bowel Syndrome: The "Other" Inflammatory Bowel Disease

As an integrative and functional nutrition practitioner and mentor to hundreds of nutrition professionals nationwide for the last 12 years, I have individually and collectively overseen thousands of patients with a myriad of chronic inflammatory conditions. In my experience, those with irritable bowel syndrome (IBS) have the most frustrating and confusing "diagnosis" for both practitioners and patients. In most cases, by the time patients reach my office, they have been through many (often 9+) practitioners, multiple tests, drugs and supplements, and are often still at square one, searching for answers, or at least a way to live without dependence on drugs or supplements. In many cases, they've been told "it's all in your head" and been dismissed or given an anti-depressant. For those clients, I not only offer tissues for tears but I also offer hope.

Who Are These IBS Patients and Why Do They Persist?

Some fast facts may be helpful to size up the problem we face in the United States with IBS. Estimates vary but based on data from the managed care literature and other sources, there are now between 40 and 60 million diagnosed IBS patients the US population, whose annual burden to the healthcare system exceeds $30 Billion.[1,2,3] The typical IBS patient is first diagnosed and treated by his or her primary care provider, though the majority are later referred to a board-certified gastroenterologist. From there, where the diagnosis is affirmed, often after expensive, invasive tests, the annual mean cost of care for IBS patients is now estimated at over $13,000 per year. The elevated cost of care often continues for life as there have been no effective long-term treatments for the IBS sufferer, be they pharmacologic or lifestyle changes. The typical patient will endure symptom-based pharmacotherapy and other empirical therapies unless the pattern existing with the condition can be broken permanently.

For the typical gastroenterologist, the IBS condition is the gift that keeps on giving as third party payers pay for the full spectrum of invasive endoscopic investigations when referred by a primary care provider who runs out of options or runs out of face-time when patients keep coming back. The primary care doctor hopes the GI expert will come up with a better solution for his or her patient. In theory, the many assays are justified so as to rule-out other conditions, despite the fact that there is no greater incidence of such diagnosis as colon cancer uncovered on colonoscopy in the IBS population than there is for the general population. If red-flags are present upon further screening however, then it wasn't IBS in the first place and the patient is in good hands.

In short, the diagnosis and treatment of IBS has become a major healthcare industry for physicians, pharmaceutical companies, and allied healthcare providers who provide everything from supplements and probiotics of dubious worth, to highly restrictive forms of elimination diets which often do no more than mask some of the GI symptoms at best, leaving the global (systemic) symptoms of the disease unresolved and the patients partially improved. Although these treatments can usually be used safely, symptoms often revert back to a less-than-optimum quality of life (QOL). However, as is obvious in the medical literature and actual experience with IBS patients long-term, this patient population is so accustomed to significant pain and suffering that anything which provides even modest relief from a portion of the worst symptoms is welcomed, then touted as "effective," and soon "recommended." These recommendations are usually based on "The Common Knowledge," that forms the basis for what we have historically believed about IBS.

The Common Knowledge

It seems that most "advisors and authorities" persist in publishing and teaching what came to be known as "common knowledge" about irritable bowel syndrome many years ago. However, as has been the case for thousands of years, be it our understanding of the shape of

the earth to our knowledge of the role of bacteria in health and disease, common knowledge is often based on partial knowledge and it is not unhealthy for the scientific community to question its validity. If we don't, we run into scenarios that have plagued science for centuries when "common knowledge" becomes dogma or "fact," perpetuated to the exclusion of any progress that might be occurring.

Much of what is found in the current literature about IBS can be summed up as follows (some are quotes and some are shortened to save time):

a. Diagnosing IBS is a "free-for-all" enterprise, because there are no actual physical attributes (i.e. inflammation, bleeding, high-temperature, blood tests, etc.) to base a diagnosis on.
b. The exact cause of IBS is unknown, it's a black box.
c. IBS can be caused by stress, whether it's from work anxieties, exams, relationship difficulties, or life events such as divorce or bereavement.
d. IBS can be treated effectively with drugs which are normally used to treat chronic depressive disorders because it is a disease of serotonin imbalance of some sort, like depression.
e. Since IBS is a syndrome and not a disease, it cannot be cured, and the best treatments consist of anti-diarrheic drugs, spasmolytic drugs, laxatives, fiber, relaxation techniques, etc.
f. Talking treatments such as cognitive behavioral therapy, hypnotherapy or psychotherapy can help relieve the symptoms. Hypnotherapy is like convincing yourself your hand feels just fine when you plunge it into scalding water.
g. IBS is a common functional disorder of the gut. A functional disorder occurs when there is a problem with the function of a part of the body, but there is no abnormality in the structure and no identifiable abnormalities upon close examination. So, in IBS, the function of the gut is upset, but all parts of the gut look normal, even when looked at under a microscope. Fact. Proven. Period. (This is why so many patients are told "it's all in your head.")
h. Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols (FODMAPS) in the diet are the cause of IBS symptoms, and the patient who strictly removes these from the diet will have great relief from IBS symptoms. (A large portion of these patients are never referred for nutritional counseling, and diet adequacy after removal of a large segment of food groups is not often addressed).
i. Intolerance to dairy products due to lactose intolerance is a common cause of IBS, as is gluten, spicy food, cold beverages, high fructose corn syrup, soy, hot food, too much food, one-size fits all foods, stress, etc.
j. Taking "probiotics" can cure IBS as many patients' IBS is caused by SIBO (Small Intestinal Bacterial Overgrowth) which is easily diagnosed by breath testing.
k. Antibiotics will cure IBS since many patients' IBS is caused by SIBO
l. SCD or Paleo diets (or other one-size-fits-all diets) will cure IBS

The literature search did not get much better from there. It became clear that most people's "common knowledge" about this highly prevalent, difficult to treat, costly destroyer of the quality of life is simply the result of conclusions based on inadequate or partial information or cognitive bias. These treatments are, for a time, somewhat helpful for some, not helpful for many, dangerous if used too long, and limited in what portion of the IBS symptoms it helps. In fact, there seems to be a growing focus on symptom relief from the primary GI displeasures like diarrhea, constipation, bloating, flatulence, cramps and abdominal pain while systemic symptoms are often overlooked, even considered mere "consequences of the stress and strain of living with IBS." Somatization is a good characterization of the current state of affairs.

Uniform Diagnostic Standards are Essential

While it is beyond the scope of this chapter to delve into basic information in how the diagnosis of irritable bowel syndrome is made, this information is readily available in the current literature

through the current guidelines for diagnosis of irritable bowel syndrome and through the AHRQ's National Guideline Clearinghouse at www.guideline.gov, as well as the last 20 years of literature where the utility of both the ROME II and ROME III criteria, with associated red-flag conditions, are discussed. [4] For years, the symptom-based approach to IBS diagnosis as described by the various ROME Committees has been in use, though it can be criticized, due to its general nature, of lacking definitive biomarkers. This has been due to the inability to resolve the actual pathophysiology of the disease by the research and clinical medical establishment, thus perpetuating the myth of IBS as a functional disease. Consequently, if researchers believe IBS is a functional disease, then efforts to seek evidence to the contrary will not take place, and biomarkers will not be found.

As recently as this year, persistent searches for diagnostic biomarkers associated with IBS continue to elude investigation. [5, 6] The bottom line is, despite the additional research material that will henceforth be discussed, the search for "the magic marker" of IBS for clinical diagnosis has continued to elude mainstream practice. However, we are growing closer based on novel research now underway. To clarify, when discussing IBS and the subtyping of IBS by specific pathology in the remainder of this chapter, we are referring to those who meet the current diagnostic standards; those with red-flags for other conditions are ruled out of the population of IBS patients.

It's a Long Look Back to the Start Line: Digestive Disease Week 2000

The annual Digestive Disease Conference held May 20 - 24, 2000 in San Diego, California is the very first time that I can find evidence presented among an expert group of Gastroenterologists that the ubiquitous irritable bowel syndrome was in fact a disease state with specific pathology. This set the trend for the next 17 years, and findings related to immunologic events in irritable bowel syndrome have been primarily in the realm of gastroenterology research, not as much in the allergy and immunology literature. After all, how many IBS patients does an allergist or immunologist see and treat per year? There is no focus clinically, nor in research, on a patient population for which American allergists provide no care.

Yet, in many cases, when physicians and nutritionists seek evidence concerning diagnosis and treatment of irritable bowel syndrome, their "evidence based assessments" are directed to the allergy literature and the expert opinion of allergists? This is, in essence, the main reason that so much about IBS is unknown to the practitioners of nutrition and dietetics. We have looked for "evidence" in the wrong places.

In a presentation at DDW 2000 titled "Is There Evidence of Increased Inflammation in IBS?" given by Nicholas J. Talley, MD, PhD, Mayo Clinic Dept. of Gastroenterology, Dr Talley presented the results of a novel experiment conducted by Dr. Hans Tornblom and colleagues from the University of Lund in Malmo, Sweden. Their subjects were ROME-criteria matched IBS patients and their findings were met with great interest. Full-thickness biopsies from the proximal jejunum were obtained. In all subjects, inflammatory infiltration of lymphocytes in the myenteric plexus was observed. These lymphocytes were situated in peri- and intraganglionic locations. The authors also noted hypertrophy of the longitudinal muscle layer and abnormalities in the interstitial cells of the Cajal (the pacemakers of the gut). Extravasation of lymphocytes occurs in response to antigen provocation, normally by pathogens seen at the intestinal mucosal barrier. However, there were no pathogens present in jejunum of the IBS patients nor a history of infectious enteritis.[7]

The findings of Tornbloom et al were provocative enough that they stimulated a new line of investigation over the next several years that continued to uncover evidence of inflammatory changes in the small bowel of IBS patients. Further, research disclosed a distinction in the nature of the inflammatory infiltrates based on a 3-class sub-typing of IBS based on the inflammatory state unique to each. To keep the information in perspective as we examine in brief the evolution of the missing pieces, it is important to keep in mind the general vision of the irritable bowel syndrome as it has evolved the past 20 years. An essential understanding of the

basics is prerequisite to appreciating the significance of the research findings I'd like to share with you. So, first a short review of clinical presentation.

Overview of Clinical Presentation, Signs, and Symptoms: GI and Systemic
We are presented with a condition which is characterized by numerous physiologic dysfunctions. A summary of key dysfunctions is:

1. Altered bowel habits presenting typically as (1) of (3) major subtypes
   a. Diarrheic-predominant IBS
   b. Constipation-predominant IBS
   c. Cyclic-predominant IBS (episodes of diarrhea and systemic symptoms followed by periods of constipation with other systemic symptoms, followed a period of cessation, then another episode of diarrhea, and so on with varying severity and duration of each period)
2. These physical symptoms are associated with various types of motility dysfunction including shortened transit time, lengthened transit time, exaggerated gastrocolic reflex, diminished gastrocolic reflex, dysregulated migratory motor complex, or combinations of the above (note the involvement of small bowel dysfunction; it is not a disease of the colon; the shock organ or primary insult is often the small bowel with the large bowel a secondary-effect organ)
3. Upregulated nociception throughout the small and large bowel
4. Upregulated stretch and tension receptors throughout the gut including apparently altered vagovagal (anti-inflammatory) responses
5. The term "upregulated HPA axis" is often used to describe the altered hypothalamic–pituitary–adrenal axis which includes manifestations of upregulated gut-brain reflex arcs (local to CNS reflex arcs and overall endocrine dysregulation)
6. Altered or impaired digestion and processing of food antigen and components (impaired assimilation of FODMAPs, impaired digestion of milk fractions including all milk fractions or a portion thereof)
7. Subpopulation with signs of altered microbiota (normal flora) in both the small bowel and the large bowel
8. Subpopulation with signs of persistent low grade enterocolitis following infectious enterocolitis which provoke IBS symptom persistence

In addition to the localized gastrointestinal symptoms associated with these dysfunctions such as the aforementioned altered bowel habits, abdominal pain and cramping, exaggerated sense of "bloating" with and without excessive flatulence (abdominal girth changes), delayed gastric emptying discomfort, incomplete evacuation discomfort, and so on, there are a host of global/systemic symptoms associated with the disease which make any focus on IBS as solely a disease of altered bowel habits and sensations short-sighted and an incorrect assessment of the conditions and the QOL-diminishing effects of the disease. These include but are not limited to:

1. An array of somatic symptoms experienced to varying degrees
2. Headache
3. Fatigue, lassitude
4. Dizziness or vertigo
5. The "fog brain" of IBS (impaired cognitive function)
6. Sense of fever or elevated temperature
7. Chills
8. Mood alteration
9. Depression/despondency/sense of sadness
10. Long term IBS can lead to chronic depressive disorders

In most cases, the amount of effort exerted by researchers delving into the global/somatic IBS symptoms has not been adequate, nor have the study designs. This has been due to the fact

that, until recently, the process of altered or diminished immunologic oral tolerance was largely overlooked, often because this aspect of the immunoregulation of the gut is as yet poorly understood, including the role of mucosal immune function and how it affects the systemic TH2/TH1 homeostasis. In large part, this is due to an inability to link these co-presenting symptoms to the "common-knowledge view" of IBS as a "functional GI disorder."

There has been a long history of cart-before-the-horse and/or chicken-vs-egg empirical speculation in the literature regarding the broad array of GI and systemic symptomology. These are irreconcilable to many practitioners attempting to treat IBS based on the "common knowledge" view of the disease, so the non-GI spectrum of symptoms is often overlooked or dismissed with one or more generalized assumptions about the causative role of stress or "patient somatization" for lack of a better guess. Also, as is often the case, systemic symptoms are often viewed as unrelated and treated individually, often by different practitioners. Until the discovery of local and systemic immune activation in IBS patients becomes more well-established, this is understandable behavior.

The same holds true for many investigators with a "treatment du jour" to promote. Despite the long-standing standard for assessing clinical response to IBS treatment being the "relief of global symptoms," [10] the assessment of treatment efficacy has been and remains focused on the degree of relief from gas, bloating, and diarrheic episodes and their reduction is deemed a success in IBS treatment. Clinically, this is a travesty in the context of what causes the QOL and degree of suffering for IBS patients to be so severe. However, as we develop the paradigm of properly-diagnosed IBS as an inflammatory disease, the holistic view of IBS-symptom spectrums that connect localized GI symptoms to the broad array of systemic symptoms makes much more sense.

When we examine the body of evidence of IBS as an inflammatory condition, the origin and causal basis of the other symptoms are then connecting by a common thread: the systemic circulation of activated immunocytes in any inflammatory response alters the balance of inflammatory mediators in all bodily compartments, and the direct actions of various mediators on body structures, tissue, organs, neurosensors and the CNS itself ties things together.

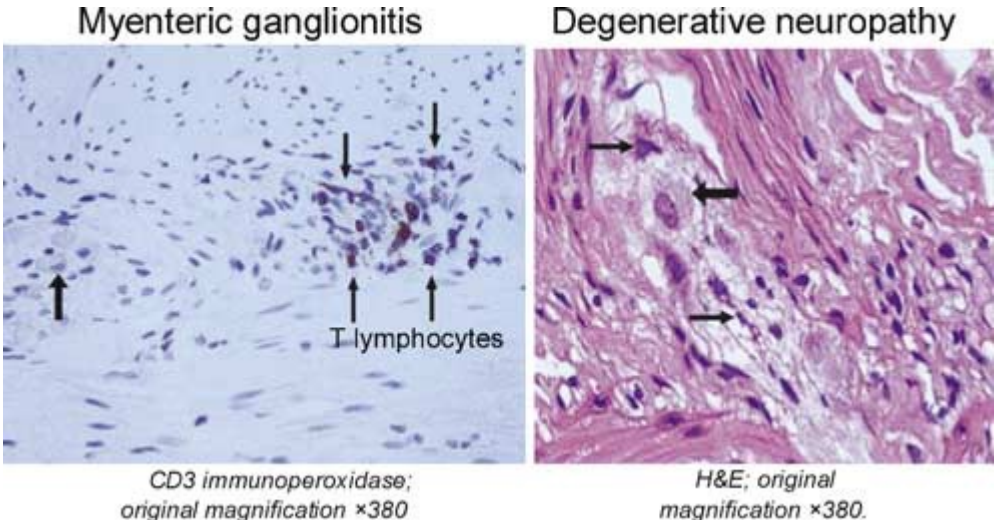
In short, *"The clinical management strategies for IBS have traditionally been based on appraisal of symptoms and empirical choice of therapy, rather than targeting treatment to the underpinning mechanism or pathophysiology."* [8] As evidence propels us toward dealing with IBS as an inflammatory bowel disease, not a functional disease, we can move away from the endless cycle of empirical treatment trials and focus instead on patient-specific clinical therapies targeted to reduce the overall inflammatory load as well as elevated levels of specific inflammatory mediators that have been quantified in IBS patients.

Inflammatory Pathology by Subtype Found

The finding of inflammatory infiltrates in the jejunum on biopsy spurred Tornblom, Lindberg, Nyberg, and Veress to continue the investigation into local and systemic immune activation and inflammation in IBS. In their 2002 study "Full Thickness Biopsy of the Jejunum Reveals Inflammation and Enteric Neuropathy in Irritable Bowel Syndrome Gastroenterology," [9] they sought to take a closer look at the nerve plexus that regulates bowel function, which is clearly dysfunctional in IBS, to seek more evidence of a pathology which could explain this dysfunction physiologically. The results were again new and instructive. In summary, 90% of the IBS patients' jejunal full-thickness biopsies showed low-grade infiltration of lymphocytes in the myenteric plexus located at both peri- and intra-ganglionic sites. There were no such intraganglionic infiltrates in the control group. In addition, 40% of the IBS patients showed concomitant intraepithelial lymphocytosis. Neuronal degeneration was also present in nearly 80% of the IBS patients, suggesting long-term elevation of inflammatory mediators at the neuronal sites which is consistent with a chronic, long term condition.

The bottom line? The evidence was presented that IBS patients suffer from inflammation and neuronal degeneration in the myenteric plexus of the jejunum. This of course is the shock-

organ for oral tolerance adaptation and long-term function as the immunoprotective barrier of the human body. Pathogens and benign antigens (dietary antigens) are processed, examined at the mucosal barrier for safety, as well as taken up both actively and passively for further examination in the mesenteric lymph nodes. From that date forward, those within the international research community performing research on irritable bowel syndrome and those responsible for the care of the IBS patient were on notice that IBS is not a functional disease; rather, it is an inflammatory disease, and should be viewed as such.[9]



Full Thickness Biopsy of the Jejunum Reveals Inflammation and Enteric Neuropathy in Irritable Bowel Syndrome Gastroenterology 2002 Dec;123(6):1972-9 Tornblom H, Lindberg G, Nyberg B, Veress B. Karolinska Institutet Department of Medicine, Huddinge University Hospital, Stockholm, Sweden

At the same 2002 Digestive Disease Week Conference, Nicholas J. Talley, MD, PhD, presented astonishing new findings by Dunlop et al at: "Irritable Bowel Syndrome: Physiology and Management."[12]

In this study, Dunlop evaluated 76 patients with IBS and 40 healthy controls. Taking full thickness biopsies of patients divided into (3) subgroups, they applied Immunohistochemical staining for lamina propria and intraepithelial lymphocytes, enteroendocrine (serotonin-containing) cells, and mast cells.

The subgroups were defined as postinfectious IBS; constipation-predominant IBS; and non-constipated, non-postinfectious IBS. They found the cell counts in constipation-predominant IBS were not significantly different from that of controls. In contrast, patients with diarrhea, but without a postinfectious history, showed increased CD3 and lamina propria lymphocytes in addition to mast cells while patients with postinfectious IBS had increased enteroendocrine cells, CD3, and lamina propria lymphocytes.

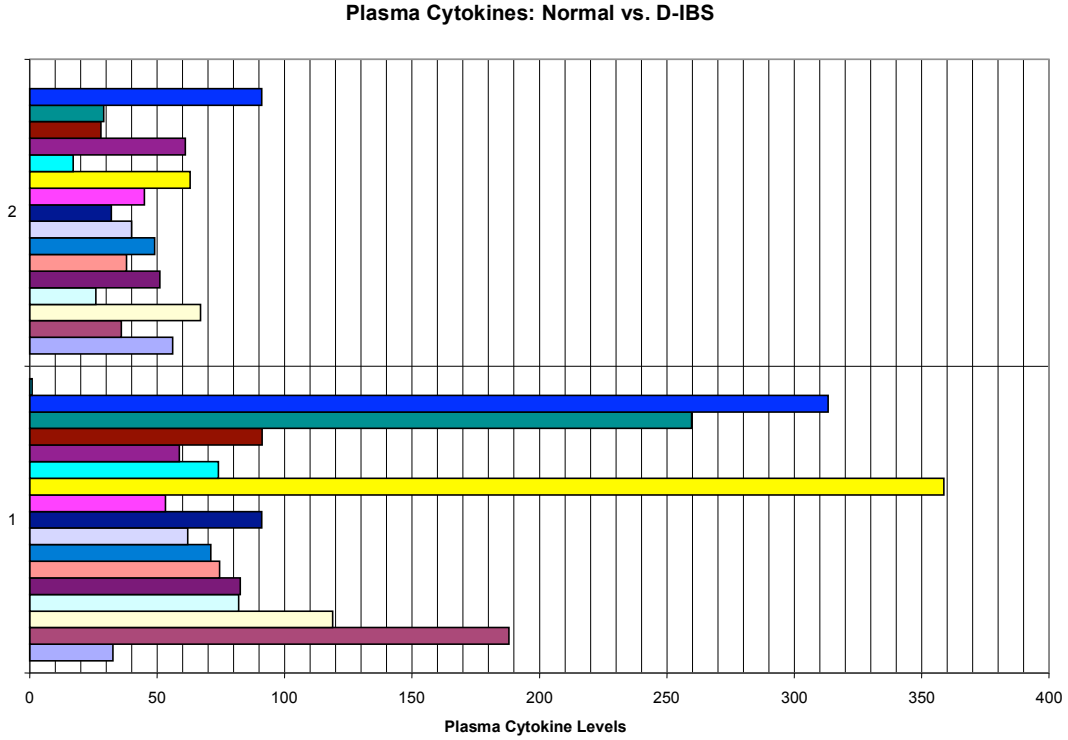
Talley proposed that subgrouping of IBS by bowel symptoms may identify distinct histomorphic phenotypes within IBS, which in turn assumes that treatment may need to be tailored to symptom subgroups based on the inflammatory pathology where present. To quote Talley: *"In view of the increasing evidence of histologic abnormalities in IBS, and providing that this is indeed a true organic bowel disease, might intervention to reduce the inflammation have utility**?** If such intervention was able to prevent the development or progression of IBS, then this would be of major clinical importance."*

Although these findings should have been a turning point in clinical research and focus, most of the money invested in IBS research in North America remained focused on GI-symptom based purported mechanisms, not what was becoming obvious. In simple terms, inflammation results in the release of mediators of various classes which upregulate local and systemic immune responses. Those mediators often have untoward effects on nerves, organs, and systems including, but not limited to, the endocrine system, nervous system (localized in the gut as well as the CNS), and the cardiovascular system. Indeed, once liberated into tissue, lymphatics and the circulatory system, their effects can be noted throughout the body. Although the bulk of research conducted has not been focused on this pathophysiologic basis for IBS, there has been sufficient work done to shape the disease state as it truly is, as well as to create what Talley noted: opportunities to tailor clinical treatment to the causal basis of the disease where possible.

The study and discovery of the inflammatory patterns seen on biopsy in IBS patients promoted a branching of investigation from solely invasive methods, which are extremely difficult to conduct, to studies seeking to identify biochemical signs or markers of inflammation. One of the earliest efforts in this line of investigation was presented to the 69th Annual Scientific Meeting and Postgraduate Course of the American College of Gastroenterology in November, 2004. Dr Fred Williams, Board Certified Gastroenterologist, reported the results of an investigation wherein the plasma levels of an array of inflammation-modulating cytokines were measured in a population of randomly selected IBS patients presenting for treatment and compared to a control group of healthy individuals (no reported health conditions). [13]

For the sake of preliminary illustration, as a thorough discussion of the clinical significance of the specific mediators measured and the specific patients' presentation is beyond the scope of this chapter, the list of mediators assayed is left off the chart. Regardless, this illustrated clearly the presence of systemic immune activation in the IBS patients.

In the following graph from Dr. William's presentation, each line represents the mean levels of a specific cytokine (interleukins, activating factors, growth factors) in the control group versus the IBS group. It was clear from this finding that the IBS population manifests altered levels of proinflammatory mediators in the plasma, and when studied closely, specific mediators correlate with specific known effects which are associated with the systemic symptoms of the IBS patients.



To my knowledge, based on my own review of available literature, and in the absence of any references to any similar prior study in all the various reviews of the IBS-related literature, this is the first time that this phenomenon was investigated and revealed in the peripheral blood of IBS patients. Other studies have found the release of inflammatory mediators in the isolated jejunum of patients presenting with IBS symptoms when the jejunum is isolated and direct food-antigen challenge is performed, but this scope and type of investigation had not been reported previously.

In 1994, Bengtsson et al developed the novel method of jejunal isolation and antigen perfusion in patients presenting with the clinical GI symptoms associated with IBS and in Celiac Disease subjects. [14] Using this method, a multi-lumen nasogastric tube is inserted into the jejunum, and (2) cuffs are inflated isolating a section of jejunum and its accompanying mucosal interface. A slurry of benign antigens, in this case a sequence of benign and common food antigens, is passed into the jejunum thus creating the ultimate blind oral challenge as no sensorial awareness whatsoever of the antigen challenge is possible by the subject. After a specific time of exposure to allow for immuno-recognition and response to occur, the section is washed out and the washings analyzed for inflammatory markers (mediators) which should not be present if immunologic tolerance is intact.

Luminal provocation with different food antigens not only activated mucosal immunocytes but clearly increased the leakage of plasma and lymphatic fluid into the lumen. Although this method is difficult to perform, it is among the most convincing methods for determining whether benign food antigens in these subjects were provoking an inflammatory response. It also showed that the inflammatory response altered mucosal stability (permeability) sufficiently to cause lymphatic fluid and plasma to leak into the isolated segment. This is but one of a series of such studies published by this team during the 1990's. Their research not only demonstrated the abnormal inflammatory response to food antigens corresponding to the presence of non-IgE mediated hypersensitivity reactions in the IBS patient population while confirming such events known to occur in celiacs, but Bengtsson was also the first to discover the phenomenon

of "intestinal food allergy" occurring in certain patients (localized IgE sensitization to jejunal antigen absent corresponding IgE antibodies in the systemic circulation).

The awareness of all these lines of investigation was and remains rare among American healthcare practitioners, unlike European healthcare communities which have an increased awareness of the role of dietary food and chemical antigens and their effects on the body, particularly inflammatory/immune. In large part, this is due to the obsession and over commitment of financial support of research into pharmaceutical solutions to health problems and diseases in the United States at the expense of broader investigation into the role of diet in both GI and non-GI disease states. The result has been a very outdated and unhelpful body of "common knowledge" as regards so-called "functional GI disorders and syndromes" at the expense of patients and the entire healthcare system.

It's the Mediators Not the Modulators
In subsequent correspondence with Professor Bengtsson to which I was privy, some of the more astonishing findings of his work were summarized by himself as follows:

"Specific inflammatory markers are recovered from the jejunal washings of the patients following localized jejunal food challenge (multi-lumen double cuffed catheters were used to isolate the test segment for food challenges). IL4, IFN-gamma, CD3, CD4, CD8 were all isolated in jejunal washings following symptom-eliciting staple food challenge of the so-labelled "food intolerance" subjects all of whom met the Rome I Diagnostic Criteria, manifest no circulating antibodies to the reactive foods, and had no history of atopy."

A mere superficial scan of the literature related to IBS from this time forward continues to shift the paradigm away from "functional disease" and the endless and expensive investigation into drugs intended to modulate GI function in IBS through action on serotonergic receptors, which are presumed to be the source of GI dysregulation in IBS (basically due to their presence and the known effects of altering serotonin levels and receptor responses). When research like this is conducted in a virtual vacuum, isolated from the research being done elsewhere investigating the local and systemic immune activation and altered immunologic tolerance to antigens manifest as inflammation in the IBS population, the erroneous paradigms and narrow interpretation of the presentation of the patients and their responses to treatment (classically poor) persist to such an extent that even so called "evidence based analysis" of the literature regarding the pathophysiology, diagnosis, presentation, and treatment of the IBS has been compromised.

This is true to such an extent that nearly all of the previously published standards for IBS diagnosis and treatment accessible through National Guideline Clearing house have been withdrawn with the exception of a rare few, limited in their scope. If we study the pharmacotherapy guidelines and the trend lines and actual clinical utility of "new IBS drugs" emergent the past few years, the limited-to-nil clinical utility of these drugs created to modulate GI function is obvious, as are the dangers of many that have come, and gone, in the process. Drugs that do not relieve the GI and global symptoms of the IBS patient long-term, and often must be discontinued after a short period of use lest dangerous side effects be suffered, have no clinical utility for those of us who see these patients seeking relief they have not found elsewhere.

However, if we focus first on the inflammatory nature of the core disease state, we can then apply specific medical nutrition therapy methods that are safe and effective. In 2006, Dinan, Quigley, Ahmed, and Scully et al published a remarkable set of findings despite the fact the array of cytokines assessed was very narrow. In their paper *"Hypothalamic-pituitary-gut axis dysregulation in irritable bowel syndrome: plasma cytokines as a potential biomarker?"* the findings can be summarized simply: IBS is characterized by an overactivation of the hypothalamic-pituitary-adrenal axis and proinflammatory cytokine increase. [15]

A total of 151 subjects, 76 patients and 75 controls, were recruited. The patients with IBS were diagnosed according to Rome II criteria. Forty-nine patients and 48 matched controls had cytokine levels measured, and a subset of 21 patients and 21 controls also underwent a corticotropin-releasing hormone (CRH) stimulation test with plasma levels of adrenocorticotropic hormone (ACTH) and cortisol measured. The remaining 27 patients and 27 controls underwent a dexamethasone (1 mg) challenge.

Cortisol and the proinflammatory cytokines interleukin (IL)-6 (together with its soluble receptor) and IL-8 were elevated in all IBS subgroups (diarrhea predominant, constipated, and alternators). There was no alteration in the anti-inflammatory cytokine IL-10. Following CRH infusion, an exaggerated release of both ACTH and cortisol was observed in patients with IBS. There was a significant correlation between the ACTH response (delta-ACTH) and the IL-6 levels. A similar relationship existed between the delta-ACTH/delta-cortisol ratio and the IL-6 levels. Dexamethasone suppression of cortisol was similar in patients and controls.

In 2007 Liebgrets T, Adams B, et al examined sets of patients representing the three most common subgroups based on clinical presentation, not pathology or history (we will discuss that approach shortly). The diarrheic-predominant, constipation-predominant, and so-called "Cyclic D and C" subgroups were examined for possible distinguishing characteristics among a limited selection of mediators measured. In their publication titled *"Immune Activation in Patients with Irritable Bowel Syndrome,"* [17] they discovered and reported the following findings which again confirmed immune activation (inflammation) in all IBS subgroups tested which were similar to the findings reported by Williams to the ACG in 2004. [13]

IBS patients showed significantly ($P < .017$) higher baseline TNF-alpha, IL-1beta, IL-6, and LPS-induced IL-6 levels compared with healthy controls. Analyzing IBS subgroups, all cytokine levels were significantly ($P < .05$) higher in diarrhea-predominant IBS (D-IBS) patients, whereas constipation-predominant IBS patients showed increased LPS-induced IL-1beta levels compared with HCs. Baseline TNF-alpha and LPS-induced TNF-alpha and IL-6 levels were significantly higher in patients reporting more than 3 bowel movements per day, urgency, watery stools, and pain associated with diarrhea.

By 2008, a clear paradigm shift began to emerge among those investigators actively engaged in this approach to IBS. Reviews of the collected evidence of localized and systemic inflammation present in IBS patients of every subtype regardless of how they are defined by clinical presentation and history, was sufficiently compelling that not only was continued investigation into the inflammatory nature of IBS encouraged but treatments based on this evidence were seen not only as justified but as an essential pursuit. For those of us interested in the pursuit of medical nutrition therapies which could ablate this inflammatory response in our patients and provide lasting relief from their symptoms and maximize their quality of life, Digiorgio summed up best what our approach to IBS as an inflammatory condition should be:

"Histopathologic data demonstrate low-grade mucosal inflammation in a subset of patients with irritable bowel syndrome (IBS). This inflammatory infiltrate is mainly represented by increased numbers of T lymphocytes and mast cells lying in the lamina propria. The close apposition of immunocytes to gut nerves supplying the mucosa provides a basis for neuroimmune cross-talk, which may explain gut sensorimotor dysfunction and related symptoms in patients with IBS. A previous gastroenteritis (due to Campylobacter jejuni, Salmonella, Shigella, Escherichia coli, and, likely, viruses) is now an established etiologic factor for IBS (hence, postinfectious IBS). Other putative causes, such as undiagnosed food allergies, genetic abnormalities, stress, or bile acid malabsorption, may also promote and maintain a low-grade mucosal inflammation in IBS. The identification of mucosal inflammation in IBS has pathophysiologic implications and paves the way for novel therapeutic options."

Indeed, as research continued forward from this point in 2008, it also became apparent that not only did one or more specific subsets of IBS patients show inflammatory activity locally (GI) and systemically (blood, plasma, CSF) but the entire population of IBS patients correctly diagnosed

based on the prevalent and accepted standards of ROME II or ROME III criteria, (absent specific red-flags for other conditions which may masquerade as IBS), have been revealed time and time again to show not only quantifiable inflammation on biopsy of the jejunum and ileocecal junction, but in all manner of systemic immune responses manifest as elevated levels of inflammatory mediators in the peripheral circulatory system as well as other inflammatory markers.

These vary widely in the literature overall as there is as yet, even in 2017, no single standard for how to design, select, and conduct investigations into the significance of various mediators and/or markers that have been found to exist in all IBS populations by an array of investigators. In large part, this is due to the fact that those doing the work select a limited number of mediators and/or markers to measure as the process of laboratory assays used are sophisticated and expensive to perform. Cytokines, for example, appear in minute quantities relative to the total blood volume, their half-lives are very short as many exist as intercellular messengers designed to modulate the wide array of potential inflammatory pathways and responses among immunocytes.

Some investigate the inflammatory patterns in the subpopulation of IBS patients who developed their constellation of symptoms following an acute enteritis episode. This is one pathway to developing IBS which has been found to precede IBS development in as much as 6% to 17% of the total estimated IBS population. It is estimated in literature reviews that anywhere from 7% to 33% of patients who experience acute bacterial enteritis go on to develop IBS. [19] Studies have shown a post-infectious persistent increase in the numbers of immunocytes, mast cells, and significant lymphocyte infiltration both in the GI mucosa and the enteric nervous system of the gut. Besides the inflammatory cells, enterochromaffin cells, cytokines and inducible nitric oxide may be related to the pathophysiologic mechanism of PI-IBS. These investigations into that subpopulation, and how to effectively treat post-infectious IBS have been spearheaded for years by Dr. Mark Pimentel. [20]

The result of his many years of work in PI-IBS have led to a widely-accepted protocol among those practitioners who have kept up with the literature related to PI-IBS, and those PI-IBS patients who meet the selection criteria have been shown time and time again to benefit from his specific antibiotic regimen. Recently Pimentel has also performed and published promising work in the area of another IBS subpopulation, those where small intestine bacterial overgrowth (SIBO) is suspected. In fact, the literature has shown that this population often develops IBS sequelae following acute bacterial enteritis with the administration of broad-spectrum antibiotics. Rather than leaving the patient with a persistent low grade inflammatory condition of indeterminate origin, evidence suggests that the suppression of gut normal flora, or "disruption of the gut microbiome" leads to an opportunistic overgrowth of bacteria which can upregulate the mucosal immune response as well as stimulate the persistent systemic immune activation leading to the disruption of overall GI motor function, sensorimotor function, nociception and immunoregulation, all of which are interactive. Again, his protocols for this subpopulation of PI-IBS have shown good results when patients are selected correctly and the treatment and the drug selection (rifaximin) and dosing are followed carefully. [21]

This need for careful assessment and not broad-brushing the IBS population as a bunch of SIBO or enteritis victims curable with rifaximin is borne out by reviews of the data which confirm that, while SIBO may play a role in the development of IBS in some indeterminate subpopulation, this cannot account for the spectrum of global symptoms seen in IBS, either in those IBS patients nor in the balance IBS patients who did not experience an episode of acute bacterial enteritis as a prelude to developing IBS.[22] There is a strong tendency among those who do see IBS for the inflammatory condition that it is, at times to be laser-focused on cause-effect conclusions, just as much as those who continue to perpetuate the mythology of IBS as a so-called "functional disease." Those persist with the dogma of Common Knowledge, instructing patients in everything from standardized lists of food elimination diets, GI symptom-based pharmacotherapy which provides some episodic relief from diarrhea, cramping, constipation,

pushing high-insoluble fiber intake to the limits of tolerance, even highly-restrictive, impossible-to-comply-with long term diets. These now include instruction in eliminating a vast array of healthy foods simply because the ingestion of high-FODMAP foods by IBS patients causes some of the localized symptoms. These symptoms are a consequence of upregulated gut nociception, upregulated or dysregulated motility, upregulated distention sensitivity (stretch receptors), exaggerated MMC due to inflammation present in the gut wall, nerve plexus, and systemically releasing mediators which target all these sites and create symptoms. In addition, there is also disruption of the antigen processing (digestion and assimilation of proteins, lipids and carbohydrates) when the jejunal mucosa is infiltrated with lymphocytes releasing inflammatory mediators and altering gut-wall permeability to macromolecule uptake.

Indeed, there are several reports of a degree of GI symptom relief from bloating, gas, and diarrhea in particular when combined with typical IBS pharmacotherapy. Unfortunately, not only is sustaining such a diet long-term very difficult, it is potentially nutritionally unsound. Worse, it directs the attention of the patient and the therapist away from the underlying inflammatory condition, local and systemic. Therefore, global symptoms are not relieved unless one is simply lucky enough to have eliminated a food on the large FODMAP list that is also an antigen for which oral tolerance has been disrupted. This occurs frequently in IBS and any disease where the jejunal mucosal immune function is upregulated and is one of the keys to propagating the systemic inflammatory response proven to exist in IBS patients of all subtypes, both in the research cited and a body of evidence not cited due to the limited scope of this chapter.

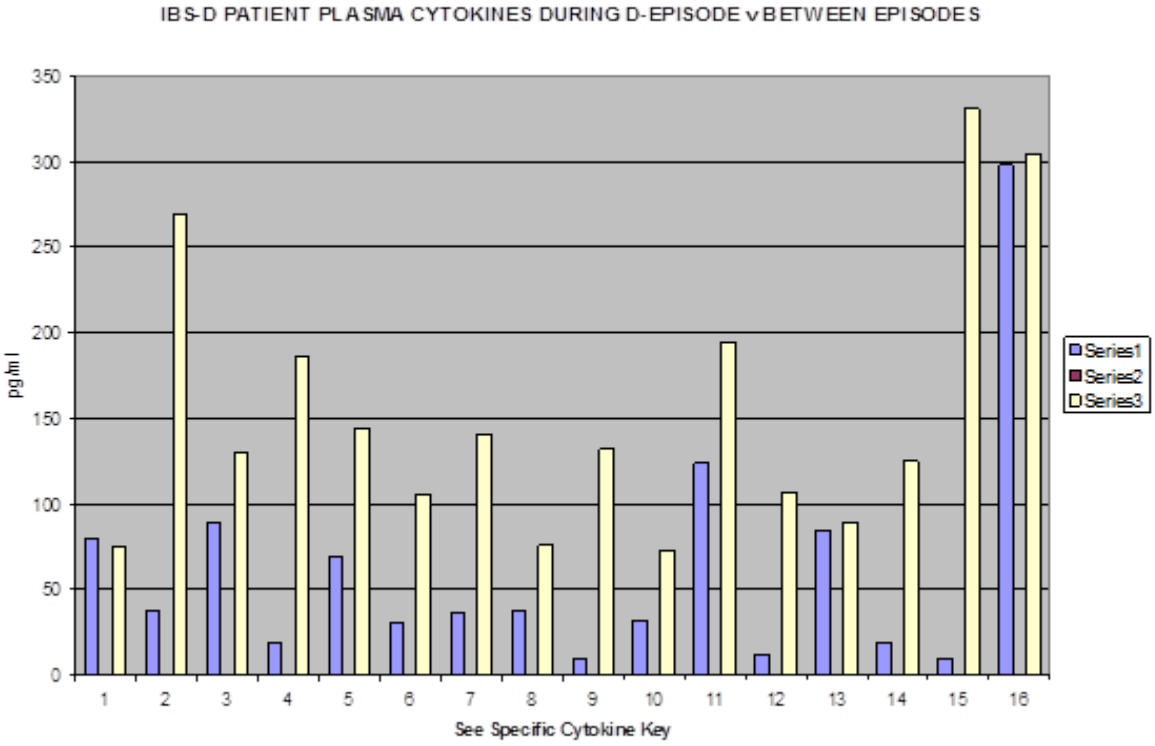
This dichotomy was recently demonstrated with exquisite clarity.[23] Twenty patients with diarrhea-predominant or mixed IBS were placed on a low-FODMAP diet for a 9-week study period. After 3 weeks, they were randomized and double-blindly assigned to receive a supplement orally of either FOS (FODMAP) or maltodextrin (placebo) for 10 days, followed by a 3-week washout period before crossover. The irritable bowel syndrome severity scoring system (IBS-SSS) was used to evaluate symptoms, and several cytokines (interleukin (IL)-6, IL-8, and tumor necrosis factor alpha) were analyzed in peripheral blood.

For those clinicians fully versed in the most current paradigm of the inflammatory bowel disease known as IBS, as it appears the investigators were, the results of the clinical trial were as such a clinician would expect. More patients reported a degree of symptomatic relief from the FODMAP diet than placebo (80% vs. 30%). The primary symptomatic impact is on GI-focused symptoms by eliminating a lengthy list of FODMAP-bearing foods. Two inflammatory cytokines were selected for measurement in peripheral blood: IL-6 and IL-8. Following the FODMAP diet period with the elimination of a wide array of foods, the proinflammatory cytokine levels were reduced. This would also in part contribute to symptomatic relief as inflammation was reduced by food elimination. However, this effect had nothing whatsoever to do with the elimination of FOS from the diet, but is related to the removal of benign antigens from the diet which, on a patient-specific basis varying from patient to patient, provoke the inflammatory response as oral tolerance is compromised in IBS.

This postulate was proven by the re-introduction of FOS-only for 10 days following the dietary elimination. There was no change in mediator levels in response to oral FOS challenge nor to placebo. **If one were able to identify the specific food antigens that provoked inflammation and elevated the cytokine levels of those patients, the degree of GI and global symptomatic relief would be far greater than the random, chance elimination of antigens by removing FODMAP foods. In addition, if the remaining unknown non-FODMAP inflammation-provoking antigens in the diet (proteins, lipids) could be identified and removed, then a diet consisting solely of safe food antigens that do not provoke or perpetuate a local or systemic inflammatory response could be created. The diet of each patient could be broader, more nutritionally balanced, and less restrictive. Thus, another problem (compliance) could be remedied.**

This approach is the basis for the use of a patient-specific oligoantigenic diet in the treatment of IBS. IBS patients do not suffer from classic IgE food allergy at any higher rate than the general population, as I will be discussing in a series of tutorials which are not included in this publication as it is beyond the scope of the chapter. However, as it has been well established by Bengtsson, Brandtzaeg,[11] and a deep well of knowledge within the immunology field, diet-induced inflammation due to loss of oral tolerance through delayed-hypersensitivity reactions (non IgE mediated) is at the core of inflammation in IBS patients regardless of the pre-IBS history. This again is suggested by the findings of FOS challenge: antigen, not FOS, provokes inflammation.

By way of example, and to introduce the reader to the classic and well-proven benefits of oligoantigenic dietary therapy, the chart below is offered in closing. This chart represents an IBS patient who presented for treatment in acute distress, (20-year history of non-PI, D-TYPE IBS). The patient was placed on an OA specific to him. After 5-days of adherence to his OA diet the patient returned asymptomatic and the mediator levels were tested. These are in violet. When the OA-eliminated foods were re-introduced, acute IBS-D symptoms returned within 48 hours and another blood specimen obtained. The results are in yellow.



1. IL-2 2. IL-4 3. IL-6 4. IL-8 5. IL-10 6. GM-CSF 7. IFN-g 8. TNF-a 9. IL-1b 10. IL-5 11. IL-7 12. IL-12 13. IL-13 14. IL-17 15. G-CSF 16. MCP-1(MCAF)

My experience adopting this patient-specific OA diet therapy is solid. I have found this method to be the most superior and consistently effective anti-inflammatory diet. Over a 12-year period my patients have enjoyed tremendous long-term relief from their GI and global (systemic) symptoms. The thousands of patients of other clinicians (nutritionists and physicians) I know who have adopted patient-specific OA diet treatment for their IBS patients since the inflammatory-basis of IBS became known, have all expressed the same high-degree of satisfaction. I look forward to the opportunity of issuing a tutorial now that the scientific basis for efficacy has emerged. It is rooted in solid evidence of the true IBS pathophysiology, the basis for the symptoms of that "other inflammatory bowel disease."

As Talley observed to his peers, the other gastroenterology experts present when the inflammatory basis of IBS was first demonstrated beyond speculation by facts:

> *"In view of the increasing evidence of histologic abnormalities in IBS, and providing that this is indeed a true organic bowel disease, might intervention to reduce the inflammation have utility? If such intervention was able to prevent the development or progression of IBS, then this would be of major clinical importance."*

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Susan Linke is a registered and licensed dietitian, Certified LEAP Therapist (CLT) and Certified Gluten Practitioner. She received her MBA from Texas Tech University in Lubbock, TX, and a Master of Science degree in Nutrition from Texas Woman's University in Denton, TX. She is a member of the Institute of Functional Medicine, and various dietetic practice groups of the Academy of Nutrition and Dietetics including Dietitians in Integrative and Functional Medicine (DIFM), SCAN, Nutrition Entrepreneurs, Medical Nutrition Practice Group and Dietitians in Gluten Intolerance Diseases (DIGID).

She is on the advisory boards for the Integrative and Functional Nutrition Academy as well as Oxford Biomedical Technologies, Inc. and is the recipient of the 2015 "Excellence in Practice Award" from the DIFM dietetic practice group.

Susan has received extensive training in immunology, adverse food reactions, and practical application of dietary treatment for chronic inflammatory conditions.

Considered one of the most experienced LEAP therapists in the country, she has spent the last 12 years training and mentoring thousands of dietitians and other healthcare practitioners nationally and internationally who are interested in improving the health of their clients by incorporating anti-inflammatory protocols as well as expanding their knowledge of functional and integrative medical nutrition therapy.

She is a sought-after speaker and lecturer, having presented at numerous local, state, and national meetings and conferences, in addition to many radio interviews and contributions to magazine articles.

Susan resides in Dallas, TX where she is the owner of an integrative and functional nutrition-based private practice, and also counsels clients through telecommute. In her spare time, her favorite thing to do is spend time visiting her 3 grandchildren who live in North Carolina.

ELLEN KAMHI
PhD, RN, AHG, AHN-BC

EUGENE R. ZAMPIERON
ND,MH,AHG

OSTEOPOROSIS – a Naturopathic Perspective

Osteoporosis is a disease of the skeletal system, which is characterized by deterioration of bone tissue, along with a decrease in bone mass. It can strike anyone at any age, although it is most prevalent in Caucasian and Asian, small boned woman over 50 years old. Osteoporosis is recognized as a major public health issue. Over 10 million Americans are afflicted, with 34 million more who may already be exhibiting signs of low bone mass, which increases the risk of developing osteoporosis. Bone mass can be determined by a bone mineral density test (BMD), such as a dual-energy x-ray absorptiometry (DXA). Low bone mass increases the risk of developing osteoporosis and fractures. Osteoporosis can effect any bone in the body, although the most common sites are the wrist, spine and hips. It is credited with more than 1.5 million fractures in both the United States and Canada per year, causing a huge amount of personal suffering and loss of quality of life. (3) (4) This disease also has a high cost to society. The cumulative economic burden of care for fractures due to osteoporosis from 2008-2028 is estimated at $474 billion dollars in the United States alone. (5)

The term, 'osteoporosis', describes the condition of the inside of the bones in people who have this disease, where large porous areas develop, weakening the bone structure. Throughout life, bone is a living tissue that maintains a balance through the bone building activity of osteoblasts, with the reabsorptive activity of osteoclasts. When factors such as advancing age cause a change in this balance towards reabsorption, bone mass decreases. After reaching a 'fracture threshold', bone that was normally able to withstand a minor stress, such as a fall or blow, becomes subject to break or fracture more easily. Osteoporosis is most often diagnosed in the senior years. However, the most important time to focus on building healthy bone is during the first 3 decades of life. Providing sufficient bone building nutrients, along with weight bearing exercise, may be the best protection against this disease. (6)

There are several risk factors that increase the chance for an individual to develop osteoporosis: family history, female (six to eight times more likely than male) especially post-menopausal, due to decreased estrogen levels, advancing age, Caucasian , low calcium intake, smoking, alcohol consumption, a sedentary lifestyle , (7) and soft drink consumption. (8) (9)

Since many of these contributing factors are self regulated, health care providers can have a direct impact on this health issue by diligently educating clients. Risk of osteoporosis is also directly linked to the use of many prescription and OTC drugs: corticosteroids/steroids, thyroid hormones, anticonvulsants, aluminum containing antacids(ironically often recommended as a calcium source by mainstream physicians), loop diuretics, gonadotropin-releasing hormones, and many others. (10) Wherever possible, health care providers can instruct clients about natural therapies that may be equally effective for specific health conditions, but present a substantially lower risk for interfering with bone density.

Drug therapies for osteoporosis include bisphosphonates, such as alendronate and risedronate. A growing list of concerns is linked to the use of these drugs, including research that suggests a link between the use of these agents and esophageal cancer. (11) A once per month tablet, ibandronate sodium, claims the advantage of greater convenience, but still has a host of possible adverse effects such as esophageal irritation, heartburn, and ulcers. In addition, it is not recommended that women with hypocalcemia take these drugs. Hormone replacement therapy was previously touted as a treatment, and may, in fact be quite useful for decreasing bone loss. However, this benefit decreases if hormone therapy is discontinued. In addition, many women refuse hormone therapy due to other known or perceived adverse effects. (12) (13) Although pharmaceutical agents can be effective, there is an increased interest in non pharmacological prevention and treatment of osteoporosis. (14)

Health care providers can be proactive on this front by supporting the improvement of nutritional status through diet and nutritional supplementation, along with suggestion for an increase in exercise training.

There are several natural interventions that promote increased bone health. These include sufficient consumption of bone supportive nutrients through healthy eating, regular exercise, and nutritional supplements including calcium, magnesium, vitamin D, boron, strontium, soy isoflavones and Vitamin K. Novel supplements such as bone morphogenic proteins are also under investigation. (15)

Exercise

Exercise has an important impact on bone health. Several studies have increased awareness on how exercise can most constructively be used to prevent the development of osteoporosis. (16)

Starting to exercise at a young age is best to achieve long term positive effects, since maximum bone mass is usually achieved during the first third of the life cycle. However, exercise at any age can improve bone health. Weight bearing exercises, including weight training, hiking, climbing stairs and walking, and other exercises that force the bones to work against gravity, are effective at increasing bone mass. (17) Researchers from the Bone & Joint Injury Prevention & Rehabilitation Center at the University of Michigan investigated a host of exercise studies from 1961 to 2009 to determine the kind of exercise that had the greatest impact on bone health and density. They concluded that three factors were most important in predicting the best exercise outcome: Strain magnitude (how much impact the exercise has on the bones and muscles), strain rate (how often maximum vs minimum strain is applied) and strain frequency (how often strain occurs in a given amount of time). (18)

A combination of these three factors determines how helpful a given exercise regime is in helping increase bone density. However, there is no consensus about the exact combination of these three factors that is most likely to maximize osteogenic activity. (19) For most individuals, practicing weight bearing exercise three times per week for 12 to 20 minutes is sufficient to increase bone density. Since each joint will respond to the strain load individually, its best to rotate exercise sites, and focus on each one for a limited time period. Continuing to exercise throughout life helps to reduce bone loss and the risk of falls. (20)

Dietary Interventions

The best approach to getting sufficient nutrients to build and maintain strong bones is by consistently making healthy food choices. As we discuss each nutrient below, food sources will be included, along with suggestions for possible supplementation, which is secondary to whole food ingestion.

Calcium

Calcium is the most abundant mineral in the human body. It is well-recognized for its importance in the development of bones and teeth, and has many other functions as well. The ability of calcium supplements to "maintain good bone health and reduce the high risk of osteoporosis later in life." is one of the few health label claims allowed by the United States FDA. The best food sources of calcium, other than dairy, include whole grains, beans, almonds and other nuts, and dark green leafy vegetables, such as kale. (21) Milk and dairy products contain a substantial amount of calcium; however, it is interesting to note that individuals who avoid dairy due to lactose intolerance do not experience a corresponding increase in osteoporosis. (22) Calcium supplements have been shown in several studies to be effective at slowing bone loss in both peri-menopausal and post menopausal

women. (23) A Cochrane Database Review Article (2004), states that "calcium supplements ….. at 500 to 2000 mg per day, are the simplest and least expensive way to prevent bone loss." (24) A comprehensive literature review published in the British Medical Journal (2010) questioned the commonly held belief in the benefits of using calcium supplements. In this meta-analysis the reviewers concluded that subjects who took a 500 mg/day calcium supplement (without Vitamin D), experienced an increased risk of myocardial infarction, when compared to those who did not take calcium supplements. These results will likely lead to further investigation of current recommendations. (25)

To maintain bone health, 1000- 1500mg/day of calcium (including food sources and supplements) is recommended (varies with age, weight, sex, etc.) by the National Academy of Sciences. (26) Sufficient calcium intake is important in preventing osteoporosis, because if the body's stores of calcium is low, calcium will be leached from bones, which can lead to decreased bone mass and the initiation or worsening of osteoporosis. While diet is the ideal source for all nutrients, calcium supplementation is often recommended to ensure that adequate amounts of this important mineral are ingested daily. This can be confusing, due to the many forms of calcium on the market, the differences in dosage levels, absorption rates, delivery forms (ie tablets, vs. liquids), cost, etc. Several studies have shown that calcium citrate is absorbed better than tricalcium phosphate, calcium lactate and calcium carbonate, (the kind of calcium in antacid tablets). (27) Calcium citrate does not tend to cause gastric distress, and has a pleasant taste. One study surmised that calcium formate is better absorbed than either calcium citrate or calcium carbonate. (28) Microcrystalline hydroxyapetite (MH) is a form of calcium that was demonstrated to be more effective at slowing bone loss than calcium carbonate. (29) MH was also shown to support bone density in a randomized double blind 2007 control study. (30) Since calcium is so intimately involved in an array of metabolic reactions, it is not surprising that there is a long list of possible interactions with pharmaceutical drugs. Examples follow: Calcium decreases the absorption of bisphosphonates, (31) levothyroxine (32) , tetracycline and quinolone antibiotics (33) Thiazide can reduce calcium excretion, leading to hypercalcemia, metabolic alkalosis and renal failure. (34) Health care practitioners can assist customers to choose a calcium supplement that best meets their needs.

Magnesium

Magnesium is the second most common mineral in the body (after calcium). Magnesium is important for many metabolic processes, including building bone, formation of ATP, and promoting calcium absorption. Dietary sources of magnesium include nuts, whole grains, dark green vegetables, fish, meat and legumes. Magnesium is often deficient in the Standard American Diet, due to eating a diet low in this nutrient, and soil depletion due to commercial farming practices such as overcroping. (35) Low levels of blood magnesium correlates with low bone density, (36) and several studies have supported the use of oral magnesium supplementation to increase bone density. (37) (38) (39) (40) Even a moderate magnesium deficiency has been documented to cause bone loss in rats. (41) Magnesium deficiency may impair the production of parathyroid hormone and 1,25-dihydroxyvitamin D, which negatively effects bone mineralization. (42) Supplementing with 250-400 mg a day of magnesium is usually recommended. Magnesium glycinate or gluconate are preferable to magnesium oxide, and are less likely to cause loose stools. Adverse effects of magnesium usually occur at higher dosages, and are most often associated with intravenous magnesium. These may include: diarrhea, drowsiness, loss of tendon reflexes, thirst, hypotension, muscle weakness and respiratory and cardiac irregularities. (43) Drug interactions include neuromuscular weakness and possible paralysis when combined with aminoglycoside antibiotics, decreased absorption of biphosphates, tetracycline antibiotics and calcium channel blockers(take at different times). Conversely,

many drugs cause hypomagnesemia, including aldesleukin, aminoglycosides and amphotericin-B(common). (44) Magnesium supplementation helps to balance a number of health issues in addition to osteoporosis, such as insomnia, headaches, chronic constipation, restless leg syndrome, anxiety and irritability, and is often the first supplement we recommend in our clinical practice, after implementing a whole food based diet.

Vitamin D

Vitamin D is essential for the formation and maintenance of bone tissue, due to several complex mechanisms, including the regulation of calcium and phosphorous absorption. If Vitamin D levels are low Parathyroid hormone (PTH) increases, and triggers osteoclasts to release calcium into the blood via bone readsorbtion. If this process continues over time it weakens bone and leads to osteoporosis. In addition, vitamin D stimulates intestinal epithelial cells to synthesize calcium-binding proteins that support the absorption of calcium in the blood. (45)

Vitamin D is called 'the sunshine vitamin' because the best source of vitamin D is from sensible sun exposure. Vitamin D is synthesized when sunlight hits the skin and transforms 7-dehydrocholesterol into vitamin D3 (cholecalciferol). D3 is shuttled to the liver where it is converted to 25-hydroxycholecalciferol, which is then transformed into 1,25 dihydrocholecalciferol (calcitriol); 10 times more potent than Vitamin D3. Magnesium and boron act as co-factors in this reaction. Food sources of vitamin D include fish and fish oils. Vitamin D deficiency is now recognized as an epidemic in the United States (46), and is especially common in dark skinned persons, the elderly, people living in northern areas, and anyone who has limited sun exposure. Deficiency can create secondary hyperparathyroidism, leading to a loss of collagen matrix and minerals, which increases the risk of osteoporosis and fractures. Poor bone remodeling due to higher osteoclast vs. osteoblast activity can be due to low levels of vitamin D, reduced synthesis of calcitriol in the kidneys or a lack of calcitrol receptors in target organs (47) Vitamin D is available as a supplement in several forms. Vitamin D 3 (cholelcalciferol) Vitamin D 2(ergocalciferol) and Alfacalcidol are three common forms. Studies indicate that alfacaldidol has been shown to prevent osteoporosis in women on high dose corticosteroids, (48) as well as increasing muscle power and walking distance in the elderly. (49) A study which compared results using alfacalcidol with ergocalciferol (Vitamin D 2) in elderly women with vertebral fractures, discovered that alfacalcidol has a greater effect than D2 at stimulating calcium absorption by bones. (50) Vitamin D 3 is more effective than Vitamin D 2, and is a better supplement choice for most individuals. (51) An exception would be vegans, who prefer not to use any product that may have been animal sourced, since the starting material for D 3 is fish or lanolin. Mechanisms of action of Vitamin D's role in building healthy bones includes increasing the number and activity of osteoblasts, (52) reducing the activity of osteoclasts, (53) and normalizing the turnover of bone in osteoporosis. (54)

Vitamin D appears to be most effective as a therapy for osteoporosis when combined with calcium. (55) While 400 IU's of oral vitamin D (cholecalciferol) is the current RDA, this level of supplementation appears to be insufficient to prevent fractures, while 700 to 800 IU/d appears to reduce the risk of hip and any nonvertebral fractures in both institutionalized and ambulatory elderly persons. (56) Vitamin D is well tolerated at doses of 400 -800 IU. Current studies are moving towards increasing the RDA of Vitamin D, and many health practitioners are already recommending much higher doses. Scandinavian countries are considering ways to increase levels of Vitamin D through both supplementation and the use of UV lights. (57)Vitamin D has a low incidence of adverse effects, although intoxication can result if higher doses are used long term. Symptoms include weakness, nausea, vomiting and poor appetite. Toxicity may be seen when serum 25(OH)D concentration is consistently >200 ng/mL (>500 nmol/L) (58) More problematic are drugs which deplete Vitamin D. These include carbamazepine, (59) chole-

styramine and colestipol. (60)

Boron

Boron is ubiquitous throughout the human body with the highest concentrations found in the bones and dental enamel. Although there is currently no RDA, boron appears to be indispensable for healthy bone function, possibly via effects on reducing the excretion and absorption of calcium, magnesium and phosphorus,

(61) and by affecting signal transmissions across cell membranes by acting indirectly as a proton donor, which influences ion gradients that are involved with cell/cell communication. (62) (63) Boron may be involved in the synthesis of steroidal vitamins and hormones, such as Vitamin D, 17 beta-estradiol and testosterone and inhibits a range of microsomal enzymes which catabolize these steroids, thus delivering a net up-regulatory effect, which could explain its bone building properties. (64) Boron clusters or carboranes have a high binding affinity for steroidal receptors (65) and are being formulated into medications such as specific protease enzyme inhibitors. (66) Boron may be beneficial in the treatment of osteoporosis, especially in the case of vitamin D, magnesium, and potassium deficiency. (67) One study found that boron supplementation as an isolated nutrient was not useful in terms of preventing bone loss. (68) Fruits, vegetables, soybeans and nuts can be rich sources of boron, but the level depends on the soil in which it is grown. A safe daily intake is estimated to be between 1 and 10 mg. Breast cancer patients are often cautioned not to use more than 3 mg a day due to references of boron's ability to increase endogenous estrogen. (69) Sodium borate and boron chelated with glycinate, aspartate or citrate are the most common forms used in dietary supplements. Toxic effects appear at intakes of about 100 mg. A fatal dose in adults is 15 to 20 g and in children 3 to 6 g. Repeated intakes of small amounts can cause accumulative toxicity, so pulse dosing is recommended, rather than continuous use.

Strontium

The mineral strontium is a powerful agent in the treatment and prevention of osteoporosis. Strontium is a naturally occurring mineral present in water and food. Trace amounts of strontium are found in the human skeleton, where it is adsorbed at the matrix crystal surface of bones. The Spinal Osteoporosis Therapeutic Intervention study is a double-blind, randomized, placebo-controlled trial, which compared two groups of postmenopausal women who already had a diagnosis of osteoporosis. One group was given two grams daily of non-radioactive strontium ranelate , while another group received a placebo. The strontium group illustrated a significant reduction (41%) in the relative risk of experiencing a new vertebral fracture. (70) Other promising studies showed reduced risks for non-vertebral fractures, including hip fractures following the use of strontium. (71) In addition to reducing the risk of fracture, strontium ranelate increased bone mineral density throughout the study, peaking at 3 years, with augmented scores of 8.2% in the femoral neck and 9.8% in the hip. Japanese pharmaceutical researchers have trade named the strontium salt PROTELOS™ and are in phase two drug trials. The mechanism of strontium's bone strengthening effect is believed to be decreased bone resorption and increased bone formation which increases bone mass, microarchitecture and strength. (72)

In the US, strontium is available as a dietary supplement in the form of strontium citrate. Theoretically, this form may have similar action to strontium ranelate, which has been used in most studies. UC Davis is investigating the use of Sodium Citrate for the prevention of osteoporosis, but the results are not yet available. (73) Most practitioners recommend that strontium should be taken at bedtime, and not at the same time as calcium supplements, since they compete for adsorption into bone matrix. It is important to ensure calcium and vitamin

D intakes are adequate when supplementing with strontium. This is underscored by earlier research on animals suggesting that increasing the intake of strontium via diet may de-mineralize bone when calcium is deficient. (74) In rats with chronic kidney failure, strontium has been shown to cause osteomalacia, a condition in which bone is softened due to lack of mineral content. (75) For this reason, it is suggested that people on kidney dialysis should not use strontium supplements.

Isoflavones

Research supports the positive effects of soy isoflavones for reducing the risk of developing osteoporosis. (76) Diets high in soy may decrease bone re-absorption in postmenopausal women. (77) Although ipriflavone, a semi synthetic flavone comparable to genistein and diadzein found in soy foods, was ineffective in restoring bone density in rats, it modulated IGF-I(insulin growth factor I), (78) which is linked to bone mineral density and increased bone remodeling through several mechanisms. (79) IGF-I (Somatomedin C) is currently being measured by holistic health practitioners as one of the parameters to assess overall aging. Ipriflavone yielded positive results on bone mass in elderly women with osteoporosis in human trials at doses of 200 mg per day, (80) and seems particularly beneficial when combined with calcium. (81) Moderate soy consumption (2-4 ounces per day) is likely a reasonable and prudent measure due to scientific validation of its positive effects, combined with a low incidence of adverse reactions. Soy can cause allergic reactions in some individuals, and may inhibit thyroid hormone synthesis. (82) Fermented soy is less likely to cause these adverse effects.

Vitamin K

Vitamin K is a fat soluble vitamin known for its effect in blood clotting, which it accomplishes by regulating the coagulation cascade via its ability to bind calcium ions (Ca2+), among other mechanisms. (83) There are three known vitamin K dependent proteins that have been isolated in bone: MGP (matrix Gla protein), protein S and osteocalcin. One of Vitamin K's roles in helping to maintain healthy bone mass is linked to its importance in the formation of osteocalcin by osteoblasts. The synthesis of osteocalcin requires both Vitamin D and Vitamin K. There are two naturally occurring forms of vitamin K: Vitamin K 1 (phylloquinone), synthesized by plants, and Vitamin K 2 (Menaquinone-n) synthesized by bacteria. The `n' signifies the number of 5 carbon chains that a specific kind of K 2 contains. Vitamin K 2 is available as both M-4 and M-7 as a dietary supplement. Research supports the use of both Vitamin K 1 and Vitamin K 2 in terms of benefits associated with osteoporosis. Vitamin K 1 supplementation has been shown to support a favorable bone biomarker profile. One study included vitamin K 1, along with Hop rho iso-alpha acids, berberine, vitamin D. The treatment group showed a significant decrease in biomarkers that indicate bone turnover. (84) However, in a double blind study which followed patients who were given 500 mcg of Vitamin K 1 for three years their bone density scores were no better than the placebo group. (85) Patients who undergo transplants have an increased risk for osteoporosis. A randomized, double blind, prospective longitudinal study investigated the effect of a dietary supplement which included vitamin K2 (180 mcg menakinon-7) on bone mass of 94 subjects who were followed for the first year after lung and heart transplantation. The outcome showed a favorable effect on bone mass density of the lumbar spine. (86) Although Vitamin K 2 is currently gaining popularity as the preferred form to use in supplementation, Vitamin K 1 is more cost effective, and therefore may be the better choice for some patients.

Vitamin K is a fat soluble substance; however the body does not store a significant amount at any given time. The need to constantly replenish vitamin K through dietary intake is decreased due to the vitamin K cycle, which

allows a small amount that is present to be used by the body several times. Vitamin K deficiency is rare, due to the reuse via the vitamin K cycle, and wide availability in the diet. Vitamin K is found in dark green vegetables such as kale, swiss chard, parsley and spinach, and to some extent in Olive and Soybean oils. Deficiency may occur in those taking anti-coagulant pharmaceutical drugs, or who have difficulty with fat metabolism. People who develop osteoporosis have been documented to have a low dietary intake of vitamin K containing foods, (87) as well as low blood levels of Vitamin K. (88) Health practitioners can emphasize the importance of eating high quality (preferably organic) green vegetables as part of the diet. If supplementation with vitamin K is recommended, common doses include the RDA amount of 65-80 mcg/day.

Bone Morphogenic Proteins

In the early 1960's, orthopedic surgeon Dr. Marshall Urist discovered a family of proteins that stimulates osteoblasts and cartilage chondrocytes, and named these proteins Bone Morphogenetic Proteins - or BMPs. The impact of Dr. Urist's contribution to medicine and healthcare was first realized in the 1990's when commercial bone-protein preparations containing BMP's and key growth factors were used by orthopedic surgeons for bone healing and spinal fusions. In 2002, the FDA approved select individual BMPs for use in surgical procedures as a more effective way to grow and heal bone. BMP's account for the major proportion of the osteoinductive potential of bone extracts. (89) BMP's bind to one of the two types of serine and threonine kinase membrane receptors, and upon binding, initiate an intracellular signaling cascade which modulate the activity of transforming growth factor beta ligands. (90) This in turn leads to the expression of the transcription factor Cbfa1 (Runx2), which results in the expression of several proteins critical for bone formation, ultimately leading to regulation of target genes involved in bone remodeling. (91) BMPs are thought to be key regulators of embryonic skeletogenesis (92), endochondral ossification (93), bone remodeling (94) (95), fracture repair (96), and bone regeneration. (97) Over 20 BMPs family members have been identified. (98) It was once thought that BMP's could only be applied locally by orthopedic surgeons for a procedure known as "screw and glue" as they attempt to mend a fracture, but recent research in animals suggest that that systemically administered BMP-6 restores the bone inductive capacity, micro-architecture, and quality of the skeleton in osteoporotic rats. Human trials are needed. (99) Some health practitioners are now recommending the use of oral BMP's for osteroporosis and osteopenia at a dosage of 200-1000 mg/day with minimum adverse effects, except for occasional GI upset in some patients.

Health care practitioners can be instrumental in educating their patients to the fact that, with intelligent dietary and lifestyle choices, osteoporosis is largely preventable for most people.

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Ellen Kamhi, PhD, RN, AHG, AHN-BC is a leader in the herbal nutraceutical industry, recognized as a consultant specializing in regulatory issues, formulation and product education. She is a professional member of the American Herbalist Guild (AHG), nationally board certified as a holistic nurse (AHN-BC), and is a medical school instructor in botanical pharmacology, and author of many books. She offers online/onground CE approved Herbal Certification Programs, and offers www.EcotoursForCures.com to experience shamanic healing traditions in indigenous areas of the world. Ellen is a wildcrafting intuitive herbalist, and is adept at radionics and dowsing. She is on the Peer Review Editorial Board of several journals/organizations, including: Alternative Therapies in Health and Medicine, Natural Medicine Journal, Natural Standard Database. Dr. Kamhi educates professionals and consumers about how to care for themselves Naturally! Her blog is recognized by Newsmax among the Top 100 Health Blogs in the country. http://www.newsmax.com/TheWire/health-blogs-topnewsmax/2015/10/13/id/695975/ .

Her passions include sharing her 4 decades of in depth herbal and nutritional knowledge with individuals that will carry natural healing arts forward into the next millennium.

www.naturalnurse.com
www.facebook.com/NaturalNurse
800-829-0918

Dr. Eugene R. Zampieron, ND,MH,AHG has over 25 years of experience as a licensed Naturopathic medical physician, professional herbalist, ethnobotanical researcher, botanical formulations inventor, professor, educator, internationally known author, lecturer, spokesman and radio personality.

DrZ, as he is known to his students and audiences, was on the founding advisory board that helped firmly establish the University of Bridgeport College of Naturopathic Medicine as the first accredited naturopathic medical college on the US Eastern seaboard , and has trained hundreds of Naturopathic doctors and physicians internationally with his encyclopedic knowledge of plants and science-based natural medicine.

Dr Z was named one of the best and most innovative Naturopathic Doctors for 2016 by the Canadian Naturopathic Doctors Development Center and practices in Woodbury, CT and at the University of Bridgeport Naturopathic medical clinic.

His websites are
www.DrZnaturally.com
www.EcoToursforCures.com
https://www.facebook.com/ecotoursforcuresjamaica/

LISE ALSCHULER
ND, FABNO

Lifestyle Factors in Cancer

Introduction

The mainstays of conventional cancer treatment, namely surgery, chemotherapy and radiation therapy, while preserving and prolonging the lives of many, present toleration challenges and often lack desired effectiveness. An integrative naturopathic approach offers an adjunctive strategy that can improve both toleration and efficacy of conventional cancer treatment. Fundamental to the naturopathic approach are diet, exercise and stress management. Diet can be used to improve tolerance to radiation and chemotherapy, and specific dietary nutrients offer synergistic antineoplastic actions. Exercise is perhaps one of the most effective strategies to both improve tolerance and outcome. Finally, the impact of stress on prognosis is proving to be significant, pointing to the important role of stress management during any form of cancer treatment.

Diet

There are several data points demonstrating a protective role of diet in cancer prevention and cancer control. Further, diet has considerable potential to optimize tolerance to conventional cancer therapies. Notably, there is evidence to suggest that patients who undergo conventional treatments without receiving nutritional support have higher complication rates. Diet can be utilized to support optimal weight, specifically to prevent weight loss during treatment, to support bowel regularity, to reduce localized areas of inflammation and pain such as headaches, arthralgia and mucositis. While the full arensal of dietary interventions is beyond the scope of this article, several dietary approaches will be highlighted.

Dietary Patterns

There are several dietary patterns and specific nutrients associated with improved survival in cancer treatment. However, when one looks across at the body of data as a whole, it is evident that the common denominator is a plant-based diet. Fruit, vegetables, and certain components of plant foods, such as fiber and polyphenols, have a large body of data supporting a protective effect against cancer. Adherence to a Mediterranean diet (a diet high in plant foods, as well as olive oil, fish, and moderate wine) has been found to be associated with reduce risk of cancer incidence in the Greek EPIC trial, comprised 25,623 participants. Adherence to the diet was assessed using a 10-point scale and every 2-point increase in the score corresponded to a 12% reduction in cancer incidence (adjusted hazard ratio, 0.88 (95% confidence interval 0.80, 0.95)). The impact of this general dietary pattern of a plant-based diet has also been studied in specific cancer patient populations.

In women diagnosed with breast cancer and treated with chemotherapy, self-report of hot flashes (HFs) after treatment for early-stage breast cancer has been associated with an approximately 25% to 30% decreased risk for additional breast cancer events, independent of the subsequent type of antiestrogen therapy. The HFs are due, in part, to lowered levels of circulating estrogen. With this in mind, the protective effect of a whole foods, vegetable-rich diet might be especially relevant to women without HFs – essentially women with potentially higher circulating estradiol levels and worse prognosis. Specifically, changes in dietary patterns to either decrease energy from fat or to increase fiber intake can alter the enterohepatic recirculation of estrogens, leading to lower circulating estrogen concentrations. A low-fat/high-fiber can be expected to reduce serum estradiol by an average of 7.5%, an effect of particular importance to women diagnosed with estrogen receptor positive breast cancer. Although this effect is modest, if it persists over years, this would have biological significance. A secondary analysis of the Women's Healthy Eating and Living (WHEL) Randomized Trial was conducted to determine if HF negative women gained specific benefit from the study diet that consisted of: 5 vegetable servings plus 16 oz of vegetable juice, 3 fruit servings, 30 g of fiber, and limited energy intake from fat to 15% to 20% of total caloric intake. Among women who reported no HFs (therefore presumably with higher estradiol levels and at greater risk) at baseline, there was a 31% lower recurrence rate in the group of women following these dietary recommendations than the HF-negative women in the comparison group (no dietary intervention) over 7.3 years of follow-up. Among HF-negative postmenopausal women, the intervention effect was more significant, with a 47% reduction in risk compared with HF- women assigned to the comparison group.

The beneficial effect of fiber specifically has been noted in other trials. For instance, women diagnosed with breast cancer who, within 12 months of their diagnosis, consume significant fiber (average consumption of 15.5 g/day of insoluble dietary fiber) experience a 49% reduction in the likelihood of having elevated CRP concentrations (OR, 0.51; 95% CI, 0.27, 0.95) compared to those who consumed an average of 5.4 g/day (P = 0.053).This suggests an anti-inflammatory effect of fiber consumption which, in turn, improves treatment toleration and is

associated with improved survival.

A dietary pattern characterized by significant reduction in the consumption of saturated fat, increased consumption of vegetable proteins with accompanying reductions in animal proteins and dairy products has been shown to significantly increase PSA-doubling time in men with prostate cancer. The slowed PSA doubling-time reflects decreased prostate cancer progression.

Colon cancer development and progression is also influenced by diet. Frequent consumption of red meat, refined carbohydrates, dairy and eggs is associated with an increased risk for developing colorectal cancer compared to infrequent consumption. There is also a significant inverse relationship between total fiber intake and risk of colorectal cancer (OR 0.57, 95% confidence interval 0.47-0.68). Vegetable fiber appears to be more protective than either fruit or grain fiber. In patients with diagnosed colon cancer, a dietary pattern that emphasizes plant foods and minimizes animal sources of protein would be expected to exert a beneficial effect on the colon, perhaps influencing progression risk.

Obesity

It is now estimated that 2.4-3.9% of cancer deaths can be attributed to obesity. In an analysis of 70 clinical trials comprising 80,000 patients with early stage breast cancer, the relative risk of dying from breast cancer was increased by 34% in obese (BMI >30) pre-menopausal women (younger than age 55y) with ER+ tumors. In other words, the absolute 10-year breast cancer mortality for pre-menopausal women with ER-positive disease was 21.5% for obese women compared with 16.6% for non-obese women. Post-menopausal obese women with ER-positive disease had a 6% increased risk of dying from breast cancer. There was no association between obesity and breast cancer death in women with ER negative tumors. Genetic analysis of pretreatment tumor biopsies has identified 121 genes with statistically significant changes in expression between obese and non-obese women. In addition, obesity is characterized by hyperinsulinemia, estrogen signaling, and inflammation – all of which play important roles in obesity-accelerated breast cancer aggressiveness.

Obesity is also associated unfavorable outcomes for patients with prostate cancer. Higher BMI (consistent with being overweight and obese) is predictive of a greater likelihood of rising PSA after surgery, indicating prostate cancer recurrence. Furthermore, overweight and obese men experience shorter times to biochemical recurrence after surgery than normal weight men.

Obesity is a known risk factor for the development of colorectal cancer as well as it progression. Obesity related dyslipidemias, increased adipokines and elevated insulin and insulin-like growth factor-1 are collectively associated with both increased colorectal cancer incidence and mortality in both men and women. Obesity also negatively impacts the effectiveness of conventional treatment with a mainstay of colorectal cancer treatment, bevacizumab. Bevacizumab is the main targeted therapy for inhibiting tumor angiogenesis by blocking the VEGF/VEGF receptor pathway. Obesity is associated with increased levels of vascular endothelial growth factor (VEGF), which could lead to resistance to anti-VEGF bevacizumab therapy. In fact, a prospective clinical trial demonstrated that in patients with metastatic colorectal cancer who were treated with bevacizumab, those who were overweight (BMI >25kg/m2) experienced significantly shorter time to progression ($p = 0.01$; HR: 4.37).

Insulin Resistance

A significant driver of malignant behavior in many cancer cell, of all cancer types, is the significant expression of insulin and IGF-1 receptors. As noted previously, insulin and IGF-1 are direct growth factors in these cancer cells. Insulin and IGF-1 stimulate cellular proliferation in malignant cells via the constitutively "turned on" insulin receptor (IR) and IGF-1 receptors (IGF-1R) which culminate in mTOR activation. Activated mTOR drives proliferation, alters mitochondrial metabolism toward anabolism (aerobic glycolysis), and decreases apoptosis. Interestingly, some cancers rely exclusively on insulin and IGF-1 for their growth, including an estimated 27% of breast cancers. Approximately 8% of these cases have upregulation of the PIK3/Akt pathway. Additionally, IGF-IR is autophosphorylated in breast cancer cells with predilection for metastasis to the brain. In vivo models demonstrate that experimental deactivation of IGF-IR attenuates the invasive and metastatic potential of these breast cancer cells thereby delaying the development of brain metastases and prolonging survival. These preclinical findings are corroborated by the fact that 25% - 40% of patients with Her2+ and those with triple negative breast cancer have significantly increased risk of brain metastasis. This clinical finding correlates with increased IGF-IR signaling

in these breast cancer subtypes.

This concept has clinical application in the dietary advice given to patients. A trial followed 87 women with metastatic breast cancer receiving first line liposomal doxorubicin and cyclophosphamide chemotherapy for a median of 15 months. Of the subjects, 87% had hormone receptor positive disease and 48% were insulin resistant, with insulin resistance defined as >2.5 HOMA-IR score. (Of note, HOMA-IR can be calculated as serum glucose (mg/dL) x plasma insulin (uU/mL)/405 with a value greater than 2.5 indicative of insulin resistance.) Even after adjusting for other prognostic factors such as age, endocrine status of tumor, visceral disease, and body mass index (BMI), patients with advanced breast cancer and insulin resistance had a statistically significant higher risk of disease progression (P = .035). The median progression-free survival was 8 months in women with insulin resistance, compared with 14 months for those who did not have insulin resistance (P = .04).

A prospective, observational study of 1011 stage III colon cancer patients reported their dietary intake during and for 6 months after conventional treatment. The median follow-up from the time of completion of adjuvant therapy was 7.3 years. Higher dietary glycemic load was associated with statistically significant worse disease-free, recurrence-free, and overall survival. Specifically, patients with stage III colon cancer who were in the highest quintile of dietary glycemic load experienced an adjusted hazard ratio (HR) for disease recurrence of 1.79 (95% confidence interval (CI) = 1.29 to 2.48), compared with those in the lowest quintile (HR = 1) (Ptrend across quintiles <.001). Increased glycemic load was associated with decreased overall survival (Ptrend across quintiles <.001). These associations were strongest for overweight patients (BMI > 25; HR 2.26). These data points support the use of a low glycemic, nutrient dense diet in people diagnosed with cancer.

Anti-inflammatory Nutrients

Plant foods and spices concentrate polyphenols which possess uniquely potent anti-inflammatory effects. The anti-inflammatory effects of polyphenols are illustrated, for instance in a parallel-designed, placebo-controlled clinical trial of 120 men and women aged 40-74 years that compared the effect of 300mg of an anthocyanin rich drink isolated from bilberries and black currants to placebo over a three week period. Consumption of the proanthocyanin-containing beverage was found to decrease NF-kappaB-controlled pro-inflammatory chemokines and IFNalpha (an inducer of NF-kappaB activation) by 45% and 40% respectively vs. 20% and 15% in the placebo group (P < 0.050). Another trial assessed the impact of 30 grams of freeze dried vegetable soup added to the daily diet of five patients with stage I non-small cell lung cancer (NSCLC) in a toxicity study group and 6 patients with stage III and IV NSCLC in a treatment group for up to 24 months. These patients were matched to 13 patients with stage III and IV NSCLC in the control group. The vegetable soup was a freeze-dried medicinal vegetable soup that included soybean, shiitake mushroom , mung bean, red date, scallion, garlic, lentil bean, leek, hawthorn fruit, onion, ginseng, angelica root, licorice, dandelion root, senegal root, ginger, olive, sesame seed, and parsley. All patients were treated with conventional therapies, including radiation, surgery, and/or chemotherapy. Those patients eating the vegetable soup had median survival of 15.5 months compared to a median survival time of 4.5 months in the control group (P<0.01). There was no adverse toxicity in the vegetable group.

In a controlled trial, 87 patients, 36 with resected colon cancer and 51 patients after polypectomy, were divided into two groups. One group of 31 patients was treated daily with a flavonoid mixture of 20 mg apigenin and 20 mg epigallocathechin-gallate and compared with a matched control group of 56 patients. Both groups were observed for 3-4 years by surveillance colonoscopy and by questionnaire. Among the 14 patients with resected colon cancer and treated with the flavonoid mixture, there was no cancer recurrence, and one adenoma developed. The cancer recurrence rate of the 15 matched untreated controls was 20% (3 of 15) and adenomas evolved in 4 of those patients (27%). The combined recurrence rate for neoplasia was 7% (1 of 14) in the treated patients and 47% (7 of 15) in the controls (P = 0.027).

In a trial of 26 men with newly diagnosed localized prostate cancer, the subjects were randomized to either 30mg lycopene or no supplement prior to radical prostatectomy. In the lycopene group, at surgery, 84% had tumors less than 4mL versus 45% in the control group. Additionally, 73% of the lycopene group and only 18% of the control group had clean margins. Prostate intraepithelial neoplasia was present in 67% of the lycopene group compared to 100% of the control group. Finally, PSA decreased by 18% in the lycopene group versus an increase of 14% in the control group.

A pooled analysis of three large prospective trials – the Shanghai Breast Cancer Survival Study (SBCSS), the Life

After Cancer Epidemiology (LACE) Study, and the Women's Healthy Eating & Living (WHEL) Study – collectively representing 9514 breast cancer survivors with a mean follow-up 7.4 years, assessed the impact of soy isoflavone. Consumption of over 10 mg isoflavones per day was associated with a 25% reduced risk of recurrence. This inverse association was seen in tamoxifen users, estrogen receptor negative and estrogen receptor positive women.

Polyphenols found in plant foods both down-regulate inflammatory NFkB and up-regulate the transcription factor Nrf2. Nrf2 is normally sequestered in the cytoplasm as an inactive complex with its cytosolic repressor Keap-1. Phytochemicals, specifically polyphenolic flavonoids, activate diverse upstream kinases, which in turn stimulate dissociation of Nrf2 from Keap-1. Once released from Keap-1 repression, Nrf2 translocates to nucleus, forms a heterodimer with small Maf protein, and binds to ARE/EpRE sequences located in the promoter region of genes encoding antioxidant and detoxifying enzymes. This effect is synergistic with chemotherapy in so far as intracellular antioxidants are required to preserve the apoptotic (cell death) cascade initiated by chemotherapy. Additionally, polyphenols directly up-regulate apoptosis the ultimate step in removing aberrant cells. There are many examples of these pro-apoptotic polyphenols such as trans-resveratrol from grapes, peanuts, berries, and red wine. Genistein from soy and curcumin from turmeric activate apoptosis.

Fasting

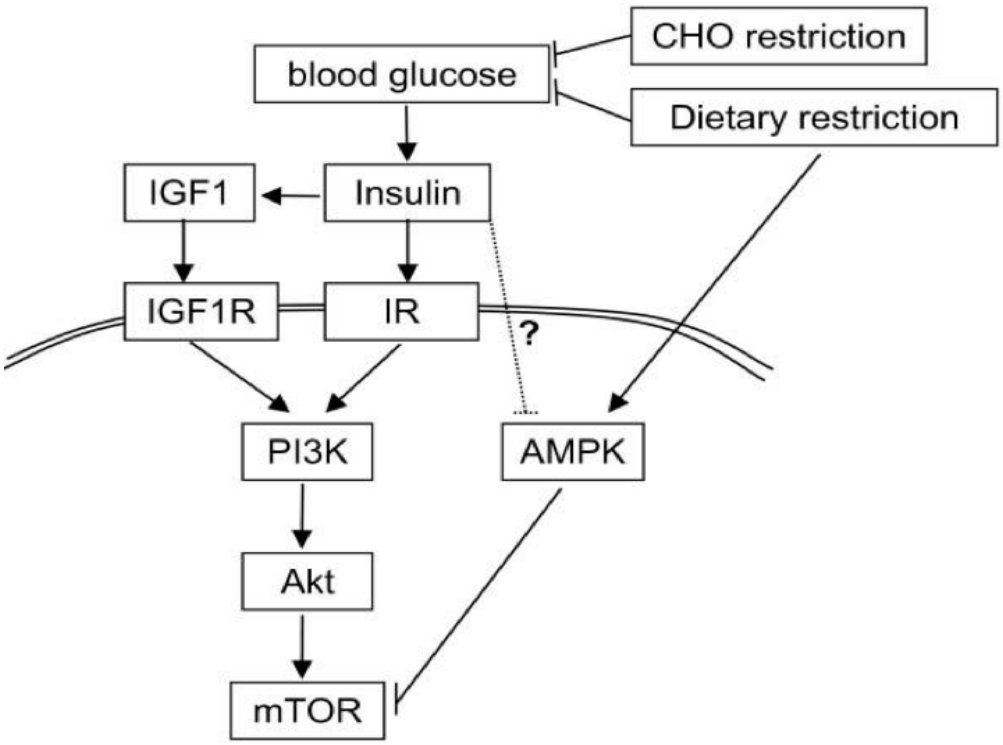
A promising approach to improve tolerance of chemotherapy is concurrent fasting during chemotherapy. This approach has gained significant momentum from the research of Valter Longo, PhD. The premise of short term starvation (STS) in an oncology context is twofold. First, when energy is scarce, cells will use energy preferentially for maintenance functions at the price of growth. Furthermore, IGF-1 levels decrease dramatically in response to short-term (36 -120 hours) of starvation. Cells throughout the body use IGF-1 to signal their growth. Thus, fasting results in growth arrest of normal cells. However, most tumor cells have mutations in pTEN, p53, and the PI3K/Akt/mTOR pathway, leading to constitutive upregulation of insulin and IGF-1 initiated proliferation pathway. Thus, in malignant cells, short term starvation and the resultant decrease in IGF-1, does not downregulate the PI3K/Akt/mTOR pathway and therefore does not arrest growth in cancer cells. This differential effect can be used concurrently with chemotherapy to preferentially protect healthy cells that will be in a dormant, maintenance and non-proliferative state. This state renders these cells somewhat immune to the effects of chemotherapy. At the same time, the malignant cells retain their proliferation during STS and so remain susceptible to chemotherapy.

The effects of STS were demonstrated in case series report of ten patients (7 females and 3 males) with cancer (four with stage IIA breast cancer, two with prostate cancer – stage II and stage IV, one with stage IA ovarian cancer, one with stage IV endometrial cancer, one with stage IV non-small cell cancer of the lung and one with stage IVB esophageal cancer). All patients received chemotherapy and underwent a water-only fast for 48-140 hours pre-chemotherapy and continued for 5 – 56 hours post chemotherapy. Patients served as their own controls and during fasted cycles they experienced less toxicity even after non-fasted accumulation of toxicity. Patients received an average of 4 cycles of various chemotherapy drugs including docetaxel/cyclophosphamide, docetaxel/carboplatin/+5-FU, carboplatin/paclitaxel, gemcitabine/docetaxel, docetaxel, doxorubicin/cyclophosphamide. Specifically, the chemotherapy received during the water fast resulted in less fatigue, weakness, and gastrointestinal side-effects.

While the benefit and safety of this approach, specifically the impact of fasting on treatment response and survival is still under clinical investigation, it could be considered empirically in patients who experience significant chemotherapy-induced toxicity to a level that is threatening their ability to complete treatment. Of note, preclinical research has indicated that fasting may reduce multidrug resistance in malignant cells , however this needs to be confirmed in human clinical trials. The exact nature of the fasting regimens are under investigation. One fasting protocol under study includes 24, 36, or 48 hour fasts prior to chemotherapy Another active clinical trial of women with gynecological cancers is studying the impact of modified fasting with daily caloric intake of <400kcal by juices starting 36 to 48 hours before beginning chemotherapy and lasting to 24 hours after ending each chemotherapy.

Although not clinically evaluated, a variation of STS can also be considered between chemotherapy treatments and as a follow-up to conventional treatment. In the absence of active treatment, diet can be used to influence the same constitutively over-active IGF-1 and Insulin stimulated PI3K/Akt/mTOR pathway in malignant cells. This proliferation pathway's activity is enhanced in the presence of IGF-1 and Insulin, both of which are reduced during caloric and carbohydrate restriction. Furthermore, dietary caloric restriction stimulates AMPk which direct-

ly blocks mTOR activation. (see Diagram 1.) The result of down-regulating mTOR is reduced proliferation. Despite the promising theoretical basis for this approach, the clinical data on the impact of caloric and carbohydrate restriction on overall survival and recurrence risk in humans is yet to be determined.



Cachexia

Of note, this approach should not be considered for any patient at risk for cachexia, a condition of significant weakness and wasting caused by inflammatory cytokines released by malignant tissue. Certain cancers such as lung cancer, pancreatic cancer and many advanced cancers carry a high risk of cachexia. Protein and essential fatty acid consumption is a clinically validated way to both prevent and delay cachexia. Protein requirements may exceed 80gm/day in people at risk for cachexia. Typically, 0.45 – 0.9g protein/2kg body weight is needed to prevent and manage cachexia. Omega-3 fatty acids, especially eicosapentanoic acid (EPA), at 2g to 3g daily is associated with weight gain and improved quality of life. Feeding (increased caloric intake) has not proven to control cachexia.

Exercise

Exercise is a critical component of a lifestyle-based support program during cancer treatment. Data collected over a median of 23 months post-diagnosis (interquartile range 18–32 months) were pooled in the After Breast Cancer Pooling Project (n = 13,302). The study found that 2.5 h (10 MET-hours/week) of moderate intensity physical activity per week was associated with a 27% reduction in all cause mortality and a 25% reduction in breast cancer mortality compared with women who did not meet the physical activity guidelines (<10 MET-hours/week). In another study, women who engaged in the equivalent of at least two to three hours of brisk walking each week in the year before they were diagnosed with breast cancer were 31% less likely to die of the disease than women who were sedentary before their diagnosis ((HR) = 0.69 (95% CI, 0.45 to 1.06; P = .045)). Women who increased physical activity after diagnosis had a 45% lower risk of death (HR = 0.55; 95% CI, 0.22 to 1.38) when compared with women who were inactive both before and after diagnosis. Conversely, women who decreased physical activity after diagnosis had a four-fold greater risk of death (HR = 3.95; 95% CI, 1.45 to 10.50).

From a cohort of 184,194 adults without colorectal cancer at baseline in 1992-1993, 2,293 participants were diagnosed with invasive, non-metastatic colorectal cancer up to mid-2007. The mean follow-up time from diagnosis to death or end-of-study was 6.8 years. Participants completed detailed questionnaires that included informa-

tion concerning recreational physical activity and leisure time spent sitting at baseline, before their cancer diagnosis, and again after their cancer diagnosis. The highest pre-diagnosis recreational physical activity category (8.75 or more MET hours per week which was the equivalent of greater than 150 minutes/week) compared with the lowest category (3.5 MET hours per week) was associated with a 28% lower risk of all-cause mortality. The same comparison for post-diagnosis recreational physical activity resulted in a 42% reduced risk of mortality. Additionally, leisure time spent sitting 6 or more hours per day on the pre-diagnosis survey was associated with a statistically significant 36% higher risk of all-cause mortality. Post-diagnosis sitting time was associated with a statistically significant 62% higher risk of colorectal cancer–specific mortality. These studies support recommendations for recreational physical activity and the avoidance of sedentary time among people diagnosed with cancer – throughout the continuum of care.

Stress Management

A third foundational component of lifestyle-based support of people undergoing cancer treatment is stress management. Elevated and prolonged stress hormones, namely cortisol, epinephrine and norepinephrine are associated with the carcinogenic process and shortened survival. The effects of stress on survival was eloquently demonstrated in a prospective trial of 217 participants with newly diagnosed metastatic renal cell cancer, all with life expectancy of greater than 4 months, with good performance status and no major concurrent diseases. All participants completed depression questionnaires, had salivary cortisol levels assessed, and provided blood sample for genomic analysis at baseline and at 4 months. The following factors were associated with decreased survival time: depression, poor quality of life, and flattened diurnal cortisol slope (with elevation of average cortisol). Genomic analyses identified up-regulation of genes involved in inflammation, immune response, and down-regulation of genes that activate programmed cell death (all $p<.0001$) as well as genes involved in cell trafficking, adhesion, oxygen transport, and hemostasis (all $p<.05$).

Based on rodent models of triple negative breast cancer, social isolation causes a heightened stress response that, in turn, increases expression of genes in adipocytes that increase glucose metabolism, lipid synthesis and leptin secretion. These metabolic changes increase the conversion of mammary carcinoma in situ to invasive carcinoma.

Mammary fat, in particular, has heightened sensitivity to stress hormones over visceral fat, making breast tissue especially vulnerable to stress. While the clinical evidence for the negative effects of stress is still developing, early evidence indicates the benefit of stress management on prognosis in people being treated for cancer. Furthermore, a more robust body of data demonstrates the improvement in quality of life that people diagnosed with cancer experience after active stress management.

Mindfulness based stress reduction (MBSR) is a particularly well-researched stress management behavior. A meta-analysis of 10 studies showed a significant improvement in psychological and physical quality of life with the practice of MBSR. MBSR has been shown to reduce depression and fear of recurrence in women diagnosed with breast cancer. MBSR lowers cortisol, reduces IL-6, lowers systolic blood pressure and improves NK cell activity – each one of which is correlated with higher quality of life and with better prognosis.

Conclusions

There is ample evidence to support the inclusion of a lifestyle-based approach in people diagnosed with cancer. A plant-based, Mediterranean style diet is the foundation of such an approach. Intermittent or continuous caloric restriction may have unique benefits to the improved toleration of treatment and overall survival. Exercise remains a potent strategy to increase overall and cancer-specific survival. Finally, stress management has direct impact on reducing the risk of recurrence and in optimizing the quality of daily living.

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Dr. Lise Alschuler, ND, FABNO practices naturopathic oncology out of Naturopathic Specialists, LLC.

Dr. Alschuler is the Executive Director of TAP Integrative, a nonprofit educational resource for integrative practitioners. She co-hosts a radio show, Five To Thrive Live! and is co-founder of the iTHRIVE Plan, a mobile web application that creates customized wellness plans for cancer survivors. Dr. Alschuler works as an independent consultant in the area of practitioner and consumer health education. She has been an invited speaker to more than 100 scientific/medical conferences, published 16 peer-reviewed articles, a co-investigator on 5 research studies, written 6 chapters for medical textbooks, and has co-authored two books, Definitive Guide to Cancer, now in its 3rd edition, and Definitive Guide to Thriving After Cancer.

P. MICHAEL STONE

MD, MS, IFM-CP

EMILY RYDBOM

B.A., C.N.C, C.N.P, C.H.N

LESLIE P. STONE

M.D., IFM-CP

Developmental Programming of Health & Disease-Applications of Functional Medicine and Nutrition in Preconception and Pregnancy: Foundations For An Implementation Program

P. Michael Stone MD, IFM-PC1,2, Emily Rydbom CNC, HN, CNP1,3, Leslie P. Stone MD, IFM-CP1.3
1Ashland Comprehensive Family Medicine- Stone Medical, Ashland Oregon
2Faculty Institute for Functional Medicine, Federal Way Washington
3GrowBaby, GrowBabyHealth.com, Ashland Oregon

Abstract: Preconception health status and nutrition impact fertility rates and successful conception outcome. The womb environment determined by the mother's lifestyle of sleep, stress, movement, and nutrition are integral in the developmental programming of health and disease of the child. Emerging understanding considers up to a three generation effect on the development of chronic disease by the adverse womb environment during pregnancy. By applying a functional medicine approach to pregnancy there are less small and large for gestational age newborns and pregnancy induced hypertension and gestational diabetes in the mothers associated with reduced incidence of hypertension, diabetes, obesity, and heart disease in the newborns by the time they are adults. Practical interventions for better preconception and pregnancy outcomes are provided.

Preconception Health- A Practical Perspective

Twelve percent of the reproductive age population in the United States, about 7.3 million American couples, suffers from infertility (1). Infertility is commonly diagnosed when people are unable to conceive after six-to-12 months without using birth control, depending on several factors, such as age. Women with recurrent spontaneous abortions are also considered infertile (2-3).

In the United States today, there are few customs to prepare for conception or pregnancy in the general population. There are cultures and traditions for the mother to be to prepare the body for receiving pregnancy. For example the Kikuyu tribe, the Bantu people of Southeast Africa—the largest ethnic group in Kenya—traditionally begin a special diet six months prior to marriage to prepare for pregnancy(4)

Research has shown that certain birth defects can be traced to nutritional deficiencies prior to conception (5). But, it's not just the mother's health that matters.

Between 1990-1993, Foresight, a British medical association for the promotion of preconception conducted a study using a nutritional and lifestyle modification preconception care program. The results were incredible. There was a tenfold reduction in the expected incidence of miscarriage and birth defects and over 80% success rate with unexplained fertility. It was evaluated that before the study was started, 60% of the women drank alcohol regularly and 57% of the women involved were previously smokers. Out of the 367 couples in the study, 327 (89%) of them successful became pregnant and 327 children were born. Among the 204 couples with infertility problems, 175 (86%) were able to achieve a healthy pregnancy. One of the most significant aspects of these results was the involvement of both partners in the program—both male and female factors were concurrently addressed. In addition to nutritional supplementation, the study included lifestyle and social modifications. A number of the couples had already tried IVF without success. Yet 65% of this group conceived naturally (6).

Both men and women play a vital role in the process of becoming pregnant, as well as contributing to the long-term health of the child. We now know that without good nutrition and lifestyle management (including stress, sleep, movement, relationships) for both men and women fertility health can become imbalanced.

Facts for Men:

1. Genes expressed from the father are directly responsible for the development of the placenta.
2. Currently 5-10% of all infertility is stress related, making stress management an integral part of conception (7).
3. Average male sperm counts have dropped by almost 50% between 1939-1990. The number of men with extremely low sperm counts tripled, and the number of men with high counts decreased (8).
4. Toxic exposure to endocrine disruptors is a very real and current issue affecting female and male fertility health.

Food to Avoid Before Pregnancy

To improve fertility and your baby's long-term health, avoid the following 3-6 months preconception:

1.) Foods that interfere with preconception health

These foods can decrease your nutrient reserves, and add to cellular damage and oxidative stress—inflammation. Living and breathing under the sun will cause some damage to your cells. This is normal. But often there are specific foods/toxins/substances/lifestyle that slow the biotransformation or detoxification pathways, increase the oxidative burden and impede cellular function. Oxidative stress is the result of this damage—causing imbalance between free radicals (damage) and antioxidants reserves (healing/balance). This stress often manifests as inflammation.

- Refined foods—white flour, white sugar, white…
- Added sugars—mainly found in what we drink like soda, fruit drinks, tea, coffee, energy and sports drinks, and flavored milks
- Natural and artificial sweeteners: agave nectar, sucrose, fructose, glucose, lactose, brown rice syrup, xylitol, corn syrup, high fructose corn syrup, corn syrup solids, sorbitol, fructose, dextrose, evaporated cane juice, erythritol, Nutrasweet® (aspartame), Splenda® (sucralose), acesulfame-K, Sweet One, Sunett, Sweet N'Low®, brown sugar, demerara sugar, stevia, invert sugar, maltodextrin, maltose, maple syrup, confectioner's sugar, turbinado sugar, fruit juice concentrate, honey, molasses, barley malt, cane sugar, coconut sugar, date sugar, caramel (10).
- High glycemic foods
- Processed foods and anything with artificial additives
- Fried foods
- Margarine (high in trans fatty acids)
- Trans Fat - increases LDL cholesterol, decreases HDL cholesterol, increases triglycerides, adds to inflammation, and even the United States Food and Drug Administration has issued a statement saying that trans fats are "not generally recognized as safe."
- Refined vegetable oils

2) Substances that interfere with preconception health

Similar to the foods above that can decrease your nutrient reserves, and add to cellular damage and inflammation, these substances should be avoided because they increase the amount of damage and imbalance to your body, decreasing your reproductive health.

- Alcohol
- Intravenous and recreational drugs
- Certain pharmaceuticals
- Check with your primary care provider to ensure you are not taking anything that could interfere with a fertile environment and put you and your partner's conception health at risk. (There are also certain pharmaceuticals that can inhibit your ability to detoxify well. The list is long, and it is important to identify which pharmaceuticals will interact with your ability to detox your body. Some of the most common pharmaceuticals that inhibit your detox pathways include antidepressants, antihistamines, and benzodiazepines.)
- Tobacco and marijuana

3.) Limit Chemical and Toxic Exposure from Endocrine Disruptors

An endocrine disruptor is a substance that alters the function and causes imbalance or damage (oxidative stress) to any of your endocrine organs. There are many endocrine organs throughout your body, starting at your head and ending at reproductive organs like ovaries and testes. Consuming a RAINBOW OF FOOD daily is your HEALTH INSURANCE for oxidative stress that occurs in your body; Red/blue/purple/orange/yellow/green/white/tan ensure that your body replenishes its antioxidant reserves, protecting your body from further damage.

4). Unmanaged Stress

We know that healthy and balanced exposures to stress during pregnancy will actually help your baby's central nervous system robustly develop. So what's the balance? Stress is a necessary part of your hormonal process, but left unmanaged and out of balance, it can lead to adrenal fatigue, chronic fatigue syndrome, depression, insomnia, inflammation, anxiety, and poor fertility health.

Did you know that in one study, 34% of infertile women became pregnant after being trained in a relaxation technique? (10)

The Dangers of Endocrine Disruptors and How to Avoid Them (11)

Bisphenol-A: BPA has been linked to everything from breast and others cancers to reproductive problems, obesity, early puberty and heart disease.
According to government tests, 93% of Americans have BPA in their bodies.

- BPA is found in cash register receipts, most canned foods, and plastics.
- Avoid the recycling label #7.
- Avoid putting a plastic lid on top of a hot cup of liquid. The steam condensates on the lid and then drips into the liquid consumed.
- Eat a rainbow of foods daily – those foods contain phytonutrients that help with detoxification of endocrine disruptors like BPA.

Dioxin: Recent research has shown that exposure to low levels of dioxin in the womb and early in life can both permanently affect sperm quality and lower the sperm count in men during their prime reproductive years.

- The American food supply is contaminated—mostly animal products like meat, eggs, dairy, and butter contain this chemical.
- Choose organic as much as possible.

Atrazine: Atrazine is widely used as an herbicide on the majority of corn and sorghum crops in the United States, and consequently it's a ubiquitous drinking water contaminant. Researchers have found that exposure to even low levels (30X lower than levels allowed by the Environmental Protection Agency) of atrazine can turn male frogs into females that produce completely viable eggs. Recent studies have also found a possible link between human birth defects and low birth weight, with atrazine exposure in the womb.

- Buy a drinking water filter certified to remove atrazine.
- Choose organic produce when possible.

Phthalates: Studies have linked phthalates to hormone changes, lower sperm count, less mobile sperm, birth defects in the male reproductive system, obesity, diabetes and thyroid irregularities.

- Avoid the recycling label #3.
- Use glass or stainless steel as much as possible.
- Avoid personal care products that contain pthalates as an ingredient.

Perchlorate: Competes with iodine and its role in thyroid health—these hormones regulate metabolism in adults and are critical for proper brain and organ development in infants and young children.

- Use a reverse osmosis water filter.
- Include iodine rich foods daily—seaweed, eggs, strawberries and whole fat dairy products

PBDEs (Fire Retardants): In 1999, a group of Swedish scientists studying women's breast milk discovered something totally unexpected—the milk contained an endocrine-disrupting chemical found in fire retardants, and the levels had been doubling every five years since 1972. These chemicals can imitate thyroid hormones in your body and disrupt its activity. The disruption is associated with lower IQ.

- Avoid reupholstering foam furniture.
- Take care when replacing old carpet.
- Use a vacuum cleaner with a HEPA filter.

Perflourinated Chemicals (PFOA): Did you know that 99% of Americans have PFOAs in their bodies and they have been shown to be "completely resistant to biodegradation." PFOA exposure has been linked to decreased sperm quality, low birth weight, kidney disease, thyroid disease and high cholesterol, among other health issues.

- Avoid non-stick pans.
- Avoid stain/water-resistant coatings on clothing, furniture and carpets.

Organophosphate Pesticides: Organophosphates can interfere with the way testosterone communicates with cells. They can lower testosterone and alter thyroid hormone levels. Despite extensive studies linking exposure to

effects on brain development, behavior and fertility, organophosphates are still among the most common pesticides in use today.

- Buy organic produce when possible.
- Check the Environmental Working Group website for the most up to date list of produce that contains the highest levels of pesticide residue.

Glycol Ethers: One outcome study in rats showed that shrunken testicles were the effect of exposure from glycol ethers. These chemicals "may damage fertility or the unborn child." Children who were exposed to glycol ethers from paint in their bedrooms had substantially more asthma and allergies.

- Avoid products with ingredients such as 2-butoxyethanol (EGBE) and methoxydiglycol (DEGME).

How & Why to Avoid Heavy Metals Before Pregnancy (11)

Lead—Lead is harmful to almost every organ system in the body and has been linked to an astounding amount of health effects: permanent brain damage, lowered IQ, hearing loss, miscarriage, premature birth, increased blood pressure, kidney damage and nervous system problems. Lead may affect your body by disrupting your hormones. In animals, lead has been found to lower sex hormone levels. Studies have also shown that children with healthy diets absorb less lead.

- Choose healthy foods daily.
- Carefully remove old paint when repainting.

Arsenic—Specifically, arsenic can interfere with normal hormone functioning in the glucocorticoid system that regulates how our bodies process sugars and carbohydrates. What does that mean for you? Disrupting this specific system has been linked to weight gain/loss, protein wasting, immune suppression, insulin resistance, osteoporosis, growth retardation and high blood pressure.

- Find a water filter that is certified to remove arsenic.

Mercury—linked to weight gain/loss, protein wasting, immune suppression, insulin resistance, osteoporosis, growth retardation and high blood pressure. Pregnant women are the most at risk from the toxic effects of mercury, since the metal is known to concentrate in the fetal brain and can interfere with brain development.

- Choose wild salmon, wild trout, wild fish

- Avoid predatory fish like shark and swordfish and limit tuna

The Toxic "Nest"

The "nesting" process that many women do before or while pregnant such as painting the nursery, purchasing new upholstered furniture, new mattresses, and new crib mattress is a common way that women exposure themselves (and their child) to toxic chemicals. If painting, try and use no VOC paints, avoid new carpeting (or choose carpets labeled by the CRI: The Carpet and Rug Institute (CRI) independently tests carpets, giving them a green label if the product has low VOCs such as Nature's Carpet and Earth Weave), air out all new furniture, or avoid buying brand new furniture.

The need to nest is understandable. Conscious nesting in the least toxic manner is important and crucial for your family's health.

Preconception Nutritional Support

Food and Nutrient Support for Phase I and Phase II Liver Detoxification: There are two phases of liver detoxification: Phase I, oxidation and Phase II, conjugation. Oxidation requires nutrients like vitamins A, E, C, B3, B6, B9, and B12, minerals and antioxidants like copper, selenium, zinc, manganese, and CoQ10, glutathione, flavonoids, phospholipids (choline and serine), and thiols, as well as branched chain amino acids (lysine, valine, and iosleucine) to make toxins that are fat-soluble into water-soluble toxins, which happens in phase II of your liver detoxification. Conjugation requires the amino acids glycine, taurine, glutamine, N-acetylcysteine, cysteine, and methionine. All of these nutrients work together to make sure that toxic exposure, whether internal (endogenous) or external (exogenous), is filtered through your liver and excreted.

Folate, B Vitamins, and Methylations Co-factors: Folate is required for the synthesis of DNA, transfer RNA, cysteine, and methionine, which are required during periods of rapid cell growth. Given the peri-conceptional period is a time of cellular growth, it was postulated that folate supplementation may improve reproductive outcomes. In a prospective cohort study of 232 women, live birth rates in women undergoing IVF were 20 % higher (95 % CI 8-31 %) among women with the highest amount of supplemental folate intake (>800 mcg/day) compared to women taking the lowest amount (<400 mcg/day). This study also suggested that folate supplementation was superior to dietary folate (12). Similarly, a prospective cohort study of women undergoing IVF in the Netherlands found that a doubling in the follicular folate level was associated with three-fold increase in pregnancy (13). From this data, women should be advised to take (at least) 800 mcg/day of folate during fertility treatments and throughout pregnancy.

Include a Rainbow of Foods daily to ensure proper phytonutrient intake and this fertility health: Phytonutrients help keep plant's vitality strong—they improve the vitality for those who intake them as well. Thousands of studies corroborate the need to include colorful fruits and veggies for optimal health, and many nutrients can impact a couple's ability to get pregnant, including carotenoids. These important antioxidants provide many benefits to both male and female reproductive health.

DR. DEANNA MINICH EXPLAINS WHY CAROTENOIDS ARE A CRUCIAL PART OF REPRODUCTIVE HEALTH:

Carotenoid Basics

Carotenoids are a family of plant pigments that provide important health benefits. Several carotenoids are pro-vitamin A (14) which means they can be converted into vitamin A in the body. Vitamin A plays a key role in eye health, the genesis of organs, immune health, and differentiation of tissue (15). All of the carotenoids, as well as vitamin A, also perform important activities as antioxidants (16). Consumption of carotenoids has been linked to a reduction of several chronic illnesses including cancer and cardiovascular disease as well as benefits to reproductive health (16-18).

The Positive Impact on Male Fertility…

Oxidative stress has the potential to significantly affect male fertility, mainly due to the negative impact of reactive oxygen species on sperm quality and function. Therefore, it is important for men to consume sufficient anti-

oxidants, such as carotenoids, to counter any excess oxidative stress and remain fertile.

In a study on humans, the blood and semen samples of infertile men had a much lower antioxidant capacity (19), including reduced levels of carotenoids and other antioxidants such as vitamin E, compared to fertile men. There was also a positive correlation between the concentrations of carotenoids and the total antioxidant capacity with the concentration, morphology, and motility of the sperm. Based on this evidence, it would appear that consuming foods rich in carotenoids benefit male fertility.

And Female Fertility

There is also a link between carotenoids and female fertility. One study reviewed the effect of several different antioxidants on the menstrual cycle of healthy, premenopausal women with regular cycles. Interestingly, they found that there was a significant variation in the level of antioxidants in the different phases of the cycle (20). During menses, antioxidant levels were lower, including those of beta-carotene, lycopene, and lutein. Additionally, there was a positive association between the level of antioxidants and testosterone and steroidal levels. The researchers stipulated that antioxidants play a role in steroidogenesis, which is the production of the sex hormones, including estrogen and testosterone. This relationship remained true even after adjusting for any potential oxidative stress.

Another area where beta-carotene might help with female fertility is through enhancing ovarian function and the synthesis of progesterone. In a study on goats, those supplemented with beta-carotene had more progesterone synthesis (21). This is an important component of fertility, as progesterone is essential for ovulation, healthy oocytes, maintaining the uterine lining, and creating a nourishing and healthy environment for the embryo. The researchers suggested that the benefits provided by beta-carotene might be due to two main factors. First, its antioxidant capacity might enhance the progesterone synthesis in the luteal cells, since steroidogenesis results in increased oxygen radicals requiring mitigation. Beta-carotene might also activate the protein kinase A second messenger system to stimulate LH (luteinizing hormone), which plays a key role in stimulating the synthesis of progesterone.

The Role in Fertilization

Carotenoids also play a role in successful fertilization (23). There needs to be the perfect balance between ROS (reactive oxygen species) and antioxidants in both eggs and sperm for fertilization to occur. In one study, consuming antioxidants led to a shorter time to pregnancy in couples who were undergoing treatment for unexplained fertility (24). Supplementation of beta-carotene positively affected those with a BMI above 25, something that makes it harder to conceive. However, it did lead to a longer time to pregnancy in women over the age of 35, which might be due to an alteration in progesterone secretion.

A Note on Obesity and Carotenoid Status

An important thing to note is that obesity might affect levels of carotenoids, and this is not due to differences in dietary intake (25). In one study, researchers found that the levels of carotenoids in obese women (based on BMI) were significantly lower than that of normal-weight women. This reduction was three times greater for the pro-vitamin A carotenoids, which includes alpha and beta-carotene and cryptoxanthin compared with the carotenoids that do not convert to vitamin A (lycopene, alpha cryptoxanthin, anhydrolutein, and lutein/zeaxanthin). It is unknown as to why this lowering occurs but could be due to a higher metabolism to vitamin A to

help with immune function and the requirement of carotenoids for antioxidant activity, since obesity is related to higher levels of oxidative stress.

Obesity is associated with both male and female fertility and the connection between fertility and carotenoids might be an element of the complex relationship between obesity and fertility (26-27). It might be reasonably inferred, based on this information,that those who are overweight or obese might wish to take extra precautions to ensure sufficient consumption of carotenoids, especially when trying to become pregnant.

Antioxidant Support: Antioxidants act to reduce the amount of reactive oxygen species, including hydroxyl radicals, superoxide anions, and hydrogen peroxide (28); when there is an imbalance of reactive oxygen species there may be an increase in sperm DNA structural damage, as well as an unclear link to female infertility (29). Commonly studied supplemental and dietary antioxidants include vitamin D, vitamin E, vitamin C, γ–carotene, and coenzyme Q10.

Prebiotics and Probiotic Rich Foods:

Prebiotics: Prebiotics promote growth and repopulation of good bacteria in the digestive tract. Found in foods typically not easily digested; this creates a situation in which certain components in these foods are only partially digested, leaving behind beneficial prebiotics that feed the good bacteria. The most common prebiotics are inulin and oligofructose.

In one study published in the Journal of Nutrition Studies it was shown that traditional diets contained over twice the amount of inulin than is present in the Standard American Diet (SAD) of today (30). SAD are greatly lacking in prebiotic foods which promote beneficial gut flora.

Prebiotic rich foods include: garlic, onions, jicama, dandelion greens, asparagus, radicchio, chicory, and endive

Probiotics are necessary and healthy bacteria that help your gut maintain balance. These friendly bacteria are a crucial part of nutrient absorption. Low gut flora or poor genus variety can increase the risk of inflammatory diseases, including autoimmune disease. 70-80% of your immunity comes from your gut lining. What happens when you don't support the health of your intestinal tract? Your vulnerability and susceptibility to immune imbalance is a consistent factor in your health.

Probiotic rich foods include: natto, kefir, sauerkraut, yogurt (with live cultures), miso, tempeh, kimchi

Colostrum Supplementation: In Colostrum, Life's First Food (31), Dr. Daniel G. Clark's states that "bovine colostrum rebuilds the immune system, destroys viruses, bacteria(32,33) and fungi, accelerates healing of all body tissue, helps lose weight, burn fat, increase bone and lean muscle mass and slows down and even reverses aging (34)

According to Clark and Dr. Bernard Jensen (35), colostrum has a therapeutic role to play in AIDS, cancer, heart disease, diabetes, autoimmune diseases, allergies, herpes (36), bacterial (37), viral and parasitic(38) infections, gingivitis, colds, the flu and much more. Colostrum has antioxidant properties, is anti-inflammatory and is a source of many vitamins, minerals, enzymes and amino acids (34)

Avoid foods that cause increased inflammation and have known associations with common food sensitivities and allergies:

- Wheat and gluten
- Dairy
- Corn
- Soy

What to do now

- Approach food with balance: lots of veggies, the more colorful the better-focus on healthy fat and protein, especially plant sources of protein
- Support your detoxification pathways
- Include antioxidants into your daily eating
- Increase your colorful fruit and vegetable intake
- Add gut supportive nutrients to improve your nutrient absorption
- Avoid foods that increase inflammation
- Meet your methylation needs by choosing foods that are high in B vitamins, iron, zinc, omega 3-fatty acids, l-methionine, and l-cysteine.
- Utilize the power of herbs and spices
- Take supplements when needed

Sleep Management for Preconception Health

Imbalanced sleep can lead to your AM wake up in emergency mode, where all the decisions that you make that day, whether it's food or interpersonal communication are based off of one single fact. You are living in a deficit from lack of sleep. You will choose foods that raise your blood sugar quickly, leaving you feeling high for a moment, just to crash you down.

This imbalance leads to cravings, sugar crashes, afternoon fatigue, eventually insulin resistance, high blood sugar, and possibly diabetes. Stop the cycle! End it now. The height of your liver detoxification and cell reparation happens from 11:00pm to 4:00am each night. Start your nighttime sleep process no later than 10:00, allowing you enough time to retrain your body to sleep by 11:00. Your brain, liver, and fertility will thank you for it.

Healthy Sleep Hygiene Can Include:

- Focus on magnesium rich foods like pumpkin seeds, dark leafy greens, broccoli, basil, cucumber, and flaxseeds.
- Take supplemental magnesium (magnesium glycinate or magnesium threonate), 200-600 mg before bedtime
- Focus on foods that help you make serotonin. Serotonin, an inhibitory neurotransmitter, helps you make melatonin. Melatonin helps you get to sleep. Foods rich in Tryptophan: Shrimp, Cod, Mushrooms, Chicken, Spinach, Turkey, Almonds, Salmon, Asparagus, Broccoli. Foods rich in Vitamin B3 (Niacin): Mushrooms, Tuna, Salmon, Lamb, Tomatoes, Summer Squash, Green Peas, Collard Greens
- Make lifestyle choices that help you make serotonin such as spending time in the sun, supplementing with inositol, and creating a healthy gut environment
- Choose nutrients that help support your gut like prebiotics, probiotics, selenium, omega 3 fatty acids, zinc, glutamine, and vitamin A, E, and C

- Take a bath with epsom salt and lavender oil
- Turn off all electronics in your room at night
- Black out your room. There should be no lights, including alarm clocks. Any light can hit the back of your retina, which stimulates brain activity.
- Prayer or meditation before bedtime.

Stress Management for Preconception Health

Chronic stress perpetuates a process that ultimately continues to do damage well after a stressful event has occurred. When we make too much cortisol and too much adrenaline, our blood sugar increases and we become insulin resistant, predisposing us to accumulate more fat mass. This hormonal imbalance can cause a myriad of common health problems: obesity, diabetes, metabolic syndrome, and infertility, to name a few.

When our stress is unmanaged (toxic), we run the risk of doing damage to an area of our brain called the hippocampus. The hippocampus regulates nerve cell production throughout life and is responsible for our memory.

Healthy Stress Management Can Include:

- journaling
- singing
- exercise and movement
- dancing
- praying
- meditation
- drinking tea
- taking a bath
- spending time with loved ones
- talking with friends and family
- massage
- asking for and receiving help
- sleeping
- designated 30 minute relaxation window during the day
- guided imagery
- mindfulness

Toxic stress exposure during preconception and pregnancy, can affect the health of your family for up to 4 generations (39). Mindfulness combined with empowered decisions help make the necessary shift toward optimal health. The choices that you make now will help teach your child the balanced way to meet any adversity that may come their way. The steps you make toward balance will have a multi-generational health impact on your family.

Quick Guide to Lifestyle Balance in Preconception and Pregnancy

Stress Management: A crucial part of managing food cravings, mood, and blood sugar.	20-30 minutes a day (it doesn't have to be all at once) of breathing, singing, journaling, prayer, gratitude, meditation, or mindfulness practice.
Sleep Hygiene: A routine that is calming and consistent at bedtime will do wonders for your daily recovery.	11P-4A is the height of your cell repair and liver detox. Sleeping a quality 8 hours a night without phones, computers, or tablets lights to disrupt your REM sleep.
Movement: Nature's #1 antidepressant, daily movement can help balance mood and gain better sleep, it also regulates healthy weight management.	20-30 minutes a day, 5-7 days a week. Choose exercise that rejuvenates you such as running, walking, hiking, yoga, swimming, and light weight lifting.
Relationships: Studies show that positive social relationships are directly associated with mental health, physical health, health habits, and longevity.	Daily check-ins and connection with your family, friends, church, school, groups, teams, and colleagues have a profound impact on your health.

Setting the Stage Developmental Programing of Disease:
Developmental Programming, Chronic Disease, and our Global Pandemic

Developmental program of health and disease (DoHaD) refers to the emerging realization that the chronic diseases of hypertension, atherosclerotic cardiovascular disease, diabetes, obesity, renal disease and others may have their origin in the environment that washed over the fetal genes while in the womb (40-41).

This understanding developed when studying the offspring of women who survived the Dutch Famine of 1944-45 (42) and the Chinese famine (1959-1961) (43). The mothers that had a calorie intake of between 400-600 calories a day during the first trimester gave birth to offspring who grew as children through adult hood with a significantly different incidence of disease compared to mothers who survived the famine during the second and third trimesters (Figure I) (41). A series of studies of this offspring population has lengthened the list of disease associations with famine during each of the three trimesters and are noted in the non-bold text in the figure below.

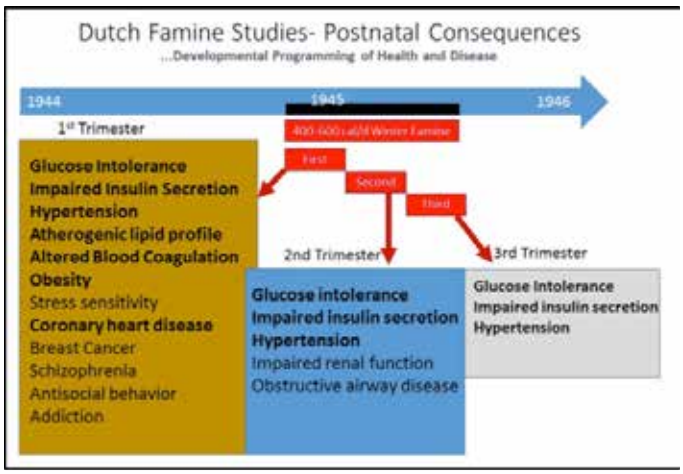

Figure 1: Chronic conditions associated with trimester famine exposure (41)

Thirty million people died during the "great leap forward" Chinese famine of 1959-1961. The impact of fetal and infant exposure to the Chinese great famine during the first trimester of pregnancy only, or during infancy only, or during both fetal development and infancy increased the risk of hypertension in adulthood. This suggests the important role of changes in exposure to famine during development and from prenatal to early postnatal life in programming cardiovascular disease risk (43)

This 9-month incubation in the milieu of maternal and paternal genetic, and epigenetic, environmental, and maternal lifestyle influencing nutrition adequacy and stress adaptation patterns health or disease. In fact, there may be a multigenerational effect. It may be the grandmother or great grandmother's womb environment that caused the altered acetylation or methylation of genetic material and mediated disease in this generation. In rodent research the alteration of one carbon metabolism cofactors (methylation factors) in the intrauterine time period can have up to a 3 generation effect. The famine studies are intriguing but the precise mechanisms are to be determined. Recent reviews summarize the emerging understanding illuminates perspective of transgenerational epigenetic influences on disease and health (44,45) The data is emerging, but doesn't it change how we think about the timeline of all health and disease?

The developing fetus is influenced by the maternal stress response, her smoking, infections, and nutrition (46). The maternal exposure to environmental toxins along with nutrition adequacy, and maternal one carbon metabolic genetic uniqueness can lead to maternofetal endocrinopathy. Together these influences, along with adequacy of placental function influenced by the paternal genome, creates a unique womb environment to which the fetus adapts. This adaptive response can lead to growth restriction, SGA, or large for gestational age birthweight. This altered metabolic physiologic profile can be perpetuated and lead to diseases in pediatric, adolescent and adult life (46).

This understanding that the environment interacting with the genome leads to phenotypic change is not new. It is the center of the nature vs. nurture discussion. But the genetic predeterminants of disease account for between 10 and 30% of disease. The epigenomic influences in the womb and the diet and nutrition influences is an exciting frontier in medicine (47). The understanding of conditions in pregnancy, in the womb affecting "the thrifty" family of genes, and epigenetically transgenerationally impacting disease occurrence has emerged since Barker published his first work in 1986 (48-50). The healthy approach to preconception and pregnancy needs to be through a functional medicine lens which is personalized, preventative, predictive, participatory, and empowering. The empowerment of the parents can influence lifestyle choices and positively impact the maternal-fetal stress axis. This care seeks to offer the right healthy intervention, at the right "dose" at the right time, with maximal health consequences and efficacy. This is consistent with the emerging perspective of precision medicine. It has a significant impact on the health of the new life.

The potential mechanisms of developmental programing have emerged and include 4 categories of scrutiny and research; 1) organogenesis and proliferation 2) disruption of endocrine environment 3) epigenetic–heritable but not fixed influences, and 4) the dynamics of telomere length. During organ development there can be disruption of organ development during differentiation (normal size organ different cell distribution) or during proliferation (normal cell profile but fewer cells and smaller size). An example is maternal dietary protein insufficiency through a low protein diet during pregnancy can lead to kidneys of normal size but 40% fewer nephrons. In humans this normal size kidney with fewer nephrons leads to increases the risk for primary hypertension. There are early findings of similar alteration in cell differentiation and proliferation in many organs including brain, pancreas and placental.

With disruption of the endocrine environment through abnormally high glucocorticoids there is an alteration in tissue maturation and function. The set point of the Hypothalamic-pituitary-adrenal-thyroid-gonadal (HPATG) axis and normal homeostatic regulation of many systems including the renal angiotensin system when disrupted increases the development of disease.

The adequacy of one carbon metabolism cofactors (vitamins and minerals, amino acids, and sulfur amides) in the setting of enzymatic single nucleotide polymorphisms affect the methylation and acetylation of DNA. The embryo and fetus is subject to both demethylation and remethylation (50). The epigenetic affect of nutrition adequacy, insufficiency, deficiency, and toxicity is heritable but not fixed. And finally, telomere length is influenced by nutrition status, attrition and aging. The developmental determinants of disease and the plasticity of health are summarized in Figure II (50).

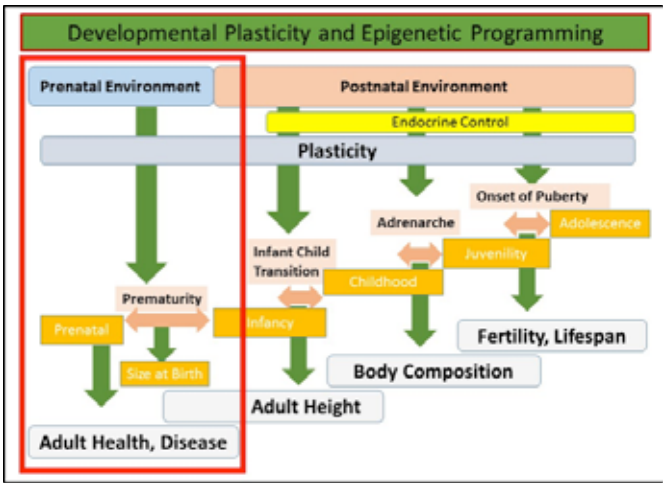

Figure II—Adapted from: Hochberg et al: Endocr Rev. 2011

Adult health and disease is influenced prenatally with the size at birth being a bell-weather of increased risk of disease (41, 48-49) and an early predictor of height and body composition (51). In the postnatal environment under the influence of the endocrine axis, in the setting of plasticity of expression adult height is projected. During childhood and early adolescence (Juvenility) body composition and fertility health is projected. And finally during adolescence- fertility and lifespan factors further shape the degree of plasticity in each of us (50).

Socioeconomic, physiologic, relationship, traumatic and the over or under abundance of nutrition stressors during pregnancy has far reaching effects on malformations (52) neurodevelopment (53-54) behavior and resilience in later life (40).

Severe stress during early pregnancy is associated with increased odds ratio of cranial neural crest malformations (1.5) and increased first trimester loss. If the severe stress was in the first pregnancy and there was first trimester loss the odds ratio of cranial-neural-crest malformation is 2.5 times greater than the incidence of other malformations (8.36 vs 3.64) (55). The severe life stress was cancer or myocardial infarction in the spouse or partner or another child in the family unit.

- The fetus develops its own intrauterine stress response independent of the mother, consistent with its modulating genetics and intrauterine environment (56).
- Antenatal maternal anxiety impacts the incidence of mental illness in the offspring (57). It is correlated with twice the incidence of behavioral and emotional problems in the male offspring by age 4 (58).

- Anxiety during pregnancy influences uterine artery resistance and blood flow to the fetus (59)
- Severe Stress increases the risk of prematurity as do periodontal infections, by 6 fold (53-54).
- The amount and type of prenatal and postnatal care impacts infant stress response (60)

The overarching role of maternal over nutrition as well as fetal undernutrition, in epigenetic programming powerfully changes the trajectory of health or disease (41, 61). Maternal food shortage during pregnancy has an epigenetic effect on methylation of the DNA in the offspring (62). Inadequate one carbon metabolism cofactors three months prior to conception and one month after conception in mothers with certain MTHFR (methylenetetrahydrofolate reductase) and CBS (cystathionine beta synthase) nucleotide polymorphisms when the fetus has certain COMT (catechol-o-methyltransferase) single nucleotide polymorphisms results in a seven fold greater relative risk of having a child develop autism (63).

Together this group of nutritional and environmental cues during fetal development can permanently affect the composition, homeostatic systems and functions of multiple organs and systems. The timing and exposure of the insults during pregnancy has well documented impact on the development of cardio-renal disease (

Table I: Timing of Exposure, Types of Exposure and Known Cardio-renal Effects1,2

Timing/exposure	**Types of Exposure**	**Effects**
Perinatal	Maternal/paternal malnutrition (Over/under), mitochondrial inheritance	Reduced # nephrons > albuminuria, reduced Glomerular Filtration Rate, Hypertension and chronic kidney disease, altered vasoconstrictor and dilatory vasculature
	Hypoxia	Increased apoptosis of myocytes and asymmetric hypertrophy of heart
	Iron deficiency, ionizing radiation and trace metals, homocysteine, tobacco, alcohol	Increased coronary vasculature to increase coronary conduction, aberrant DNA methylation of cytosine's
	Modification of histone methylation and acetylation	Heart and Kidney abnormalities of CRS
Intrauterine	Hormones and methylated compounds (insufficient folate, methionine)	Insulin Resistance, reduced beta cell mass, impaired glucose tolerance, obesity and DM
	Hyperglycemia, excessive glucocorticoids, free fatty acids, oxidative stress	Increased Angiotensin- 1-Receptor expression, renal and cardiac structural abnormalities, myocardial and vascular structural changes and hypertension

Placenta	Insufficiency, monozygotic twins	Although direct effects on adult Cardiorenal syndrome is being studied, Effects on intrauterine growth and birth weight could have potential effects of Cardiorenal syndrome.

1Nistala R, MR Hayden, VG DeMarco, EJ Henriksen, DT Lackland, JR Sowers: Prenatal programming and epigenetics in the genesis of the cardiorenal syndrome. Cardiorenal medicine 2011;1:243-254. 2Christian P, C P Stewart: Maternal Micronutrient Deficiency, Fetal Development, and the Risk of Chronic Disease J. Nutr. 140: 437–445, 2010.

Predispositions to these morbidities, as well as osteoporosis, some cancers (CA), aging, and sex-specific disease appear malleable based on availability of micronutriture, complexity of maternal/fetal gut microbiota, dietary fatty acid and protein composition, and toxic exposure, although debate remains about the efficacy of individual nutrient levels in pregnancy (62-64).

Common Nutrient Deficiencies and Co-Factors for a Healthy Pregnancy

The nutrients included for healthy intervention reflect our belief in the likelihood of maternal and fetal benefit with potential reduction of risk in the F1 and possibly F2 generations. For example, maternal carnitine insufficiency treated with 2000 mg of carnitine avoids a striking rise in free fatty acids, which are thought to be the main cause of insulin resistance and gestational diabetes (65). Because GDM is associated with LGA offspring and because these offspring experience a greater than aver- age risk for adult disease, especially adult onset DM (AODM), it is reasonable to expect a reduced incidence of chronic disease if maternal carnitine insufficiency is recognized and treated. Iron status, more commonly assessed in pregnancy, is not only important in hematopoesis and neurological and cognitive development (66) but plays a crucial role in carnitine synthesis, (67) although carnitine precursors may be more important (68).

ZINC

Zinc deficiency affects 1 in 5 world habitants (71). And it is an important cofactor for more than 300 identified zinc metalloenzymes (69). Zinc insufficiency in late pregnancy disrupts neuronal replication and synaptogenesis, (70) and maternal deficiency is associated with decreased DNA, RNA, and protein content of the F1 brain. Zinc supplementation reduces the risk of preterm birth, though not SGA (71).

VITAMIN D

Vitamin D deficiency is under investigation for its role in protection against DM, CV, some CA, osteoporosis, and optimization of immune function (72). Vitamin D might be an important mediator in gut homeostasis and in signaling between microbiota and host (73). The intestinal microbiome in both newborns and lactating mothers influences infant and childhood food allergy and eczema. Supplementation with probiotics reduces incidence of these conditions in the offspring by 35% through 4 years of age (74) and possibly through adolescence (75). Use of Lactobacillus rhamnosis and L reuteri appear most effective (76).

FOLATE

Folate's role in preventing neural-tube defects is well described. Lesser known is the commonness of single-nucle-

otide polymorphisms such as methylene tetrahydrofolate reductase (MTHFR) that limit methylation of folic acid and their crucial role in such disparate conditions as pregnancy-induced hypertention (PIH) and autism. MTHFR polymorphisms affect just under 50% of most ethnic groups. If B-vitamin supplementation is inadequate during the period from 3 months before conception to 1 month postconception and if the maternal genome carries MTHFR and cystathionine beta synthase (CBS) polymorphisms while the fetus is affected by catechol-O-methyl transferase, the offspring experience a 720% rise in the risk for autism (63). PIH is more common in people carrying the MTHFR C677T polymorphism, (77) raising the possibility of preventive therapy using the methylated form of folic acid, 5-methylene tetrahydrofolate. SGA babies are born more commonly to mothers with PIH-affected pregnancies, and these neonates fall within the highest quartile of risk for adult obesity, DM, HTN, and CVD (78).

ESSENTIAL FAT: DHA

Essential fat, particularly docosahexanoic acid (DHA) supplementation in the second half of pregnancy has been shown to result in higher maternal and cord RBC-phospholipid-DHA, longer gestation duration, and greater birth weight, length, and head circumference. In addition, the DHA supplementation in pregnancy was associated with fewer infants born at <34 wk of gestation and shorter hospital stays for infants born preterm (79).

A 2016 Kansas University, DHA Outcomes Study (KUDOS), found a significant reduction in early preterm births with a supplement of 600 mg DHA per day compared to placebo. The objective of this analysis was to determine if hospital costs differed between groups--applied a post-hoc cost analysis of the delivery hospitalization and all hospitalizations in the following year to: 197 mother-infant dyads who delivered at Kansas University Hospital. The hospital cost saving of DHA supplementation amounted to $1678 per infant. Even after adjusting for the estimated cost of providing 600 mg/d DHA for 26weeks ($166.48) and a slightly higher maternal care cost ($26) in the DHA group, the net saving per dyad was $1484. Extrapolating this to the nearly 4 million US deliveries per year suggests universal supplementation with 600 mg/d during the last 2 trimesters of pregnancy could save the US health care system up to USD 6 billion.

Applying a Developmental Programming of Health Perspective to Pregnancy.

In addition to the before mentioned preconception, and lifestyle factors discussed there are additional common insufficiencies and deficiencies in our clinic population that affect both organogenesis and proliferation. Each trimester different nutrients help uniquely with development (Table II). In addition to these major ones—other common deficiencies such as magnesium have been identified in the American pregnancy population (80). Indeed, many of our patients were insufficient in vitamin D, carnitine, zinc, magnesium, DHA, EPA by diet recall and serum studies. In addition there were the common single nucleotide polymorphisms in our population that when combined with a diet low in folate and the B vitamins is associated with increased relative risk of autism (63).

Recognizing all these factors that influence maternal/fetal health and recognizing the powerful use of food, nutritional bridges and empowering maternal education, we developed a customized nutrition and lifestyle program. The program includes group nutrition and lifestyle education and online supplementary education unique for each of the three trimesters and the postnatal period. There is a supplement bridge to augment the changing diet preferences and to address the documented nutritional insufficiencies in the setting of selected single nucleotide polymorphisms. The program as implemented reduced pregnancy induced hypertension and gestational diabetes mellitus through this family of epigenetic and metabolic modulation. By reducing the frequency of large for gestational age and small for gestational age newborns at least in part by reducing pregnancy induced

hypertension and gestational diabetes the expectation is that there will be a decreased risk of obesity, diabetes, hypertension and cardiovascular disease by the time these infants become adults.

Table II: Macronutrient (Protein, Fat, Carbohydrate) and Micronutrient (Mineral, Vitamins and Phytonutrient) Emphasis preconception, pregnancy, postpartum.

Nutrients	**Pre-conception**	**1st Trimester**	**2nd Trimester**	**3rd Trimester**	**Postnatal**
Protein	Complete adequate 0.8 g/kg	Carnitine, Methionine Cysteine, 0.8g/kg	Complete adequate 1.1-1.2 g/kg	Complete Adequate 1.1 -1.2g/kg	Complete Adequate
Fat	EFA, DHA	Omega 3	Omega 3	Omega 3	Omega 3
Carbohydrates	Complex	Complex	Complex, fiber-rich	Complex, fiber- rich	Complex
Probiotics	Immune balance	Immune balance	Immune balance	Immune balance	Immune balance
Minerals	Iodine, Fe, Mg, Zinc, Ca, Se	Iodine, Selenium	Iron, Mg, Ca	Iron, Zinc, Mg	Fe, Ca
Vitamins	Methylation factors, D,E,A,C	D, B6,B12, Folate,	E, D,C	C,A	B Vitamins, D
Phyto-nutrients: Main reason	Full range of colors of fruits and veggies	Colors: oxidative stress	Colors: Organ formation	Colors: Newborn Preference	Colors: Antioxidant balance

Program Results and Outcomes

The aggregated occurrence rate of the two maternal conditions- gestational diabetes mellitus and pregnancy induced hypertension and the two newborn outcomes- small for gestational age and large for gestational age was significantly lower in our clinic population than comparison populations that share similar age, socioeconomic status, locality, gravidity, parity and ethnicity even with the small study size (n=110 study population n=553 comparison population. Both the pregnancy induced hypertension and gestational diabetes incidence was lower in the mothers with the functional nutrition approach(81).

OUTCOMES AND APPLICATION

A Customized Nutritional Enhancement For Pregnant Women Appears to Lower Incidence of Certain Common Maternal and Neonatal Complications though preliminary suggest that the customized and individualized approach to nutrition and lifestyle intervention is highly likely to be responsible for reduction of Pregnancy Induced Hypertension (High Blood Sugar), GDM (Gestational Diabetes Mellitus), SGA (Small for gestational age) neonates, and LGA (large for gestational age) neonates.

- We know that SGA neonates pose the highest risk of chronic disease outcome as adults.
- We know that PIH is associated with SGA neonates.
- We know that GDM is associated with an increased autism risk if diagnosed within the first 26 weeks of pregnancy.
- We know that LGA neonates are associated with mothers who have GDM.
- We know that Autism risks increase in mothers who have GDM.

Summary:

The preconception and perinatal period represents a unique opportunity for real change in lasting health outcomes. There is no more amenable phase in the human lifecycle for introducing habits that will lead to healthier lives for mothers and their babies. People are open to what will improve the health of their offspring, and not too surprisingly, this time period appears to present a critical window of opportunity for epigenetic and biometabolic intervention with positive outcomes that transcend generations (82).

The growing body of evidence suggests that generational reductions in the chronic diseases of obesity, HTN, DM, CVD, osteoporosis, allergy, and mental illness could be achieved through addressing preconception, intrauterine, and postnatal developmental programming (83-86).

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P. Michael Stone MD, MS, IFMCP is the medical director of Ashland Comprehensive Family Medicine, a 9 clinician functional medicine primary care insurance based clinic in Ashland Oregon. With Emily Rydbom CNC,

CNP, CHN and Leslie Stone MD IFMCP the GrowBabyHealth program has been developed. In his early career he delivered 1500 children. He lectures internationally on wide ranging topics of one carbon metabolism, nutrition adequacy and inadequacy, the nutrition physical exam, and developmental programing of health and disease. Leslie Stone and Michael have 4 grown children and 3 grandchildren.

He is faculty with institute for functional medicine and consultant to Tallahassee Family Medicine Residency and Florida State University on Functional medicine. The greatest impact on multigenerational health occurs during pregnancy and it is the greatest opportunity for change. mstone@ashlandmd.com

He received his MD at University of Washington Seattle and His Graduate Degree in Nutrition at Washington State University. He completed Residency and Fellowship at UCLA Ventura in Family Medicine. Additional Certification in Functional Medicine.

Emily Rydbom, B.A., C.N.C, C.N.P, C.H.N is a Certified Nutrition Consultant and Certified Nutrition Professional, Board Certified in Holistic Nutrition through the National Association of Nutrition Professionals. She is the owner

of GrowBaby, and mother of 2 and has been practicing the functional nutrition approach to pregnancy for over 5 years. She co-published the "Customized Nutritional Enhancement for Pregnant Women Appears to Lower Incidence of Common Maternal and Neonatal Complications" study - Global Advances in Health and Medicine with Dr. Leslie Stone and others. She has an active clinical practice with Dr. Stone, helping women reach their nutrition and pregnancy health goals. Emily's passions include empowering women during the preconception, pregnancy, and postnatal time period, while reaching Spanish-speaking populations worldwide, and teaching families about healthy nutrition and lifestyle balance from 6 months-5+ years. Her postgraduate training is through Bauman College, with an undergraduate degree completed at Southern Oregon University.

Leslie P. Stone, M.D., IFM-CP, board certified in family practice, with a fellowship in surgical obstetrics. She is an International lecturer on developmental programming of disease and application of individualized functional medicine care during pregnancy. Her passion is helping parents capture the miraculous during pregnancy by changing habits, their lives and empowering life in and out of the womb She is the primary consultant for GrowBabyHealth.com, an individualized nutrition and lifestyle program promoting generational health. She has been delivering babies since 1982 and has delivered nearly 5000 children. She is owner of Ashland Comprehensive Family Medicine—Stone Medical in Ashland Oregon where she continues to practice.

Her ongoing clinical research centers around aspects of the developmental programming of health, functional medicine approach to pregnancy, and comparing birth practices including vaginal births after cesarean and water births with other birthing experiences.

Her undergraduate degree from Washington State University in Physiological Psychiatry was followed by her MD from University of Washington Seattle, Internship in OB/GYN Oregon Health Sciences University, Residency at UCLA in Family Medicine, Surgical Obstetric Fellowship at UCLA Ventura and further Certification in Functional Medicine.

Growbabyhealth.com. and Ashlandmd.com

Rammohan V. Rao
CAS, RYT, PhD

Dale E. Bredesen
MD

INTEGRATIVE APPROACHES TO ALZHEIMER'S DISEASE

ABSTRACT

Alzheimer's disease (AD) is an age-associated, progressive neurodegenerative disease that is characterized by severe memory loss, unusual behavior, personality changes and a decline in cognitive function. These losses relate to the death of brain cells and the breakdown of the connections between them. While the exact cause is still unknown, environmental as well as genetic factors are thought to contribute to the disease progression. No cure exists for Alzheimer's and the drugs currently available to treat the disease address only its symptoms and with limited effectiveness. An integrative approach that combines the best of conventional medicine and treatment with non-conventional approaches, including diet, lifestyle, and other nonpharmacological interventions, has the potential to delay/reverse the progression of this disease.

Introduction

Alzheimer's disease (AD) is a progressive, age-associated, inexorable loss of cognitive function. Symptoms including memory losses typically appear after age 60, with some early-onset forms of the disease linked to a specific genetic defect. The disease is characterized by the presence of senile plaques and abnormal Tau tangles often starting in the hippocampal area of the brain. No cure exists for Alzheimer's and the drugs currently available to treat the disease address only its symptoms and with limited effectiveness. As the disease progresses, patients become totally dependent upon caregivers and eventually require comprehensive care. Thus, Alzheimer's disease presents a considerable problem in patient management, as well [1-4]. One in eight older Americans has AD. An estimated 5.5 million Americans are living with Alzheimer's dementia although this number does not account for those individuals that are potential victims but not yet diagnosed with the disease. Efforts to find a cure for AD have so far been disappointing and the drugs currently available to treat the disease address only its symptoms and with limited effectiveness. It is believed that therapeutic intervention that could postpone the onset or progression of AD would dramatically reduce the number of cases over the next 50 years [2,3,5-8].

Signs & Symptoms of AD

The underlying pathogenesis is a loss of neurons in the hippocampus, cortex and subcortical structures. There are different stages of the disease as it progresses from early onset to late onset. Frustration, hostility, and irritability are common emotional features exhibited by AD patients. Early disease shows a loss of short term memory, inability to learn new information, mood swings, and difficulty in finding words, forgetting immediate names and losing items. As the disease progresses, memory starts deteriorating and patients lose sense of time and place. Symptoms vary between individuals and in addition to memory loss there are other warning signs that individuals may experience to different degrees. The signs and symptoms at different stages of the

disease provide a general idea of how functional abilities change during the course of the disease. It is necessary to understand and recognize these signs and symptoms so as to explore treatments and other lifestyle changes that may provide some relief and help to maintain a level of independence [2,3,5-8].

Etiology & Pathology

Although the disease was first described in early 1900's, the exact cause of Alzheimer's disease remains unclear. There is compelling evidence that genetic predispositions underlie the development of Alzheimer's disease. However, the most obviously genetic cases are also the rarest. Most cases identified are 'sporadic' with no clear family history. It is probable that environmental factors have to interact with a genetic susceptibility to cause development of disease. Several competing hypothesis exist to explain the causes of AD.

1) Cholinergic hypothesis According to this hypothesis AD begins as a deficiency in the production of acetylcholine, a vital neurotransmitter. Four of the first-generation anti-Alzheimer's drugs were based on this hypothesis but the therapeutic benefits from these drugs are temporary and the cognitive decline continues after a short term improvement.

2) The Glutamatergic hypothesis. Abnormal glutamate levels resulting in uncontrolled glutamate activity triggers neuronal destruction in the memory and learning areas of the brain that can lead to cognitive dysfunction. The drug memantine that blocks glutamate excitotoxicity is currently approved for AD and has been associated with a moderate decrease in clinical deterioration with a mild positive effect on cognition, mood and behavior [9].

3) Protein abnormalities. Accumulation of misfolded protein products of Amyloid precursor protein (APP) and the microtubule protein Tau in the form of toxic aggregates results in loss of neurons in the cerebral cortex, hippocampus and subcortical structures [10,11]. The progression of AD depends on the accumulations of these aggregates and the subsequent cerebral degradation that follows. The destruction of cerebral tissue triggers the behavioral changes associated with Alzheimer's dementia [10,11].

4) The Aβ-amyloid Prion hypothesis. Studies from our laboratory and others suggest that AD may also arise due to a cellular imbalance in the trophic support [12]. According to this model APP is a molecular switch signaling either neurite extension, synaptic maintenance, and caspase inhibition, or neurite retraction, synaptic reorganization, and caspase activation [12,13]. In support of this model, the four peptides derived from the amyloidogenic processing of β-amyloid precursor protein (APP) namely, sAPPβ, Aβ, Jcasp, and C31—have been shown to mediate neurite retraction, synaptic inhibition, caspase activation, and programmed cell death [5,13]; whereas, in contrast, the two peptides derived from the non-amyloidogenic processing of APP—sAPPα and αCTF—mediate neurite extension, and inhibit Aβ production, caspase activation, and programmed cell death [5,13]. These findings suggest a new model of Alzheimer's disease as a trophic vs antitrophic signaling imbalance [12-15] and a positive feedback in

the form of Aβ amyloid prionic loops that selects and amplifies the disease process at the molecular species level [5,14,15].

5) Infectious hypothesis. There are increasing number of reports of various pathogens that have been identified in the brains of patients with Alzheimer's disease—from viruses such as *Herpes simplex* [16] to oral bacteria such as *P. gingivalis* [17] to fungi such as *C. glabratus* [18]. We have reported a subtype of AD—type 3 AD as a result of exposure to specific mycotoxins, typically associated with molds such as *Stachybotrys*, *Penicillium*, or *Aspergillus* and is most commonly inhalational (IAD) [7,8], resulting in a phenotypic manifestation of chronic inflammatory response syndrome (CIRS). However, other biotoxins, from the *Borrelia burgdorferi* of Lyme disease or from other tick-borne pathogens, or aquatoxins such as those from dinoflagellates, may also trigger CIRS and AD-like symptoms [7,8]. The laboratory abnormalities are frequently accompanied by nasal colonization by MARCoNS (multiple-antibiotic resistant coagulase-negative *Staphylococcus*) [7,8]. All the above mentioned findings raise the possibility that a subset of AD (we designated it as type-3 AD) may be accompanied by an active infection [7,8]. This also raises the attractive possibility of amyloid beta initiating an antimicrobial response/anti-toxin response to the presence of these pathogens [7,8,19,20]

6) Other Theories. In addition, recent studies have also pointed to the role of the apolipoprotein E4 (ApoE4) as a major genetic risk for Alzheimer's disease [2,21,22]. ApoE4 protected early hominids from their pathogen-laden environment but now promotes AD in modern humans who live about twice as long as their distant ancestors. About 2.5% of the population has two ApoE4 genes, giving them a 10—12 fold risk of developing AD [21-24].

In addition to its possible role in enhancing amyloid beta clumping and blocking amyloid beta clearance [25-30], ApoE4 lowers the body's production of an anti-aging protein called SirT1 both in lab tests and in the brains of deceased AD patients with ApoE4. ApoE4 acts as a transcription factor and binds DNA with high affinity, including the promoter regions of 1700 different genes associated with sirtuins and aging, insulin resistance, inflammation and oxidative damage, accumulation of amyloid plaques and tangled tau among others [31,32]. These results offer an exciting new possibility to design therapeutics that would block the coordinated action of these 1700 ApoE4-associated genes in their Alzheimer's risk induction [31,32].

Whatever be the theory/mechanism, a critical unmet need is the development of a drug(s) that could be taken long-term to prevent people at risk from developing AD, and, for those already with AD, ameliorate the symptoms and prevent progression. Considering that several mechanisms have been identified to play a role in AD pathogenesis, introduction of a combination therapy in preference to monotherapy will be needed to address all of these mechanisms therapeutically for optimal clinical efficacy [33].

Treatment for AD

Efforts to find a cure for Alzheimer's disease have so far been disappointing. In the last 10 years, of the 244 compounds that went to clinical trials only one was approved. The USFDA (U.S.Food and Drug Administration) approved drugs temporarily relieve some of the symptoms but are often associated with several side effects [2]. Many studies have indicated that non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen and aspirin delay the onset and lower the ultimate risk of AD. Prolonged intake of these drugs results in a greater risk of developing fatal stomach ulceration and gastrointestinal bleeding [34]. Scientists are also looking at several methods to diagnose AD earlier, before symptoms appear, which can allow for earlier pursuit of treatment [35,36].

Recently, Dr. Dale Bredesen reported in a series of manuscripts, a more advanced and effective protocol, dubbed ReCODE™ for Reversal of Cognitive Decline. The protocol described the reversal of cognitive decline in patients with pre-Alzheimer's conditions and early Alzheimer's disease. Furthermore, using the protocol, Dr Bredesen was able to identify specific subtypes of Alzheimer's disease [3-8] and also recognized the role of specific toxins *(as mentioned above-section 6, infectious hypothesis)* that contributed to a specific subtype of AD [7,8] The protocol supports the idea that addressing the many contributing factors of AD as a group, rather than individually, could potentially reverse the disease's early progression. Those factors include nearly 100 biochemical, genetic, and functional imbalances that require correction and optimization to reverse cognitive decline. Some of these components include but is not limited to vitamins E, C, D and folic acid, zinc, smoking, weight reduction, cellular levels of homocysteine, antioxidants, adrenal hormones, exposure to toxins, metal toxicity and inflammatory markers [3,5-8].

Integrative approaches to reverse AD

Listed here is an integrative program—factors that anyone can use to prevent, delay or potentially reverse memory loss and other symptoms that characterize AD.

1. Metabolic parameters and hormones. The integrative approach that we describe here involves metabolic enhancement to reverse/delay the AD symptoms. Hence metabolic analysis is necessary and suitable interventions are needed to optimize the metabolic parameters. This includes among others hs-CRP, fasting glucose, fasting insulin, hemoglobin A1c, homocysteine, 25-hydroxycholecalciferol, vitamin B12, alpha-tocopherol, TSH, free T3, free T4, serum zinc, serum copper, copper:zinc ratio, ceruloplasmin, pregnenolone, testosterone, progesterone, AM cortisol, albumin:globulin, lipid profile, urinary mercury:creatinine, Lyme antibodies, VEGF, VIP, HLA-DR/DQ, and BMI [5-8]. Optimizing all the above mentioned metabolic parameters in a comprehensive way has provided cognitive benefits, both in symptomatic and asymptomatic individuals [5-8].

2. Diet. Inflammation is a key feature of AD and one of the ways to block or lower the inflammatory response is by consuming an anti-inflammatory diet by eliminating simple carbohydrates, trans fats and processed foods [4]. Consumption of foods low in glycemic

index, high in fiber and including fruits, vegetables especially cruciferous vegetables and sulfur rich foods is also recommended. Intake of omega-3-rich oils and foods rich in alpha-linolenic acid (flax and walnuts), helps to curb inflammation [4-8]. Practicing intermittent fasting (IF) by waiting at least 12 hours between dinner and breakfast triggers a hypoglycemic state in the brain, leading to autophagy and lipid catabolism and liberation of brain protective ketone bodies particularly β-OH-butyric acid, all of which results in enhancement of brain plasticity and improvement in cognition [37-39].

3. Stress. All efforts need to be made to reduce stress. High cortisol levels associated with stress can damage the memory centers of the brain. Relaxing walks, yoga, meditation and music are some of the recommended stress busting interventions [40-42].

4. Physical and mental exercise. Having an active physical exercise regimen helps to reverse/delay the AD symptoms. This could be walking, swimming, cycling, gardening or just an active exercise at the gym. Physical exercise in any form for at least 30 minutes each day is recommended [43,44].

The brain is plastic, so stimulating and challenging the brain through mental exercises also helps to improve cognitive impairment [45]. Activities involving multiple tasks or requiring communication, interaction, and organization offer the greatest protection [46,47].

5. Yoga and Meditation. Yoga and meditation not only protect the brain against age-related cognitive decline but also offer other health benefits including, but not limited to, improvement of depression, anxiety and stressful states. In addition, they also contribute to the increase in size and volume of the hippocampus[48]. Patients with early and moderate AD can incorporate yoga asanas by practicing the poses gently paying greater attention to focus and detail. Yoga poses bring stability to the body and calm the mind, thereby reducing anxiety and stress [4,48].

Yoga is comprehensive in that it combines physical poses, with breath control exercises (Pranayama) and meditation all of which are excellent tools to keep the nervous system calm and balanced. These techniques can be easily imparted to the patients with early and moderate AD. There is some evidence from studies with healthy volunteers that use of certain breathing techniques (such as breathing solely through one nostril or the other) may improve different aspects of cognitive function [48,49].

Similarly meditation may reduce stress proteins, increase the beneficial effects on lipid profile, lower oxidative stress, strengthen neuronal circuits and enhance cognitive reserve capacity all of which reduce the risk for age-related neurodegeneration [4,50].

6. Sleep. Sleep has an important function in ensuring metabolic homeostasis. Sleep helps to maintain a healthy immune system, balance our appetites, makes us less susceptible to degenerative diseases or infections, improves memory and enhances cognition. Poor sleep prolongs reaction time, reduces learning and triggers impaired performance in cognitive tests. Good quality sleep has numerous benefits: a) It triggers a dramatic

increase in the flow of cerebrospinal fluid in the brain that washes away harmful toxins that build up in the brain and thereby improves cognition; b) specific fear and stressful memories are wiped out during the slow-wave sleep; c) Sleep helps to forget some of the redundant information that we learn each day. Sleep is accompanied by specific pruning of noisy synaptic circuits that in turn helps to consolidate memories [51-53].

7. Herbs. Several anti-inflammatory herbs, neuroceuticals and cogniceuticals have been shown to improve cognition. These include among others, Ashwagandha, Bacopa, Turmeric, Ginger, Cat's claw, Guduchi and Gotu Kola that act as antioxidants, free radical scavengers, anti-virals, anti-inflammatories and regulators of the immune system [3,4].

The biggest hurdle to drug delivery into the central nervous system (CNS) is the presence of the blood brain barrier (BBB) that severely limits access to the CNS. This could be avoided by considering several novel method of herbal delivery. Thus, herbs can be taken individually or as a combination and may be administered as oral capsules or prepared as oil extracts and given transdermally, transcranially or intra nasally [3,4].

Intra nasal administration (called NASYA in Ayurveda) is a therapeutic procedure that involves delivery of dry herbal powders or medicated oils. The delivery is rapid, bypasses the BBB and directly targets the CNS [54-58].

Transdermal administration involves application of warm herbal oil on the body and massaging the areas with gentle or deep hand strokes. A significant brain functional activation changes together with increased cerebral blood flow was observed in participants who received a massage. Massage also lowered the levels of serum cortisol, arginine-vasopressin and chromogranin-A with concomitant increases in circulating lymphocytes and in regional cerebral blood flow. Application of medicated oil followed by a gentle massage may relax the tight junctions between endothelial cells in the CNS vessels thus allowing entry of solutes and other components into the CNS [59-62].
Transcranial oleation therapies are non-systemic and non-invasive. Therapies include Shirodhara (gentle dripping of herbal oil on the forehead), Shirobasti (a leather dam is created over the head of a patient and warm herbal oil is retained for an hour), ShiroAbhyanga (herbal oil is applied on the head followed by a gentle massage), and ShiroSeka (herbal oil is poured on the scalp in a continuous stream). Application of medicated oil through the above mentioned techniques may relax the tight junctions between endothelial cells in the CNS vessels thus facilitating the entry of solutes and other herbal components into the CNS [3,63-66].

Conclusions. Approximately 360,000 new cases of AD are diagnosed annually in the U.S.A. AD is extremely costly to patients, their families, and society as a whole. The prediction is that by the year 2030, $375 billion will be spent annually in the United States on AD [2,67]. AD-associated cognitive decline may be driven in large part by metabolic processes. Memory loss in patients AD and at least the early phase of AD, may be reversed, and improvement sustained, with the integrative program described here Furthermore, whereas the normalization of a single metabolic parameter, such as vitamin

D3, may exert only a modest effect on pathogenesis, the optimization of a comprehensive set of parameters, which together form a functional network, may have a much more significant effect in reversing/delaying memory loss.

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Rammohan V. Rao (Ram) holds a doctorate degree in Biochemistry & Neurosciences and works as a Research Associate Professor of Neuroscience at the Buck Institute for Research on Aging, Novato, CA (https://www.buckinstitute.org). His research focus is in the areas of chronic stress, neuronal cell death and mechanisms of age-associated neurodegenerative diseases with special emphasis on Alzheimer's disease. Ram has more than 15 years of research and teaching experience in Neuroscience and has published more than 50 peer reviewed papers in scientific journals and chapters in a couple of text books. Ram has supervised, trained and mentored several high school students, college interns, research technicians and post-doctoral fellows.

Ram also completed the academic training at the California College of Ayurveda (CCA) and received his certification as Clinical Ayurvedic Specialist (CAS). He serves as a faculty at the California College of Ayurveda and teaches in their Nevada city location (http://www.ayurvedacollege.com/college/). Ram is also a dedicated Hatha yoga practitioner and is a Registered Yoga Teacher (RYT) from Yoga Alliance USA. In his spare time he conducts workshops, seminars and cooking classes on Yoga, Ayurveda, Meditation & Pranayama (YAMP) techniques. Ram has published several articles in major Yoga/Ayurveda journals and has been a featured speaker in several meetings and symposia. He is a member of the National Ayurvedic Medical Association (NAMA), member of the Research Board of the Association of Ayurvedic Professionals of North America (AAPNA) and Science Editor of Ayurveda Journal of Health.

Dr. Dale E. Bredesen, MD is internationally recognized as an expert in the mechanisms of neurodegenerative diseases such as Alzheimer's disease. His research focuses on the mechanisms of cell death in the nervous system and has led to a new approach to Alzheimer's disease therapeutics. Dr. Bredesen earned his undergraduate degree at Caltech, his MD at Duke University, and completed his neurology residency at UCSF. He was an NIH Fellow in the laboratory of Nobel Laureate Stanley Prusiner.

In 1989, Dale joined the faculty at UCLA where he was awarded the Elizabeth R. and Thomas E. Plott Chair. In 1994, he was recruited to the Burnham Institute to direct the Program on Aging, and then in 1998 became the Founding President and CEO of the Buck Institute for Research on Aging. He has held faculty positions at UCSF, UCLA and the University of California, San Diego. He recently completed a term as a member of the National Advisory Council on Aging. The Bredesen Laboratory studies basic mechanisms underlying the neurodegenerative process, and the translation of this knowledge into effective therapeutics for Alzheimer's disease and other neurodegenerative conditions, leading to the publication of over 200 research papers. His group has developed a new approach to the treatment of Alzheimer's disease, and this approach has led to the first description of reversal of symptoms in patients with MCI and early Alzheimer's disease, with the ReCode protocol (https://www.mpi-cognition.com/protocol-overview/).

TERRY WAHLS

MD, FACP, MBA, IFMCP

Dietary Approaches to Treating Multiple Sclerosis Fatigue and Other Neurodegnerative Diseases

This paper is a rewrite of two grants, one related to multiple sclerosis and the other related to amyotrophic lateral sclerosis. I provide a discussion of the research that supports the use of a dietary approach to reducing symptoms and improving the quality of life in these two disease states. I briefly summarize the potential mechanisms by which dietary changes are having a favorable impact on autoimmune and neurodegenerative disease states. The details for the low saturated fat diet advocated by Dr. Roy Swank can be found in his book, The Multiple Sclerosis Diet Book, and the Swank MS Foundation website, http://www.swankmsdiet.org. The details for the Wahls™ diet I have used in my clinical trials, which is a modified Paleolithic diet, can be found in my book, The Wahls Protocol: A Radical New Way to Treat All Chronic Autoimmune Conditions; the companion cookbook, The Wahls Protocol Cooking for Life: A Revolutionary Modern Paleo Plan to Treat All Chronic Autoimmune Conditions; and my website, www.terrywahls.com

Multiple Sclerosis

Fatigue is one of the most common and disabling symptoms of multiple sclerosis (MS), diminishing quality of life and contributing to early exit from the workforce (1, 2). The etiology of MS-related fatigue is complex, involving neurotransmitter and circadian rhythm dysfunction(3), adding to the challenge of effectively reducing the negative impact of fatigue on quality of life. This symptom is not eliminated by any of the current MS treatments. Instead, fatigue is managed separately using multiple interventions, including disease-modifying drugs and stimulants, exercises, energy conservation, and stress management techniques(4). Among the pharmacological agents used to treat MS-related fatigue, the most common are amantadine and modafinil. However, studies investigating their effects have provided conflicting results regarding tolerability and efficacy (5-7), and thus non-pharmacological therapies such as diet, which is both safer and more cost-effective, may be preferable. Exercise augmented by electrical stimulation can also be modestly effective for reducing perceived fatigue, as reported by both Coote et al.(8) and Chang et al.(9). Consistent with these findings, we have reported statistically and clinically significant reduction in fatigue severity in persons with progressive MS (pwPMS), using a multimodal intervention consisting of a modified Paleolithic diet, stress reduction, exercise, and electrical stimulation of muscles(10, 11).

The above-described findings regarding the effectiveness of non-pharmacological treatments in MS are particularly interesting in light of emerging data supporting the notion that environmental rather than genetic factors are the predominant causes of MS(12). Given that food consumed is a major component of the environment, it is conceivable that improving the quality of the diet may have a significant impact on the development of MS-related fatigue.

Nutrition scientists have shifted from single-nutrient (i.e., supplement-based) to dietary-plan interventions in treating or preventing diseases, including psoriasis(13), cancer(14, 15), and neurological diseases(16). A combination of Self-Determination Theory and motivational interviewing (technique that assists the subject in finding her or his internal motivation for adopting and sustaining changes in diet and lifestyle) increases the probability that changes in health behavior are adopted and sustained(17-25), particularly when the spouse is included in the process. The proposed study will compare two dietary plans for the treatment of MS-related fatigue: the low saturated fat diet (Swank) and the modified Paleolithic diet (Wahls Elimination).

Dr. Roy Swank was one of the first to use a dietary plan in treating MS, and did so based on his observation that

high levels of saturated fat in the diet were associated with the risk for MS in Norway(26, 27). This led to his development of the theory that a diet high in saturated fats causes more rapid disease progression.

Dr. Swank followed 144 patients with varying levels of disability, ranging from mildly to more severely disabled. These individuals had agreed to consume a diet containing <20 grams of saturated fat per day and to report their dietary compliance, monitoring clinical outcomes over time(28-33). The patients were classified as either "good" dieters, consuming <20 grams of saturated fat per day, or "poor" dieters, consuming >20 grams of saturated fat per day. In addition, the patients were classified according to performance on a 6-point scale, where performance refers to physical and mental performance in everyday situations. Points were given as follows: 0=normal performance and normal neurology; 1=normal performance but abnormal neurology; 2=slightly to moderately impaired performance and abnormal neurology (able to work part- or full-time and ambulant); 3=severely limited performance (unable to work); and abnormal neurology but ambulant; 4=severely limited performance and non-ambulant; and 5=dead.

In this study, the number of relapses and progression of disability correlated strongly with the amount of dietary saturated fat consumed(29-34). Moreover, individuals with the mildest disability (performance grade of 0–1) at the time of adopting the low saturated fat diet were more likely to experience fewer relapses and were much less likely to have died due to MS-related complications(32, 33). These patients also experienced much less deterioration in their ability to ambulate than those who consumed >20 grams saturated fat(32, 33). The 50-year follow up is a strength of the Swank study; the absence of a control group and lack of brain imaging is a limitation.

A more recent study by Yadav et al.(35) used a vegetarian version of the Swank diet, also known as the McDougall diet. This study used a randomized design with control group. Measures included the Fatigue Severity Scale (FSS), Short Form 36 (SF36) quality-of-life scores, lipids, weight, body mass index (BMI), and MRI images of the brain, at baseline and at one year. Favorable changes in weight, body mass index, and lipids were observed, but no statistically significant difference in MRI findings, SF36 quality-of-life scores, or FSS scores were reported(4).

The Paleolithic diet as described by S. Boyd Eaton(36) in 1985 in the New England Journal of Medicine included a discussion of the health implications of adopting a diet that more closely resembled that of our Paleolithic ancestors. Dr. Loren Cordain provided more specific recommendations for a modern version of the Paleolithic diet in the American Journal of Clinical Nutrition(37) and the British Journal of Nutrition(38). His version of the modern Paleolithic diet stressed the consumption of meats, vegetables, and fruits; it excluded grains, legumes, and dairy(36, 37), and excluded nightshade vegetables (potatoes, tomatoes, peppers, and eggplants)(38) for persons with rheumatoid arthritis. The Paleolithic diet was recently tested for its impact on various biomarkers, and in healthy individuals it was associated with improvements in blood pressure, BMI, levels of plasminogen activator inhibitor-1(39), lipid profile, insulin sensitivity, and arterial distensibility (as measured by brachial artery responsiveness to ischemia)(40). In a study of patients with type 2 diabetes, the Paleolithic diet was shown to be more satiating per calorie than the American Diabetes Association (ADA) diet(41). In a crossover study comparing the Paleolithic diet to the ADA diet in free-living humans, the former was superior to the ADA diet with respect to improving blood pressure, the lipid profile, and glycemic control(42). Finally, in a randomized controlled study of obese persons with metabolic syndrome, comparison of the Paleolithic diet to an isoenergetic diet based on dietary guidelines of the Dutch government, the Paleolithic diet was associated with improved blood pressure, fasting levels of lipids, and weight loss(43).

In a previous pilot study, we used a modified version of the Paleolithic diet as part of a multimodal intervention, in pwPMS (either secondary or primary progressive multiple sclerosis (SPMS and PPMS))(10, 11).

Our study diet (modified Paleolithic) stressed the consumption of more vegetables, with a target of 6 to 9 cups of vegetables and fruit per day, and recommended somewhat less meat than the Paleolithic diets tested in the previously mentioned studies. At enrollment our study subjects were consuming less than 1.5 servings of vegetables per day, but raised this to an average of 8 servings per day by month 12(11). Notably, the number of mean daily servings of vegetables is inversely correlated with the risk of developing obesity(44), which in turn is a risk factor for developing MS(12, 45) and a common comorbid diagnosis for those with MS. In particular, increased consumption of vegetables is associated with lower expanded disability status scores (EDSS)(46). It is thus likely that the modified Paleolithic diet proposed for this study will also be associated with favorable impact on lipid profiles, insulin sensitivity, blood pressure, body weight, and BMI. A diet low in saturated fats would also likely be associated with a favorable impact on blood pressure, lipid profile, body weight, and BMI.

Our published data suggest that a multimodal intervention (modified Paleolithic diet, targeted vitamin supplementation, stress-reducing practices, exercise, and electrical stimulation of muscles) greatly reduces MS-related fatigue in pwPMS(10, 11) and improves mood and cognition (in press J of American College of Nutrition). It is unknown which component of the multimodal intervention contributed the most to the observed reduction in fatigue. However, several subjects spontaneously reported that deviations from the study diet resulted in a sharp worsening of their fatigue, and that this was resolved with stricter adherence to the study diet. We also have data from a pilot randomized controlled trial showing that significant reductions in perceived fatigue (as assessed by FSS) occurred as a result of a modified Paleolithic diet intervention in individuals with RRMS.

In our current studies we focus on a diet-only vs. the previously tested multimodal intervention, because it will permit us to establish specifically the effects of diet on MS symptoms such as fatigue. Moreover, because we are studying persons who have RRMS rather than progressive forms of MS, the subjects are likely to be employed and more active in performing activities of daily living and work. Indeed, whereas many of the subjects in our progressive MS studies were very sedentary and needed electrical stimulation to be able to perform exercise, those with RRMS were less likely to be sedentary and could exercise without assistance if they chose to do so. Based on feedback from our most recent application to the NMSS, we are using a comparator diet instead of a study design in which the subjects are first observed and then retested. To enhance compliance by subjects and reduce the rate of dropout (which was high among subjects in the control group when they were randomly assigned to this group), we are using a second diet, the Swank diet, which is also popular among the MS community. We are currently comparing the effects of this low saturated fat diet to a modified version of the Paleolithic diet that we used in our pilot studies to treat MS-related fatigue. This new diet, the Wahls Elimination diet, is more closely aligned with Paleolithic diets in the literature referenced above. The main difference is that it eliminates a few additional foods to which some individuals may be sensitive, including grains, dairy, legumes (including soy), eggs, and nightshades, but continues to stress a high intake of vegetables. Our hypothesis is that subjects following the Wahls Elimination diet will have a statistically greater reduction in the fatigue severity and greater improvement in quality of life scores than subjects following the low saturated fat diet.

Study diets:

Study diet 1. The modified Paleolithic (Wahls Elimination) diet, which stresses more vegetables than the other Paleolithic diets that have been studied previously, and places a limit on daily meat consumption; like other Pa-

leolithic diets, it excludes all grain, legumes, and dairy (except for clarified butter or ghee).

Study diet 2. The low saturated fat diet (Swank) severely restricts fats, reducing saturated fat in particular to less than 15 grams per day.

Study diet 1. The modified Paleolithic (Wahls Elimination) diet, which stresses more vegetables than the other Paleolithic diets that have been studied previously, and recommends 6-12 ounces of meat per day. Like other Paleolithic diets, it excludes all grain, legumes, and dairy (except for clarified butter or ghee). The diet will also exclude eggs. Nightshade vegetables/spices will be excluded during the first 12 weeks on the diet and then re-introduced during the second 12 weeks on the diet if the subject desires. Specific guidance will be provided to subjects about how to re-introduce nightshades into the diet.

Study diet 2. The low saturated fat diet (Swank) restricts saturated fat in particular to ≤ 15 grams per day and limits unsaturated fat to 20-50 grams (4-10 teaspoons) per day.

Dietary supplements currently taken by the study participant will be reviewed by study staff. Staff will ask subjects to discontinue over the counter dietary supplements that contain the study supplement ingredients (fish oil, vitamin D, B12, folate, and/or multivitamins) and use study supplements instead. Participants will be told to continue taking all other dietary supplements they have been using and to not begin any new supplements until after they complete the study. If the subject reports that their personal physician or neurologist had initiated the use of the dietary supplements we are asking them to discontinue, we will send a letter to their treating physician, detailing which supplements have been discontinued and which supplements have been initiated as part of the study protocol. If the provider believes it is clinically safe for the subject to resume the supplement that provider had recommended, the subject may resume taking the supplement.

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is a disease that causes the death of neuron cells that control voluntary muscles. The disease is associated with stiff muscles, muscle atrophy, muscle twitching, steadily declining strength, and worsening disability(47). Symptoms may start in one limb, with bulbar symptoms (problems speaking or swallowing), or more rarely, with problems breathing. Approximately 5 to 10% of ALS cases are directly inherited from the parents with the remaining 90 to 95% considered sporadic(48). In the sporadic cases there appears to be a complex interaction between environmental exposures and genetic vulnerability that contributes to the development of ALS, severity of symptoms at initial diagnosis, and speed of decline(48).

The environmental factors that have been shown to increase the risk of developing ALS include previous exposure to heavy metals (mercury and lead), pesticides and other organophosphates, and organic solvents; history of electrical shock; and history of traumatic brain injury and physical injury(49). Epidemiologic evidence linking viral infections and ALS has not been documented to date(48, 49).

Modifiable risk factors related to diet that influence the risk of developing ALS and the speed of the decline have been identified. Smoking increases the risk(49), while diets higher in vegetable and fruit intake(49-51) and in omega-3 fatty rich foods(52) lower the risk of developing ALS and slow the speed of the decline.

In addition, autoimmune processes have been identified as a potential factor in the development of ALS(53, 54). There is a case report of an individual who was initially believed to have a motor neuron disease, possibly ALS,

whose symptoms, physical findings, and laboratory findings regressed over a 23-month period while following a gluten-free diet(55). In a subsequent case control study, Gadoth found that a higher percent of individuals with ALS (59.1%) than controls (28.6%) had HLA-specific alleles that increase the risk of developing Celiac disease. All controls had no evidence for IgA antibodies to transglutaminase and/or gliadin (antibodies associated with Celiac disease or gluten sensitivity), while 15.3% of the ALS patients did have elevated auto-antibodies(56), suggesting that gluten sensitivity may be a factor for some individuals with ALS. Other autoimmune diagnoses and processes have been noted in the presence of ALS. Other autoimmune diagnoses that have preceded the diagnosis of ALS include asthma, lupus, celiac disease, myasthenia gravis, polymyositis, Sjögren's syndrome, ulcerative colitis, and systemic lupus erythematosus(57-59).

In previous pilot studies, we have utilized a modified Paleolithic diet as part of a multimodal regimen (10, 11) in a single arm, non-randomized study in the setting of progressive multiple sclerosis (MS) or as the sole intervention(60) in a randomized wait list control study in the setting of relapsing-remitting multiple sclerosis to successfully treat multiple sclerosis–related fatigue. Through Dr. Wahls' social media presence, where she advocates for dietary approaches to reducing symptoms and improving quality of life in people with chronic neurological, neurodegenerative, and autoimmune disorders, she has been contacted by persons who have ALS, have adopted and stayed compliant with the modified Paleolithic diet, and have experienced an improved quality of life. Based on the favorable experience in the pilot studies in the settings of relapsing-remitting multiple sclerosis and the individual favorable reports in the setting of ALS, we have proposed to conduct a study of the impact of a modified Paleolithic diet and stress-reducing practices in the setting of ALS.

We are using functional medicine principles to create diet and lifestyle interventions to reduce symptoms and improve quality of life. Functional Medicine addresses the interaction of genetic vulnerability and environmental factors, particularly diet and lifestyle, that contributes to 70 to 90% of the risk of developing chronic disease. The root causes of poor health--toxin body burden, hormone disruption, inadequate digestion and assimilation of nutrients, structural damage, infection, dysbiosis, and microbiome compromise--are addressed with the patient using motivational interviewing and patient activation(61). We utilize motivational interviewing techniques (20, 24) that stress self-determination to assist participants in identifying and amplifying their internal motivation to adopt the recommended diet and stress-reducing practices. Because the dietary interventions have been associated with reduced MS symptoms (improved energy, reduced pain, and improved mental clarity), we have been remarkably successful at helping people eliminate the excluded foods from their diet (gluten-containing grains, casein-containing dairy products, and eggs) and add the encouraged foods (green leafy vegetables, sulfur-rich vegetables, deeply pigmented vegetable and berries, and omega-3 rich foods).

We achieved this success by providing a 2-week run-in to determine if the subject and family have implemented the study diet, assess their desire to continue the study diet, and work with them to implement the study diet as a family intervention (as opposed to an individual intervention). Because subjects have been supported as they find their internal motivating factors, implement the dietary interventions as a family, and experience symptom reduction, participants have largely been very successful at implementing and sustaining the recommended study diet. We also collaborated with a medical anthropologist to conduct interviews of study participants and their families to understand the factors associated with higher and lower levels of success with adopting and sustaining the study diet. We modified enrollment processes and study procedures to reflect what we learned and improve the retention of our study subjects. We provided a more detailed description of the study diet during the screening process and stressed that the greatest levels of success are achieved when the family supports

the study diet. We continued the coaching support using motivational interviewing for subjects and offered to include the family as well. These modifications have allowed us to achieve the extraordinary levels of change to the diet over 12 months that is depicted in Figure 1. We anticipate similar levels of success with the proposed study.

Discussion

Studies involving a dietary and/or a multimodal intervention that included several diet and lifestyle interventions have been conducted for multiple sclerosis with favorable results. Our research team is continuing to use dietary interventions in the setting of multiple sclerosis. We are now proposing to use our dietary intervention in the setting of early ALS.

Non-pharmacologic approaches to treating neurological and psychiatric disorders have increased. Prior to 2006 there were very few published papers on dietary approaches to neurodegenerative diseases. However, in the last decades many more papers, including review papers with over 500 reviews, are now findable with the search terms "diet" and "neurodegeneration." This is a reflection of the increase in animal model studies and human clinical trials using dietary approaches to treat underlying neurological and/or psychiatric disorders. There is greater recognition of how a lifetime of physical activity interacts with underlying genetic vulnerability to influence the risk of developing a neurodegenerative disease and the severity of the disease once it has developed(62-65). Thanks to the basic science work that is ongoing, our understanding of the complex biological systems that contribute to the health of the brain (and the rest of the body) continues to deepen. This has allowed us to recognize how the gut-brain axis influences mood and cognition and the risk of developing neurodegenerative and/or demyelinating illnesses(66-69). Furthermore, which foods a person consumes has a major impact on the microbiota, which contributes at least in part to the underlying mechanisms by which dietary approaches to treating autoimmune and neurodegenerative disorders are likely successful(70-72). According to Dr. Bruce Ame's triage theory, the body prioritizes the use of nutrients when the dietary intake is insufficient for optimal function(73). Eating diets that are relatively devoid of vegetables and micronutrients increases the risk of accelerated aging and neurodegeneration(73-76). The Wahls™ diet, was specifically designed to be maximally nutrient dense. It is possible that one mechanism by which the Wahls™ diet was helpful was improved nutritional adequacy of the diet, which led to improved utilization of nutrients according to Dr. Ame's triage theory, thus reducing the probability of long latency diseases, such as neurodegenerative diseases, and improving cellular health in the brain of our MS patients.

Dietary changes were not the only factor that contributed to the recovery of our clinical patients or the patients in our studies. We taught our patients and study participants stress-reducing practices, gave them personalized exercise programs, and taught them how to increase physical activity level. The research demonstrates that the severity of stressful life events and use of underlying stress management practices impact the probability of acute MS relapse and severity of MS related symptoms(77, 78). Exercise and the lifetime of physical activity influences nerve growth factor production(62-65) and risk of developing and/or the severity of neurodegenerative disease (79-83).

Conclusion

In summary, dietary interventions such as the Swank Diet, the Wahls™ Diet and the Wahls Elimination Diet influence the risk of developing and the severity of autoimmune and neurodegenerative diseases through multiple mechanisms, including higher levels of nutritional sufficiency in the diet through the triage theory, favorable shifts in the microbiome, and favorable gene expression.

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Dr. Terry Wahls is a clinical professor of medicine at the University of Iowa where she conducts clinical trials. The focus of the research is the impact of diet and lifestyle on chronic disease with a particular focus on multiple sclerosis and amyotrophic lateral sclerosis.

Her interest in using dietary and lifestyle interventions developed as result of her own health challenges. She is also a patient with secondary progressive multiple sclerosis, which confined her to a tilt-recline wheelchair for four years. Dr. Wahls restored her health using a diet and lifestyle program she designed specifically for her brain and now pedals her bike to work each day. This has led to the development of a research program to understand the mechanisms that underlie her recovery. She collaborates with other researchers to investigate how diet and lifestyle changes impact gene expression, metabolomics and the microbiome.

In addition she teaches the public about the benefits of a nutrient dense diet, stress reducing practices and increasing physical activity. She is the author of The Wahls Protocol: How I Beat Progressive MS Using Paleo Principles and Functional Medicine, The Wahls Protocol: A Radical New Way to Treat All Chronic Autoimmune Conditions Using Paleo Principles (paperback), and the cookbook The Wahls Protocol Cooking for Life: The Revolutionary Modern Paleo Plan to Treat All Chronic Autoimmune Conditions.

You can learn more about her work from her website, www.terrywahls.com. She conducts clinical trials that test the effect of nutrition and lifestyle interventions to treat MS and other progressive health problems. She also teaches the public and medical community about the healing power of the Paleo diet and therapeutic lifestyle changes that restore health and vitality to our citizens. She hosts a Wahls Protocol Seminar every August where anyone can learn how to implement the Protocol with ease and success. Follow her on Facebook (Terry Wahls MD) and on Twitter at @TerryWahls. Learn more about her MS clinical trials by reaching out to her team MSDietStudy@healthcare.uiowa.edu.

Clinical trials in which Dr. Wahls research team is participating

The link to the National MS Society funded study

http://www.nationalmssociety.org/About-the-Society/News/National-MS-Society-and-University-of-Iowa-Launch

Two studies in Bastyr University that ask patients with MS or Parkinson's disease about whether they are following the Wahls™ diet.

http://bastyr.edu/research/studies/complementary-alternative-medicine-care-multiple-sclerosis-cam-care-ms

http://bastyr.edu/research/studies/complementary-alternative-medicine-care-parkinsons-disease-cam-care-pd

Links to two MS papers by Dr. Terry Wahls

https://www.dovepress.com/randomized-control-trial-evaluation-of-a-modified-paleolithic-dietary--peer-reviewed-article-DNND

https://www.dovepress.com/multimodal-intervention-improves-fatigue-and-quality-of-life-in-subjec-peer-reviewed-article-DNND

DAVID BRADY

ND, DC, CCN, DACBN

Functional Models of Autoimmune Disease; Molecular Mimicry, the Hygiene Hypothesis, Stealth Infections, and Other Potential Drivers of an Epidemic.

*Author: David M. Brady, ND, DC, CCN, DACBN**

*University of Bridgeport, Division of Health Sciences, Human Nutrition Institute, Bridgeport, CT, USA

Abstract:

Autoimmune disorders have been on a steep rise in the industrialized countries over the past several decades and while research has been starting to develop a detailed understanding of pathophysiology and many of the underlying mechanisms, any meaningful incorporation of this information into clinical medicine has been painfully slow. Concepts of molecular mimicry, the hygiene hypothesis, intestinal hyper-permeability (leaky gut syndrome) and aggressive use of predictive antibody testing are explored in this article with examples given on how emerging information on these phenomena may aid the clinician in a new, more proactive, approach to management of these conditions.

1.0: Introduction

There is simply no doubt that the incidence of autoimmune disorders has been rising sharply over the past several decades in the Western industrialized countries, particularly the United States (See figure 1) (1). A broad array of disorders considered immune-dysregulatory and autoimmune in nature, encompassing both those classically categorized as Th1 and Th2-dominant, are included in this phenomenon. The question is why has there been such a sharp rise in the incidence of these disorders? The answers may very well be found in the current medical research, but you would probably never know it by visiting a doctor. This may be because this situation serves as an example of the giant chasm that often exists between medical research, which is often outstanding, and the practice of clinical medicine, which often leaves quite a bit to be desired when it comes to the management of chronic disorders with high morbidity but low mortality.

The typical allopathic clinical approach to autoimmune disorders focuses on the management of symptoms with various anti-inflammatory medications and often the use of chemotherapeutics, and very potent immunosuppressive agents with nasty potential side-effects like leukemia and lymphoma (2). While these approaches admittedly can provide substantial symptomatic relief to the patient, they do not really get to the cause of these conditions and some research suggests that these approaches may result in a furthering of the pathological process. However, modern research into autoimmune phenomenon suggest radically different approaches may be required to reverse the above cited trends, including a strong emphasis on very early detection with predictive auto-antibodies, a focus on optimizing gastrointestinal mucosal immune function and the microbiome, eradication of infectious agent triggers with antimicrobial therapy, and even the seemingly bizarre use of parasitic agents therapeutically. Some of these concepts have a long history in naturopathic and functional models of medicine, but now are emerging as hot areas of emphasis in mainstream medical research journals and investigative communities in immunology.

2.0: Molecular Mimicry

The concept of molecular mimicry is really a simple one, and it is an area attracting considerable research related to the genesis of autoimmune disorders. Simply stated, environmental exposure to specific antigens (including dietary peptides and those expressed by microbes), can in genetically susceptible individuals induce cross-reactions with structurally similar amino acid motifs associated with specific host tissues. There are now multitudes of associations that have been firmly established between immune incompatibility with specific dietary-derived antigens, as well as the overgrowth of certain opportunistic and pathogenic gastrointestinal bacteria, and the presence of specific autoimmune disorders (See table 1)(3). While some of these associations have been known for quite some time, mechanisms of causality are rapidly being established in the research. However, patients suffering from disorders like rheumatoid arthritis (RA), ankylosing spondylitis (AS), and autoimmune thyroiditis (i.e., Hashimoto's or Grave's disease) who visit a rheumatologist or endocrinologist do not routinely have stool analysis of their GI microbiota or food sensitivity testing performed. This is ironic, particularly in the case of opportunistic microbial overgrowth in the gut, as the conventional medical paradigm typically assumes an infectious cause, doesn't it? Perhaps this is just another example of resistance to significant change in clinical approach within medicine, even in the face of compelling evidence to do so, as it would then require a least a passive admission that something so seemingly simple was missed for so long.

Pishak et al have demonstrated that the mucous membrane of healthy people is colonized by Bifidobacteria, Lactobacilli, Bacteroides, Escherichia and Enterococci; as contrasted with the mucous membrane in RA subjects which is mainly colonized by aerobic opportunistic conventionally pathogenic enterobacteria (i.e., enteropathogenic Escherichia, Citrobacter, Enterobacter, Klebsiella, etc.), Staphylococci, Enterococci and other anaerobic bacteria (Bacteroides, Peptococci, Peptostreptococci, etc.) (4). They have also reported the observed phenomenon that as RA exacerbates and then enters remission, which is a common occurrence across the spectrum of autoimmune disorders, the composition of the subject's GI microbiota correspondingly also changes between the aberrant pattern detailed above and the one typical of normal subjects. The data of Tiwana et al suggests an increased immune response to Klebsiella in patients with AS, ulcerative colitis (UC), and Crohn's disease (CD) and to Proteus in patients with RA (5). Alan Ebringer and his group in the United Kingdom have established over the course of many years that a substantial percentage of patients diagnosed with RA have chronic stealth infection with Proteus mirabilis in the upper urinary tract (6). His group has also established the specific amino acid motifs of cross-reaction between the Proteus hemolysin and the RA-associated HLA-DR molecules, as well as those between the Proteus urease enzyme and hyaline cartilage, containing type XI collagen, the type only found in the small joints affected in RA. His successful treatment protocol includes antibiotic therapy, such as ciprofloxacin (sometimes in combination with NSAIDs, DMARDS, and immunosuppressive agents as needed), with the added use of natural blocking agents such as cranberry juice, vitamin C for urine acidification, and plenty of fluids (7).

Oral bacterial infection with Porphyromonas gingivalis, the primary cause of periodontal disease, may also play a role in peptide citrullination, theorized to be involved in the loss of self-tolerance and development of autoimmunity in RA, according to Liao et al (8). Clearly one of the challenges to the acceptance of bacterial and viral agents as the cause of these autoimmune diseases has been that there is no universally observed association or one specific universally-causative agent. This issue is addressed head-on in research by Harkiolaki et al using a mouse model of multiple sclerosis (MS) when he states: "We show that a microbial peptide, common to several major classes of bacteria, can induce MS-like disease in humanized mice by cross-reacting with a T cell receptor

(TCR) that also recognizes a peptide from myelin basic protein, a candidate MS auto-antigen. Structural analysis demonstrates this cross-reactivity is due to structural mimicry of a binding hotspot shared by self and microbial antigens, rather than to a degenerate TCR recognition. Thus, these data suggest a possible explanation for the difficulty in incriminating individual infections in the development of MS."(9). A similar phenomenon is also likely in play across a multitude of autoimmune disorders, and is not something unique to MS.

Researchers have now gone beyond establishing mere associations between the presence of various microbes and autoimmune disorders. Some have actually experimentally induced autoimmune disease by infecting animals with specific pathogens. Mazmanian et al inoculated a wild-type mouse with the bacterium Helicobacter hepaticus to create an experimental mouse version of the autoimmune disorder inflammatory bowel disease (IBD) (10). H. hepaticus activates Th17 cells which release cytokines associated with inflammation, such as IL-17, which cause symptoms of the disease. They then introduced Bacteroides fragilis expressing the polysaccharide A (PSA) to the gut of the animals where the PSA molecule was taken up by dentritic cells and presented on their surface, activating CD4 T cells and regulatory T cells (Tregs). The Tregs release IL-10 which suppresses the inflammatory action of IL-17, alleviating the IBD in mice. In summary, the researches induced autoimmune disease by introducing specific bacteria to the gut, and resolved it by introducing another, making a compelling argument for a causal relationship between the GI microbiota and autoimmune activity.

Autoimmune thyroid disorders also have been linked to bacterial and viral infections, mainly GI overgrowth of the opportunistic organism Yersinia enterocolitica. Petru et al state; "Yersinia shows on its surface saturable binding sites for TSH. TSH receptor antibodies could be produced in selected individuals having been infected with bacteria showing TSH receptors. It may, therefore, be assumed that the gram-negative bacterium Yersinia enterocolitica may have an active part in triggering immunogenic thyroid diseases." (11). Other researchers have shown a much higher prevalence of Yesinia serum antibodies in patients with thyroid disease versus controls. However, once again, there is no universal causality established, as autoimmune phenomena is a complex issue and seems to be potentially fueled by a multitude of potential antecedents, triggers, and mediators. For example, dietary antigens have also been linked to autoimmune thyroid disease. Celiac patients have approximately 10 times the rate of auto-immune thyroid diseases (such as Hashimoto's thyroiditis and Grave's disease) as non-celiac individuals, reflective of the affinity of gluten-gliadin antigen-antibody complexes for thyroid tissue (12). It may be no coincidence that the emergence of an apparent epidemic of autoimmune diseases has corresponded with the ever-increasing consumption of poor-quality modern processed foods known to both negatively alter the GI microbiome and to contain a constant (often hidden) stream of offending dietary antigens, including gluten-containing grains.

While all of these associations may be interesting to researchers, what does this really mean to a clinician? Some critics would argue that there is a lack of interventional data to suggest eradication of these associated organisms and/or avoidance of these dietary antigens positively affects patient outcomes. This may be true in some instances, but it has been well established, for instance, by Ebringer that successful treatment of Proteus clinically helps those with RA (7), and dietary elimination of gluten-containing grains is entirely accepted as the most viable intervention in Celiac disease. One potential issue in play is that by the time a patient is diagnosed with autoimmune disease there is often already substantial host-tissue damage. Perhaps the horse has already left the barn? However, what if potential triggers were routinely screened for and removed by health care providers, particularly in those with a family history of autoimmune disorders? The entire course of the disorder might be favorably altered, and many of these disorders might potentially never emerge clinically. In the naturopathic

and functional medicine models, there is a strong emphasis on both early detection and interventions that target the underlying pathophysiologic basis and underlying dysfunction of a disease process. Therefore, in these models the goal is to take clinical actions to reduce the potential for the disease process to progress. This also seems to intuitively make sense even in those who already have established disease; even though you may not be able to undo the damage already done, you can likely - if nothing else- slow down the train. This is particularly true since the interventions required pose little or no risk and are also relatively inexpensive; including probiotics, antimicrobial botanicals and volatile oils, mucosal-supporting nutrients and botanicals, and dietary modulation. Substantially improved molecular methods to assess the GI microbiota, utilizing PCR-DNA analysis, are also now available to clinicians at relatively low cost with rapid turn-around time (13).

3.0: The Hygiene Hypothesis

The concept of the hygiene hypothesis is also one that is quite simple, with the complexity being in the details. The thought that we have induced dysregulation into our immune system's by virtue of living in too clean of an environment and the over eradication of infection is not new (See figure 1), but it has gained favor with researchers who have begun to work out exactly why this may be the case. Some of these concepts were elegantly addressed by Weiss in an editorial in the New England Journal of Medicine entitled Eat Dirt-The Hygiene Hypothesis and Allergic Disease (14). While there is no doubt that modern public health measures, such as adequate sewage systems, water treatment, the use of antibiotic agents, and various other aspects of modern hygiene have lessened deadly infectious outbreaks and have prevented unnecessary deaths. However, as with most things, there is a yin and yang. This "new clean world" has likely resulted in a lack of adequate sampling of our environment, including a lack of exposure to all of the microbes that we share our planet with, particularly while we are young and our immune systems are developing the delicate balance between adequate defense and tolerance. In a 2010 paper in Nature Reviews-Immunology entitled Farm Living-Effects of Childhood Asthma and Allergy authors Mutius and Vercelli state: "Numerous epidemiological studies have shown that children who grow up on traditional farms are protected from asthma, hay fever and allergic sensitization. Early-life contact with livestock and their fodder, and consumption of unprocessed cow's milk have been identified as the most protective exposures. Studies of the immunobiology of farm living point to activation and modulation of innate and adaptive immune responses by intense microbial exposures and possibly xenogenic signals delivered before or soon after birth"(15). Does this mean that our children who are: 1) growing up in more urban and suburban environments; 2) living in comparatively sterile homes; 3) drinking chlorinated water; 4) being bathed and scrubbed daily with anti-bacterial soap; 5) not being allowed to play in the dirt; 6) being given antibiotics every time they have a sniffle… are actually being harmed from an immunologic perspective and will carry this dysfunction with them throughout their entire lives? This is likely the case, and one of the reasons why, as parents of two young boys, my wife and I constantly try and balance the need for cleanliness with allowing them to be children and dig in the dirt, play in the stream in our backyard, and otherwise sample their living environment.

4.0: The Role of Parasites

As reported by David Gutierrez in NaturalNews, researchers in a study conducted at the University of Nottingham, point out that humans and gastrointestinal parasites might have co-evolved in a way that the parasites actually help regulate the human immune system to prevent allergies (16). They believe that over the course of millions of years, gastrointestinal parasites have evolved the ability to suppress the human immune system as a survival mechanism. Because parasitic infestation has been so common throughout human evolutionary history, the human immune system has in turn evolved to compensate for this effect. This means that if the parasites are re-

moved, the immune system may actually function too strongly, resulting in maladaptive immune responses such as asthma, allergies, and eczema. To test this concept the researchers studied over 1,500 children in rural villages in Vietnam where parasitic infestation with hookworm is extremely common and allergies are not. Eradication of parasitic infection resulted in skyrocketing incidence of allergy, including dust mite sensitivity, supporting the hypothesis that parasites were modeling their immune response.

With issues such as the hygiene hypothesis, and the role of parasites in immune function in mind, gastroenterologist and researcher Dr. Joel Weinstock, originally at the University of Iowa, and now Tufts University, has performed novel work with subjects with inflammatory bowel disease (IBD) (17). IBD was unheard of before the 20th century. Beginning of 20th century incidence is thought to be about 1:10,000 and is now 1:250. Similar data exists with the incidences of asthma, hay fever, DM, MS, etc. Weinstock conducted various studies of IBD patients and treated them with the therapeutic parasite Trichuris suis, a porcine whipworm, which was an ideal choice as it only remains viable in the human GI tract for a short time and must be continually administered. The organism, when introduced into patients with IBD; 1) induced changes in regulatory T cell function; 2) blocked T cell proliferation; 3) altered cytokine production and expression of innate immunity; 4) altered the intestinal flora; and 5) generally produced a lessening of symptoms and severity of disease. Pharmaceutical agents are now being developed along these lines to treat IBD.

5.0: Intestinal Hyper-permeability (aka: "Leaky Gut Syndrome")

Leaky gut syndrome for much of the past twenty years seemed something that just functional medicine doctors talked about. Not any longer! Prestigious researchers such as Alessio Fasano at the University of Maryland, have been researching the role of intestinal permeability in the pathogenesis of autoimmune disorders and bringing this concept full-speed to the conventional medical research community through his publications in top-tier immunology and gastroenterology journals (18). In a 2009 article in Scientific American he eloquently brought the topic to the lay audience with his article Surprises from Celiac Disease, where he described that his theory that leaky gut contributes to Celiac disease and autoimmunity was initially greeted with skepticism by his colleagues (19). Fasano has proposed that in order for autoimmune disease to manifest there must be three factors present, and he equates these to a triangle, or three-legged stool, where if any are not present the disease cannot exist. These three factors include; 1) an environmental trigger (i.e., antigen), 2) genetic susceptibility (i.e., an HLA pattern that is particularly efficient at presenting the antigen to the immune cells, such as the presence of the HLA-DQ2 and HLA-DQ2 pattern in Celiac disease), and 3) intestinal hyper-permeability (i.e., "leaky gut syndrome"). He goes on to opine that by far the easiest of these three factors to alter clinically is intestinal permeability. Much of his work involves the study, and future therapeutic manipulation, of a protein which alters intestinal permeability by the name of zonulin.

Sapone et al, from a paper in Diabetes in 2006, expands on the role of zonulin and leaky gut in autoimmune disorders saying, "Zonulin, a protein that modulates intestinal permeability, is upregulated in several autoimmune diseases and is involved in the pathogenesis of autoimmune diabetes. Zonulin upregulation seems to precede the onset of the disease, providing a possible link between increased intestinal permeability, environmental exposure to non-self antigens, and the development of autoimmunity in genetically susceptible individuals (20)". Fasano summarizes the role of intestinal mucosal health and hyper-permeability in autoimmunity best in a 2005 paper when he states, "Together with the gut-associated lymphoid tissue and the neuroendocrine network, the intestinal epithelial barrier, with its intercellular tight junctions, controls the equilibrium between tolerance and immunity to nonself-antigens. When the finely tuned trafficking of macromolecules is dysregulated in genetically

susceptible individuals, both intestinal and extraintestinal autoimmune disorders can occur (18)."

Functional medicine and naturopathic physicians, and other nutritionally-minded providers, have been addressing the issue of leaky gut for a long time with effective natural agents, including; L-glutamine, N-acetyl-glucosamine, anti-inflammatory botanicals and bioflavonoids, mucilaginous herbs, zinc-carnosine, omega-3-fatty acids and more. However, one popular nutrient that is used frequently as an immune modulator in autoimmune conditions is vitamin D. However, most clinicians are not aware of the role vitamin D plays directly in intestinal permeability. According to Kong et al in their 2008 paper entitled Novel Role of the Vitamin D Receptor in Maintaining the Integrity of the Gastrointestinal Barrier, "In vitro experiments demonstrate that the VDR mediates the activity of 1,25(OH)2D3 that induces junction protein expression and strengthens the tight junction complex. These data are consistent with, and explain at least in part, the observation reported in the literature that vitamin D deficiency is linked to increased incidence of IBD in human population (21)."

Another possible role for vitamin D in the treatment of autoimmune disease, including MS, involves antimicrobial action. In addition to the previously cited findings by Harkiolaki et al regarding molecular mimicry induced by various GI bacteria in MS (9), researchers like Dr. Charles Stratton at Vanderbilt University have made clear associations between MS and Chlamydia pneumonia (22), and others, including Dr. Donald Gilden, have implicated various viral triggers in MS (23). It has also been shown that the human cathelicidin antimicrobial peptide (CAMP) gene is a direct target of the vitamin D receptor and is strongly up-regulated in myeloid cells by 1,25 dihydroxyvitamin D3 (24). Meaning, as vitamin D levels rise, so does the production of this endogenous antimicrobial peptide in the body, and this may account for some of the clinical benefit observed with vitamin D therapy in MS and other autoimmune disorders.

6.0: Predictive Autoantibody Testing (A True Application Preventive Medicine?)

In a 2007 Scientific American article entitled New Predictors of Disease, Abner Louis Notkins stated "Molecules called predictive autoantibodies appear in blood years before people show symptoms of various disorders. Tests that detect these molecules could warn of the need to take preventive action (25)." While some of these tests have been used for many years in a very selective manner, often simply to confirm the presence of a disease strongly suspected by clinical presentation and examination. However, the development and availability of low-cost autoantibody arrays has ushered in the possibility to use autoantibody testing in a much more proactive screening strategy to predict the future emergence of autoimmune disorders so that preventive action can be initiated early to short-circuit the disease process (26). Table 2 outlines some of the available predictive autoantibody tests, their positive predictive value (PPV), and the years before clinical diagnosis that they generally appear in the blood of subjects with specific disorders (27-29).

According to Aristo Vojdani, Ph.D. (30), autoantibodies could:

- Predict the risk of falling ill
- Project the probability of contracting a particular disease so that the potential patient could consider preventive therapy:

- Primary prevention: Remove environmental factors that trigger disease
- Secondary prevention: Modulate the destructive process before onset of clinical symptoms

• Anticipate the timing of a disorder, revealing how soon a disease is likely to cause symptoms

• Project the course of a disease

- Predict the severity and probable rate of progression of a disease

• Classify the disease

- In a patient with an established disease, autoantibodies can help define the nature of the condition as autoimmune or non-autoimmune.

As inexpensive tests for predictive autoantibodies continue to be developed, they could become part of a routine check-up, particularly by preventive physicians such as naturopathic and functional medicine physicians.

7.0: Summary

It is hoped that this article will help the physician to develop a comprehensive conceptual framework from which to view autoimmune disease and to institute a new proactive clinical model from which to evaluate patients. Physicians should look for immune dysregulatory conditions with a strong emphasis on: 1) very early detection with predictive auto-antibodies; 2) a focus on optimizing gastrointestinal mucosal immune function and the microbiome; 3) the eradication of infectious triggers with antimicrobial therapy; 4) the detection and elimination of food sensitivities; and 5) the promotion of an anti-inflammatory lifestyle.

Author Biography:

Dr. David M. Brady is a Connecticut and Vermont licensed naturopathic medical physician, a doctor of chiropractic, and certified clinical nutritionist. He is the vice president of Health Sciences, director of the Human Nutrition Institute, and associate professor of clinical sciences at the University of Bridgeport. He is also the chief medical officer for Designs for Health, Inc. and Diagnostic Solutions Labs, LLC, and practices at Whole Body Medicine in Fairfield, CT, specializing in functional and nutritional medicine. He is the bestselling author of the book The Fibro Fix. Learn more at DrDavidBrady.com and FibroFix.com.

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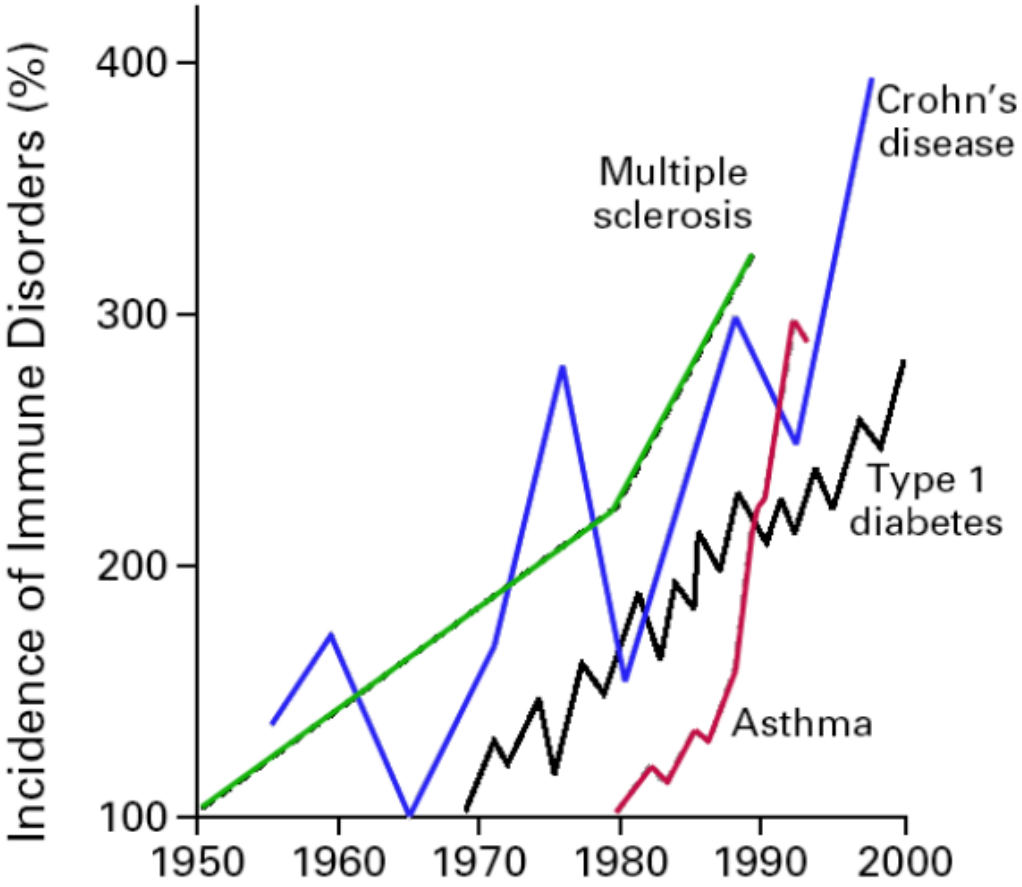
Microbe Species	Disorder
Klebsiella	Ankylosing Spondylitis
Citrobacter, Klebsiella, Proteus, Porphyromonas	Rheumatoid Arthritis
Yersinia	Grave's Disease & Hashimoto's Dz.
S. Pyogenes	Rheumatic Fever
Camphylobacter	Gullian Barre Syndrome
Chlamydia	Multiple Sclerosis
E. coli, Proteus	Autoimmunity in general

Disease/Disorder	Autoantibody Tests	Positive Predictive Value	Years Prior to Clinical Diagnosis
Addison's Disease	*Adrenal cortex antibodies	70	10
Celiac Disease	*Anti-tissue transglutaminase *Anti-endomysial antibodies *HLA-DQ2 or DQ8 antigens	50-60% 50-60% 100%	7
Hashimoto's Thyroiditis	*Anti-thyroid peroxidase antibodies (postpartum)	92%	7-10
Primary Biliary Cirrhosis	*Anti-mitochondrial antibodies	95%	26
Rheumatoid Arthritis	*Rheumatoid factor *Anti-cyclic citrullinated peptide	62-88% 97%	14
Scleroderma	*Anti-centromere antibodies *Anti-topoisomerase I antibodies	100%	11
Sjogren's Syndrome	*Anti-Ro and La antibodies	73%	5
SLE	*RNP, Sm, dsDNA, Ro, La, and cardioliptin antibodies	94-100%	7-10
Type I Diabetes	*Pancreatic islet cell *Insulin *65 kD glutamic acid decarboxylase *Tyrosine phosphatase-like protein	43% 55% 42% 29%	14



Figures and Table Legends and References

Figure 1: Rising Incidence of Autoimmune Disorders

From: Bach JF. The effect of infections on susceptibility to autoimmune and allergic diseases. N Engl J Med. Sep 2002;347(12):911-20.

Table 1: Selected Associations of Microbial Overgrowth and Autoimmune Disorders

Modified from: Mayes MD. Epidemiologic studies of environmental agents and systemic autoimmune diseases. Environ Health Perspect 1999;107(suppl. 5):743-748

Table 2: Selected Predictive Autoantibody Tests

Dr. David M. Brady

Dr. David M. Brady has over 25-years of experience as an integrative practitioner and academic. He is a licensed naturopathic medical physician in Connecticut and Vermont and a board certified clinical nutritionist. Dr. Brady is also a prolific author of medical papers and research articles on fibromyalgia and has dedicated a large part of his professional career to helping people recover from this mysterious disorder. He currently serves as the Vice President for Health Sciences, Director of the Human Nutrition Institute, and Associate Professor of Clinical Sciences at the University of Bridgeport in Connecticut. He maintains a private practice, Whole Body Medicine, in Fairfield, CT and is also the Chief Medical Officer for Designs for Health, Inc. and Diagnostic Solutions Labs, LLC. He is an internationally sought-after presenter on nutritional, functional and integrative medicine and has appeared on the speaking panel of the largest and most prestigious conferences in the field. Dr. Brady is a highly dedicated champion and advocate for patients suffering with a fibromyalgia diagnosis. He is the author of the book The Fibro-Fix from Rodale, Inc. and hosted the extremely popular and informative online Fibro-Fix Summit You can learn more at DrDavidBrady.com, FibroFix.com, and FibroFix-Summit.com.

GARRY D'BRANT

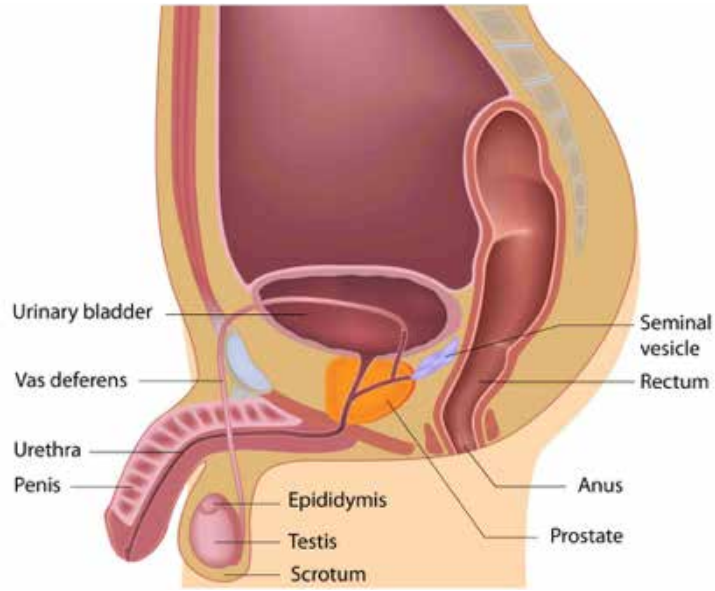
DC CTN LCSW DACBN CDN DIPLAC

The Prostate Gland:
Natural Ways to Nourish and Support the Prostate

The prostate gland is a small but powerful gland that plays a key role in men's bodies and their health. In this article I'll detail its function, natural ways to support it, and ways to prevent and deal with BPH, prostatitis and prostate cancer. (I won't discuss the conventional medical treatments for these various conditions, because these treatments are well documented.

This gland is actually made up of many tiny spongy ducts, fluid-producing glands and muscle that are surrounded by a sturdy but thin layer of connective tissue, encased by a buffering layer of fat. It's located beneath the urinary bladder and in front of the rectum in men and has a very important function in the male body: It produces some of the fluid that nourishes and protects sperm cells, especially following ejaculation. The part of the fluid produced by the prostate is made up of hormones and proteins including acid phosphatase, albumin, calcium, citric acid. prostate specific antigen (PSA) and zinc. The rest of this fluid is produced by the seminal vesicles, which are located just behind the prostate. The urethra, which runs through the prostate, carries urine and semen out of the body through the penis.

Figure 1: Anatomy of the male reproductive system:



In men in their 20's, the prostate is about the size of a walnut and few problems occur with it at this stage of life. By age 40, many men report having some prostate concerns, including increased pressure to urinate and/or restricted flow. It is estimated that by age 50, nearly 50% of men are experiencing some level of prostate difficulties. These difficulties occur due to the increased size of the prostate as men age. Normally walnut-sized, the aging prostate can grow to be the size of a golf ball or lemon in men at this age.

By age 80, approximately 80% of men experience significant prostate concerns, and the prostate may have grown to the size of a baseball. It is estimated that almost all men will experience some prostate problems through continued prostate growth if they live long enough.

There are three zones in the prostate. They are:

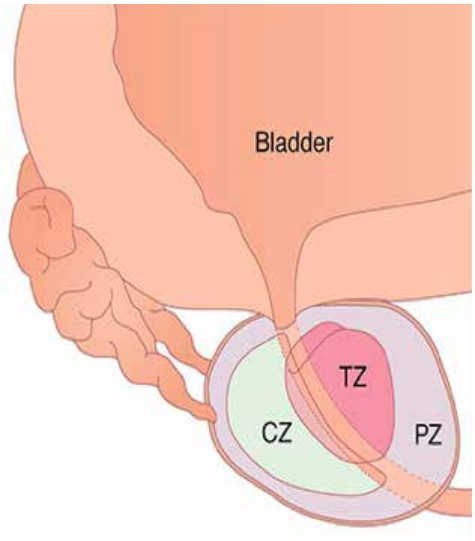
1. The peripheral zone (PZ), which contains most of the actual prostatic glandular tissue. When a man gets a digital rectal examination, the doctor is feeling the rear or back surface of the prostate, which is part of the peripheral zone.

2. The central zone (CZ), which is the area that encompasses the ejaculatory ducts.

3. The transition zone (TZ) is the area surrounding the urethra as it enters the prostate gland. It's fairly small in young men but grows as we age

Figure 2: Zones of the Prostate Gland

Hitachi Medical Systems America, Inc.



Prostate Conditions

Here are the three most common prostate conditions that men suffer from:

1. Prostatitis - Inflammation of the prostate, which can result in a host of significant symptoms. There are three main types of prostatitis, including acute prostatitis, chronic bacterial prostatitis and chronic non-bacterial prostatitis. Approximately 90% of all prostatitis cases fall into the chronic non-bacterial type, which occurs most typically in younger men (with an average age of 30). Painful urination is the most common presenting problem with this type. Other common symptoms include:

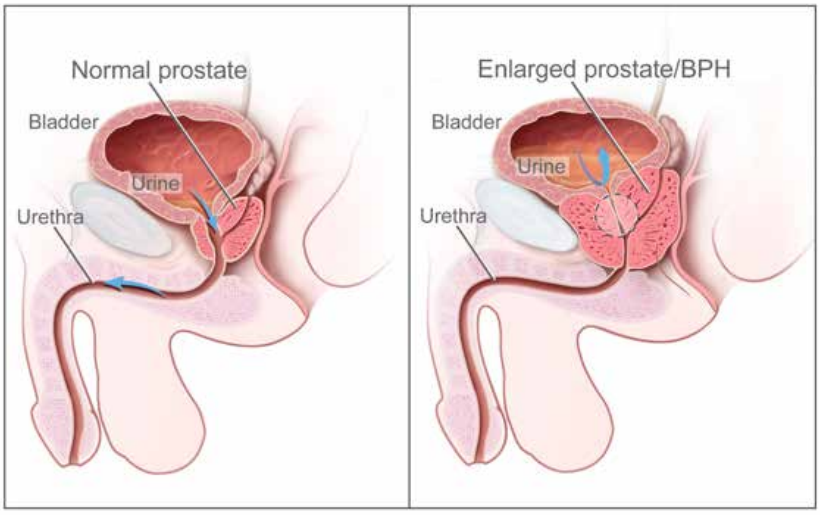
- pelvic pain
- low back pain
- difficulty in starting urine flow
- painful ejaculation
- perineum pain
- testicular pain
- fatigue
- flu-like symptoms
- depression
- erectile dysfunction

2. Benign Prostatic Hyperplasia (BPH) - An enlargement of the prostate, which occurs with age and may have a variety of symptoms associated with it, including:

- increased urge (pressure) to urinate
- difficulty in starting urine flow
- inability to stop urine flow at completion (dribbling)
- frequent stop and starting of urination
- pain during urination
- decreased strength of urine flow
- an urge to urinate again quickly after finishing
- waking up to urinate several times nightly

Most cases of BPH occur in the transition zone of the prostate gland. Only about 20% of prostate cancer occurs in this zone.

Figure 3: Comparison of Normal Prostate with Enlarged Prostate (BPH)



3. Prostate Cancer (CaP) - The most common type of cancer in men after skin cancer. Although this disease is rare in men under age 45, the older a man gets, the more likely he will develop it. If there's a family history of prostate cancer, this approximately doubles the risk. Annually, about 1.1 million men are diagnosed with prostate cancer worldwide, with about 300,000 dying each year. In American men, prostate cancer accounts for one-third of all new cancers. Prostate cancer is more common among African American men (they have a 60% higher risk than Caucasian men, and twice the risk of dying from it) and less common in Pacific Island, Native American and Native Alaskan men. Prostate cancer affects one man in every six, and a substantial percentage of men never have any symptoms. This is important in understanding that prostate cancer can be a very slow developing cancer that some men will never even know they had.

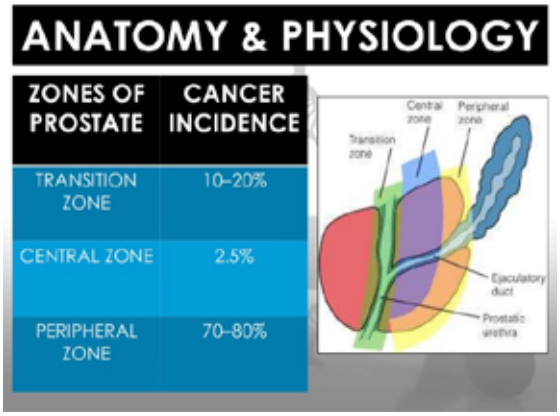
When there are symptoms associated with prostate cancer, they include:

- frequent urge to urinate, especially at night
- painful (often burning) during urination

- difficulty starting urine flow
- difficulty in being able to contain urination
- decreased strength of urine flow
- blood in urine or semen
- erectile dysfunction
- painful ejaculation
- pain or stiffness in lower back, hips or upper thighs

About 70 to 80 percent of prostate cancer occurs in the peripheral zone of the prostate.

Figure 4: Where Prostate Cancer Happens

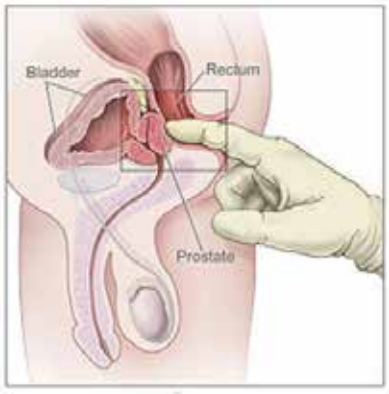


Screening Methods for Prostate Cancer

Digital Rectal Examination (DRE)

The digital rectal examination (DRE) is a prostate cancer screening technique most commonly performed by a urologist, in which the doctor inserts a gloved and lubricated finger in the rectum in an attempt to find any bumps, hard areas or unusual contours in the prostate gland. As mentioned earlier, prostate cancer often begins in the peripheral zone, which is in the posterior portion of the prostate gland and therefore is accessible through digital examination. It should be noted that this test is not foolproof, partly because almost 20% of prostate cancers occur in the transition or central zones, which make them impossible to feel from a DRE. So it should be used as a screening tool to help determine whether further testing (a biopsy) should be done.

Figure 5: Digital Rectal Examination



Prostate Specific Antigen (PSA)

I think it is important to mention prostate specific antigen (PSA) and the growing controversy within the international scientific and medical communities over its role in screening for and diagnosing prostate cancer. While it's safe to say that an elevated PSA level can indicate the presence of prostate cancer, it's not the only reason that an elevated PSA level may be present. Conditions such as BPH can also elevate PSA levels, as can older age, prostatitis, recent ejaculation, bike riding, certain urologic procedures such as cystoscopy, and some medications including the male hormone testosterone.

Research conducted within the past 10 years has shown that the previously held standard of an elevated total PSA value of over 4 nanograms per milliliter doesn't necessarily indicate the need for biopsy. If your PSA levels are above 4, it doesn't conclusively mean that you have CaP, and in fact about 15 percent of men have CaP with PSAs below 4. Studies have indicated that measuring the percentage of the free portion of PSA (fPSA), the part not bound to protein, may be an important marker in assessing CaP risk, along with determining PSA velocity (the rate of change in PSA levels).

Low fPSA is found in men with CaP, in contrast to men who don't have the disease. In men with borderline high total PSA (between 4 and 10 nanograms per milliliter), a lower fPSA reading is a strong corollary for the presence of CaP and should be followed more closely with a MRI guided biopsy.

Having a high PSA velocity (PSAV) is another strong indicator for the presence of CaP, and MRI guided biopsy should be considered as well. The general consensus among medical professionals is that the PSA levels should be measured at least 3 times over an 18 month period to get a more accurate understanding of the PSAV.

Further complicating the matter: Many men do not have their PSA levels checked for the first time until they are in their fifties, by which time either BPH or CaP may already be present. This makes it hard to identify exactly what role PSA plays in the detection and early development of CaP, since in many cases there is no baseline PSA reading in the individual being tested.

Inflammation and the Prostate Gland

In this author's opinion, inflammation is at the root cause of all three of the major conditions associated with the prostate gland discussed here.

A review of Western medical literature reveals a significant correlation between BPH and cardiovascular disease, in that they share three major risk factors: diabetes, hypertension and obesity. The diabetes connection may be the most studied, but it's my belief that as we see a greater percentage of the population becoming obese and diabetic, the connection between BPH, prostate cancer, and diet and metabolic functioning will be further solidified. Excessive insulin levels experienced by non-insulin dependent diabetics may be a significant factor in the enlargement of the prostate gland, whereas a diet high in red meat and dairy consumption can increase the risk of getting prostate cancer.

More recent research conducted in Europe indicates that for every 4 inches that's added on a man's waist, his likelihood of developing prostate cancer increases by up to 13 percent, and it increases his rate of mortality from it as well, by 18 percent.

Other lifestyle factors that impact prostate cancer risk (and have garnered the attention of researchers in the

past several years) include smoking and smoking history; alcohol consumption; body mass index; and exercise regularity and intensity. If you aren't currently smoking or don't have a history of heavy smoking, consume less than 2 alcoholic drinks daily, maintain a BMI between 19 and 25, and exercise at a moderate intensity for at least 150 minutes a week, then you're 40 percent less likely to die from prostate cancer then other men in the U.S.

If we work with the supposition that inflammation is at the root cause of all three of the major prostate dysfunctions described above, then our exploration of natural substances that support and nourish the prostate gland will start there. Many of the natural products described in the following section will have benefit for all three conditions, some more so than others.

Natural Substances That Support and Nourish the Prostate Gland

1. Zinc -

Figures 6 through 14: Excellent food sources of zinc

Oyster, white mushroom, spinach, pumpkin seeds, lean pork, roast beef, toasted wheat germ, cashews and chickpeas.

Zinc levels tend to decrease in men over 50. This is important because the prostate gland relies heavily on this trace mineral to stay healthy and vital. Zinc levels are found in substantial concentrations inside the healthy prostate gland—in fact, these levels have been found to be much higher in the cells of the prostate gland than in those of any others tissue in the body, indicating that adequate levels of the mineral may play a significant role in maintaining prostate health.

The presence of adequate zinc increases sperm count and mobility. It also indicate lower levels of estrogen and prolactin, thereby protecting sensitive prostate tissue from hormonal damage.

Food sources of zinc include beans, beef, chicken, dark chocolate, mushrooms, nuts, oysters, pork, pumpkin seeds, spinach and squash seeds.

Supplementing with a minimum of 15mg of a bioactively available form of zinc daily (Albion zinc arginate, for example) is recommended to somewhat reduce the risk of invasive prostate cancers. However, this level of supplementing also showed a higher rate (66%) of reduction in risk of advanced prostate cancer, which suggests that supplementation with zinc may be helpful to some men with this condition.

Prostate cancer cells appear to lose their ability to accumulate zinc, whereas healthy prostate tissue has approximately 10 to 15 times higher concentration than other body tissues, thereby suggesting that keeping zinc levels high in men may be a critical factor in preventing prostate cancer. It is recommended that men over 40 consider supplementing with zinc daily.

Recommended dose is between 15 to 50 milligrams daily.

2. Pygeum Bark (Pygeum Africanum)

Figures 15 & 16: African Cherry Tree and its Bark

G Baldwin & Co.

Pygeum is found in the bark of the African Cherry tree and is rich in phytosterols. Phytosterols are derived from plants and can inhibit the absorption of cholesterol from the small intestines, thereby effectively lowering low density lipoprotein (LDL) levels. Beta-sitosterol, one of these phytosterols, shows a significant anti-inflammatory action in the prostate by inhibiting the production of prostaglandins some of which are naturally pro-inflammatory.

Other components of pygeum that are beneficial to the prostate gland include pentacyclic triterpenes, which reduce inflammatory enzymes and decrease edema, and ferulic esters, which decrease levels of prolactin (a hormone that increases testosterone uptake by the prostate gland). These components work synergistically to negate the biochemical and physical changes associated with BPH.

Pygeum has also been shown to be effective in the treatment of Prostatitis, which can develop from infectious or non-infectious causes. Furthermore, pygeum has demonstrated some benefit for men experiencing sexual and reproductive dysfunction.

Recommended dose is between 250 to 400 milligrams daily.

3. Saw Palmetto (Serenoa repens)

Figures 17 & 18: Saw Palmetto Plant and Saw Palmetto Berries

GreenMedInfo.com

A species of North American palm with berries is historically one of the most widely used natural plant remedies for treating the prostate gland. It may benefit the prostate by several actions, including blocking the conversion of testosterone to its powerful androgen metabolite dihyrdrotestosterone (DHT). This androgen, along with excess accumulation of estrogens, is believed to be responsible for many hormonally induced cancers in men, such as prostate cancer as well as BPH. DHT is converted from testosterone by the enzyme 5-alpha-reductase.

Research has demonstrated that saw palmetto is an effective inhibitor of 5-alpha-reductase, which means that less DHT will be produced, thereby alleviating the symptoms of BPH. Studies have shown that saw palmetto is as effective in inhibiting 5-alpha-reductase as the drug finasteride (Proscar), one of the most commonly used drugs for treating BPH.

Saw Palmetto—when combined with other nutrients like Stinging Nettles, lycopene and selenium—has been shown to help men reduce urine flow issues and support healthy erectile function.

Recommended dose is between 300 to 500 milligrams daily.

4. Lycopene

Figures 19 through 26: Excellent food sources of lycopene

Tomato, papaya, red grapefruit, red and yellow sweet peppers, guava, carrots, asparagus, mango

Lypocene is found most abundantly in tomatoes and tomato products and is significantly higher in cooked tomatoes rather than raw ones This naturally occurring carotenoid is responsible for giving fruits and vegetables a reddish color, and can also be found in apricots, carrots, mangos, papayas, pink grapefruits, pink guavas, red cabbage, sweet red peppers, and watermelons. Additional food sources of lycopene include: asparagus, chili powder, dried herbs, rose hips and strawberries.

Lycopene has a significant impact on the prostate gland in that it seems to deter the growth of normal prostate cells; in one study, men with the highest blood level concentrations of lycopene demonstrated a significantly reduced risk of getting prostate cancer. Furthermore, CaP patients who were supplemented with lycopene showed a decreased rate of prostate cancer growth.

Lycopene works by reducing inflammation through reduction of oxidative stress on prostate tissue. It may also slow the rate of new blood vessel growth (angiogenesis), which is a primary way that prostate cancer develops.

Recommended dose is between 5 to 15 milligrams daily.

5. Stinging Nettle (Urtica dioica)

Figures 27 & 28: Stinging Nettles Plant and Close Up View

Oregon State University

The root portion of stinging nettle seems to have the most anti-inflammatory effect and has therefore been most effective in treating BPH. One of the active ingredients in stinging nettle root that seems to have a potent effect is lignans (any class of polyphenolic compounds, including those found in plants that have significant antioxidant and estrogenic properties). Lignans have been shown to bind to the sex hormone binding globulin (SHBG), thereby displacing hormones such as testosterone, DHT and estrogen. The important result of these actions is to effectively limit prostatic hyperplasia.

Additionally, the rich levels of mineral content in stinging nettle root may act to strengthen the pelvic connective tissue, thereby further limiting the development of BPH.

Recommended dose is between 200 to 500 milligrams daily.

6. Pomegranate (Punica granatum)

Figure 29: Pomegranate fruit and seeds

Pomegranate is a fruit bearing shrub that got its origins in modern-day Iran. It's been cultivated since ancient times throughout the Mediterranean region and in India. Its juice is most commonly associated with health benefits, but the peel and oil also possess anti-cancer properties. Specifically, pomegranates interfere with tumor cell growth, cell development cycles, invasiveness and the development of new tumor blood vessels.

Research has indicated that pomegranate inhibits pro-inflammatory DNA-related protein by inducing beneficial

gene expression. Furthermore, the fruit reduces the production of cancer stimulating androgen receptors in prostate cells, and has been shown to suppress testosterone synthesis.

Recommended dose is 100 to 120 milligrams daily.

7. Pumpkin Seed (Curcubita pepo)

Figure 30: Pumpkin seeds

nuts.com

Pumpkin seed oil has been demonstrated to inhibit testosterone as well as DHT's effect on stimulating prostate cell growth, thereby decreasing the incidence and severity of BPH. Pumpkin seed oil also is rich in carotenoids and omega-3 fatty acids, both of which reduce the likelihood of developing BPH. This oil is also a great source for the mineral zinc, which is beneficial in preventing prostate cancer.

Although not a great source of vitamin E in the form of alpha-tocopherol, pumpkin seed oil nevertheless has been shown to provide vitamin E in a wide variety of forms (alpha-tocopherol, gamma-tocopherol, delta-tocopherol, alpha-tocomonoenol and gamma-tocomonoenol), which may contribute to its significant antioxidant capacity, thereby reducing inflammation.

Recommended dose is between 50 to 80 milligrams daily.

8. Curcumin (Curcuma longa)

Figure 31: Curcumin Root and Powder

GreenMedInfo.com

This a naturally occurring chemical compound found in the spice turmeric. Turmeric, with its vibrant orange, yellowish color, has long been associated with Asian cultures both for its uses in food and beauty products.

Curcumin may be a true superstar in the field of antioxidants, with many important health benefits for the entire body and very definitely for the prostate gland. Research conducted with a group of BPH sufferers who were given curcumin supplementation showed significant reduction in symptoms such as urinary infections, difficulty in urination and incontinence. It is believed that curcumin actually may inhibit the hormonal compounds that stimulate prostate growth.

In regards to prostate cancer, curcumin also shows great promise. It initiates apoptosis (cell death) of prostate cancer cells and controls inflammatory responses through the master regulator, nuclear factor-kappaB (NF-KB), which is a protein complex that regulates DNA transcription. Curcumin also disrupts the spread of cancer cells and lessens the metastasis of cancer cells in the prostate. And it slows the development of angiogenesis in prostate cancer cells, slowing the rate of cancer development.

Recommended dose is between 100 to 300 milligrams daily.

9. Green Tea (Camellia sinensis)

Figures 32 & 33: Green Tea Field and Individual Green Tea Plant

Green tea catechins (a type of flavonoid found in certain foods and rich in antioxidants), especially epigallocatechin-3-gallate (EGCG) have shown tremendous efficacy in preventing prostate cancer. One clinical trial demonstrated a 90% effectiveness rate on prostate cancer prevention in men with premalignant lesions who were given green tea catechins.

Green tea catechins, most predominantly EGCG, have shown their effectiveness in reducing the marker prostate specific antigen (PSA) and other tumor promoters such as vascular endothelial growth factor in research subjects. Additionally, those men suffering from prostate cancer who were tested and received green tea supplementation reported a higher quality of life than those who did not receive them.

Recommended dose is between 300 to 400 milligrams daily.

Soybean: (Glycine max)

Figure 34: Soybeans

These well known and versatile legumes are native to East Asia but are now grown throughout the world, and they're used to make tempeh, natto, soy paste, tofu, soy milk, soy sauce, miso, edamame and textured vegetable protein.

Multiple population studies of Asian men found that they had a lower risk and lower incidence of prostate cancer than men living in Western countries. The decreased risk rate for getting prostate cancer went from 42 to 75 percent lower in these studies. Interestingly, this protective effect from soy consumption was lost on second generation Asian men, whose parents moved to Western countries and ate less soy or abandoned it altogether.

The mechanism by which soy protects the prostate tissue appears to come from the isoflavones found in soy (genistein, diadzein and equol). Isoflavones are phtyoestrogenic compounds found in some plants, particularly red clover and soy ,which have been found useful in lowering blood lipid levels, ameliorating menopausal symptoms, protecting against osteoporosis and enhancing prevention of hormone-related cancers.

Animal studies have indicated and later human studies have supported that isoflavones inhibit prostate tumor growth by acting directly on the tumor cells themselves, and also by decreasing tumor neovasculature (growth of new blood cells). Genistein, in particular, showed a very definite effect in diminishing prostate cell proliferation.

Recommended dose is between 200 to 300 milligrams daily

An important consideration when thinking about soy supplementation is the potential risks associated with soy consumption. Soy is phytoestrogenic, which means that although derived from a plant, it has estrogenic properties that can cause hormonal imbalances.

Additionally, most soy grown in the world today is GMO, which means that it is not the same soybean that was eaten centuries ago. A genetically modified crop such as soy may have significant negative health effects that have not fully been studied or recognized, and organically derived soy should be sought at all times.

Lastly, soy allergy and/or intolerance is a well documented condition that affects thousands of people throughout the world. Many direct symptoms such as itching, hives and swollen throat can be seen within minutes of taking soy if a true soy allergy is present. However, if the person consuming soy is intolerant but not allergic to soy, symptoms may take a longer time to appear and can include, nausea, vomiting, diarrhea, headache, etc.

More Ways to Nourish the Prostate Gland

Other things to consider in supporting the prostate gland include using spices and herbs in combination, such as ginger, green tea, oregano and rosemary; this combination has been studied for its effectiveness in treating prostate cancer cell growth. One test result showed a 78 percent reduction in prostate cancer cell growth in lab experiments.

Another delicious way to help the prostate: Eat more garlic and scallions. Researchers found that men who ate more than 10 grams of garlic and scallions (roughly 3 cloves of garlic or 2 tablespoons of scallions) daily had a 50 percent decreased risk of prostate cancer, compared to men who ate less than 2 grams a day.

Developing a holistic plan for supporting and nourishing your prostate can involve taking herbs and nutrients. These can help treat an already existing condition or can be used in a preventative manner, given the large number of American men who suffer from some sort of prostate inflammation as they age.

Other areas to consider exploring include Chinese healing techniques such as Qigong and Tai chi for helping with energy blockages and strengthening the flow of chi and blood in the body. Taking Chinese herbs can also assist in removing stagnation (deficiency of blood/chi with subsequent slowing and pooling of those essences) from the body. Additionally, practicing yoga, meditation and mindfullness in one's daily life may be of use in restoring balance and lowering stress, which in my opinion is at the root of many of our modern-day diseases.

All of these practices, along with the herbs and nutrients described in this article, should be discussed and coordinated with the patient's holistic health practitioner. Each person's needs may vary, and lifestyle considerations as well as medications a person may be taking need to be evaluated in developing a truly nourishing prostate support program.

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Dr. Garry D'Brant is an award-winning alternative healthcare provider who has been in practice for over 39 years, providing compassionate and knowledgeable care to his patients. His private practice, D'Brant Infinite Wellness in Glen Cove, NY, includes chiropractic, body-centered psychotherapy, nutrition, naturopathic medicine, anti-aging therapies, and traditional Chinese medicine. Using a holistic "whole person" approach, Dr. D'Brant is passionate about his focus on balancing the physical, emotional, and spiritual aspects of each patient, helping them make whatever lifestyle adjustments are needed to optimize the conditions for peak function, and supporting them in believing in their own innate ability to heal themselves.

Dr. D'Brant is a licensed chiropractor, a certified dietician/nutritionist and clinical nutritionist, a certified traditional naturopath, and a licensed clinical social worker, as well as a 20-year student of Medical Qigong. He's a Diplomate of The American Chiropractic Board of Nutrition and of the Shanghai Research Institute of Acupuncture. Dr. D'Brant is also certified in and is a senior trainer in Primary Emotional Energy Recovery—a body-centered therapy founded by John Lee—as well as in Energetic Clearing Technique, a body-centered emotional release technique founded by Judith Johnson.

A featured presenter at the NAVEL Expo, Long Island's largest natural health expo, Dr. D'Brant has appeared numerous times on TV and radio and lectures nationally on a wide variety of natural health topics. He lives on Long Island, NY, and is the father of four. His comprehensive website on natural healing is drdbrant.com, and he can be reached at 516-609-0890

IZABELLA WENTZ
PHARMD, FASCP

Supporting a Patient with Hashimoto's Thyroiditis through Nutrition

Hashimoto's thyroiditis is an autoimmune condition that results in the destruction of the thyroid gland, eventually leading to hypothyroidism. Hashimoto's is the most frequently occurring autoimmune condition, with an estimated prevalence rate between 12% and 26% in the general population,1,2 and the leading cause of hypothyroidism in the United States, accounting for 90-97% of cases.1-3

Testing for Hashimoto's

Clinicians working with people with Hashimoto's should be aware of the primary tests used to diagnose and monitor the condition. Blood tests, thyroid ultrasound, as well as a biopsy of the thyroid gland can be used to diagnose Hashimoto's. Blood tests are the most accessible option and most commonly used method to determine a diagnosis of Hashimoto's.

The thyroid stimulating hormone (TSH) test is the most commonly utilized screening and monitoring test for thyroid disease. TSH is made by the pituitary gland, which sends signals to the thyroid to increase production of thyroid hormones when levels are low. An elevated TSH test is indicative of hypothyroidism but is not diagnostic of Hashimoto's.

In recent years, the National Academy of Clinical Biochemistry indicated 95% of individuals without thyroid disease have TSH concentrations below 2.5 µIU/L, and a new normal reference range was defined by the American College of Clinical Endocrinologists to be between 0.3 and 3.0 µIU/ml in healthy adults without thyroid disease. Elderly individuals over the age of 80, however, may have a TSH value that is above 2.5 µIU/ml without any evidence of autoimmune thyroid disease.4

Thyroid peroxidase (TPO) antibodies, and thyroglobulin (Tg) antibodies are the primary anti-thyroid antibodies detected in Hashimoto's thyroiditis and are present in 90% and 80% of those affected, respectively.5 These anti-thyroid antibodies indicate that there is an active autoimmune process happening in the thyroid gland. However, it can take many years before enough gland damage occurs to affect the thyroid's ability to adequately produce thyroid hormones and before a change in TSH is noted on lab testing. Thus, thyroid antibodies can be used to diagnose Hashimoto's and may be present for decades before a change in TSH is observed.5

Thyroid antibodies are thought to have a positive correlation with the aggressiveness of the condition, indicating a greater attack on the thyroid gland.6 Seronegative Hashimoto's has been recently described as a less aggressive version of the condition, where thyroid specific antibodies are not detected, however the hypoechoic pattern of the thyroid gland characteristic of Hashimoto's is found on thyroid ultrasound.7

Thyroid hormones can also be assessed. Most circulating thyroxine (T4) and triiodothyronine (T3) are protein-bound; unbound T4 and T3 are the active forms of the hormone available to the body. Total T4 and total T3 levels reflect both the bound and unbound hormones, while free T4 and free T3 testing measures just the active, unbound hormone levels.

A full thyroid work-up for people with Hashimoto's should include TSH, free T3, free T4 and thyroid antibodies (inclusive of TPO and Tg antibodies). A baseline thyroid ultrasound should also be utilized.

Symptoms

Many symptoms of Hashimoto's result from hypothyroidism and include the classical hypothyroid symptoms of cold intolerance, hair loss, fatigue, weight gain, forgetfulness, muscle aches, constipation, a loss of the outer third of the eyebrow, and infertility.

However, some individuals with Hashimoto's may also experience symptoms typically associated with hyperthyroidism, such as irritability, palpitations and anxiety due to a transient hyperthyroidism that results from a flood of thyroid hormones into the blood stream secondary to breakdown of thyroid tissue.

In addition to experiencing symptoms of hypo- and hyperthyroidism, many people with Hashimoto's also experience a variety of other inflammatory symptoms, especially gastrointestinal distress, such as irritable bowel syn-

drome (IBS), gastroesophageal reflux disease (GERD), diarrhea, constipation, bloating, rashes, allergies, adrenal fatigue, and nutrient deficiencies.

Furthermore, recent studies point to the role of high titer of thyroid antibodies resulting in symptoms such as distress, obsessive-compulsive symptoms and anxiety, even in euthyroid (having thyroid hormone levels within the normal reference range) subjects.8,9

Pharmacotherapy

The standard of care for Hashimoto's hypothyroidism is the use of thyroid hormone medications to bring a patient into the euthyroid state. As thyroid hormone receptors are present in every cell of the body, medication optimization is an important step in helping a person with Hashimoto's feel better.

The medication levothyroxine is the drug of choice per conventional treatment guidelines. Chemically, levothyroxine contains one tyrosine molecule with four attached iodine molecules and is often referred to as T4. T4 has been described as a pro-hormone, as it needs to be deiodinated in the body to produce liothyronine, a more physiologically and metabolically active thyroid hormone which contains three molecules of iodine (T3).

T3-containing medications, liothyronine sodium, are also available, as well as T4/T3 combination medications, including desiccated thyroid extract products, and compounded medications made by compounding pharmacists.

While treatment guidelines suggest that most Hashimoto's patients can be well controlled with levothyroxine,4 a new paper on the quality of life in people with Hashimoto's thyroiditis found that people with Hashimoto's thyroiditis may continue to experience symptoms despite levothyroxine treatment.10

In 2014, Dr. Wilmar Wiersinga, a Dutch endocrinologist and top thyroid researcher, stated that "Impaired psychological well-being, depression or anxiety are observed in 5–10% of hypothyroid patients receiving levothyroxine, despite normal TSH levels. Such complaints might hypothetically be related to increased free T4 and decreased free T3 serum concentrations, which result in the abnormally low free T4:free T3 ratios observed in 30% of patients on levothyroxine. Evidence is mounting that levothyroxine monotherapy cannot assure a euthyroid state in all tissues simultaneously, and that normal serum TSH levels in patients receiving levothyroxine reflect pituitary euthyroidism alone."11

New research supportive of the role of T3 in thyroid care is emerging, and a 2013 study conducted by the National Institutes of Health concluded that: "DTE (Desiccated Thyroid Extract) therapy did not result in a significant improvement in quality of life; however, DTE caused modest weight loss and nearly half (48.6%) of the study patients expressed preference for DTE over L-T4. DTE therapy may be relevant for some hypothyroid patients."12

In a survey of 2232 people with Hashimoto's, the majority reported feeling best with a TSH under 2.0 µIU/ml and showed a preference for products that contained both T4 and T3 hormones, such as natural desiccated thyroid or compounded T4/T3 medications.13

Thyroid hormone therapy should be individualized with the patient in mind. Each person with Hashimoto's should be evaluated by a physician who specializes in thyroid hormone optimization.

Goals of Integrative and Complementary Methods

While conventional treatment protocols offer many lifestyle interventions for the treatments of other chronic conditions, most primary care physicians receive very little training in lifestyle interventions for Hashimoto's.

A functional and integrative approach to Hashimoto's can address many of the residual symptoms experienced by people with Hashimoto's, reduce thyroid antibodies, and can in some cases even prevent the progression into other types of autoimmune disease. Additionally, through the use of functional medicine and integrative approaches, this writer has documented numerous Hashimoto's remission stories, resulting in thyroid antibodies becoming seronegative, often along with a reduced need for thyroid hormone replacement.14-21

Integrative Approach to Hashimoto's

New research from Dr. Alessio Fasano and colleagues has focused on the "three-legged stool of autoimmunity." Dr. Fasano has found that three primary factors need to be present in order for autoimmunity to develop: 1) genetic predisposition, 2) a trigger, and 3) intestinal permeability.

These three factors together create "the perfect storm" of autoimmunity, and it has been found that eliminating triggers or the intestinal permeability can lead to a remission of autoimmunity.22,23

It may take some detective work to identify triggers, and even the root causes of intestinal permeability – some root causes have not yet been identified, and we may not have the tools to resolve them, but helping to support a person's body though nutrition should always be the first approach to improving the outcomes of the condition. The integrative approach to helping people with Hashimoto's focuses on addressing nutrient depletions, food sensitivities, stress response, detoxification, and any underlying or chronic infections.21

Nutrition Support

Multiple nutritional approaches have been reported to help the prognosis of Hashimoto's and/or other autoimmune conditions, including a gluten-free diet, iodine-free diet, the Specific Carbohydrate Diet, GAPS Diet, paleo diet, autoimmune paleo diet, soy-free diet, dairy-free diet, low FODMAPs diet, and the Body Ecology Diet. Vegetable juicing and elemental diets may also play a supportive role.14-21, 24

The connecting thread behind these diverse dietary approaches is that they all remove various reactive foods. Most of the diets also include animal proteins, are more nutrient dense than the standard American diet, and eliminate processed foods. As many of these diets limit carbohydrates, they are also likely to be helpful for people with Hashimoto's due to blood sugar balancing effects.

Reducing the intake of goitrogenic vegetables, which can block the intake of iodine into the thyroid gland, has been a common recommendation for people with iodine deficiency hypothyroidism, however, as Hashimoto's is not an iodine deficiency-related thyroid condition, but rather an autoimmune condition, that recommendation is not relevant for most with Hashimoto's.25-27

Fluoride, which was historically used as a thyroid-suppressing agent due to its antagonistic effects with iodine, however, may be a relevant substance to avoid for those with Hashimoto's. Hypothetically, fluoride, when occupying iodine receptors, can initiate inflammation in the thyroid gland, acting as a catalyst in the autoimmune response. Using a reverse-osmosis water filter can be helpful in reducing one's exposure to fluoride.28-31

Blood Sugar Balance

According to a 2012 Polish study, "Carbohydrate metabolism disorders in the form of type 1 diabetes connected with an autoimmune process, as well as type 2 diabetes connected with the increase of the insulin resistance, occurred in average of half of the patients with Hashimoto's thyroiditis."32 Blood sugar imbalances can exacerbate the autoimmune response in Hashimoto's and may lead to increased levels of anxiety and thyroid antibodies. Balancing blood sugar levels should be one of the priorities for everyone with autoimmune thyroiditis. Reducing the intake of carbohydrates, excess fruits and sugars, while increasing the intake of healthy fats can be a helpful measure for people with Hashimoto's.

Food Sensitivities

People with Hashimoto's often present with numerous food sensitivities, and testing may show IgG antibodies to various food proteins. IgG antibodies are also thought to be the same types of antibodies that target the thyroid gland in autoimmune disease, thus removing IgG reactive foods may attenuate the IgG response to the thyroid gland.33

Gluten, the protein found in wheat, rye and barley, is a known trigger of intestinal permeability.

Various studies have looked at the rates of celiac disease in people with Hashimoto's. All of the studies have found celiac disease to be more common with Hashimoto's, but the incidence rates have varied.34-37 While a 2006

Brazilian study found an incidence rate of celiac disease at only 1.2% of people with Hashimoto's, a 2007 Dutch study found that 15% of subjects with Hashimoto's had Celiac disease.34,37 One study, focused on patients with co-occurring celiac disease and Hashimoto's, found that most people with these concurrent conditions were able to regain thyroid function—as manifested by a reduction of TSH, normalization of thyroid antibodies and a reduced need for medications—after implementing a gluten-free (GF) diet.37

In this author's experience, a small subset of clients have been able to achieve remission of Hashimoto's with a GF diet as the sole intervention. However, very little has been published on the topic of the effects of a GF diet in individuals with Hashimoto's who do not have celiac disease.

As there is no current research supporting the use of dietary interventions for Hashimoto's, with the exception of a GF diet for those with co-occurring celiac disease, during May 2015, this author conducted a survey of 2232 people with Hashimoto's who are readers of the www.thyroidpharmacist.com website. Seventy-six percent reported that they believed that they were gluten sensitive (another 16% of respondents were not sure).13

Most people that reacted to gluten reported feeling the reaction in their gut (constipation, diarrhea, cramping, bloating, nausea, gas, acid reflux, burning or burping) and in their brain, with symptoms such as headaches, dizziness, brain fog, anxiety, depression, fatigue and insomnia.13

Overall, 88% of survey respondents with Hashimoto's who attempted a GF diet felt better, with 86% reporting an improvement in digestive symptoms. Improvements in mood, energy levels and weight reduction were reported in 60%, 67%, and 52% of people with Hashimoto's who undertook a GF diet, respectively.13 Notably, only 3.5% of survey respondents reported being diagnosed with celiac disease,13 suggesting that a person with Hashimoto's does not have to have celiac disease to benefit from a GF diet.

Limiting sugar was reported as "helpful" for 81% of those surveyed. Additional common food sensitivities reported by survey respondents include soy, dairy, eggs, nuts, seeds, nightshades and grains. Survey results indicated that people with Hashimoto's may also be more sensitive to the effects of caffeine, which can exacerbate heart palpitations and anxiety.13

It should be noted that this sample was comprised of readers of www.thyroidpharmacist.com, and not the typical patients presenting at an endocrinology clinic. As the author advocates nutrition as an integral approach to Hashimoto's, it is possible that the respondents were biased towards a GF diet. Nonetheless, until more published research becomes available, these results can be used as a guide for clinicians helping people with Hashimoto's.

Nutrient Density

In addition to GF diets, the other most helpful dietary interventions included sugar-free, paleo, autoimmune paleo, grain-free, dairy-free, and low glycemic index diets. Survey respondents who tried these approaches reported feeling 75-81% better.13

Incorporating nutrient-dense "healing" foods also supported symptom improvement. Homemade bone-broth helped 70% of those that tried it, while green smoothies helped 69%, and fermented foods helped another 57%.13

While one study found that vegans had a lower incidence rate of hypothyroidism compared to lacto-ovo vegetarians and people eating the standard American diet,38 out of 292 survey respondents with Hashimoto's who attempted the vegan diet, 87 said it made them feel better, 83 said it made them feel worse, and 122 did not see a difference.13

In contrast, out of 1793 survey respondents with Hashimoto's who tried a GF diet, 88% (1580 respondents) reported that it made them feel better, less than 1% (13) that it made them feel worse, and 11% (200) did not see a difference.13

This author's clinical experience has shown that some individuals were able to achieve remission of Hashimoto's following the transition from a vegan diet to a paleo-like diet.

More research is needed on the role of specialized diets in autoimmune thyroid disease. Until then, clinical experience has indicated that the most helpful approaches have been found to be the GF diet, sugar free diet,

paleo diet, grain-free diet, dairy-free diet, autoimmune modified-paleo diet, and the low glycemic index diet.13

Food sensitivity testing, elimination diets and rotation diets may further improve outcomes.21

Nutrients Required for Proper Thyroid Function

Selenium, iron, vitamin A, vitamin E, the B vitamins, potassium, iodine, and zinc are all required for proper thyroid function. Other nutrients, although not directly involved in thyroid function, are also essential for proper immune, gut, liver and adrenal function.

People who are diagnosed with Hashimoto's should be tested for vitamin D, vitamin B12, and ferritin deficiency. While iodine deficiency is a known cause of non-autoimmune hypothyroidism, Hashimoto's does not seem to correlate with iodine deficiency. In fact, iodine excess has been recognized as a trigger for Hashimoto's, and an upper intake limit of 400 mcg of iodine per day has been suggested for those with Hashimoto's. Testing for the remaining nutrients required for thyroid function is not readily accessible, and clinicians have the option of relying on the use of clinical assessments, advanced functional medicine nutrient testing as well as multivitamin supplements. Supplements containing up to 150 mcg of iodine have been found to be tolerated by people with Hashimoto's without increasing thyroid antibodies.5,24,34-36

Vitamin D

Adequate Vitamin D levels have been associated with a lower likelihood of developing Hashimoto's. Vitamin D levels should be checked at regular intervals, especially in the winter months. There are two available tests: 1,25-dihydroxyvitamin D (1,25(OH)2D) and 25-hydroxyvitamin D (25(OH)D). The latter is preferred. Blood levels of 25(OH)D should be between 60 and 80 ng/L for optimal thyroid receptor and immune system function.39-40

Sources of vitamin D include cod liver oil, fatty fish, fortified dairy and orange juice, eggs, and sunlight. Despite dietary interventions and sunlight, many people may still require an oral vitamin D3 supplement to reach their target range.

Vitamin B12

Vitamin B12 is naturally found in animal products including fish, meat, poultry, eggs, milk, and other dairy products. However this vitamin is generally not present in plant foods, and thus vegetarians and especially vegans are at a greater risk for deficiency.

Low levels of B12 can contribute to fatigue and are often found in people with Hashimoto's. Normal levels of B12 are between 200-900 pg/mL, yet levels under 350 are associated with neurological symptoms. If B12 levels are below 800, a person may still benefit from supplementation. Patients with Hashimoto's and low B12 levels should be screened for parietal cell antibodies, which may be present in up to one-third of patients with Hashimoto's.41-43

Options for B12 replacement include capsules, sublingual tablets, liquids, and injections. The sublingual route may offer an advantage for those with absorption issues, and it is more convenient than injections. Methylcobalamin versions of B12 are highly bioavailable, do not require intrinsic factor for activation, and are generally preferred over cyanocobalamin versions.

Selenium

Selenium deficiency has been identified as an environmental trigger for Hashimoto's, and multiple studies have been done on the role of selenium in autoimmune thyroid disease. While several studies reported no benefit and a Cochrane review found insufficient evidence, many other studies reported the benefit of selenium in autoimmune thyroid disease.5, 44-50 Testing for selenium deficiency is not routinely performed; however a 200 mcg dose of selenomethionine was found to reduce thyroid peroxidase antibodies by 50% over the course of three months.49 Patients who start selenium often report feeling calmer, potentially due to a reduction in thyroid tissue breakdown.50

Selenium is a trace mineral that is incorporated into proteins to make antioxidants including glutathione peroxi-

dase. This type of protein, known as a selenoprotein, prevents damage from the hydrogen peroxide generated from the conversion of iodide to iodine by breaking down the hydrogen peroxide into water particles. This allows for the removal of the cells affected by oxidative damage, leads to the preservation of tissue integrity, and prevents the convergence of white blood cells in the thyroid gland.47

The Recommended Daily Allowance (RDA) for selenium is 55 mcg, while the Tolerable Upper Intake Level (UL) is 400 mcg.51 A study done in South Dakota did not find any signs of toxicity at levels as high as 724 mcg; however, changes in nail structure, a sign of toxicity, were reported with selenium intakes of 900 mcg per day in China.52 Most reported toxicity cases have been associated with industrial accidents and manufacturing errors. Some symptoms of selenium toxicity that have been reported include GI disturbances, hair loss, changes in hair and nails, peripheral neuropathy, fatigue, irritability, garlic-smelling breath, and a jaundice-like yellow tint to the skin.52,53

While the RDA of selenium may usually be found in multivitamin/mineral combinations, that will not be sufficient for TPO antibody reduction. Studies have been done to test the minimal dose of selenium for thyroid antibody reduction, and that dose was established to be 200 mcg daily; even a 100 mcg dose did not produce a statistically significant TPO antibody reduction.49

Hypochlorhydria/Achlorhydria

Studies have found that people with Hashimoto's and hypothyroidism often have hypochlorhydria (low stomach acid) or achlorhydria (lack of stomach acid).54

An inadequate amount of stomach acid can make it more difficult for patients to digest proteins, making them more fatigued and more likely to develop food sensitivities, especially to gluten, dairy and soy as these proteins are amongst the most difficult to digest, and are also the most commonly eaten proteins in the standard western diet. Furthermore, low stomach acid can contribute to small intestinal bacterial overgrowth, which can be a trigger for intestinal permeability and was reported to be present in 54% of people with hypothyroidism in one study.55

Additionally, having low stomach acid makes individuals more susceptible to acquiring gut infections such as Helicobacter pylori (H. pylori), Yersinia, other bacteria with lipo-polysaccharide residues, and parasites, which may contribute to the antigenic burden commonly found in autoimmunity.

Nutrient depletions of iron and B12 are sometimes secondary to hypochlorhydria or achlorhydria, and supporting proper stomach acid production may be a useful measure in helping to address deficiencies, restoring proper digestive function, resolving fatigue and preventing the development of new food sensitivities.56, 57

Betaine hydrochloride (HCl) with pepsin, taken at the end of a protein-containing meal, can be a supportive supplement for restoring stomach acid levels. However, root causes of low stomach acid, such as H. pylori infection should also be explored and addressed.

Clinicians should be familiar with instructing their clients on proper dose titrations of betaine HCl with pepsin, having the client start with one dose per protein-containing meal, then watching for responses such as a slight burning sensation in the throat or esophagus. The patient should be instructed to increase the betaine by one dose until the burning sensation is perceived; at that point, the target dose can be estimated to be one dose less than the dose at which the burning sensation was experienced.

Intestinal permeability support

Supporting intestinal barrier function though the use of digestive enzymes, omega-3 fatty acids, zinc, L-glutamine, and curcumin can be helpful in healing the intestinal barrier and improving immune regulation.

Overall, survey respondents reported the following supplements as helpful: vitamin B12 (76%), vitamin D3 (74%), digestive enzymes (73%), iron (63%), omega-3 fatty acids (65%), selenium 200 mcg (63%), betaine HCl with pepsin (59%), curcumin (56%), zinc 30 mg (52%) and L-glutamine (51%).13 (The numbers in parentheses represent the percentage of people who reported "feeling better" after incorporating these supplements).

Additional interventions

Supporting a person's nutrition status can help put some cases of Hashimoto's into remission and will help most people with the condition feel better.

Additional integrative methods that may be used in conjunction with medications and nutrition may include stress reduction, emotional support, adrenal support, detoxification protocols, and addressing chronic infections that may be present in those who do not immediately respond to initial nutritional interventions.

Pathogens can contribute to the antigenic load of Hashimoto's through various mechanisms, including leading to intestinal permeability, the "bystander effect" (when a pathogen is inside the target organ), as well as molecular mimicry (when proteins on the pathogen are similar to proteins on the target organ).

Common pathogens that have been identified in people with Hashimoto's include H. pylori,58-59 Yersinia entercolitica,60-62 Borrelia burgdorferi (one of the bacteria that causes Lyme disease)62 as well as an overgrowth of bacteria in the small intestine.55 Epstein Barr Virus (EBV) has also been implicated in triggering Hashimoto's and other autoimmune conditions.63- 65 Reactivations of EBV can potentially exacerbate Hashimoto's symptoms.65

The treatment of chronic infections and toxins in Hashimoto's is beyond the scope of this article; however any person who has not responded to three months of nutritional therapy should be investigated for the presence of infections and toxins.

Further discussion on Hashimoto's, infections, detoxification and a functional medicine root cause approach can be found in Hashimoto's Thyroiditis: Lifestyle Interventions for Finding and Treating the Root Cause.21

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Izabella Wentz, PharmD, FASCP is an internationally acclaimed thyroid specialist and licensed pharmacist who has dedicated her career to addressing the root causes of autoimmune thyroid disease after being diagnosed with Hashimoto's Thyroiditis in 2009.

Dr. Wentz is the author of the New York Times best-selling patient guide Hashimoto's Thyroiditis: Lifestyle Interventions for Finding and Treating the Root Cause and the recently released protocol-based book Hashimoto's Protocol: A 90-Day Plan for Reversing Thyroid Symptoms and Getting Your Life Back.

As a patient advocate, researcher, clinician, and educator, Dr. Wentz is committed to raising awareness on how to overcome autoimmune thyroid disease through The Thyroid Secret Documentary Series, the Hashimoto's Institute Practitioner Training, and her international consulting and speaking services offered to both patients and healthcare professionals.

ANGELA GRASSI
MS, RDN, LDN

The Functional Nutrition Approach to Treating Polycystic Ovary Syndrome

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders, affecting 9-18% of women. 1 The condition is characterized by hyperandrogenism, ovulatory dysfunction and polycystic ovarian morphology. Despite the high prevalence, PCOS is commonly overlooked and undertreated. An international study showed nearly 50% of women saw three or more health professionals or waited for more than two years before receiving a diagnosis of PCOS. Few women were satisfied with information about PCOS given to them at diagnosis, with over half reporting not receiving any information about long-term complications of PCOS or emotional support. 2

In the past, PCOS has been viewed primarily as a reproductive disorder as women are at an increased risk for infertility (PCOS is the leading cause of ovulatory infertility), miscarriage, pre-term births, and endometrial cancer. Yet, PCOS is mainly an endocrine disorder with increased rates of insulin resistance, type 2 diabetes, gestational diabetes, hypertension, and cardiovascular disease that extends beyond their reproductive years.3-5 A study published in Diabetes showed that the prevalence of type 2 diabetes in middle-aged women with PCOS was 6.8 times higher than that of the general female population of similar age. 4

Lifestyle management involving modifications to diet, taking appropriate nutrition supplements, exercise, stress management, and sleep hygiene, are the primary treatment approaches to prevent or ameliorate these health risks as well as to improve fertility, and optimize health.

Nutrition Strategies for PCOS

Diet modifications are an important treatment for women with PCOS, yet the optimal diet for women with PCOS hasn't been determined. A systematic review and meta-analysis published in the Journal of Nutrition and Dietetics found that the type of diet didn't matter as much as weight loss itself. Losing weight improved both metabolic and reproductive parameters associated with PCOS. This review, however, only included six studies. 6

Eating plans such as modifying glycemic index (GI) and glycemic load (GL), or modifying carbohydrate, fat or protein amounts have been shown to reduce metabolic markers associated with PCOS and improve fertility. 6

Compared to women without PCOS, women with the condition have higher levels of insulin and inflammatory markers. 7 Researchers have investigated the use of an anti-inflammatory diet in women with PCOS with good results.

In this study, 100 overweight PCOS women ate a reduced calorie diet for 12 weeks. The diet consisted of 5 small meals with 25% proteins, 25% fat, and 50% carbohydrates. The diet was designed to be moderate to high fiber with an emphasis on anti-inflammatory foods such as fish, legumes, green tea, and low-fat dairy. Chicken, red meat, added sugars were limited. 8

The results were encouraging. The mean weight loss was 7.2% with significant reductions in cholesterol, blood pressure and fasting glucose levels. C-reactive protein levels were reduced by 35%, and 63% of the women regained menstrual cyclicity.

The DASH diet which is also designed to be rich in antioxidants, has also been investigated in women with PCOS. Women who followed the DASH diet for eight weeks saw significant reductions in insulin and CRP levels, along with improvements in waist circumference measurements. 9

PCOS is a heterogeneous condition that affects women differently. Many different nutrition approaches are available to women with PCOS, requiring personalized recommendations. Women with PCOS are encouraged to work with a registered dietitian nutritionist skilled in PCOS, for individualized nutrition counseling and strategies that work best for their unique needs.

Nutrition Supplements for PCOS

Research is expanding into what benefits nutrition supplements can potentially offer to women with PCOS. Here are some of the many promising supplements.

N-acetylcysteine

N-acetylcysteine (NAC), is a powerful antioxidant and amino acid. NAC is a derivative of L-cysteine, a precursor to glutathione, and is involved in fighting oxidative stress and inflammation. NAC has also been shown to protect insulin receptors, influence insulin receptor activity and insulin secretion from pancreatic cells. Therapeutic dosage of NAC in studies is 1.6 to 3 g/daily. NAC is well tolerated with minimal side effects.

A systematic review and meta-analysis showed that compared with metformin, NAC significantly improved BMI, total testosterone, insulin, and lipid levels, equally as well in women with PCOS. 10

The review also showed NAC had significant improvements in pregnancy and ovulation rates as compared to a placebo among PCOS women. However, NAC was not associated with greater benefits to metformin for improving pregnancy rate, spontaneous ovulations, and menstrual regularity. 10

Inositol

Both myo (MYO) and d-chiro inositols (DCI) have been well studied in women with PCOS and are showing promising results as a first-line treatment. MYO in particular has been shown to improve insulin sensitivity as well as egg quality and ovulation. Newer research is finding that a combination of MYO and DCI in the ideal 40:1 ratio that mimic's the body's own tissue levels, works better than either inositol alone for improving metabolic aspects and restoring hormone balance. 11

Inositols are pseudovitamins found in foods such as fruits, beans, cereals, and buckwheat. MYO and DCI work as inositol-phosphoglycan mediators, or "secondary messengers" that regulates activities of hormones including FSH, TSH and insulin. Therapeutic dosage is 2 to 4 grams MYO daily with 50 to 100 mg DCI daily. Inositol is well tolerated with minimal side effects. It may have the potential to lower blood sugar, especially in those talking insulin sensitizers or other supplements that may also lower blood sugar.

Vitamin D

Studies in PCOS show an inverse relationship between vitamin D and metabolic and hormonal disorders. A systematic review published in Nutrients, however, found no evidence that supplementation with vitamin D reduced or mitigated metabolic and hormonal dysregulations in women with PCOS. 12

Vitamin D receptors have been located on the oocyte. Vitamin D supplementation (10,000 IU/month), has been shown to improve fertility in women with PCOS by increasing the number of mature follicles and improving menstrual regularity. 13

Fish Oil

Fish oil offers many benefits to women with PCOS including helping to reduce elevated triglyceride levels, improving fatty liver, and reducing inflammation. Fish oil was also found to reduce testosterone and regulate menstrual cycles in both overweight and lean women with PCOS. 14

Vitamin B12

Results from the Diabetes Prevention Program Outcomes Study show that metformin affects the absorption of vitamin B12, by causing alterations of the vitamin B12-intrinsic factor complex in ileum. B12 deficiency is progressive over time in metformin users. Consequences decreases in vitamin B-12 concentrations—such as macrocytic anemia, neuropathy, and mental changes—can be profound. 15

Since the average dose of metformin in the PCOS population is rather high (1,500 mg to 2,000 mg daily), it's recommend for PCOS patients who take metformin to have their vitamin B12 levels checked annually and supplement their diets with vitamin B12. Sublingual methylcobalimum form is best absorbed.

Berberine

Berbrine is a Chinese herb that has been used for thousands of years as a treatment for diabetes and infertility that is showing promise in helping women with PCOS. Berberine is an alkaloid extracted from Chinese herbs such as hydrastis cacadensis (goldenseal), berberis aquifolium (oregon grape), erberis vulgaris (barberry), berberis aristata (tree turmeric) and coptidis rhizome (huanglian).

As a potent insulin sensitizer, berberine's insulin and glucose lowering effects have been compared with that of metformin. In their study, Wei and colleagues randomly selected 89 women with PCOS to receive either berberine (500 mg, 3x daily), metformin (500mg, 3x daily), or a placebo for 3 months. All women were instructed by a nutritionist to reduce carbohydrate and fat intake although no calorie range was provided. After 3 months of treatment, women who took berberine saw greater reductions in body fat loss than metformin or placebo. Berberine lowered insulin and glucose levels similarly to metformin. Women with PCOS who took berberine saw significant reductions in total cholesterol, LDL, and triglyceride levels and a significant improvement in HDL levels compared to metformin. 16

Berberine has also been found to reduce androgens, inflammation, cholesterol, fatty liver disease, and blood pressure in women with PCOS. 17, 18

Berberine has been shown to assist in weight loss and central body fat loss in women with PCOS. According to a study published in Evidence-based Complementary and Alternative Medicine, berberine targets fat cells to impair the appetite hormone leptin and the lipoprotein lipase enzyme, to reverse fat storage. Berberine has been shown to slow the release of free fatty acids while boosting fat burning in the mitochondria, which lowers cholesterol levels and prevents fat storage. 17

Due to its many positive health benefits, berberine has been suggested as a way to possibly prevent many of the metabolic disorders associated with PCOS.

PCOS is a complex and overlooked condition with significant long-term metabolic risk factors that persist throughout a woman's lifespan. Modifications to diet and nutrition supplements play a crucial role in helping women with PCOS to improve their fertility, optimize their health, and prevent disease.

— Angela Grassi, MS, RDN, LDN, is an internationally known nutrition and health expert on PCOS. Angela is the co-author of The PCOS Nutrition Center Cookbook: 100 Easy and Delicious Whole Food Recipes To Beat PCOS and the bestselling, The PCOS Workbook: Your Guide to Complete Physical and Emotional Health. Angela's third book, PCOS: The Dietitian's Guide, now in its second edition, is the most comprehensive evidence-based nutrition resource available on PCOS.

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MARLISA BROWN
MS, RD, CDE, CDN

Is Your Diet Putting Your Health at Risk?

Do You Have Celiac Disease or Gluten-Sensitivity?

Are You at Risk?

When it comes to our own health, most of us usually accept our daily aches and pains as something which is normal for us. We tend to distance ourselves from the thought that our health could one day decline until it does, and then we are forced to deal with it.

None of us can predict the health challenges we'll encounter in our lifetime, but your body often does give clues, all you have to do is to pay attention and know what to look for. In the case of celiac disease, the symptoms show up in hundreds of different ways the more you know the easier it will be to get diagnosed.

What Is Celiac Disease?

Celiac disease is thought to have been around for thousands of years, and it may have started back when we switched to a diet that included wheat. Even though celiac disease has been around for so long, science has just begun to understand how to diagnosis and treat it as well as the risks associated with it. It wasn't that long ago that, celiac disease was considered a rare European disease. Recent research has discovered that celiac disease can affect as many as 1 in 133 in North America alone— approximately 3 million people. Celiac disease is an inherited disorder and if you have celiac disease there is a chance that some of your immediate family members may also have celiac disease. Celiac disease affects about 1 percent of the population in the world, including in North Africa, Asia, and South America. And yet as many as 84 percent of the people living with celiac disease will go undiagnosed. Recent research as also shown that the number of people developing celiac disease in the past 50 years has increased 4-5x,and the reason for this still remains unknown.

Celiac disease is caused by a reaction to the protein gluten (pronounced glOO-ten). Gluten is found in wheat, rye, and barley, so when you eat these starches, or when they are added to your food or medications, you are consuming gluten. It is the protein part of wheat, rye, and barley that contains gluten. Gluten is actually a mix of proteins, specifically gliadin and glutenin. When people suffer from food allergies or sensitivities, they are reacting to the proteins in those foods, therefore these proteins should be avoided. Celiac disease is not considered an allergy, but it is rather sensitivity to the gluten found in food. This sensitivity will cause an autoimmune response any time that the protein gluten is ingested. It used to be thought that celiac disease was a gastrointestinal problem because many who suffered with celiac disease also experienced gastrointestinal symptoms, but it has since be found that only a percentage of those with celiac will experience gastrointestinal symptoms, and since it is an autoimmune disease there can be hundreds of different symptoms that will vary from person to person. Therefore gluten must be avoided at all times to stop this autoimmune response. Depending on whom you speak to, celiac disease may be referred to as sensitivity or as a gluten intolerance, but no matter how you say it, if the diagnosis is celiac disease, gluten can never be consumed again. In addition to being found naturally in grains, gluten is also added to many foods. You may ask why add gluten to food? Well, gluten is the "glue" that holds the ingredients together, giving breads and other foods that crispy, light texture which we all enjoy.

WHAT IS GLUTEN?

"Gluten is a combination of several proteins that are complex and not easily digested by humans. For most people, this incomplete breakdown of gluten peptides doesn't cause a problem and the gluten fragments pass without trouble through the digestive tract. For certain people with the genetic susceptibility to gluten-related disorders, the undigested gluten can create problems. When gluten is ingested and reaches the small intestine, it can trigger an immune response leading to increased intestinal permeability and, ultimately, to inflammation in genetically susceptible individuals." Dr Alessio Fasano the Director of the Center for Celiac Research and the Mucosal Immunology and Biology Research Center at Mass General Hospital for Children

Since celiac disease is aggravated by the gluten found in the foods we eat, it often affects the digestive system since this is the root of its absorption, however it is not a digestive disease it is an autoimmune disease, and so symptoms will not always be gastrointestinal in nature. Celiac usually "presents itself in the small intestine, a 22-foot-long organ covered with tiny hair like projections called villi. It is through the villi that our bodies absorb nutrients. Celiac disease will cause a flattening of the villi, making it difficult for our gastrointestinal tract to function normally. When being tested to identify celiac disease generally not enough villi samples are taken, and therefore the flattened villi may not be identified and the disease can easily be missed.

Celiac disease can affect every person differently; some may have stomach pains or be depressed and tired all the time, others may feel sick only once in a while, and still others may feel just fine. However no matter what their symptoms are, if they consume gluten the damage is being done. Celiac disease can develop at any age, from infancy to old age, so it is difficult to know when to look out for it. And because it can show up in many ways, your doctor may attempt to test or treat you for other ailments, such as Crohn's disease, chronic fatigue, irritable bowel syndrome, thyroid disorder, osteoporosis, diverticulitis, or rheumatoid arthritis—anything and everything but the celiac disease. Because there are no "typical" symptoms of celiac disease, it is not usually the first thing doctors think of. It's no wonder that so many who have celiac disease 75% to 83% still remain undiagnosed. It has been shown that most people with celiac disease will spend an average of about 11 years going to doctors and specialists before they figure out what the cause of their problems is. Numerous studies have shown that many people diagnosed with other diseases, such as irritable bowel syndrome, are actually are suffering with undiagnosed celiac disease.

How do we get celiac disease? We don't know how, but we now know that it runs in families (about 99 percent of people who have celiac disease will have at least one of the genetic markers HL DQ-2 or HL DQ-8) and if you have a first-degree relative (sibling or parent) with celiac disease, you will have a much higher chance of also having celiac disease. That is why if someone in your family has celiac disease, it is important that you be tested for it as well.

The following checklists will help you evaluate your risk.

Recognizing Symptoms of Celiac Disease

Section A

Put a check next to any of the health problems below that you have:

——— Anemia
——— Behavioral changes
——— Bloating, gas, or abdominal pain
——— Bones that break easily
——— Bone or joint pain
——— Bruising
——— Chronic fatigue
——— Delayed growth as a child
——— Dental enamel problems
——— Depression or irritability
——— Diarrhea or constipation
——— Discolored teeth or enamel problems
——— Canker sores
——— Dry eyes
——— Edema (swelling, especially found in hands and feet)
——— Epstein–Barr
——— Failure to thrive (in children)
——— Fatigue
——— Frequent bowel movements
——— Frequent infections
——— Frequent illness
——— Hard-to-flush stools
——— Inability to lose weight
——— Indigestion
——— Infertility
——— Irritability
——— Joint pain
——— Lactose intolerance
——— Learning difficulties
——— Memory problems
——— Menstrual problems
——— Migraines
——— Mouth sores and ulcers (canker sores)
——— Nutritional deficiencies (such as iron, calcium, or vitamins A, D, E, and K)
——— Reflux (heartburn)
——— Seizures
——— Short stature
——— Skin problems and rashes
——— Tingling or numbness in hands and feet

——— Unexplained weight loss
——— Unexplained weight gain

Count how many items you have checked in Section A:
If you have checked 2 or more of the items in this section, and the source of these symptoms has not been identified you should consider being screened for celiac disease.

Not everyone who has celiac disease will have symptoms!. Please check any of the following health problems with which you have been diagnosed:

——— Addison's disease
——— Alopecia areata
——— Anemia
——— Autoimmune disorders
——— Autism
——— ADHD
——— Central and peripheral nervous system disorders
——— Dermatitis Herpetiformis
——— Down syndrome
——— Family history of celiac disease (any relative with celiac disease)
——— Gastro-intestinal malignancies
——— IBS (irritable bowel syndrome)
——— Inflammatory bowel disease (Ulcerative colitis, Crohn's disease)
——— Intestinal lymphomas
——— Hepatitis
——— IgA deficiency
——— Infertility
——— Intestinal cancer
——— Juvenile idiopathic arthritis
——— Lymphoma
——— Myasthenia Gravis
——— Non-Hodgkin's lymphoma
——— Osteoporosis
——— Pancreatic insufficiency
——— Peripheral neuropathy
——— Primary biliary cirrhosis
——— Psoriasis
——— Recurrent aphthous ulcerations
——— Rheumatoid arthritis
——— Sarcoidosis
——— Scleroderma
——— Selective IgA deficiency
——— Sjögren's disease
——— Systemic lupus erythematosus

——— Thyroid disease
——— Turner syndrome
——— Type 1 diabetes (DM1) (in you or any of your first-degree relatives)
——— Williams syndrome

Count how many items have you checked in section B:

If you have checked 1 or more of the items in this section, and any items in section A consider being screened for celiac disease.

You may think, "These lists are so long—they can't all be linked to celiac disease, can they?" But since celiac disease affects your immune system through your gastrointestinal system the symptoms will be different for each individual based on their genetic differences. This autoimmune attack can lead to illness and the development of many disease states. How you are affected depends on your body's weak spots, which will influence where your immune system decides to attack. For instance, it has long been known that there is a relationship between type 1 diabetes and celiac disease. This is why the American Diabetes Associations "Standards of Care" recommends that anyone with type 1 diabetes should be screened annually for celiac disease and their first-degree relatives should be screened as well.. More recently, scientists have been looking at the chromosomal abnormalities that are similar among those with type 1 diabetes and those with celiac disease. There is some speculation on the relationship between celiac disease which is an autoimmune disorder, and type 1 diabetes (type 1 diabetes is caused by an immune system attack of the beta cells in the pancreas). Who knows, is it possible that in some individuals gluten could be the a trigger for this attack? Research is on going studying the relationship between celiac disease and these disorders, only the future will tell? One way to determine your potential risk can be taking a look at the specific diseases that are most commonly associated with celiac disease, and by evaluating your symptoms and your family history.

Useful and Not-So-Useful Medical Tests

It is estimated that 1 in 100 people worldwide suffers from celiac disease. The easiest way to screen for celiac disease is with blood tests. Unfortunately none of the tests alone are 100 percent accurate, nor can they be used to rule out celiac or to diagnose you. But they can help indicate a potential risk. Before getting screened for celiac disease it is important to make sure that you are still eating gluten, because if you are already following a gluten-free diet, you must start eating gluten for several months prior to being tested for celiac disease, otherwise the test results may not be accurate.

When Screening for Celiac Disease, These Blood Tests Should be Used:

1. **IgA -Tissue transglutaminase antibody (-tTG):** If this test is positive, it is likely that you could have celiac disease, but it is not conclusive in itself.

2. **IgA Gliadin antibodies (AGA):** These tests are the older gliadin tests, are not as accurate as the newer tests, but they are still sometimes ordered.

3. **.IgA Endomysial antibodies (EMA):** This test has mostly been replaced by the anti-tTG test, and it is expensive and it is rarely ordered.

4. **Deaminated gliadin peptide antibodies (-DGP):** This test is a new version of the older AGA tests, and its accuracy is higher than that of the original tests. This is the best test when someone also has an IgA deficiency (see note below).

** Please note that when being screened for celiac disease it is also important to have a total serum IgA test, which is used to identify an IgA deficiency. Some of the screenings rely on the IgA to identify celiac disease; IgA deficiencies are common with celiac disease and if you have an IgA deficiency, the results of celiac screening may not be accurate.*

Genetic Tests

About 99 percent of patients who have celiac disease also have one or both of the genes HLA-DQ2 and HLA-DQ8. Thus, if an individual comes back negative on the above blood tests but has symptoms of celiac disease and are positive on either the HL-DQ2 or HL-DQ8 tests, they could have celiac disease. If they do not have the genetic markers it is unlikely that they have celiac disease.

- *Please note, your doctor can order these tests for you also DNA testing is also available.
- If you are positive on any one of the blood tests, go directly to the diagnostic tests.
- If you are negative on all the blood screening tests but have checked several items in section A or B, and no other cause of your illness has been found, talk to your doctor about being tested further for celiac disease.
- If you are negative on all the blood screening tests but have checked off anything in section A or B, and have a relative who is suffering from celiac disease, talk to your doctor about further celiac testing.
- If you are either positive or negative on the blood tests and do not want to go for diagnostic tests right away, you can do a simple DNA test, as noted above. This test—which is sometimes covered by insurance—will isolate whether or not you have the gene or DNA that is found in 99 percent of those who develop celiac disease. If you do not have this genetic marker, it is very unlikely that you could have celiac disease. If this test is positive, you should talk to your doctor about testing further.

Diagnostic Tests

If you are positive on any of the blood tests, make sure you follow up by having an endoscopy of the small intestine (it is important that this is done in the duodenum or jejunum areas), this is the only way to accurately diagnose celiac disease. Blood tests are a good screening tool, but they cannot currently be used alone to diagnose celiac disease. The endoscopic procedure is used to identify any flattened villi in the small intestine which is what is indicated when someone has celiac disease. Villi are the fingerlike covering on the lining of your intestines and are responsible for nutrient absorption. An endoscopy, along with a biopsy, is the only way to get a conclusive diagnosis for celiac disease. You will need to have an endoscopy with multiple (4-6) samples taken in a maize pattern from the duodenum/duodenum bulb, since celiac disease can be patchy and can easily be missed during testing. Taking a number of samples from various locations will give you a better chance of being properly diagnosed; there is a linear relationship between the number of samples taken and the number of people who will be diagnosed with celiac disease. The endoscopic procedure is a relatively quick, painless procedure that

will be done while you are under anesthesia. Try to find a specialist or gastroenterologist who works often with patients who have celiac disease. A gastroenterologist is a doctor who specializes in treatment and diagnosis of gastrointestinal problems. Some doctors work more extensively with celiac patient's than others and are more likely to take sufficient samples giving a higher probability of an accurate diagnosis. Often when a diagnosis of celiac disease is missed, it is due to either an insufficient number of samples taken or a misinterpretation of the test results. If a diagnoses of celiac is not found, and an individual is suffering from gastrointestinal issues it is important to have a full range of tests done to rule out any other illness. If nothing is found, consider being retested for celiac disease or looking into other possibilities such as gluten-sensitivity and food intolerances.

In Europe they sometimes allow children to be diagnosed without an endoscope when the following rules apply; they must have symptoms of celiac disease, have positive findings with the blood work 10x the normal titer, have one or more of the genetic markers, and they must respond favorably to a gluten-free diet. However 10x the usual values is unusual, and this is currently only being used in Europe. The endoscopic test is still the gold standard for diagnosing celiac disease.

Another Sign of Celiac Disease

A skin disorder called dermatitis herpetiformis (DH), a prickly, itchy skin rash usually found on elbows, knees, and buttocks is closely associated with celiac disease. If a person has dermatitis herpetiformis and it has been sampled and shown to be positive for D.H., no further testing is needed to confirm the diagnosis of celiac.

Celiac Sprue vs. Refractory Sprue

A very small percentage of people with celiac disease will not experience improved health even after six months to a year on a strict gluten-free diet. These individuals may have developed refractory sprue. Treatment options may include a combination of therapies such as steroids and immune-suppressive drugs, along with a gluten-free diet.

Refractory sprue is thought to be a malignant condition, and people with this condition are often malnourished and have weakened immune systems. Close monitoring by a physician is necessary, as in many cases malabsorption and malnutrition progress despite treatment, and nutrition may have to be delivered via alternate routes, such as TPN (total parental nutrition)—IV feeding that bypasses the gastrointestinal tract completely and delivers nutrients directly into the bloodstream. This is why discovering refractory sprue as soon as possible is essential, it may be best to recommend these patients to a celiac research center.

It is unknown why refractory sprue develops. One theory is that since it is usually only found in older adults, it may have developed due to celiac disease having been present and untreated for many years. Left unchecked and untreated, refractory sprue condition can lead to many complications as well as higher risk for cancer. It is thought that something as simple as following a gluten-free diet early after diagnosis on can prevent this condition from developing.

Misdiagnosis and Multiple Conditions:

There are other possible reasons for flattened villi that may not be caused by celiac disease,. For example some blood pressure medications and autoimmune suppressant drugs may produce flattened villi as a side effect. If someone has had no symptoms of celiac disease, had negative findings on the blood work, and is taking medi-

cations that could have affected their villi and their diagnosis is uncertain they should be reevaluated at a celiac research center to re confirm their diagnosis of celiac disease.

If someone has had symptoms and a positive diagnosis of celiac disease but is not responding favorably to a gluten-free diet, first check with an registered dietitian who is an expert with gluten-free diets to make sure they are compliant with a gluten-free diet and are not making any errors. If compliance is good, consider a secondary diagnosis to be at the root of the continued symptoms, such as SIBO (small intestinal bacterial overgrowth) or FODMAPS, or lactose intolerance, or fructose intolerance. Have a gastroenterologist evaluate to see if there is a secondary diagnosis at the root of this.

WHEN WORKING WITH YOUR DOCTOR

Since celiac disease and gluten sensitivity is often missed, it can sometimes be difficult to get medical professionals to agree that you may need to be retested. When advocating for your health remember the following:

You have the right . . .

- To be heard.
- To have all your questions answered.
- To be retested if you do not have any diagnosis that explains your symptoms.
- To a second opinion.
- To see a specialist (such as a gastroenterologist that specializes in celiac disease).
- To be taken seriously. Just because they haven't found the root of your illness doesn't mean it is all in your head.
- To bring copies of your test results to a celiac research center.
- If diagnosed to see a Registered Dietitian who specializes in celiac disease.

Gluten Sensitivity:

It is possible to pass screening and diagnostic tests and still be at risk, but if you do not have symptoms, the risk is minimal. If you do have symptoms, and were positive on the genetic panel consider being retested for celiac disease. If you have symptoms and do not wish to have repeat testing done, and no other medical explanation is found, consider experimenting with a test diet, you could have a gluten sensitivity.

A gluten sensitivity is an intolerance to the protein gluten which is not caused by celiac disease. Ingestion of gluten causes an immune response and usually gastrointestinal symptoms. It is unknown at present if it is also the cause of autoimmune issues. The diagnoses of gluten sensitivity at this time is a diagnoses by elimination, (rule out celiac disease or other health problems, rule out a wheat allergy, implement a gluten-free diet, if a person responds favorably to a gluten-free diet then a diagnoses of gluten sensitivity is found. These findings where first presented in June 2011 by a panel of experts June 2011:

Professor Alessio Fasano

Professor Carlo Catassi
Dr Anna Sapone
Professor David Sanders

In looking at gluten related disorders some have estimated that 4-6 % US population has gluten sesnsitivity,1 % has celiac disease and 5-7% has a wheat allergy

There is no cure for celiac disease or gluten sensitivity; the only treatment is to follow a gluten-free diet. Although it's understandable that anyone would want to start feeling better right away, it's generally not recommended to start the gluten-free diet if you are still being tested for celiac disease, as it may interfere with your diagnosis, since your villi will begin to heal. And if you start the diet without being diagnosed, you may not be as committed to following the diet and your family members would not be alerted to be screened, as well.

TIP
Prior to starting a gluten-free diet, it is important to first undergo needed medical tests to rule out the possibility of any serious health problems.

If You Have Celiac Disease
Following a gluten-free diet works by allowing those villi covering your small intestine to heal and return to normal so that you can once again absorb all the nutrients from food. This, in turn, allows your immune system to improve. Many people who start the diet after discovering that they have celiac disease will begin to feel better within a few days. However for the villi to heal it may take several years for adults and about 6 months for children..

If You Have Gluten Sensitivity
Villi are not affected with gluten sensitivity, only symptoms are used to evaluate a favorable response. Usually implementation of a gluten-free diet provides immediate relief from symptoms.

Today there is a huge amount of research being done with both celiac disease and gluten sensitivity, and information is changing practically daily. There is some recent research about ATI's in wheat being responsible for some reactions and we should see more about this with continued research.

Today scientists are even looking for different ways to treat celiac disease. One approach is to develop medications to help the body handle the gluten protein so that if a small amount of gluten is ingested accidently, the response would not be as severe. Only the future will show us the newest research in these areas.

Presently, however, there is no magic bullet. If you are diagnosed with celiac disease, or gluten sensitivity following a gluten-free diet must be taken seriously. It is a lifelong commitment that takes dedication. You may have already spent years feeling terrible and frustrated because you have been going to doctor after doctor, feeling like no one is helping. Initially, you may feel overwhelmed when you realize all the changes you will need to make to follow a gluten-free lifestyle. In Chapter 2, you will find an easy quick-start plan to begin following a gluten-free diet. It is also important to find a registered dietitian who specializes in celiac disease to answer any questions and to help you identify problem-solving issues.

If you're a parent who has a child with celiac disease, it may be difficult to explain why he or she can no longer have their favorite foods. You may feel uncomfortable about asking your friends or family to make special dishes

for you or asking about all the ingredients in the recipes. Going on vacation can be challenging, since all food is usually eaten out. You may also sometimes feel it is just easier to stay home!

The good news is that today there is much more information available to help you follow a gluten-free lifestyle, including organizations, web sites, and support groups. Supermarkets are starting to carry more gluten-free foods, and more and more companies are producing and selling thousands of gluten-free foods on the internet. There's beginning to be a much greater awareness of celiac disease and gluten sensitivity—even many restaurants now have gluten-free options listed on their menus. Receiving a diagnosis of celiac disease can be difficult, but with patience and education, you can lead a normal, happy, and healthier life.

Can Eating Less Gluten Improve Everyone's Health?

There are times you might consider a gluten-free diet even if you are sure you don't have celiac disease. Gluten is a large protein which is difficult to digest, if you are suffering from another health problem especially a gastro-intestinal problem like inflammatory bowel disease a large protein like gluten may make you feel unwell, even if you are not suffering from celiac disease or a gluten sensitivity.. In addition, many parents of autistic children report an improvement in their child's behavior when they put their child on a gluten-free diet and there is current research being done in this area.

Why is gluten causing so many problems today? Perhaps because it is a larger protein that is difficult to digest, or maybe because we are adding gluten to so many foods. There is so much more to learn, but it is important to note that following a gluten-free diet can help a lot of people.

Some people even follow gluten-free diets as part of just a diet craze, unfortunately this confuses many people and makes it so restaurants and friends may not always realize that even a crumb can make someone ill if they have celiac disease or gluten sensitivity.

Using the tips and meal plans found later in this book can make it easier for you to live gluten-free while having a lot more options.

Quick and Easy Tips to Getting Diagnosed with Celiac Disease:

CELIAC DISEASE:

- Start by reviewing the list of possible symptoms that can be found with celiac disease to see if you may have indications that you should be tested.
- To get tested start by using the blood tests that are shown earlier in this chapter. When you get tested you must be eating gluten as part of your regular diet for the blood tests to be accurate.
- Blood testing is just a screening method, only an endoscopic procedure with a positive biopsy can diagnose celiac disease. You cannot be diagnosed with just blood tests.
- To have the best chance of being diagnosed a doctor should take at least 4-6 samples in the duodenal portion of your small intestine.
- Just because a test is negative it is not 100% certain that you don't have celiac disease, remember celiac

disease is patchy and can be missed.

- If you are diagnosed with celiac disease the only treatment is 100% removal of gluten in your diet.

Gluten Sensitivity:

- Gluten Sensitivity is not celiac disease.
- Most people with gluten-sensitivity will have gastrointestinal problems following the consumption of any gluten.
- There are currently no tests for diagnosing gluten-sensitivity.
- To diagnose gluten-sensitivity you need to rule out celiac disease, wheat allergies and any other health problems. If a person responds favorably to a gluten-free diet then a diagnoses of gluten-sensitivity is found.
- Currently the only treatment for gluten-sensitivity is removal of gluten from your diet.

There are no pills, shots or other treatments currently available to treat celiac disease or gluten-sensitivity. The only treatment at this time is 100% removal of gluten from the diet.

MARLISA BROWN MS, RD, CDE, CDN

REGISTERED DIETITIAN *CERTIFIED DIABETES EDUCATOR
* AUTHOR*CHEF* PROFESSIONAL SPEAKER

Marlisa works with organizations and individuals looking at healthful products, programs and services.

www.MarlisaSpeaks.com
www.GlutenFreeEasy.com
Blog www.GlutenFreeEZ.com
@MarlisaBrownRD
Marlisa@TWellness.net

Marlisa is president of Total Wellness Inc., for more than 20 years working with more than 24,000 clients specializing in diabetes, cardiovascular disease, weight loss, gastrointestinal disorders, celiac disease, medical nutrition therapies personal development, nutrition/culinary programs, corporate wellness and more.

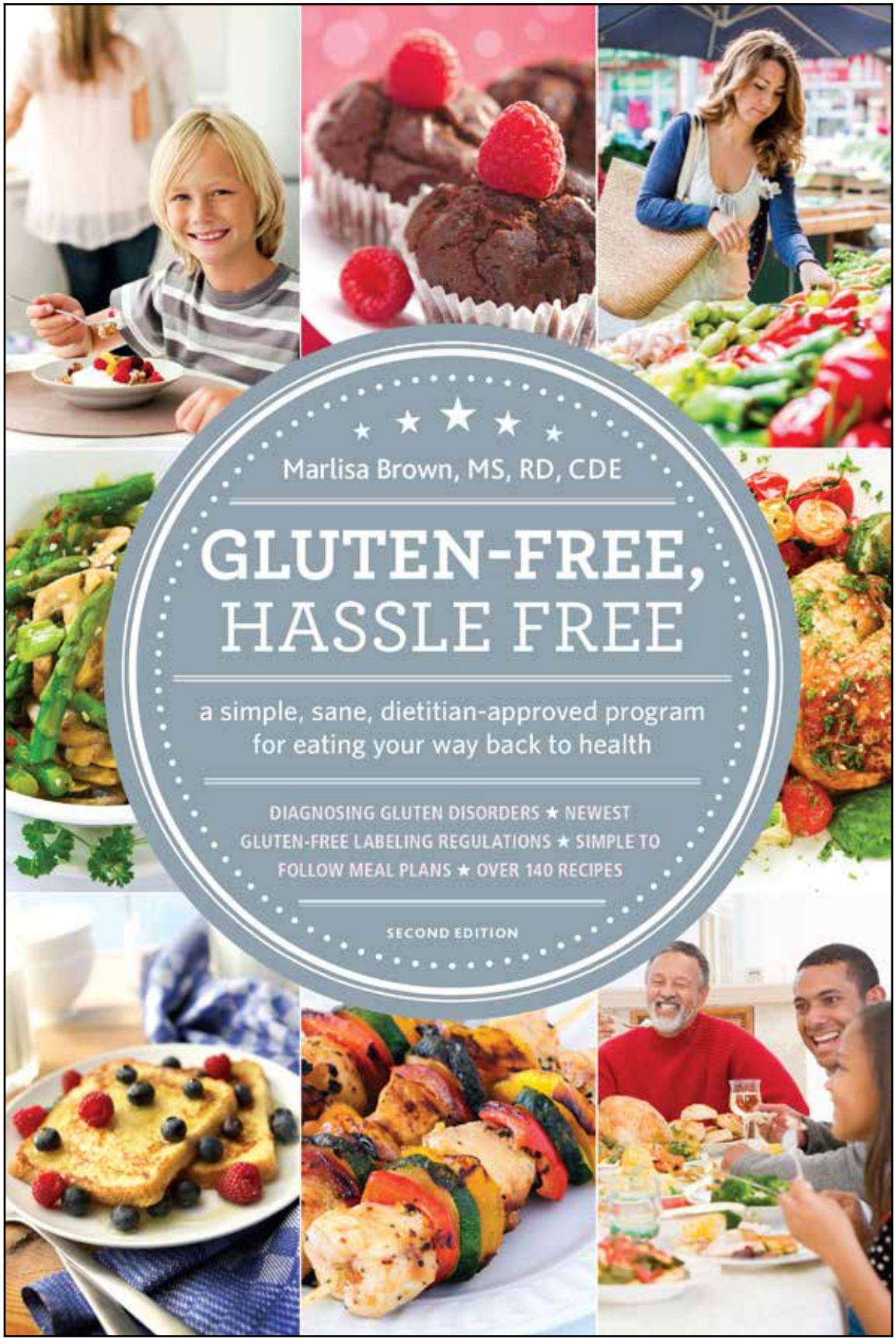
Marlisa has given hundreds of presentations; some of her clients include the NY Jets, The Kennedy Space Center, Pratt and Whitney, Honeywell, Hofstra & Adelphi Universities Lilco, Guardian Life, Brookhaven National Labs, Goldman Sachs, Guardian Life, Tiffany, Dean Witter Reynolds, Pall Corp, Bank of New York, Sony, Liz Claiborne, and Ethicon and more. In addition Marlisa worked at the corporate office of Lackmann Culinary Services as their Wellness Coordinator for over a ten year period.

Marlisa has made numerous television appearances including Fox 5, Fios, CNN, 5 years on "International Healthy Cooking" for The American Heart Association where Marlisa wrote and appeared on every show and she has recently piloted a diabetes cooking show "Defeating Diabetes in Your Kitchen", in addition she has been a member of the dLife TV Professional Council.

Marlisa has a bachelor's degree in marketing 1982 and a graduate degree in nutrition 1994 from C.W. Post/Long Island University, and she has also studied at the Culinary Institute of America.

Marlisa is author of "Gluten-Free Hassle Free", "The Gluten-Free Hassle-Free Cookbook" and "Easy, Gluten-Free". In addition she has contributed to many publications including, Salute, Scholastic, Shape, Food Service Management, Newsday, Parenting Magazine, Weight Training for Dummies, and Sports Nutrition Medicine and Rehabilitation . She has also written and contributed to many programs including, Richard Simmons' Food Mover Program, cookbooks, recipe cards and web site, Kathy Smiths' Project You II for Diabetes, Jorge Cruises' The 3-Hour Diet Cookbook, and Leslie Sansones' Walk Away the Pounds, (green, yellow, and red meal plan).

Marlisa has served as an officer on many boards including the nutrition chair for the International Association of Culinary Professionals, BOD member of The Gluten Intolerance Group of Long Island and past president, media representative, and public relations chair of the New York State Dietetic Association. Marlisa is a recipient of the 2011 Diabetes Educator of the Year from the DCE of The American Dietetic Association, The Emerging Dietetic Leader Award from the American Dietetic Association, Dietitian of the year from The Long Island Dietetic Association, Best Of Long Island from the L.I Press 2008/2009/2010/2011, and the Community Service Award from C.W. Post/Long Island University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DC, IFMCP

Tackling Chronic Health Conditions

In This Chapter

* Combating cancer, chronic fatigue, and cardiovascular diseases
* Dealing with diabetes, fibromyalgia, and lupus
* Managing migraines and multiple sclerosis
* Battling osteoporosis and Parkinson's disease

Chronic health conditions are those that last a long time and are difficult to shake. Fortunately, this is the area of medicine where functional medicine tends to shine. While conventional medicine battles chronic illness with powerful pharmaceutical medications that often weaken the body in the process, functional medicine works to strengthen the body so that can more effectively rid itself of disease. In this chapter, I provide the guidance you need to equip your body to battle a host of chronic illnesses — from cancer and cardiovascular disease to osteoporosis and stroke.

<Remember>

Doses in this chapter are for adults.

Combatting Cancer

Cancer is uncontrolled growth of abnormal cells that may be caused by numerous factors, including genetic susceptibility, inflammatory agents in the diet and other sources, health conditions (insulin resistance, diabetes, and obesity, for example), and exposure to environmental contaminants and toxins (pollution radiation, herbicides, pesticides, and so on). You can't control everything in the world around you, but you can control most of what you put into your body.

Start by adopting a healthy diet and lifestyle, with a focus on increasing protein consumption. For people without cancer, I recommend consuming about 0.36 gram of protein per pound of body weight daily. If you have cancer, increase your daily consumption of protein to 0.45 to 0.90 gram of protein per pound. For example, if you weigh 200 pounds, then you should consume at least 200 @@ts 0.45 = 90 grams of protein daily. Double that to get the upper limit, which would be 180 grams in this example. Also supplement a healthy diet with the following:

Supplement	***Dosage***
Diindolylmethane (DIM)	150 mg twice daily
Vitamin A (retinyl palmitate and beta-carotene)	2,500 IUs retinyl palmitate and 2,500 IUs beta-

	carotene daily (see Appendix A for precautions)
Vitamin C (mineral ascorbates)	1,000 mg daily
Whole beta glucan	500 mg one or two times daily
Vitamin D3	2,000 to 10,000 IUs daily, depending on blood levels (see Appendix A)
Vitamin E (mixed tocopherols)	400 IUs daily
Vitamin B12 (methylcobalamin, sublingual fast-dissolving tablet)	1,000 to 5,000 mcg daily
Folate (5-MTHF)	1,000 to 2,000 mcg daily
Curcumin	1 to 2 grams daily
Resveratrol	75 mg one or two times daily
S-acetyl glutathione	200 mg one or two times daily
Fermented wheat germ extract	5.5 grams one or two times daily
Glucoraphanin (from broccoli extract) (SGS)	100 mg twice daily
Calcium glycinate chelate	150 mg daily
Magnesium bis-glycinate chelate	125 mg twice daily
Potassium glycinate	50 mg twice daily
Selenium glycinate	100 mcg twice daily
Zinc glycinate chelate	20 mg twice daily

If you're receiving medical treatment for cancer, consult with your doctor before taking supplements. Certain supplements may interfere with chemotherapy and other medications.

In addition to diet and supplements, do what you can to reduce stress in your life. Consider centering disciplines, such as yoga, Qigong, tai chi, and mindfulness mediation. Make sure you're getting approximately eight hours of sleep per night.

Easing Chronic Fatigue Syndrome (CFS) and Fibromyalgia

Chronic fatigue syndrome (CFS) is unexplained fatigue lasting more than four months that significantly interferes with your functioning and is often associated with body aches, foggy brain, poor sleep, increased thirst, gastrointestinal issues (including irritable bowel syndrome), persistent infections (including sore throats, sinusitis, and the common cold), feeling worse the day after exercise, and multiple chemical sensitivities. Fibromyalgia is closely related to CFS but is characterized more by pain than by fatigue; many of those with fibromyalgia have tender knots in the muscles commonly referred to as *trigger points*.

To recover from CFS and fibromyalgia, you need to degunk and re-energize your body, starting with your diet. Adopt a healthy diet, replacing manufactured foods with whole foods — fresh, organic vegetables, fruits, nuts, legumes, seafood, lean meats, and healthy fats. Steer clear of dairy, grains (especially in the form of breads, baked goods, pasta, and cereals), refined sugars and other processed foods, legumes, and starches. Drink eight ounces of pure water every two hours. Limit consumption of alcohol and caffeine. (A paleo diet is a good option; for guidance, check out *Living Paleo For Dummies*, by Kellyann Petrucci (John Wiley & Sons, Inc.).)

The vast majority of CFS patients also need to be treated for yeast overgrowth.

If you have either CFS or fibromyalgia, apply the Sleep, Hormonal support, Infections, and Nutritional support (SHIN) protocol:

- **Sleep:** Make sure you're getting about eight hours of sleep nightly.
- **Hormonal support:** Get tested for and address any hormone problems and nutritional deficiencies (see Chapter ? for more about diagnosing and treating hormone imbalances related to the adrenal and thyroid glands).

* **Infections:** Clean up bowel, parasitic, bacterial, fungal, and sinus infections by supplementing your diet with the following digestion and immune system support:

Supplement	***Dosage***
Probiotics (*Saccharomyces boulardii*; a proprietary blend of a multistrain probiotic containing *Lactobacillus acidophilus, Bifidobacterium longum,* and *Lactobacillus plantarum;* and *Bifidobacterium lactis* HNO 19 (HOWARU Bifido))	250 mg of *Saccharomyces boulardii* twice daily 50 billion CFUs of the proprietary blend daily 50 billion CFUs of HOWARU Bifido once daily
Monolaurin	200 mg twice daily
L-lysine	150 mg twice daily
Bee propolis	100 mg twice daily
Cinnamon bark extract	100 mg twice daily
Grape seed extract	100 mg twice daily
Olive leaf extract	50 mg twice daily
Oregano extract	300 mg twice daily
Ginger	300 mg twice daily
Turmeric extract	200 mg twice daily
Olive extract	100 mg twice daily

* **Nutritional support:** Take the highest quality multivitamin/mineral formula available containing the more utilizable forms of the B vitamins and all of the minerals in the form of glycinated chelates. Specifically, make sure you're supplementing your diet with the following:

Supplement	***Dosage***
D-ribose	5 grams three times daily
Iron (ferrous bis-glycinate chelate)	30 mg up to twice daily, depending on blood levels (see Appendix A)
Vitamin B12 (methylcobalamin, sublingual quick-dissolving tablet)	5,000 to 10,000 mcg once daily
CoQ10 (Kaneka Q10)	200 to 400 mg daily
Vitamin D3	2,000 to 10,000 IUs daily, depending on blood levels (see Appendix A)

To relieve the pain that accompanies CFS and fibromyalgia, take the following supplements:

Supplement	***Dosage***
White willow bark extract	600 mg one or two times daily between meals
Boswellia	100 mg one or two times daily between meals
Turmeric	200 mg one or two times daily between meals

You can stop all treatments after 6 to 12 months. Stay on the multivitamin/mineral, sleep support, D-ribose, and CoQ10 indefinitely.

Dealing with Cardiovascular Conditions and Stroke

Your *cardiovascular* system, consisting of your heart, veins, and arteries, circulates blood throughout your body. Over time, this system begins to show signs of wear and tear as it become subjected to *vascular insults* — injuries caused by anything from high blood pressure and fluctuating glucose levels to exposure to nicotine and alcohol. In addition, several cardiovascular conditions, including atherosclerosis, heart arrhythmia, and high blood pressure, increase the risk of stroke, so it's important to address any of these underlying conditions.

The natural cures approach to treating cardiovascular conditions and stroke is to provide the body with the nutrients it needs to prevent and recover from inflammation, oxidative stress, autoimmune dysfunction, altered gene expression, and tissue damage. In this section, I provide guidance on how to strengthen your cardiovascular system overall and then go on to address specific conditions, such as arrhythmia, atherosclerosis, heart attack, and stroke.

Improving cardiovascular health

To improve cardiovascular health, adopt a healthy diet and lifestyle. Following are more specific recommendations:

* **Eat 30 percent fewer calories daily.** *Caloric restriction* (CR) reduces oxidative stress, inflammation, and autoimmune dysfunction and increases cellular energy.

  One simple way to lower your calorie intake is to eliminate wheat from your diet. Wheat stimulates the appetite; cutting wheat from your diet eliminates about 400 calories daily.

* **Fast for about 12 hours daily seven days a week.** Fast from three hours before bedtime until you wake up the next morning to give your digestive and cardiovascular systems a break.

* **Eat low on the glycemic index (GI).** Make most of what you eat protein and non-starchy vegetables and fruits. Eat eight servings of low-GI vegetables and two servings of low-GI fruits daily. Avoid sugary and processed foods.

* **Eliminate trans fats.** Trans fats are mostly in the form of hydrogenated and partially hydrogenated oils used in processed foods and to fry foods in fast-food restaurants. Trans fats increase your risk of heart disease, stroke, type 2 diabetes, and other chronic conditions.

  Eat mono- and select polyunsaturated fats, instead. Monounsaturated fats (MUFAs) are found in nuts, avocados, and most vegetable oils, including olive, sunflower, safflower, peanut, and sesame oils. Good sources of polyunsaturated fats (PUFAs) are walnuts, flaxseed, fatty fish (especially salmon, mackerel, tuna, sardines, and herring), algae, leafy green vegetables, and krill.

* **Check for and treat vitamin and mineral deficiencies.** Vitamins C, E, and B9 (folate) and the mineral selenium play key roles in cardiovascular health.

* **Consume 45 to 50 total grams of dietary fiber daily.** You can supplement with psyllium husks, if necessary.

* **Enhance your diet with heart-healthy supplements.** Antioxidants and anti-inflammatories, such as resveratrol, quercetin, red wine, green tea, dark chocolate, and flavonoids (especially diadzein and genistein from non GMO soybeans), provide strong support for a healthy cardiovascular system.

* **Stay physically active.** If possible, engage in aerobic exercise for 30 minutes at least every other day, along with strength training at least three days a week.

* **Reduce stress.** Chronic stress increases your risk for heart disease and many other illnesses. Although you can't eliminate stress from your life, you can make reducing stress a top priority and take steps to manage stressful situations (and people) more effectively.

* **Get sufficient sleep.** Try to sleep approximately eight hours nightly. If you're having trouble sleeping, see Chapter 16 for suggestions.

You may be able to reduce your risk for many cardiovascular conditions, including atherosclerosis and stroke, by lowering your homocysteine

levels. *Homocysteine* is an abrasive molecule that can scrape the inside lining of the arteries, increasing fatty plaque deposits. You should have your homocysteine levels checked occasionally; a healthy level is 5 to 8 micro-mol/L. To reduce homocysteine levels, follow the homocysteine lowering protocol:

Supplement	***Dosage***
Vitamin B2 (riboflavin 5'-phosphate)	25 mg twice daily
Vitamin B6 (pyridoxine 5'-phosphate)	10 mg twice daily
Vitamin B12 (methylcobalamin, sublingual fast-dissolving tablet)	1,000 mcg daily
Folate (5-MTHF)	2,000 mcg daily
Trimethylglycine	500 mg twice daily
SAMe	200 mg twice daily

Alleviating angina

Angina is chest tightness or pain caused by insufficient blood supply to the heart. Angina can be caused by atherosclerosis (hardening or narrowing of the arteries), hypoglycemia (low blood sugar), or inflammation affecting the cardiovascular system. The first step to preventing and treating angina is to adopt a heart-healthy diet and lifestyle; see the earlier section "Improving cardiovascular health" for details.

Seek immediate medical attention for any chest tightness or pain. Angina is an early warning sign that you're at an increased risk for heart attack.

In addition to adopting a heart-healthy diet and lifestyle, increase the nitric oxide concentration in your blood. Nitric oxide is a powerful *vasodilator* (it expands the blood vessels). To increase your body's nitric oxide production, supplement your diet with the following:

Supplement	***Dosage***
L-arginine	2 grams twice daily (see Appendix B for precautions)
Citrulline	500 mg twice daily
S-acetyl glutathione	200 mg twice daily
Aspirin	81 mg daily

Take L-arginine, citrulline, and glutathione on an empty stomach for best results.

Additional nutrients for treating angina include the following:

Supplement	***Dosage***
Magnesium bis-glycinate chelate	125 mg twice daily
Acetyl-L-carnitine	350 mg twice daily
CoQ10 (Kaneka Q10)	100 to 400 mg daily
Omega-3 essential fatty acids (EFAs)	1 gram yielding 180 mg EPA and 120 mg DHA four times daily
Vitamin E (mixed tocopherols)	400 IUs daily
D-ribose	5 grams three to four times daily (see Appendix B for precautions)
Vitamin D3	2,000 to 10,000 IUs daily, depending on blood levels (see Appendix A)

Calming an erratic heartbeat: Arrhythmia

Arrhythmia is any abnormal heartbeat, including *arterial fibrillation* (fluttering), *tachycardia* (beating too fast), and *bradycardia* (beating too slow).

The first step is to get tested for food allergies and sensitivities (see Chapter 13) so that you can confirm or rule out those conditions. Eliminate caffeine, nicotine, alcohol, aspartame, and monosodium glutamate from you diet to see whether symptoms improve.

Next, adopt a healthy diet, and supplement your diet with the following nutrients, if necessary:

Supplement	***Dosage***
Magnesium glycinate chelate	125 mg twice daily
Potassium glycinate complex	300 mg one or two times daily, only under close medical supervision
Omega-3 essential fatty acids (EFAs)	1 gram yielding 180 mg EPA and 120 mg DHA four times daily
Selenium	100 to 200 mcg daily
Copper glycinate chelate	1 to 4 mg daily
Vitamin C (mineral ascorbates)	1,000 mg twice daily
Vitamin D3	2,000 to 10,000 IUs daily, depending on blood levels (see Appendix A)
D-ribose	5 grams two to three times daily (see Appendix B for precautions)

CoQ10 (Kaneka Q10)	100 to 400 mg daily

Improving circulation: Atherosclerosis

Atherosclerosis is inflammation and fatty plaque buildup on the interior walls of the arteries, restricting blood flow. Atherosclerosis takes a long time to develop and doesn't start to produce symptoms until the blockage is fairly advanced. Your doctor can perform a variety of tests to determine the level of plaque buildup in your arteries. To prevent and reverse the course of inflammation and plaque buildup, start by adopting a heart-healthy diet and lifestyle; see the earlier section "Improving cardiovascular health" for details.

To determine your risk of developing atherosclerosis, your doctor may order a test to evaluate the level of lipoprotein (a) in your blood. Lipoproteins are molecules made of fats and proteins. Lipoprotein (a) is made in the liver and can accumulate in the endothelium, contributing to atherosclerosis, inflammation, and the formation of *foam cells* — immune cells formed in response to excess cholesterol. Lipoprotein (a) can contribute to blood clot formation. The vertical auto profile (VAP) blood test or Advanced Cardiovascular Test (ACT) will include this measurement, which is not performed with traditional testing.

Cook in a way that minimizes the formation of *atherogenic compounds*, which promote the formation of fatty plaque in the arteries. Store vegetable oils, butter, meat, dairy, and nuts in airtight containers. Avoid cooking at very high temperatures. For high-temp cooking, use palm or coconut oil; use olive oil for medium heat.

Making your own exercise drink

Exercise in the morning after a 12-hour fast. Blend the following ingredients to make your own exercise drink and drink it during breaks in your exercise session to maintain healthy veins and arteries:

* 8 ounces of fresh orange juice diluted with water to 24 ounces
* 10 grams of D-ribose
* 40 grams whey protein
* 2 grams buffered vitamin C powder
* 3,000 mg of L-glutamine powder
* 2 grams of acetyl-L-carnitine powder
* 2,000 mg of L-arginine powder

A recent study also shows that a combination of moderate wine (red or white) consumption five days a week and regular exercise (at least twice a week) reduces the risk of cardiovascular disease, including atherosclerosis. Moderate consumption in the study meant 0.3 to 0.4 liters (about two and a half glasses) daily for men and 0.2 to 0.3 liters (one to two glasses) daily for women. However, I recommend that you drink no more than a couple ounces of wine daily.

To help keep your blood vessels clear of plaque, make sure you're getting sufficient amounts of the following nutrients:

Supplement	***Dosage***
Omega-3 essential fatty acids (EFAs)	1 gram yielding 180 mg EPA and 120 mg DHA four times daily
Vitamin E (mixed tocopherols)	400 IUs daily
Trans resveratrol	200 mg twice daily
N-acetyl cysteine	1 to 2 grams daily
CoQ10 (Kaneka Q10)	100 to 400 mg daily
Vitamin K2 (menaquinone-7)	45 mcg as twice daily
Vitamin D3	2,000 to 10,000 IUs daily, depending on blood levels (see Appendix A)
Magnesium glycinate chelate	125 mg twice daily
Whey protein	40 grams daily
B vitamins (High quality formula with the more bioavailable forms in a substantial dose)	Follow label instructions (see Appendix A)
Vitamin C (mineral ascorbates)	1,000 mg twice daily

Atherosclerosis has been linked to high levels of homocysteine in the blood. See the earlier section "Improving cardiovascular health" to find out how to lower your homocysteine levels.

Recovering from a heart attack

A *heart attack (myocardial infarction)* occurs when the blood supply to part of the heart muscle is totally cut off. Symptoms range from mild indigestion and heartburn to crushing tightness in the chest radiating down the arms and into the upper back and jaw, possibly accompanied by profuse sweating, ringing in the ears, and a drop in blood pressure.

If you're experiencing heart attack symptoms, call 911 immediately. Emergency medical attention can stop a heart attack in its tracks. Popping an aspirin may also help, but call 911 first and take aspirin only if directed to do so by medical personnel. If you're allergic to aspirin or are having a stroke due to a ruptured blood vessel, taking an aspirin is likely to do more harm than good.

For general recommendations on improving cardiovascular disease and preventing heart attacks, see the earlier section "Improving cardiovascular health." Consider supplementing your diet with the following heart attack prevention nutrients:

Supplement	***Dosage***
Omega-3 essential fatty acids (EFAs)	1 gram yielding 180 mg EPA and 120 mg DHA four times

	daily
Vitamin E (tocopherols and tocotrienols)	400 IUs daily
Trans resveratrol	200 mg twice daily
N-acetyl cysteine	1 to 2 grams daily
CoQ10 (Kaneka Q10)	100 to 400 mg daily
Vitamin K2 (menaquinone-7)	45 mcg twice daily
Vitamin D3	2,000 to 10,000 IUs daily, depending on blood levels (see Appendix A)
Magnesium bis-glycinate chelate_	125 mg twice daily
Whey protein	40 grams daily
B vitamins (High-quality formula with the more bioavailable forms in a substantial dose)	Follow label instructions
Vitamin C (mineral ascorbates)	1,000 mg twice daily
L-carnitine tartrate	340 mg twice daily
D-ribose	5 grams two to three times daily (see Appendix B for precautions)
ALA (controlled release)	600 mg 15 to 30 minutes before breakfast and dinner

Lowering high blood pressure (hypertension)

Blood pressure is the measure of force of the blood pushing against the walls of the blood vessels. Normal blood pressure is 120/80 mm Hg (millimeters of mercury); anything over 140/90 mm Hg is considered high. (The top number is *systolic pressure*, measured when the heart muscle is fully contracted; the bottom number is *diastolic pressure*, measured when the heart muscle is fully relaxed.) Having high blood pressure (hypertension) increases your risk of developing cardiovascular disease.

Standard blood pressure measurements can be inadequate and often misleading. I recommend getting an EndoPAT assessment, which looks at small artery elasticity, which conventional blood pressure measurements don't consider. Visit www.itamar-medical.com for details and to search for a provider near you that can conduct the assessment.

The first step in addressing high blood pressure is to adopt a healthy diet and lifestyle, as explained in the earlier section "Improving cardiovascular health." You'll be surprised at how much your blood pressure drops simply by eliminating sugar and high-glycemic foods.

Conventional medicine typically treats high blood pressure with several different classes of medications, including diuretics (which stimulate elimination of fluids), beta blockers (to block adrenaline and slow the heartbeat), calcium-channel blockers (to relax blood vessels), and angiotensin-converting-enzyme (ACE) inhibitors and other vasodilators (to expand blood vessels). Nature provides equivalents for all of these manufactured pharmaceuticals. Talk to your healthcare provider about

the possibility of replacing any of your current medications with these natural alternatives or adding one or more of these to your current treatments (don't self-medicate):

Supplement	***Dosage***
Natural diuretics	
Vitamin B6 (pyridoxal 5'-phosphate)	35 mg twice daily
Taurine	250 mg twice daily
Celery	Four stalks daily
Magnesium bis-glycinate	125 mg twice daily
Protein	0.36 grams per pound of body weight
CoQ10 (Kaneka Q10)	100 to 400 mg daily
Acetyl-L-carnitine	350 mg twice daily
Natural beta blocker	
Hawthorne berry	400 mg daily
Natural vasodilators	
L-arginine	2 grams twice daily (see Appendix B for precautions)
Citrulline	500 mg twice daily
Omega-3 essential fatty acids (EFAs)	1 gram yielding 180 mg EP and 120 mg DHA four times daily
Monounsaturated fatty acids (MUFAs)	10 ounces daily
Potassium	125 mg twice daily (see Appendix A for precautions)
Magnesium bis-glycinate chelate	125 mg twice daily
Vitamin C (mineral ascorbates)	1,000 mg two to three times daily
Vitamin D3	2,000 to 10,000 IUs daily, depending on blood levels (see Appendix A)
CoQ10 (Kaneka Q10)	100 to 400 mg daily
Natural calcium channel blockers	
ALA (controlled release)	200 mg daily
Magnesium bis-glycinate chelate	200 mg daily
N-acetyl cysteine	500 mg daily
Vitamin C (mineral ascorbates)	1,000 mg daily
Vitamin E (tocopherols)	400 IUs daily
Natural angiotensin-converting enzyme (ACE)	

inhibitors	
Seaweed (dried wakame)	3.3 grams daily
Sardines (valyl-tyrosine)	3 grams daily
Bonito fish (Sarda orientalis)	1.5 grams daily
Hydrolyzed whey protein	30 grams daily
Omega-3 essential fatty acids (EFAs)	4 grams daily with a ratio of 3 parts EPA to 2 parts DHA
Egg yolks	Several pastured eggs per week
Pomegranate	125 mg daily
Natural angiotensin receptor blockers (ARBs)	
Potassium	250 mg daily (see Appendix A for precautions)
Trans resveratrol	200 mg daily
CoQ10 (Kaneka Q10)	100 to 400 mg daily
Gamma linolenic acid (GLA)	250 mg twice daily

Nitric oxide is a powerful vasodilator that also reduces inflammation, oxidative stress, and cardiovascular immune dysfunction. See the earlier section, "Angina," for details on increasing your body's nitric acid production.

Getting the straight story on cholesterol

If you've been diagnosed with high cholesterol, don't worry—it may not be a problem. Don't rush to go on a low-fat diet or take statin drugs, which can do more harm than good. Neither your overall cholesterol level nor your ratio of "good" HDL to "bad" LDL cholesterol necessarily affects your risk of cardiovascular disease. A traditional lipid panel indicating your total cholesterol, HDL, LDL, and triglycerides can give you a very limited picture.

What drives the risk of cardiovascular disease is LDL particle size and the number of small, dense LDL particles. Picture the lining of your arteries as a tennis net. LDL particles the size of tennis balls won't pass through the net, but if they're the size of golf balls, they will. Small LDL particles pass through the lining of the arteries, get stuck there, and trigger the formation of fatty plaques. Small LDL particles along with a high homocysteine levels, elevated lipoprotein (a), and other factors can be better assessed through a vertical auto profile (VAP) blood test rather than a traditional lipid panel.

Insist that your doctor order an *expanded lipid panel*, which reports LDL particle size and number. If the number of small LDL particles is abnormally large, take steps to reverse this unhealthy trend:

* Work toward achieving your ideal weight and body fat composition—less than 18 percent body fat for men and less than 28 percent for women.

Body mass index (BMI) charts are readily available online to give you a ballpark idea of healthy weights based on your height.

* Adopt a Mediterranean-style diet, including plant sterols, soy foods (non-GMO), almonds, fibers, okra, and eggplant.
* Team up with your healthcare provider to combine lipid-lowering medications with nutritional and nutraceutical therapies, including the following:

Supplement	***Dosage***
Curcumin	250 mg twice daily
Red yeast rice	500 mg twice daily (See note following table)
Quercetin	250 mg one to two times daily
Lycopene	4 mg twice daily
Green tea extract	250 mg twice daily
Trans resveratrol	40 mg twice daily
N-acetyl cysteine	250 mg twice daily
DGL licorice	100 mg twice daily
Berberine	200 mg twice daily
Phytosterols	800 mg twice daily
Aged garlic extract	600 mg twice daily
Omega-3 essential fatty acids (EFAs)	1 gram yielding 180 mg EPA and 120 mg DHA four times daily

Niacin (B3) significantly increases HDL and HDL particle size and lowers lipoprotein a levels and has been shown to reduce cardiovascular disease and events by 26 percent and total mortality by 11 percent over six years. Take 1 to 4 grams daily of niacin as nicotinic acid (*not* nicotinamide or hexanicotinate) while monitoring for possible undesirable side effects, which may include hyperglycemia, gout, hepatitis, flushing, elevated homocysteine, bruising, and palpitations (see Appendix A for precautions). Try one or more of the following techniques to lessen the flushing effect of niacin (tingling or itchy red skin that passes within about 30 minutes):

* Take a slower delivery form. I use a product that includes a wax coating to minimize flushing.
* Start by taking 100 mg daily and increase your dosage by 100 mg each week until you reach the maximum dosage.
* Take with food. Apple, applesauce, or apple pectin is best.
* Avoid alcohol.
* Take your niacin every day. If you start and stop, your body needs to readjust again.
* Take with baby aspirin.
* Take 200 to 500 mg of quercetin daily.

Recovering from a stroke

A *stroke* is a loss of brain function due to interrupted blood flow to the brain, caused by a blocked or ruptured blood vessel. Symptoms may include weakness along one side of the body, slurred speech, vision loss, confusion, sudden intense headache (unlike anything you've ever experienced), dizziness, impaired balance, and unconsciousness. *Silent strokes* are those that go unnoticed, but over time, a series of silent strokes may cause significant brain damage.

If you have symptoms of a stroke, have someone drive you to the nearest emergency room immediately or call 911. Immediate medical treatment can prevent debilitating brain damage.

Stroke is highly preventable. Get tested to gauge your stroke risk and adjust your diet and lifestyle accordingly to lower your risk. Here are some dietary recommendations.

* Increasing consumption of oily fish, nuts, seeds, pastured animal products, and plenty of colorful vegetables rich in antioxidants. Dark purple organic fruits and vegetables (berries, grapes, eggplant, and cabbage) are best for preventing stroke.
* Eliminating refined sugar from your diet. Eating sugary fruit in moderation is okay, but avoid fruit juices, organic or otherwise. An 8-ounce glass of OJ contains as much sugar as a soda; you'd eat *one* orange at a sitting, *not* ten.
* Consume at least 4 grams of fish oil daily and supplement with cod liver oil for additional DHA (docosahexaenoic acid), as necessary. Seventy-five percent of your brain is fat, and 25 percent of that fat is from DHA.
* Cut down on saturated fats from dairy and red meat and eliminate trans fats (hydrogenated and partially hydrogenated oils) entirely. Buy only grass-fed, organic, non-GMO, pastured animal products. Never eat margarine or fried foods.
* Consume only non-GMO foods. Visit www.nongmoshoppingguide.com to find out what's safe and what's not. (Almost all soybean products and canola oil have been altered by genetic modification, so be very selective when purchasing those.)
* Take the following supplements for stroke prevention:

Supplement	***Dosage***
Vinpocetine	5 mg twice daily (***Note:*** Don't use if you've had a stroke due to a brain hemorrhage)
DHA (cod liver oil)	2 grams daily
CoQ10 (Kaneka Q10)	200 to 400 mg daily
Vitamin E (tocopherols)	400 IUs daily
ALA (controlled release)	600 mg twice daily 15 minutes before meals
Phospatidylserine	100 mg twice daily
L-carnitine	400 mg twice daily

Vitamin D3	2,000 to 10,000 IUs daily, depending on blood levels (see Appendix A)

Delving into Diabetes and Other Blood Sugar Illnesses

Numerous chronic illnesses involve the body's inability to regulate blood glucose (sugar) levels. With *type 1 diabetes*, the pancreas produces too little or no insulin, resulting in elevated blood glucose levels. Symptoms include increased urination and thirst, blurred vision, tingling pain in the hands or feet, and weight loss despite normal or increased eating. With *type 2 diabetes (insulin resistance),* the body doesn't use insulin properly to convert sugar into energy. As a result, the pancreas produces even more insulin, and the body converts the sugar into fat instead of into energy, leading to weight gain. Without effective treatment, the overworked pancreas eventually gives out, and the person experiences symptoms identical to those of type 1 diabetes and requires insulin injections.

Metabolic syndrome is a cluster of conditions, including increased blood pressure, elevated blood sugar, excess body fat around the waist, and abnormal cholesterol levels that increase the risk of diabetes, heart disease, and stroke. Diabetes and related conditions are occurring in epidemic proportions worldwide.

The cause of type 2 diabetes and metabolic syndrome isn't solely genetic but *epigenetic,* the interplay of nature and nurture — genetics influenced by environmental factors, primarily diet. Food and other substances you ingest are more than mere sources of energy and building blocks for bodily tissues and fluids. Everything you consume "talks" to your genes, and a thousand calories of broccoli says something a whole lot different than does a thousand calories of soda. Consuming a certain amount of junk food can transform a perfectly healthy human being into someone with metabolic syndrome or type 2 diabetes.

If you're taking medication for diabetes, such as insulin, consult with your doctor before making adjustments to diet and lifestyle or taking any supplements to treat your diabetes. Your doctor needs to monitor your blood glucose levels closely and adjust your medication as these natural treatments kick in and your body requires less or no medication to regulate glucose levels. Taking more insulin than your body needs can be deadly. If your blood sugar dips too low, creating a condition called hypoglycemia, you may experience blurred vision, rapid heartbeat, sudden nervousness or mood change, unexplained fatigue, headache, or hunger. Eat or drink something sugary, such as a tablespoon of honey, some juice, or a hard candy, and seek immediate medical attention.

Eliminating problem foods from your diet

Whether you have type I or type II diabetes or metabolic syndrome, dietary and lifestyle changes can help to level out your blood sugar levels. Adopt a healthier diet and lifestyle, as explained in Chapter 2, with a focus on eliminating the following toxins and junk:

* **Trans fats:** Eliminate all processed foods from your diet, because even if the label indicates 0 (zero) trans fats, the product may contain up to 0.5 grams of trans fats in accordance with government labeling laws.
* **Sugar:** Read labels and look for ingredients that end in *-ose:* glucose, fructose, sucrose, and so on. These are all sugars.
* **Problem foods:** Eliminate wheat (gluten) and dairy (casein) products from your diet, or get tested for sensitivities, as explained in Chapter 13, and adjust your diet accordingly.
* **Artificial sweeteners:** No study has ever proven that artificial sweeteners help people lose weight. These are manufactured toxins, and some may even stimulate insulin production contributing to weight gain.
* **Food additives, monosodium glutamate (MSG), colors, and preservatives:** Many are known to be harmful. You're rolling the dice when eating this stuff.
* **Genetically modified organisms (GMOs):** Changing the protein structure of wheat, corn, soy, and other produce is like playing Russian roulette with foods. The human body didn't evolve over millions of years to process these foods effectively. In fact, your immune system may reject these foods, causing inflammation and other serious health conditions. Eat nature-made foods, not those developed in labs.
* **Hormones, antibiotics, herbicides, and pesticides:** Commercial (non-organic) produce and livestock are loaded with these toxic substances. Eat organic.
* **Bisphenol (BPA):** BPA leaches into your food from plastic containers and wrap, increasing the risk of diabetes and other health conditions. Drink out of glass bottles and glasses instead of plastic cups and containers. Use glass, porcelain, or stainless steel containers instead of plastic containers. Never microwave plastic containers or plastic wrap.

Your doctor should also monitor your HgbA1c levels to determine how your body has processed sugar over the past 120 days. Sugar binds to the proteins of certain tissues, causing oxidation and inflammation. The goal is 4.8-5.2. Anything over 6 is a problem.

Retooling your diet is one of the best ways to address two of the other prime contributors to diabetes and related illnesses: body weight and body fat. Work toward achieving your ideal weight and body fat composition — less than 18 percent body fat for men and less than 28 percent for women. Body fat percentage is more important than weight, but it's harder to measure. You can purchase body fat scales that measure electrical impedance to estimate your ratio of fat to muscle (electricity passes more easily through muscle than it does through fat).

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Boosting your body's ability to regulate glucose level

Here are some additional suggestions for boosting your body's ability to regulate its blood glucose levels:

* **Start your day with a blood-sugar stabilizing smoothie.** Replace your cereal, muffin, toast, bagel, or (egad!) donut, with a healthy smoothie. See Chapter 2 for a recipe, but if you're waking up with a blood glucose level above 125 mg/dl, then leave out the fruit.

  Not all breakfast smoothies are created equal. Even health food stores carry poor quality products loaded with artificial colors and flavorings, sweeteners, and inferior ingredients. You're better off blending your own smoothie using quality, organic ingredients from reputable producers.

* **Consume at least 50 grams of fiber daily.** Mix it up with soluble and insoluble fiber.

* **Minimize alcohol consumption.** Two ounces daily is healthy. Much more than that is unhealthy.

* **Drink oolong or unsweetened green tea.** Drink 1 cup after meals.

* **Exercise.** Engage in aerobic exercise 30 minutes a day five days a week and some sort of strength training three days a week. Do something physical on your non-exercise days. Take a long walk or bike ride, go swimming, or do yard work.

* **Reduce stress.** Your blood glucose level rises in response to stress so that you have enough energy to deal with the stress. Try to prevent stressful situations from arising and learn to deal more effectively with such situations. Honing your communication and problem-solving skills goes a long way toward reducing stress. Centering disciplines, such as qigong and yoga, are very helpful, as well.

* Take the following supplements to help your body regulate blood glucose levels:

Supplement	***Dosage***
ALA (controlled release)	200 mg 15 to 30 minutes prior to each meal
Cinnamon	200 mg twice daily
Gymnema	200 mg twice daily
Green tea extract (EGCG)	200 mg twice daily
Chromium glycinate chelate	200 mcg twice daily
CLA (derived from pure, non-GMO safflower oil)	1.5 grams twice daily
Vitamin D3	2,000 to 10,000 IUs daily, depending on blood levels (see Appendix A)

Brown seaweed blend	500 mg 20 to 30 minutes before meals that contain carbohydrates
Acetyl-L-carnitine	350 mg twice daily
Multivitamin/mineral (highest quality product available with the better forms of each vitamin and mineral, see Appendix A)	Follow label instructions
Omega-3 essential fatty acids (EFAs)	1 gram yielding 180 mg EPA and 120 mg DHA four times daily

Supplementing for type 1 diabetes

If you have type1diabetes, follow my earlier recommendations for diet and supplements to control blood sugar levels naturally. In addition, you'll need to take insulin. I also recommend the following supplements:

Thiamine	100 mg twice daily
Biotin	10,000 mcg twice daily after meals
Fenugreek	300 mg twice daily
Bitter gourd	150 mg twice daily

Dealing with Autoimmune Disorders

An autoimmune disorder occurs when the body's immune system attacks healthy body tissue, such as blood vessels, the thyroid gland or pancreas, joints, muscles, red blood cells, or skin. Autoimmune disorder is at the root of many illnesses, including celiac disease (Chapter 13), Hashimoto's thyroiditis (Chapter 18), type 1 diabetes (previous section), and lupus and multiple sclerosis, which I cover in this section.

Living well with lupus

Lupus is an inflammatory disease in which the immune system attacks healthy tissues of the joints, skin, blood cells, kidney, heart, and lungs. Symptoms include fatigue, sensitivity to sunlight, rash (usually on skin exposed to the sun), swollen lymph nodes, hair loss, low-grade fever, joint and muscle pain, neuropsychiatric disorder, and accelerated atherosclerosis. Testing for lupus antibodies in the blood can confirm or rule out lupus.

As with almost all autoimmune diseases, genetic susceptibility combined with intestinal permeability and environmental stressors are implicated in the onset of lupus. You can't do anything about your genetic susceptibility, but you can treat a leaky gut and reduce or eliminate environmental stressors. Here's how:

* **Heal your gut.** See Chapter 14 for more about curing a leaky gut.

* **Adopt an anti-inflammatory diet.** See Chapter 2 for more about healthy eating. Eliminate the following from your diet:
    * **Inflammatory substances:** Saturated fats, caffeine, alcohol, and fried foods, because they cause systemic inflammation
    * **Artificial coloring and flavoring:** Especially tartrazine (FD & C Yellow 5)
    * **Alfalfa products:** Alfalfa contains an amino acid called L-canavanine that may increase inflammation
* **Get tested for food allergies and insensitivities and adjust your diet accordingly.** See Chapter 13 for more about food allergies and sensitivities. Wheat/gluten and dairy/casein are the usual culprits, but there could be others.
* **Consume healthy fats.** Eat oily fish caught in the wild (not farm-raised), including mackerel, lake trout, herring, salmon, and sardines. Add flax seeds to your morning smoothie and salads. These omega-3 essential fatty acids can serve as anti-inflammatories.
* **Detox.** Enroll yourself in a supervised detoxification program for a minimum of ten days.

In addition to adopting an anti-inflammatory diet, take the following supplements to support a healthy gut and regulate your immune system:

Supplement	***Dosage***
Colostrum	10,000 mg daily
Proline-rich polypeptides extracted from bovine colostrum	Four sprays in mouth, hold for 30 seconds, and swallow, twice daily early morning and before bed, for a total of 16 mg daily
Omega-3 essential fatty acids (EFAs)	1 gram yielding 180 mg EPA and 120 mg DHA four times daily
Vitamin D3	2,000 to 10,000 IUs daily, depending on blood levels (see Appendix A)
MSM	1,000 mg two to three times daily
Boswellia	1,500 mg two to three times daily
Indole-3-carbinol	150 mg twice daily

Managing multiple sclerosis

Multiple sclerosis (*MS*) is disease in which the immune system attacks nerve fibers and *myelin,* the fatty substance that surrounds and insulates nerve fibers, interfering with communication within the brain and between the brain and body. *Sclerosis* refers to the scar tissue of the damaged myelin. Symptoms include brain fog, impaired vision and balance, brain shrinkage, and muscle weakness.

Don't stop taking any medication your doctor prescribes. Instead, work with your doctor to complement medical treatment with nutrition and other natural remedies. Find a functional medicine doctor that can help you through your journey. Visit www.functionalmedicine.org, click Find a Practitioner, and use the resulting form to conduct your search.

To treat MS, follow these guidelines:

* **Stimulate your muscles.** Any physical activity stimulates the muscles. You can also try whole body vibration, in which you stand, sit, or lie down on a machine that vibrates your entire body. If you're having trouble with *foot drop* (the front of your foot drops as you walk), you can purchase products to help with that, including WalkAide (www.walkaide.com) and Bioness (www.bioness.com).
* **Improve your sleep.** Increasing the quantity and quality of the sleep you're getting is crucial.
* **Reduce stress.** Try to prevent and avoid stressful situations (and people) and learn to deal more effectively with stress. Honing your communication and problem-solving skills goes a long way toward reducing stress. Centering disciplines, such as qigong and yoga, are very helpful, as well.
* **Heal your gut.** Many chronic health conditions, including MS, are related not only to what you eat, but also to how efficiently you absorb nutrients from your food and the permeability of your digestive system (leaky gut syndrome).
* **Get tested for food allergies and insensitivities and adjust your diet accordingly.** Wheat/gluten and dairy/casein are the usual culprits, but there could be others.
* **Improve your diet.** Avoid excessive sugar consumption in any form (sucrose, glucose, fructose, lactose, honey, corn syrup, and so on). Eliminate wheat/gluten from your diet regardless of test results or what your doctor says. Eat natural whole foods, including organic vegetables, fruits, meats, seafood, nuts, and seeds.
* **Supplement your diet with the following:**

Supplement	***Dosage***
Co Q10 (Kaneka Q10)	200 to 400 mg daily
B vitamins in their better forms	B6 (pyridoxal 5'-phosphate): 35 mg twice daily Folate (5-MTHF (5-methyltetrahydrofolic acid)): 5 mg twice daily B12 (methylcobalamin): 5,000 mcg sublingual quick-dissolving tablet once daily
Vitamin C (mineral ascorbates)	1,000 mg two to three times daily
Vitamin D3	2,000 to 10,000 IUs daily, depending on blood levels (see Appendix A)

Vitamin E (tocopherols)	400 IUs daily
Calcium citrate	250 mg twice daily
Magnesium glycinate	350 to 400 mg twice daily
Omega-3 essential fatty acids (EFAs)	1 gram four times daily with an emphasis on higher levels of DHA as found in cod liver oil
Digestive enzymes (protease, amylase, and lipase)	50,000 to 100,000 USP of protease, 50,000 to 100,000 USP of amylase, and 8,000 to 15,000 USP of lipase with meals

Mitigating Migraines

A *migraine* is a throbbing headache on one side of the head accompanied by extreme sensitivity to light, nausea, and vomiting. If you have recurrent migraines, consult your doctor, who can perform tests to diagnose or rule out glaucoma, hypertension, brain tumors, or other conditions that may be causing your migraines. Other possible causes include dramatic blood sugar fluctuations; food allergies; certain foods including chocolate, cheese, citrus fruits; caffeine and alcohol (especially red wine); monosodium glutamate; aspartame; and severe stress and sleep deprivation.

Adopt a healthy diet, and avoid any food triggers: refined sugar, caffeine, alcohol (especially red wine), salt, chocolate, and the others listed previously. Better yet, team up with a functional medicine doctor to develop a personalized nutritional plan. In addition to making dietary adjustments, consider taking the following supplements, which can reduce the frequency, severity, and duration of migraines:

Supplement	***Dosage***
Magnesium bis-glycinate chelate	125 mg twice daily
Co Q10 (Kaneka Q10)	100 to 400 mg daily
Folate (5-MTHF)	5 mg daily
Vitamin C (mineral ascorbates)	1,000 mg three times daily
Vitamin D3	2,000 to 10,000 IUs daily, depending on blood levels (see Appendix A)
Omega-3 essential fatty acids (EFAs)	1 gram yielding 180 mg EPA and 120 mg DHA four times daily
Niacin (nicotinic acid)	500 mg immediately at first sign of migraine (see note following table)
ALA (controlled release)	600 mg before meals
Butterbur	75 mg twice daily
5-HTP (controlled release)	100 mg two to three times daily
Riboflavin	200 to 400 mg daily

Feverfew	300 mg daily

Niacin is likely to cause a flushing effect — red, itchy skin — that's not dangerous and passes within 30 minutes. Refer to the earlier section "High cholesterol," which includes a discussion on mitigating these effects.

Strengthening Your Bones: Osteoporosis

Osteoporosis means "porous bones." It's an inflammatory condition in which bones lose density over time. Symptoms include unexplained back pain, loss of height, a stooped posture, a *dowager's hump* (curvature or bowing of the upper back), and bones that fracture easily.

As with most illnesses, preventing osteoporosis is easier than curing it. Build a strong bone bank in your childhood, adolescent, and early adult years. After the age of 35, your bone bank has more withdrawals than deposits.

If you have symptoms of osteoporosis or are over the age of 35 and are concerned about your bone density, get a bone density x-ray (DEXA).

If you have osteoporosis or simply want to take steps to improve your bone density, follow these suggestions:

* Test for and treat any food allergies or sensitivities, with a focus on gluten sensitivity.
* Adopt a healthy diet and lifestyle. Eliminate sugar, soda, caffeine, salt, and alcohol, all of which raise the body's acidity and contribute to bone loss. Consume a low-glycemic, anti-inflammatory diet.
* If you smoke, stop.
* Engage in weight-bearing exercise. Your bones need resistance to develop strength.
* Treat hormonal imbalances (see Chapter 18).
* Expose your skin to sunlight several times a week without getting sunburn. Doing so raises your vitamin D level. (Contrary to popular belief, drinking milk doesn't increase bone density.)
* Eat unprocessed, whole foods: vegetables, fruits, nuts, seeds, wild fish, and pastured animal products.
* Avoid unnecessary medications, including antacids, prednisone, and many others.
* Try the following supplements, which can help improve bone density:

Supplement	***Dosage***
Vitamin D3	2,000 to 10,000 IUs daily, depending on blood levels (see Appendix A)
Vitamin K2 (menaquinone-	45 mcg twice daily (see

7)	Appendix A for precautions)
Calcium and phosphorous (MCHC)	2.2 grams twice daily (see Appendix A)
Choline and silicon	60 mg as choline stabilized orthosilicic acid twice daily
Strontium	680 mg in divided doses daily for just one year in high-risk patients then reduce dosage. Until long-term safety data is available don't take high-dose strontium indefinitely.

* Get hormone levels tested and supplement only if necessary. (See Chapter 18 for details.)

Taking the Punch out of Parkinson's Disease

Parkinson's disease is a central nervous system disorder characterized by a reduction in *dopamine,* a neurotransmitter that regulates movement and emotional response. This reduction in dopamine results in tremor (shaking), stooped-forward posture, impaired movement (as if wearing cement boots), depression, anxiety, apathy, difficulty chewing, urinary incontinence, constipation, insomnia, and loss of libido. Pharmaceutical medications, including levodopa, are used to control symptoms, but they lose their effectiveness over time and may cause undesirable side effects, such as *dyskinesia* — involuntary movement.

Don't stop taking any medications your doctor prescribes. Instead, team up with your doctor to add natural remedies to your medication regimen and strive toward decreasing the amount of medication required to control symptoms.

Instead of merely increasing dopamine levels or stimulating dopamine receptors in the brain, the natural cures approach targets the cause of the decrease in dopamine. In Parkinson's disease you need to extinguish the fire, not just the smoke by doing the following:

* **Drink one to two cups of coffee (not decaf) daily.** Opt for organic coffee with no added sweeteners. Caffeine protects against Parkinson's.
* **Adopt an anti-inflammatory diet.** Increase consumption of sulfur-containing foods, such as cruciferous vegetables (broccoli, cauliflower, brussels sprouts, and kale), which provide the raw material for glutathione, a powerful antioxidant.
* **Avoid processed food.** Eat only organic, pesticide-free produce; fish caught in the wild; and organic, pastured livestock free of antibiotics, growth hormones, and steroids.
* **Get glutathione injections three or more times a week.** Glutathione makes brain cells more sensitive to dopamine and helps detoxify the liver and lungs. Intravenous glutathione must be administered by a qualified healthcare professional. N-acetyl cysteine and ALA (alpha-lipoic acid) increase glutathione, as well, but these too should be administered intravenously for optimum results.

* **Supplement your diet with the following nutrients:**

Supplement	***Dosage***
Vitamin E (tocopherols)	400 IUs daily
Vitamin C (mineral ascorbates)	1,000 mg two to three times daily
Vitamin D3	2,000 to 10,000 IUs daily, depending on blood levels (see Appendix A)
N-acetyl cysteine	1 to 2 g twice daily
ALA (controlled release)	600 mg twice daily 15 minutes before meals
DHA (cod liver oil)	550 mg twice daily
CoQ10 (Kaneka Q10)	200 to 400 mg daily
Phospatidylserine	100 mg twice daily
Vinpocetine	5 mg twice daily (See Appendix B for precautions)

* **Follow the homocysteine lowering protocol.** See the earlier section

Scott J. Banks has just joined another world-class group of chiropractic doctors. He has completed Level 2 advanced training for Sigma-Computer Assisted Instrumentation and Spinal Decompression and is certified by The International Medical Advisory Board on Spinal Decompression and Disc Centers of America What this means is that Dr. Scott J. Banks is one of a few doctors in the U.S. to have this level of training. So, what that really means is when a patient chooses to partner with Dr. Banks for health-related issues, that patient can rest assured that he/she is in the most capable hands (literally and figuratively) in the field of Alternative Medicine and Chiropractic care.

In 2013, Dr. Banks joined an elite group of Institute for Functional Medicine Certified Practitioners. He is uniquely trained in the functional medicine model to identify and treat the root causes of illness, disease and chronic disorders. By shifting the traditional disease-centered focus of medical practice to a more patient-centered methodology, Dr. Banks concentrates on the whole person, not just an isolated set of symptoms. As a Functional Medicine practitioner, he spends time with his patients, listening to their histories and looking at the interactions among genetic, environmental, and lifestyle factors that can influence long-term health and complex, chronic disease. As a valued Institute for Functional Medicine Educator, Dr. Banks has been assisting the IFM faculty in facilitating at IFM's course, AFMCP.

Always striving to further his medicinal knowledge and offer additional health-oriented solutions for his patients, Dr. Banks is also a Certified Gluten Practitioner. He has the expertise to identify and treat gluten-related disorders, such as non-celiac gluten sensitivity (NCGS) and celiac disease.

Dr. Banks was voted winner Best of Long Island in the Alternative Medicine category 2016 and 2017..

In 2015 Dr. Scott J. Banks, introduced his private label supplements to enhance and sustain wellbeing for all of his patients and clients. Please visit www.spinelife.com, http://spinelifestore.com/dr-banks-functional-medicine-solutions/ or call 877-698-4826 for more information on Dr. Banks and his products.

Dr. Banks', Natural Cures for Dummies (Wiley), April 2015, ranked #1 on Amazon and awarded winner of USA Best Book Awards 2015 by USA Book News in Alternative Medicine category.

Dr. Scott J. Banks, DC, IFMCP, holds a Bachelor of Science Degree from Farleigh Dickinson University, a Doctor of Chiropractic from New York Chiropractic College and is a Clinical Nutritionist. As an Adjunct Professor at Nassau Community College, in Garden City, New York he teaches Anatomy and Physiology. He has been in clinical practice, Banks Chiropractic and Wellness Center, for more than 30 years with offices on Long Island, New York.

MICHAEL POSNER
DC

Healing at the Speed of Light

I make it my business to search out the very best clinically proven quality products in today's marketplace. I use everything myself first, so that what I say is not just hearsay, but rather from personal experience. I must admit, that I am very skeptical, but at the same time, I am open minded about trying new things. I cannot ask for more than that from you, the reader of this chapter. I will share with you real experiences that I have had, rather than just theory. So here we go!

Did you know that **LASER** is an acronym for **L**ight **A**mplification by **S**timulated **E**mission of **R**adiation? While light from the sun has been used over the centuries for healing, modern scientists have progressed in leaps and bounds with their remarkable inventions of devices that use light as a healing modality. Yet the remarkable invention of a powerful, dual head, robotic laser technology has truly raised the bar and transformed and accelerated the body's ability in the areas of natural healing, pain relief, reduction of inflammation and cell growth. The results I have seen are so truly profound that this could be considered one of the greatest advancements in the field of Laser technology today.

My objective here is not to bore you with all the different types of lasers, nor do I want to discuss the physics of how they work. Rather, I would like to speak about the amazing testimonials, my own healing, and the benefits that I have personally witnessed with the patients at my clinic utilizing a MLS Class 4 Laser. It is my heartfelt desire to make people more conscious about the benefits of laser for pain, inflammation, and cellular healing. Although some explanations might not speak to the scientific mind, I am determined to keep it simple for the layperson.

Let me begin with my personal experience. My thumb was crippled with arthritic pain and weakness. I also had a trigger finger that would get stuck with any movement; I had little to no range of motion. My thumb was completely weak, and was useless for any activity. This resulted from over 30 years of doing Chiropractic and massage. Before seeking medical treatment, I tried everything natural, Chiropractic, Massage, Acupuncture, nutritional supplements, topical balms. You name it, I tried it.

The hand specialist offered me a cortisone shot as the first line of treatment. If that didn't work he said I needed surgery. I was disappointed because I did not want the side effects of cortisone and did not want surgery, so I left the office. As a chiropractor, I always seek the natural remedies as my first line of action. Within 2 weeks, the condition of my thumb had so deteriorated, that I became desperate. Realizing that everything up to this point had failed, I submitted to the cortisone injection. The effects of this shot worked for about 6 weeks and then when it wore off, my thumb was even worse than before.

I purchased the MLS Laser to treat my thumb. After the first treatment, to my total amazement, my thumb was completely asymptomatic. That lasted for about a day or two and then some of the pain came back but I had complete ranges of motion. My finger no longer got stuck. After about 5-6 treatments my finger returned to normal and I had zero symptoms, total strength and I could now use my thumb, working without incident. It has been over 6 months and my thumb has been healed! The MLS laser fixed me!

Why MLS Laser?

The innovative and patented ***Multiwave Locked System*** **(MLS®)** Therapy Laser was developed to produce an efficient and simultaneous effect on pain, inflammation, and edema, exceeding the limits of traditional LLLT (low power) and concerns of HP (high power) laser therapy. MLS

technology delivers therapeutic wavelengths, 808nm (anti-edema and anti-inflammatory) and 905nm (analgesic), allowing a tissue penetration depth of 3-4 cm. An energetic synergy is created when delivering these wavelengths that produces greater anti-inflammatory and analgesic effects than either can produce on its own, while minimizing the risk of thermal damage. It is this unique combination and synchronization of continuous and pulsed emissions that characterizes MLS and distinguishes it from other Class 4 lasers.

Unlike early-generation Class 4 technology, MLS® Laser Therapy has the capability to deliver controlled laser energy. This unique feature provides a more accurate therapeutic dose delivery, which means consistent and repeatable results.

With high levels of efficacy, safety, and consistency, MLS Laser Therapy can help health care practitioners relieve pain and restore lives.

Multiwave Locked System (MLS®) Laser Therapy is a patented, FDA cleared technology designed to produce an efficient and simultaneous effect on pain, contracture, inflammation, and edema within a short period of time. The control system that generates the MLS pulse synchronizes the emissions to achieve optimum results. Due to this unique synchronization, the various therapeutic effects not only take place at the same time, but reciprocally reinforce each other, without the risk of thermal damage.

Characteristics of MLS Laser Therapy

THE EVOLUTION OF THERAPEUTIC LASERS

- Class 3b Lasers

> *Less effective, but safe*
>
> Because they are stationary, Class 3b lasers allow you to control dosing at appropriate wavelengths. However, they do not evoke as rapid and dramatic a stimulatory response as high-power alternatives.

- High-power Class 4 Lasers

> *Powerful, but potentially dangerous*
>
> While some Class 4 lasers can provide a stimulatory response, they do not always provide appropriate wavelength options. They can also cause collateral tissue damage due to excessive heat. As a result, the user must keep the laser in motion at all times, making dosing control nearly impossible.

- MLS Laser Therapy

> *Effective and safe*
>
> MLS Laser Therapy combines stationary application for exceptional dosing control with the appropriate combination of wavelengths. By delivering separate but simultaneous wavelengths for both anti-edema and analgesic effects, this laser evokes a rapid, powerful stimulatory response without the threat of tissue damage.

What is a high powered deep tissue MLS Laser Therapy?

MLS laser therapy is a non-invasive, safe and effective treatment modality where light is used to relieve pain, reduce inflammation, promote wound healing and soft tissue repair. MLS laser is

the only multi-wave locked system, dual wave, fully robotic laser therapy system on the market. This means deeper penetration with no heat produced allowing faster healing with no known side effects. It has been cleared by the FDA since 2009.

MLS laser therapy is a medical breakthrough therapeutic device with unparalleled applications and treatment outcomes. The laser works by converting light into biochemical energy, resulting in normal cell function, which causes symptoms (pain) to disappear. The primary biological action of the laser results from stimulation of cellular transport mechanisms in the mitochondria, cell membranes and epithelial tissues. This action causes the release of vasodilating (enlarging or expanding) chemicals, the stimulation of DNA and RNA (building blocks) synthesis, an increase in enzyme production, an increase of superoxide dismutase (antioxidant) activity, normalization of tissue PH, and increased ATP production (healing of the cells from the inside).

The increase of vasodilatations and nitric acid (blood supply), and improved microcirculation, will increase the supply of cellular nutrition and detoxification, thus promoting tissue repair and remodeling (which means faster healing). Significant reduction in edema (swelling) is also evident, which also leads to pain reduction.

How is the treatment done?

Most treatments are fully robotic, although there are some cases where manual treatments are indicated. The laser placed 8 inches above the skin, allowing the healing energy to properly penetrate tissue, where it interacts with various intercellular bio-molecules, resulting in the restoration of normal cell function. The laser treatment enhances the body's natural healing processes. Light energy is converted into biochemical energy. Think of this like photosynthesis is in plants. The result is, that normal cell functions are restored. The process results in the disappearance of symptoms, and increases the speed at which your body heals. Other effects include stimulation of the immune system response, improvement of lymphatic drainage, and the enhancement of the body's natural healing processes.

The beneficial physiological changes noted above are the result of tissue regeneration and cellular stimulation. This is possible because we are using the newest, most powerful and only robotic laser available, which allows our patients to live a pain free life, without having to suffer using dangerous drugs.

10 Benefits of MLS Laser Therapy

1. Anti-Inflammatory: MLS Laser Therapy has an anti-edema effect as it causes vasodilation, but also because it activates the lymphatic drainage system which drains swollen areas. As a result, there is a reduction in swelling caused by bruising or inflammation.

2. Analgesic: MLS Laser Therapy has a beneficial effect on nerve cells. It blocks pain transmitted by these cells to the brain which decreases nerve sensitivity. Also, due to the decreased inflammation, there is less edema and less pain. Another pain blocking mechanism involves the production of high levels of pain killing chemicals such as endorphins and enkephalin from the brain and adrenal gland.

3. Accelerated Tissue Repair and Cell Growth: Photons of light from lasers penetrate deeply into tissue and accelerate cellular reproduction and growth. The laser light increases the energy available to the cell, so that the cell can take on nutrients faster and get rid of waste products. Because of exposure to laser light, damaged cells are repaired faster.

4. Improved Vascular Activity: Laser light will significantly increase the formation of new

capillaries in damaged tissue, which speeds up the healing process, closes wounds quickly and reduces scar tissue. Additional benefits include acceleration of angiogenesis, which causes temporary vasodilation and an increase in the diameter of blood vessels.

5. Increases Metabolic Activity: MLS Laser Therapy creates higher outputs of specific enzymes, greater oxygen and food particle loads for blood cells.

6. Trigger Points and Acupuncture Points: MLS Laser Therapy stimulates muscle trigger points and acupuncture points on a noninvasive basis, providing musculoskeletal pain relief.

7. Reduced Fibrous Tissue Formation: MLS® Laser Therapy reduces the formation of scar tissue, following tissue damage from cuts, scratches, burns or surgery.

8. Improved Nerve Function: Slow recovery of nerve functions in damaged tissue can result in numbness and impaired limbs. Laser light speeds the process of nerve cell reconnection and increases the amplitude of action potentials to optimize muscle healing.

9. Immunoregulation: Laser light has a direct effect on immunity status by stimulating immunoglobulins and lymphocytes. Laser emissions are absorbed by chromophores (molecule enzymes) that react to laser light. Upon exposure to the laser, the enzyme flavomononucleotide is activated and starts the production of ATP (adenosinetriphosphate), which is the major carrier of cell energy and the energy source for all chemical reactions in the cells.

10. Faster Wound Healing: Laser light stimulates fibroblast development in damaged tissue. Fibroblasts are the building blocks of collagen, which is the essential protein required to replace old tissue or to repair tissue injuries. As a result, MLS® Laser Therapy is effective post surgically as well as in the treatment of open wounds and burns.

Conditions We Treat

Back Pain

- Decreases pain and inflammation
- Accelerates healing of soft tissues
- Accelerates healing of disc and nerve root
- Decreases thickening of hypertrophic tissue
- Reduces chance of having back surgery

Sciatica

- Pain in the buttocks and down the thigh and leg (below the level of the knee)
- Most often due to disc herniation and degenerative arthritis
- Results in numbness, pain, and muscular weakness
- Laser therapy is the safest, most effective treatment for nerve pathology

Post-Operative Pain

- Strong antimicrobial effect means less infection post operative.
- Decreased scar tissue formation
- Less pain/ less activity intolerance
- Increased collagen and fibroblast growth means stronger tensile strength.
- Decrease post operative rehabilitation by 30%-50%.

Neuropathy

- Nerve pathology secondary to impaired circulation (Diabetes, chemotherapy, medications, degenerative vascular disease).
- Symptoms include; pain, burning, numbness, tingling, loss of balance.

- Several medications available that only treat the symptoms. Until laser therapy, nothing was available to address the root cause.
- Laser therapy increases blood flow (vasodilation and neo-capillary growth), decreases pain and inflammation, and accelerates the healing of the peripheral nerve endings.

Arthritis

- Arthritis is a form of joint disorder that involves the inflammation of one or more joints.
- There are over 100 types of arthritis.
- Laser therapy has been clinically shown to decrease inflammation in the joints, increasing blood flow to the areas of arthritis leading to an overall decrease in pain and inflammation.

Herniation

- Damage to outer layers of disc (annular fibers) resulting in the migration of gelatinous material (Nucleus Pulpous) to the periphery, which can result in neurological symptoms.
- Traditional treatments aim to decrease inflammation (epidural injections) and surgical removal of damaged disc material.
- Laser therapy is the only treatment which safely helps to control inflammation as well as actually heal the outer fibers of the damaged disc!
- Laser therapy can actually increase the tensile strength of the outer fibers of the disc making it stronger and more resilient.

Additional Conditions We Treat

- Ankle Pain
- Achilles Tendonitis
- Ankle Sprain
- Arm Pain
- Arthritis
- Back Pain
- Carpal Tunnel Syndrome
- Cervical Radicular Pain
- Disc Herniation
- Jaw Pain
- Foot Pain
- Golfers Elbow
- Headache
- Hip Arthritis
- Hip Bursitis / ITB Syndrome
- Knee Arthritis
- Knee Pain
- Knee Sprain
- Leg Pain
- Metatarsalgia
- Neck Pain
- Patella Pain
- Peripheral/Neuropathy Diabetic/Nerve)
- Plantar Fasciitis

Remarkable Testimonials From My Patients

I came to see Dr. Posner after years of trying to get my neck pain to go away. I am a physical therapist and exercise trainer, I saw every type of doctor and tried all kinds of therapies to get relief with no satisfaction. Being in the healing profession myself, I left no stone unturned and did it all. From epidurals to cortisone and exercise, nothing worked. I then saw Dr. Posner for MLS laser treatment along with Chiropractic and within about 8 visits I was pain free. I am an enthusiastic tennis and racquetball player and didn't stop during the treatment and I still got the results. That really impressed me! Thank you, Dr. Posner and the MLS robotic laser.

Denise B.

I suffered with sciatica on and off for years. I had multiple epidural shots with only minor relief. Physical therapy didn't help either. I didn't know what to do. Drugs, at best, helped with the pain temporarily, but I couldn't take the gastric side effects. My boyfriend heard about Dr. Posner and his laser and recommended that I see him. After 10 visits the numbness and pain was almost completely gone and I am looking forward to my next visit. I have not felt this good in years. If you suffer with sciatica I highly recommend that you see Dr. Posner He's the best!

Terry M.

I was doing some renovations for Dr. Posner and he told me about MLS laser. I am a very skeptical person and continued to question the validity of Dr. Posner's claims. Rather than trying to convince me with his words he took me into the office and gave me a treatment on my thumb which suffered recurrent tendonitis, was jammed multiple times and strained and sprained over the course of many years.

Just for a little background, I played goalie on a soccer team most of my life (now 45) and had multiple injuries to my hands. Dr. Posner gave me one treatment and I must admit my skepticism immediately left as I now can move my thumb and it is completely pain free. Truly this laser immediately took away my skepticism (and pain). I must now say that this is an incredible technology (only one treatment).

I am still doing work for him weeks later and my thumb still feels good. If you are skeptical as well, try the laser you might be as amazed as I was. I am planning on resuming treatment as soon as my job with him is done.

Dan V.

I am a practicing Chiropractor and a friend of Dr Posner's. I am an avid hockey player and play regularly as I am on a team, and playing also helps me to keep my sanity. About a week ago I injured my hamstring muscle and had a hard time walking so obviously, I could not play hockey. After trying several therapies and treatments I was no better. I recalled Dr Posner telling me about his laser so I went to see him. After one treatment, I was completely better and pain free. I could not believe it! MLS laser rocks and I am completely impressed. Thank you so much!

Dr. Davin H.

I have been suffering with cervical arthritis and disc problems for over 20 plus years. I have tried so many different therapies to include, pain management doctors, physical therapy, nerve blocks, epidurals, anti inflammatory drugs, pain killers, vitamins, massage, chiropractic, acupuncture, just about everything out there. After receiving about 12 MLS laser sessions I have to say that I am pain free for the first time in years. The doctor told me to come in once every month or two to maintain the results and I am happy to do that. What a pleasure to finally be out of pain! I am very thankful for MLS laser treatments and I believe that this is the future for pain management and healing.

Sharon E.

My name is Nicole and I have had trouble with my neck for years. It got to the point where I had a daily constant headache which affected my daily routine. I was very cranky, irritable, wasn't able to sleep and unable to concentrate at work.

I have gone to other Chiropractors 2-3 times a week for about a year and nothing helped – still the same irritable, insomniac and in pain person.

Not too long ago, I was rear-ended in a car accident – which made my neck 100 times worse. Oh boy, did I have a HORRIBLE constant migraine!

After meeting with Dr. Posner and doing my research – his experience really stood out! He adjusted me and used the laser 2 times per week. The Laser was phenomenal, it helped reduce my pain and inflammation almost immediately.

I'm happy I took the time to choose the best place for my care! Dr. Posner has helped me dramatically and I saw significant improvement – I am now able to live day to day without constant headaches! It's all due to effective adjustments and laser treatments from Dr. Posner!

Thanks Dr. Posner – you're awesome!

Nicole C.

I came to see Dr Posner after injuring my calf jogging. I usually jog 18 miles per week, but I was unable to put any weight on that leg. I limped into his office and after the first treatment felt improvement but still couldn't run. After the third treatment, I was good to go and resumed my jogging without any further pain or problems. I am so impressed with how the MLS Laser worked so quickly. I recommend this laser with all my heart to anyone who hurts or is an athlete!

Sharon S.

Frequently Asked Questions

What does laser therapy have over other forms of therapy?
It does not require the use of drugs or surgery, there are no known side effects, and it is quick/convenient. Studies have shown that it is equal to or more effective than other forms of physical therapy. These studies were performed at many prestigious institutions, including Harvard University.

Does it hurt? What does the treatment feel like?
There is little or no sensation during treatment. There is no pain associated during laser application. Laser treatment is relaxing and some people even fall asleep.

How long does the treatment take?
The typical course of treatment is 10 to 15 minutes, depending on the size of the area being treated. Treatments are typically received 2 to 3 times a week. Treatment plans are determined on an individual basis.

How many treatments does it take?
This depends on the nature of the condition being treated. The typical treatment protocol is between 6 and 12 visits. Conditions such as severe arthritis may require ongoing periodic care to control pain.

How long before results are felt?
You may feel improvement in your condition (usually pain reduction) after the 1 to 3 treatments. For some more chronic conditions it may take up to 6 visits to feel the benefits of laser therapy. Not everyone responds to laser therapy and results cannot be guaranteed.

Are the results long lasting?
MLS Laser Therapy is about healing. It's not about masking or covering up a condition. When you feel better from this therapy... it's because you are better. Therefore, results have been found to be quite long lasting.

Can it be used in conjunction with other forms of treatment?
Yes, MLS Laser Therapy is sometimes more effective when combined with other forms of therapy, including physical therapy, chiropractic, massage, soft tissue mobilization, electrotherapy, and following surgery.

How do I know if laser therapy is right for me?
We will evaluate your condition and perform a complete laser therapy examination to determine if you are a candidate for this procedure. Call us to schedule your evaluation or a consultation. Consultations are always at no cost to the patient.

Can laser therapy be used over medical implants or over metal?
Yes, laser therapy is a light treatment. No heating is involved with the surgical or metal implants. It can be used safely with no side effects. It is extremely effective for post-operative wound healing. Many hip and knee replacement patients see us for care.

Michael Posner graduated from NY Chiropractic College in 1983 and has a successful Wholistic family practice in Huntington Village, N.Y. He integrates many different therapies for his patients which include Acupuncture, Massage Therapy, Functional Nutrition, Extracorporeal Shock Wave Therapy, Weight Management, and his latest addition, MLS Laser Therapy. He has devoted numerous years teaching Tai Chi, Chi Kung and Meditation in NYC, on Long Island and has done workshops in Costa Rica.

Dr. Posner is well known as a gifted healer in the chiropractic profession and is well regarded by his loyal patients and the community at large. Because of his many years of training in meditation, yoga and as a black belt in the martial arts, as well as his mastery in the practice of Tai Chi and Chi Kung, he developed a profound level of sensitivity in his hands. He constantly amazes his patients with his ability to magnetize immediately to the problem areas in his patients' bodies. He then delivers a gentle, precise adjustment to the problem areas, removing their blockages.

As the stressors of daily life accumulate, they have a detrimental impact on one's health in many ways which they may or may not realize. Those nagging aches and pains in our bodies can be traced to nervous system interference and joint dysfunction.

Drawing upon his vast experience, Dr. Posner reflects on the "unique wholeness" of each person and considers how stress damages their overall health and wellbeing. He looks to the brain and nervous system to find the source of their neck, back, shoulder, joint and headache problems and then removes these interferences with pin-point accurate, gentle adjustments.

When the structure is balanced and the supporting muscles are relaxed and retrained, the Innate Intelligence of the body does what it does best, which is to heal itself. This differs from conventional medicine, which often just manages the symptoms through medications and does not get to the root of the problem. Dr. Posner's primary goals are to get his patients out of pain fast and restore them to their normal daily activities, back to doing the things they love. He is dedicated to teaching his patients how to harmonize their emotions, quiet their minds and return to their attunement within, through deep breathing, Chi Kung and meditation practices. This helps to align body, mind and Spirit, thereby producing vibrant health and wellbeing to last a lifetime.

FREDERICK TINARI

DC, MS, DACBN, DCBCN

Applied Kinesiology

Cutting Edge in Holistic Health

Frederick Tinari DC, MS, DACBN, DCBCN

Applied Kinesiology (AK) is an examination system that aids a doctor in a patient's exam and treatment. The combined terms "applied" and "kinesiology" describes the basis of this system. Kinesiology is the study of motion and biomechanics, while Applied is the application of the findings. AK incorporates the evaluation of chemical, mental and structural aspects of health. Through the use of manual muscle testing used by AK and combined with traditional methods of diagnosis practitioners are able to evaluate the functions of the body through non-invasive means. Applied Kinesiology is truly a unique system within the healing arts, and it has become a dynamic movement within the healthcare arena.

George J. Goodheart Jr. DC is known as the father of Applied Kinesiology. A graduate of National College of Chiropractic, Class of 1939, he began practicing with his father in Detroit, Michigan. Soon after, he enlisted into the United States Air Force where he served from 1941 until 1946, achieving the rank of Major before his honorable discharge.

Applied Kinesiology originated when Dr. Goodheart began treatment on a twenty-four year old male patient. This young man was unable to pass a job required physical due to his inability to move one of his arms forward. Dr. Goodheart observed in his examination of the patient that when he attempted to push the arm forward his shoulder blade shifted to the outside. This is called Winging of the Scapular. The muscle associated with this the Serratus Anterior and one of its jobs is to hold the scapular to the chest wall thereby allowing the arm to move in a normal manner. With testing each of the different muscles, Dr. Goodheart was able to isolate the Serratus Anterior muscle in this patient and found it to be weak. Concentrating on this muscle, Dr. Goodheart was able to find that there were also nodules that needed to be addressed. By working on this particular muscle and reducing the nodules within the muscle, the muscle was shown to strengthen and the patient's arm was able to move forward. The patient was able to pass his required physical exam and thus began the development and growth of Applied Kinesiology.

If this method of testing could help one patient, then why not all of his patients? Dr. Goodheart began to study the origin and insertions of all the muscles in the body. He also studied the Chapman Reflexes, developed and named for Frank Chapman, DO in 1937. Dr. Goodheart found that by stimulating the Chapman Reflexes, he could strengthen certain muscles within the body, making them stronger. He termed these reflexes Neurolymphatic points.

Over time, Dr. Goodheart found that specific muscles were associated with vascular reflexes, acupuncture meridians, organs, glands, vitamins and minerals and subluxations of the spine, joints and or skull. He studied cranial manipulation and sacral-occiputal technique (SOT) under Major Bertrand DeJarnette DC, DO. With Janet Travell, MD, he studied her work in trigger point therapy and myofascial pain syndrome. Dr. Goodheart continued to add what he learned from his studies and blend it into his developing Applied Kinesiology.

It was in 1964; at a meeting of The American Chiropractic Association that Dr. Goodheart first taught his evolving technique to his peers. It was generally well received by those doctors in attendance. From this point on other doctors began to follow his teachings and use his techniques and Applied Kinesiology began to grow. As those doctors using the AK techniques began to flourish, the International College of Applied Kinesiology (ICAK) was formed in 1976. It

was founded to promote the continued growth, research and development of AK. Beginning originally in the United States with mainly chiropractors as members, it quickly expanded to include all types of healthcare practitioners. Doctors in Europe found Applied Kinesiology to be most intriguing and wanted to learn more. The ICAK quickly expanded into Europe and became a truly international organization. It was in Europe where the vast majority of those drawn to learn more about Applied Kinesiology and join the organization were traditional medical doctors. Today, including the United States, the ICAK has members in Australia, Austria, Benelux, Brazil, Canada, Germany, Korea, Russia, Sweden, Switzerland and the United Kingdom. The numbers continue to grow as new members are added almost daily representing additional countries.

As in most new things that grow, problems arose. Since the method name, Applied Kinesiology was never trademarked, nor copy righted from its inception, it paved the way for anyone who knew even a basic muscle test to use the phrase AK when treating patients. This regrettably allowed individuals with no formal training, or expertise in Applied Kinesiology to utilize the basic parts of AK and market themselves as an expert in the field. This in turn left the medical field and the public to question the validity of Applied Kinesiology.

Following many years of turmoil and legal filings, the ICAK was finally able to trademark the term Professional Applied Kinesiologist, (PAK). This meant that only those health care providers that fulfilled the ICAK requirements would be able to use the term PAK when treating and marketing their practices. These included being a professional healthcare provider licensed to diagnose, this includes Allopathic (MD), Osteopathic (DO), Chiropractic (DC), Naturopathic (ND), Dentist (DDS), Acupuncturists (LAC), Psychologist (Ph.D.) and Veterinary (DVM). Applied Kinesiology is a complicated system of analysis, evaluation and treatment protocols that takes a competent practitioner to perfect. Those individuals that wish to become an advanced PAK practitioner need to complete an Applied Kinesiology certification program. An advanced diplomat status may be achieved through further study and testing.

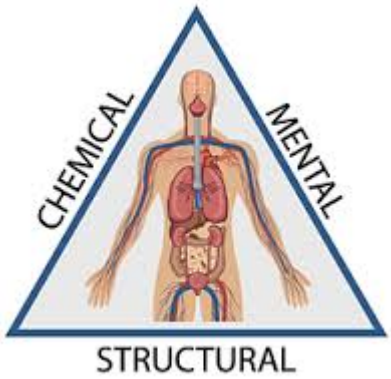
Muscle testing is the basic tool used by a Professional Applied Kinesiologist. It has been found that there are many different aspects of life that influence our health, muscle testing (AK) helps to isolate those muscles that are being affected resulting in abnormal muscle function. Dr. Goodheart found that with proper treatment the muscle function can return to normal thereby alleviating patient distress.

Applied Kinesiology adds another dimension to the examination and treatment of patients. It truly uses the body's own language to aide in the diagnosis of the patient and offers an assortment of tools to help in rectifying of issues for the patient. Athletes seem to appreciate AK best. This is due to the testing methods' ability to detect subtle changes in an athlete's muscle function. Applied Kinesiology helps to expedite healing allowing athletes to return to their sport of choice when the body is in balance.

Even though muscle testing is the basis of Applied Kinesiology, it is still based in science and is an art unto itself. Anyone can push on a muscle and deem it muscle testing, however a true PAK takes years of study and practiced learning in order to truly be an Applied Kinesiologist. Proper muscle testing involves knowing the exact function of the each particular muscle being tested and the associated muscles that are recruited. This includes the origin and insertion of each of these muscles as well as the neurolymphatic and neurovascular points associated with them. Also important are the organs and spinal segments related to each of these muscles and how they are affected by them.

When testing a muscle there are four (4) responses that are looked for and evaluated: 1- Muscle tests normal, 2- Muscle tests weak, 3- Muscle is pathologically weak, 4- Muscle is

hypertonic. To correct any of the above issues requires numerous possibilities and are very complex. Doctors' David Walther, D.C., Benjamin Markham, D.C and Robert Blaich, D.C. developed a flow chart of Applied Kinesiology, this aids a PAK in the assessment, treatment and correction of patient issues in a step by step format.



The basic concept of Applied Kinesiology is the Triad of Health. Dr. Goodheart believed that there are three main factors that form an equilateral triangle when addressing health. The triangle is comprised of the Chemical on the left, made up of vitamins and minerals, foods and medications. Allopathic physician expand this side with the addition of medications/drugs while holistic practitioners expand this side with foods, vitamins and minerals. The right side of the triangle is the Mental/Spiritual side. Again allopathic doctors expand this side with the addition of medications/drugs, while holistic practitioners utilize meditation, counseling, yoga etc… The base of the equilateral triangle is of course the Structural side. Chiropractors, physical therapists, physiatrists, osteopaths and orthopedists concentrate and expand the structural side. Different practitioners emphasize different sides of the triangle while treating patients, but together they create an equal sided triangle. In Applied Kinesiology doctors strive to maintain a balance between all three sides of the triangle therefore helping to balance their patients.

Balance also includes the analysis of the movement and posture of the patient. A patients' posture and gait can reveal many interesting aspects of their health. If an overall structural balance is not present then pain is common and increased wear and tear to joints can result. This is true also of organ and gland issues. Remember that each organ is related to a particular muscle area of the spine and associated with corresponding vitamins and minerals and acupuncture meridians. AK works to balance the structural and well as the functional aspects of the body allowing the body to work at healing itself.

Applied Kinesiology is an exciting area of study. Dr. Goodheart had the genius to weave various principles together resulting in what has become a cutting edge field of examination and diagnosis. It attracts doctors and professionals who have a thirst for knowledge above and beyond what they have learned in school. The incorporation of many other disciplines into the study of AK helps to give these professionals the added tools in order to treat their patients and to address the health issues that plague the public today.

For more information on the ICAK see: http://www.icak.com

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6405 Metcalf Ave. Suite 503, Shawnee Mission, KS 66202

Frederick Tinari, DC, MS, DACBN, DCBCN
1311 Broadway Avenue
Holbrook, New York, 11741
631-467-8224
Fax: 631-585-7575

Frederick Tinari, DC has been a chiropractor and nutritionist for over thirty-four years. Undergraduate studies were done through the SUNY system of New York where he receive a BS in biology while minoring in chemistry. He completed his DC degree at National College of Chiropractic in Lombard, IL and his MS degree in Clinical Nutrition from the University of Bridgeport. At the completion of chiropractic school he was certified in Acupuncture in Illinois and holds a certification in Applied Kinesiology.

Dr. Tinari previously held executive board status in the ICAK as membership chairman.

Dr. Tinari is currently a member of the ACA Council of Nutrition. He is board certified diplomat of the American Clinical Board of Nutrition and is a board certified diplomat of the CBCN; Chiropractic Board of Clinical Nutrition. Dr. Tinari currently is serving a board position in the ACBN.

When at National College of Chiropractic he was president of the student chapter of the ICAK. While a student himself, he took the ICAK 100 hour course several times under Drs. George Goodheart, Gerard Achilly, Jerry Morantz, and Richard Caskey and thus began his love of the field. He was directly involved in the teaching of basic AK techniques and muscle testing methods to fellow students. He was also a student intern at the Achilly-Morantz Clinic in Harvey, IL.

Dr. Tinari has a love of healing. His passion for nutrition and educating his patients on lifestyle changes to better their health is what draws people to his office. Dr. Tinari's warm personality, knowledge of his given fields and caring aspect infuse his patients and are infectious. He has been practicing in Holbrook, New York where he returned following the completion of his education.

GITA PATEL
MS RDN CDE CLT LD

Blending Science with Spices for Feeding Health

Health is something we do for ourselves, not something that is done to us; a journey rather than a destination; a dynamic, holistic, and purposeful way of living…Elliott Dacher, M.D.

Diabetes mellitus is a major health care problem worldwide both in developing and developed countries. Many factors, including age, obesity, lifestyle and diet are involved in the etiology of diabetes mellitus. To prevent and manage diabetes mellitus drugs and diet are the two major approaches currently used. There is a resurgence of interest in using diet to manage and treat diabetes mellitus.

Recent data shows that 40% of US adults are likely to be diagnosed with type 2 diabetes (T2DM) in their lifetimes. (1) Diabetes mellitus (DM) is a chronic, progressive illness that requires continuing medical care and patient self-management to prevent acute complications and reduce the risk of long-term co morbidities. This emphasizes the need to identify the most practical, cost-effective strategies and interventions for promoting health in diabetes. In view of their specific health benefits, potential to influence glycemic control, reduce cardiovascular disease risk and modulate inflammation, there is reason to consider the inclusion of functional foods. There is still much to be learned about the role of functional foods in terms of dose, timing and duration, however, this is an exciting area of continued study.

Feeding health through good nutrition could be the primary foundation for diabetes management. Nutrients in whole, unprocessed plant foods affect many functions in the body, including neutralizing inflammation, improving digestive health, and preventing diabetes related complications to name a few. People with diabetes may have little control over many aspects of the disease, but we all have control over the foods we choose to eat on a daily basis. Eating slowly and mindfully allows one to really taste the food while preparing the food for digestion, absorption and assimilation. When we eat a variety of plant foods including herbs and spices, it allows us to experience all six of our taste sensations… sweet, salty, astringent, sour, pungent and bitter.

Healthy cooking, functional foods, good hydration, mindful eating of whole unprocessed nutrient rich plant foods can help reduce blood pressure and stress, improve cardiovascular health and postprandial blood glucose spikes. Consuming the Standard American diet leaves us overfed in calories yet undernourished in key micronutrients such as phytonutrients and fiber. Many of these phytonutrients function as antioxidants. We cannot store antioxidants in the body like we store certain nutrients such as some vitamins, minerals, fat and carbohydrate, so we need to consume antioxidant rich plant foods everyday in order to neutralize the free radicals we generate naturally in the body, some from the foods we eat, and some from environmental exposure. Antioxidants are our first line of defense from free radicals. Plant foods, especially herbs and spices, are the only source of these two important micronutrients, phytonutrients and fiber, in our food supply.

Diabetes mellitus is a metabolic disorder characterized by altered glucose tolerance and impaired fat and carbohydrate metabolism. (2) Along with behavior change, medications and physical activity, food choices play a critical role in diabetes management. The role of functional foods in chronic disease risk reduction and management has received increasing attention over the past several years. Our roles as professional health care providers is to encourage, motivate and educate patients and clients to develop eating habits that support health and improve quality of life. Though numerous foods have demonstrated hypoglycemic, hypocholesterolemic, anti-atherogenic, and anti-inflammatory effects, in this chapter, I will mostly focus on medical culinary use of select herbs and spices.

FUNCTIONAL FOODS:

The International Food information Council defines a functional food or medicinal food as "Foods or dietary components that may provide a health benefit beyond basic nutrition and may play a role in reducing or minimizing the risk of certain diseases and other health conditions." (3,4)

"It is the position of the Academy of Nutrition and Dietetics to recognize that although all foods provide some level of physiological function, the term functional foods is defined as whole foods along with fortified, enriched, or enhanced foods that have a potentially beneficial effect on health when consumed as part of a varied diet on a regular basis at effective levels based on significant standards of evidence." (3) There is evidence that some food components in plant foods, not considered nutrients in the traditional sense, (such as phytochemicals, phytoestrogens, flavonoids, lignins, isoflavons, phenolic compounds) may provide positive health benefits; such foods are functional foods. (3)

Functional foods include the healthful components in plant foods such as fruits and vegetables; whole grains, beans and legumes; herbs and spices; nuts and seeds, fish oils, fermented foods, calcium in milk, fortified or enhanced foods and beverages such as vitamin D in fortified milk; and functional foods can also include dietary supplements. Functional attributes of many traditional foods are being discovered, while new food products are being developed with beneficial components. (3,4) Foods marketed as functional foods fall into three general categories:

- Conventional foods containing natural bioactive food compounds. Most vegetables, herbs, spices, fruits, grains, dairy, cocoa and fish contain bioactive food compounds that provide benefits beyond basic nutrition. Examples would be the antioxidant vitamins in orange juice, isoflavones in soy-based foods, and prebiotics in bananas and probiotics in yogurt.

- Modified foods containing bioactive food compounds through enrichment or fortification, such as n-3 fatty acids in margarine spreads and eggs.

- Food ingredients that are synthesized, such as indigestible carbohydrates, which provide prebiotic benefits like oligosaccharides or resistant starch (3)

The consumption of whole grains not only because of its fiber and indigestible carbohydrate content but also because of the presence of phenolic compounds is considered to have significant health benefits in both the prevention and management of chronic diseases (i.e. cardiovascular disease, diabetes, and cancer). (5)

Adiponectin is a hormone secreted by adipose tissue that normally circulates at a high concentration in the blood. This beneficial hormone regulates both fat and glucose metabolism and has anti-atherogenic and anti-diabetic properties. Adiponectin improves insulin sensitivity by reducing the levels of free fatty acid in blood, enhancing insulin action, stimulating glucose utilization, increasing liver fatty acid oxidation, and decreasing fatty acid synthesis in the liver. High levels of circulating adiponectin can help improve lipid profile, improve blood glucose control, and reduce inflammation.

Intake of cereal fiber from whole beans and legumes and other plant foods, is associated with higher adiponectin concentrations in patients with type 2 diabetes. Circulating levels of adiponectin decrease as fat stores in the body increase. It is therefore beneficial to eat a high fiber, plant-based diet containing antioxidants and phytonutrients for both diabetes and weight management.

Resistant starches are starches that escape digestion in the small intestine. Natural resistant starch is fermented in the large intestine similar to prebiotic fibers. They provide some of the health benefits of both soluble and insoluble fiber. Natural resistant starch is found in whole grains, seeds, beans, legumes, under-ripe fruit (i.e. green bananas) and is especially prevalent in cooked starches that have been cooled (i.e. beans, lentils, legumes, pasta salad, potato salad, and sushi rice). Soluble fiber feeds the intestinal bacteria (microbiome) while insoluble fiber aids in digestion by trapping water in the colon, and inactivates many intestinal toxins. (7) The benefit of resistant starches for diabetes is a lowered contribution of carbohydrate energy and the benefit of delayed digestion that in turn helps reduce postprandial blood glucose spikes.

"All disease begins in the gut"…Hippocrates. The gastrointestinal tract hosts a large and diverse number of different microorganisms, known as intestinal microbiota. The human gut microbiome and its metabolites impact human health and disease. The gut is the seat of immune responses. Prebiotics and probiotics, too, have recently garnered publicity due to their purported health benefits. In the last several decades, type 2 diabetes has increased dramatically. The connection between the gut microbiota and diabetes is now the subject of great interest. The foods we eat strongly influence the composition and diversity of the gut microbiome.

Plant foods provide fiber and prebiotics, food for the microbiome, which promote digestive health. Beans, lentils, legumes, whole grains and many vegetables and fruits also provide us with resistant starch, which acts as a prebiotic for the microbes, promoting digestive health. The microbiome interacts with its host, assisting in digestion and detoxification, supporting immunity, protecting against pathogens, and maintaining health. The micro-biome and its metabolites have now been associated with multiple disease states including obesity, diabetes, digestive disorders, osteoporosis, autoimmune diseases and even mental health. This chapter will, however, focus on the functional foods --herbs and spices that may be helpful to individuals with diabetes. Attention will be given to the

purported mechanism of action, cautions/precautions, and suggested culinary uses.

"To eat is a necessity, but to eat intelligently is an art". La Rochefoucauld, Maxims, 1665

Herbs and Spices:

"Herbs and spices, in use since approximately 5,000 B.C.E., are among the richest sources of phytonutrients and antioxidants and can play a central role in cooking. Herbs are from the leaf, while spices are any other part of the plant, like buds (i.e., cloves), bark (i.e., cinnamon), roots (i.e., ginger, turmeric), berries (i.e., peppercorns) and aromatic seeds (i.e., cumin)." (6,7)

Conventional dietary methods to treat diabetes mellitus include the use of culinary herbs and/or spices. Spices have long been known for their antioxidant, anti-inflammatory, and anti-diabetic properties. Spices and herbs add delicious variety to the foods we eat. But spices and herbs are much more than flavor enhancers — they are nutritional powerhouses. They are sources of plant phytonutrients. Many phytonutrients have antioxidant, anti-inflammatory or even anti-cancer properties, and in the case of dried herbs and spices, these phytonutrients can be very concentrated. So herbs and spices do more than perk up the flavor of your food — they put a natural pharmacy in your kitchen.

Spices can make food richly flavorful and aromatic, but they make it hot only if you add fresh, powdered or flaked Chile peppers. That heat comes with a few benefits — spicy hot food reduces the need for salt, plus it helps the body sweat and potentially remove toxins.

One key reason that world cuisines taste different from each other is the distinctiveness offered by the herbs, spices and other aromatic ingredients that are traditional to each one.

Bitter Melon (Momordica charantia; Family: Cucurbitaceae) resembles a light green, pointed cucumber and is used as a vegetable cooked with potato, onion and or tomato, pickled or occasionally dried. Soak the cut bitter melon in water, squeeze the water out and then cook with onions and tomatoes or tomato sauce to reduce the bitter taste.

Bitter melon fruit and seeds have been shown to potentially help improve glucose tolerance and reduce blood glucose in individuals with T2DM (8). The hypoglycemic effect is dependent on viable beta cell function. Bitter melon contains a mixed sterol, charantin that lowers blood glucose, and also contains polypeptide-p, an insulin-like polypeptide (9). Possible mechanisms include increased insulin secretion, tissue glucose uptake, liver muscle glycogen synthesis, glucose oxidation, and decreased hepatic gluconeogenesis. (10) Additive hypoglycemic effects have been reported when large quantities of bitter melon curry were consumed while taking chlorpropamide (Diabinese) (11).

Fenugreek (Trigonella foenum-graecum; Family: Fabaceae/Leguminosae) seeds contain 45.4% dietary fiber (32% insoluble and 13.4% soluble) and are associated with reduced glycemia and cholesterolemia. Fenugreek's hypoglycemic effect has been documented in humans and animals with both Type 1 (T1DM) and T2DM (12).

When taken with food fenugreek delays gastric emptying, slows carbohydrate absorption, and inhibits glucose transport. Its constituent, 4-isoleucine, appears to stimulate insulin secretion. Fenugreek may reduce blood glucose levels and might have additive effects on glucose levels when used with medications to lower blood glucose; thus, glucose levels should be closely monitored. (12).

Fenugreek contains constituents that may inhibit platelet aggregation. Patients on antiplatelet or anticoagulant drugs who take fenugreek in amounts greater than are used in normal cooking should be monitored closely (12,13).

Fenugreek seeds or powder (ground seeds) may be used in pickles, vegetables, rice dishes and curries. The powder may be added to flour in baked foods or pancake batter. The seeds can be sprouted for adding to salads or cooked with rice, beans or vegetables. Fenugreek leaves are eaten in India as a fresh green vegetable or added to rice, dried bean dishes, potatoes or flour to make a variety of breads.

Cinnamon (Cinnamomum aromaticum, synonyms Cinnamomum cassia, Cinnamomum ramulus; Family: Lauraceae) has a long history both as a spice and as a medicine. Added to improve taste and aroma of food, cinnamon has been shown to have potent antioxidant activity. There are many varieties of cinnamon; the spice purchased in food stores contains a combination of different varietals.

Polyphenolic polymers such as hydroxychalone found in Cinnamomum verum and Cinnamomumum cassia are thought to be responsible for potentiating insulin action, thereby lowering glucose levels. These polyphenolic compounds increase phosphorylation of the insulin receptor, which increases insulin sensitivity. Increased insulin sensitivity improves blood glucose control and serum lipid levels. Cinnamon extracts also may activate glycogen synthetase and increase glucose uptake (11). Though cinnamon consumption is associated with a statistically significant decrease in levels of fasting plasma glucose, total cholesterol, LDL-C, and triglyceride levels, and an increase in HDL-C levels, no significant effect on hemoglobin A1c was found. (14)

Individuals with diabetes and on blood glucose lowering pharmacueticals, who use cassia cinnamon in amounts larger than are typically used in cooking, must monitor blood glucose levels closely.

Cinnamon's versatility lends itself to sweet and savory dishes. Add cinnamon to your breakfast oats, baked goods or meat marinades. Sprinkle it on roasted vegetables or sautéed leafy greens. Mix it into black bean dishes.

Ginger (Zingiber officinale, synonym Amomum zingiber; Family: Zingiberaceae). In laboratory models of diabetes, ginger seems to increase the release of insulin and lower cholesterol levels. Preliminary in vivo research suggests ginger might increase insulin levels and/or decrease blood glucose levels. Theoretically, taking ginger in quantities greater than those used in cooking, along with hypoglycemic medications might cause hypoglycemia, requiring a medication dose change (11). Ginger might slow blood clotting (6,7).

Fresh ginger can be pickled with garlic and enjoyed with food. Likewise, ginger, fresh, crystalizied or dried powder, can be added to a variety of foods during cooking. Grated ginger can be added to hot water or green or black tea for a ginger tea--an especially enjoyable and tasty combination is fresh or powdered ginger combined with cardamom! Ginger root is a cornerstone of Asian cooking, imparting a slightly sweet, slightly hot flavor. It goes well with garlic in many Thai, Indian, and Chinese dishes. Try a ginger and honey tea when you're under the weather, or add fresh or powdered ginger to smoothies. Fresh ginger root keeps in the fridge for several weeks, longer in the freezer.

Turmeric (Curcuma longa, synonym Curcuma domestica; Curcuma aromatica; Family: Zingiberaceae) is a root similar to ginger (11). A 9-month curcumin intervention (1500 mg daily) in a prediabetic population significantly lowered the number of prediabetic individuals who eventually developed T2DM compared to placebo. In addition, the curcumin treatment appeared to improve overall ɣ-cells function, with very minor adverse effects. (15) Furthermore, limited research is suggesting a potential for decreased blood glucose and HbA1c levels in person with diabetes.

Curcumin, the active ingredient in turmeric, has anti-inflammatory and antioxidant effects. Taking large quantities of supplemental curcumin along with medications that slow clotting could have an additive effect and might increase chances of bruising and bleeding. (11).

Turmeric is added to all vegetables, beans, legumes, grains, flours, and yogurt along with a source of fat such as oil or ghee and spices and is used daily in Asian Indian cooking. Fresh grated turmeric mixed with limejuice, salt and herbs is eaten as a condiment during the winter months in India.

Add turmeric to rice or to hot oil before sautéing onions and garlic. Add it to curry dishes, marinades and salad dressings. When you use turmeric in savory dishes, use black pepper, too, because a compound in black pepper helps your body absorb turmeric's beneficial compounds.

Cumin (Cuminum cyminum, synonym Cuminum odorum; Family: Apiaceae/Umbelliferae) is used regularly in Asian, Indian and Mexican cooking and may have hypoglycemic effects. Individuals using hypoglycemic medications must monitor blood glucose if taking large doses of cumin whether in foods or as supplements. (11).
Cumin along with ginger, cinnamon, black pepper and green tea has been shown to prevent and/or inhibit protein glycation. Protein glycation has been implicated in several pathophysiologies associated with aging and

diabetes. Inhibition of the formation of protein glycation is believed to play a role in the prevention of diabetes related complications (16). Cumin is added to stir fry vegetables, grains, yogurt beverages, and legume and beans dishes – think chili!

Garlic: (Allium sativum; Family: Alliaceae or Liliaceae) Garlic's active ingredients allicin and allyl propyl disulphide have hypoglycemic effects and have been shown to improve blood glucose control. Researchers have noted the association of garlic use with increased serum insulin levels and improved insulin sensitivity (17). Garlic consumption has been associated with slower progression of cardiovascular disease in epidemiological studies although results of clinical trials are limited (18).

Metabolic effects of time-released garlic powder tablets (Allicor) 300 mg two to three times daily, in combination with metformin or an oral sulfonylurea, for 4-24 weeks suggests significant reduction in fasting blood glucose, serum fructosamine, cholesterol, and triglycerides compared to placebo in patients with T2DM (19, 20).

Most cuisines use garlic in their cooking; it is easy to add garlic to flavor a variety of foods during cooking or in salad dressings and pesto.

Onion: (Allium cepa; Family: Alliaceae or Liliaceae) The bulb of the onion shows hypoglycemic actions and inhibits platelet aggregation. Theoretically, individuals taking hypoglycemic agents and consuming over 50 gms (1.76 oz) onion in medicinal amounts must monitor blood glucose; medication dosage might need to be adjusted (11). Onions can be enjoyed raw or cooked and can be added to most foods during cooking.

Coriander (also known as Cilantro): (Coriandrum sativum; Family: Apiaceae/Umbelliferae) has shown hypoglycemic activity in animal models; however, currently there is not enough research on humans. Despite lack of substantial data on cilantro and DM health, coriander is a rich source of vitamin C, calcium, magnesium, potassium, and iron (11), and thus, in its own right does play a role in functional nutrition and health promotion. Again, additive effects of using coriander along with other potentially hypoglycemic herbs and/or antidiabetic medications could have implications for glycemic control and blood sugars should be monitored.

Coriander is widely used in many ethnic cuisines and can be easily added to most vegetables and salads (think salsa), bean, legumes and lentil dishes, and can be used to make pesto.

Cloves (Syzygium aromaticum, synonyms Caryophyllus aromaticus, Eugenia aromatica, Eugenia caryophyllata, Eugenia caryophyllus; Family: Myrtaceae) contain a volatile oil, eugenol, which inhibits platelet activity and can slow blood clotting (6,7). Eugenol contributes to the mild anesthetic and analgesic properties of clove by inhibiting prostaglandin biosynthesis. Preliminary research suggests that clove extracts mimic the action of insulin (11). Whole cloves can be added to grains, beans, legumes and vegetable preparations. Ground cloves can be added to black or green tea or hot water for a hot beverage.

Cocoa (Theobroma cacao, synonyms Theobroma sativum; Family: Malvaceae or Sterculiaceae) seeds are a significant source of naturally occurring flavanoids, which are anti-inflammatory, antihypertensive, and antithrombotic, increase insulin sensitivity as well as increase postprandial insulin secretion, thus potentially improving glycemic control. (21,22) Because of its cardioprotective effect, (dark chocolate > 60%, preferentially 80% cocoa) long-term daily intake of dark chocolate (46-100 gms) can be part of a healthy diet (22)

Because of their anti-inflammatory, antiatherogenic, antihyperlidemic, and insulin sensitizing effects, there are many other functional foods (i.e. green tea, pomegranate seed, figs, dates, Jack fruit, Bengal gram, maitake mushrooms, goji berries (lycium fruit) that modulate disease pathophysiology and promote health. As such, it is important to include and enjoy eating a variety of plant foods in one's daily diet. There is ongoing research in the area of phytochemicals in herbs, spices, and other functional foods.

The potency of herbs/spices consumed as functional foods (culinary use) is typically at a dose lower than the medicinal (tea, extract, capsules, tinctures) preparations. Medicinal doses of many of these functional foods are contraindicated in certain populations such as pregnant women, children and individuals with multiple chronic conditions. Individuals with diabetes who are using herbs and spices to improve diabetes management must monitor blood glucose closely and discuss the use of any herbs with a qualified healthcare professional. An important part of the healthcare team, RDNs and DTRs can communicate efficacy of functional foods as well as

concerns to physicians and other care providers.

Bitter melon, fenugreek seeds, cinnamon, ginger, turmeric, cumin, garlic, onion, coriander, cloves, and cocoa are examples of food and spices that can be used frequently in cooking. These functional foods have a beneficial effect on health. Research to date is showing potential impact on blood glucose, coagulation status, lipid levels, and blood pressure, it is important to be aware of the additive effects of these functional foods when consumed in quantities greater than used in normal cooking especially while concomitantly taking medications to reduce blood glucose, blood lipids or control coagulation.

"The doctor of the future will give no medication, but will interest his patients in the care of the human frame, diet and in the cause and prevention of disease." ~Thomas A Edison.

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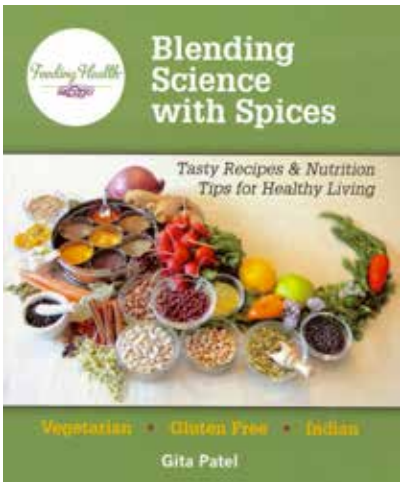

Gita Patel MS RDN CDE CLT LDN is a registered dietitian, certified diabetes educator, and certified LEAP (Lifestyle Eating and Performance) therapist specializing in diabetes, women's health, heart disease, vegetarian nutrition, healthy aging, migraines, IBS, IBD, Celiac disease, gastrointestinal problems with food allergies, food sensitivities and food intolerances. Gita partners with individuals and organizations that need the science of nutrition translated into a healthy vegetarian lifestyle. Gita is an author, speaker and counselor.

Her vegetarian cookbook, ***Blending Science with Spices: Tasty Recipes & Nutrition Tips for Healthy Living,*** is the culmination of her traditional Indian background, the varied foods she grew up eating, and her extensive training in modern nutritional science. With current research connecting the effect of what we eat on how we feel, food preparation is the one place where I can reflect daily on that fundamental relationship. Helping people feed their health is my goal in life.

Gita has taught nutrition through vegetarian cooking in a variety of venues, including television, and shares her extensive background in modern nutritional science through a combination of education and practice.