Nutrition and Integrative Medicine

A Primer for Clinicians

Edited by
Aruna Bakhru, MD, FACP

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This book is dedicated to my mother, Gita Bakhru, who is the embodiment of unconditional love in my life. Ultimately, it is love that heals. It is the love within the physician that heals the patient, and it is love, loving kindness that will heal our planet.

Aruna Bakhru, MD, FACP

Disclaimer

The purpose of this book is to educate the reader. The publisher, editor, and the authors have no liability or responsibility to any person(s) or entity with respect to any alleged loss or damage or injury caused directly or indirectly by information contained in this book. The information presented here is not a substitute for medical consultation or treatment.

Aruna Bakhru, MD, FACP

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Preface

As a practicing internist for over 25 years, I realized long ago that standard medical care did not have all the answers. There were many times that I found myself unable to help chronically ill patients. Over the years of my practice, chronic illness and the toll it has taken on the population of the United States and the rest of the world, the cost of care, and the burden on the caregivers has only continued to increase. The financial ramifications for the industry, government, society, and families are unsustainable in the long term. We can kick the can down the road only for so long. Amazingly, the answers are available but in separate pieces: the ancient healing sciences of Ayurveda, yoga, Chinese medicine, nutrition, homeopathy, plant essential oils, the use of light and sound in healing, mind–body medicine, the detrimental effects of toxins and electromagnetic/microwave frequencies on the human body. I could go on, but the list is in the book. Even as a trained physician, I did not understand the value, the importance, and the absolute imperative of nutrition. Vitamins were something you took as a kind of insurance in case you were missing something in your diet. The USDA food groups were what you explained to your patients, before sending them off to the dietician as you certainly did not, and still do not, have the time to go over what they were eating. I recall being taught that Vitamin B12 levels should be checked only in the elderly, what I found in actual practice was that a great number of my patients complaining of fatigue had low B12 levels, even though they were young. I eventually, as a standard practice, started getting baseline B12 levels in all of my patients and discovered that almost half of them were deficient in B12. Of course, I did not check the entire spectrum of B vitamins as that was not cost-effective; however, I did recommend that in addition to B12 injections, they take organic, whole food-based B complex vitamins. To this day, I am not certain what is causing this. I suspected the environment and recently read that autoimmune disease was exploding possibly as a result of EMF exposure. Then came the 1-25 hydroxyvitamin D3; again I found that almost a majority of my patients were deficient and those who were not, did not seem to get sick. To my amazement, I found that most over-the-counter vitamins were petroleum-based and actually harmful and I had to seek out organic, non-GMO, whole food-sourced vitamins.

The cell membrane is mainly comprised of fatty acids. An imbalance or a deficiency of essential fatty acids causes the cell membrane to lose its flexibility and become stiff and impermeable. Paradoxically, the diet and nutrition industry has exploded into a billion-dollar business. Yet, the American population is more obese than ever. People obsess over their carbohydrate, fat, and protein intake without realizing the subtle component of food. Where was it grown? How was it treated, what chemicals were used? What kind of seeds, what were the soil conditions? What additives were added? Excitotoxins added to processed food have now been demonstrated to cause inflammation in the body and the vascular system resulting in a whole host of problems ranging from migraines to restless leg syndrome and more. It is the responsibility of the food industry to pay attention to the health ramifications of their additives, beyond taste and food preservation.

Now research is coming out that epigenetics rather than genetic factors are the major cause of chronic disease. From Chapter 10 we learn, “In effect, the epigenetic effects of diet, via the many activators and suppressors of chromatin remodeling enzymes that food contains, can deprogram or reprogram vast quantities of genes regulating metabolic pathways, which in turn can influence the development of chronic, long-latency, and degenerative diseases.” Also, “Food, when not artificially sterilized, is comprised of other organisms, that is, all food has a microbiome.” This is powerful information indeed! Chapter 1 is entirely devoted to the microbiome of the human superorganism while Chapter 10 is devoted to the microbiome of our food and food as information. Research is now beginning to show that bacteria, fungi, and parasites in our gut actually effect our brain and thought process, causing a craving for the type of food that the parasite requires, rather than what is healthy for our body and mind.

Then, there is water—water that composes over 75% of our bodies. Research, as is being done at the Pollack laboratories, is desperately needed, yet is not a priority for funding. A deep understanding of water is essential. What kind of water are we putting into our body? Microwaved? Chemically treated? All water is not equal. We know that healing springs and waters exist. Why is it that some waters are healing and others not? It is not simply a matter of toxins in the water. Water seems to act as a source of information. The best analogy that I can think of is, imagine water as a blank computer disc upon which information can be imprinted. This water then, if assimilated by our body carries information into our system, which as we know consists of over 75% water as stated earlier. Yet, if you drive down our highways, what do you see? Water towers with Cell towers wrapped around them! Imagine the consequences of drinking, showering, washing clothes in this water? Also, there is not a remote corner of our world's oceans that you could go to, dip a slide or test tube in, and not come up contaminated with PCBs and dioxins. Our enzymatic systems and pathways are overwhelmed by the unprecedented toxic chemicals they are faced with in this century.

We are heading blindly toward more and more technology, 4G now 5G wireless networks, tethered to our cell phones, unable to exist without them. Getting more disconnected from nature, from the Earth, from each other. Over 500 Facebook friends but no one to talk to, families pull out their phones and everyone is immersed in their own phone as they sit together but are not together. Cell phones have added much value to our lives no doubt, but cautious responsible use is recommended. They have become a source of addiction, not to mention that as electromagnetic beings we need to be mindful of the unknown effects that these invisible waves are having on us. The scanner at the grocery checkout emits a red beam at the level of the groin! What effects could that be having on our human system and what can be done to mitigate their harmful effects?

The teeth are approached as inert objects, sitting in our gums that help us to chew food. If there is a cavity, it is drilled and filled, or God forbid a root canal is performed causing the bacteria to proliferate throughout the dentinal tubule system of the teeth, then into the bloodstream and spreading through the body, changing the microbiome, causing disease in the areas of weakness, where they settle. We have forgotten that our teeth are made of cells and respond to good nutrition as well as a supportive environment. Thankfully, I read that work is being done regarding filling cavities with the person's own stem cells, which is a much better approach.

Homeopathy is decried as placebo medicine because we do not understand it. A lack of understanding does not invalidate the reality that it is, in fact, an elegant system of vibrational medicine. A dead body is dissected in medical school, but the living vibrationally alive human is not yet fully understood. Jacques Benveniste was a French immunologist who was the head of INSERM's Unit 200, performing research on immunology and allergy. In 1988, he published a paper in the journal *Nature* that caused an international controversy. The research was co-authored by four laboratories worldwide in Canada, Italy, Israel, and France. He diluted a solution of human anti-IgE antibodies in water so that there was no possibility that even a molecule of the antibody remained in the water solution. Human basophils still responded to the solution as though they had encountered the original antibody. This effect was reported only when the solution was shaken violently during dilution. This heretical view cost Jacques his laboratory, his funding, and his reputation. The journal retracted the paper. Later, a Swiss chemist Louis Rey published a paper in *Physica A*, 2003 claiming to show that "even though they should be identical, the structure of hydrogen bonds in pure water are very different from that in homeopathic dilutions of salt solutions." Luc Montagnier, a Nobel prize laureate whose research paper on "Electromagnetic Signals Are Produced by Aqueous Nanostructures Derived from Bacterial DNA Sequences" 2009 was also questioned on his beliefs about homeopathy, to which he replied: "I can't say that homeopathy is right in everything. What I can say now is that the high dilutions are right. High dilutions of something are not nothing. They are water structures which mimic the original molecules. We find that with DNA, we cannot work at the extremely high dilutions used in homeopathy; we cannot go further than a 10^{-18} dilution, or we lose the signal. But even at 10^{-18}, you can calculate that there is not a single molecule of DNA left. And yet we detect a signal" (Enserink, December 2010).

Another interesting finding regarding water came from The University of Michigan astronomers, Cleeves and Bergin published in *Science* 2014, that about half the water on Earth may be older than the solar system. I could not but help draw a parallel to the legend of the river Ganges in India which is said to have originated from the "heavens" and not of this Earth. I could be wrong, but it is a curiously interesting study. The Ganges river water has been extensively studied for its unique bacteriostatic properties.

We know there is electricity running in the body as evidenced by the brain waves, the EKG, the muscle action potential, and in fact, science has now shown that there is electrical as well as neurotransmitter activity at the neuromuscular junction. In a study published in the *Proceedings of the National Academy of Sciences*, January 2007, UC San Diego said that "modifying electrical activity in the adult brain can alter neurotransmitters and receptors." We already know, of course, that messages are conducted along nerve fibers in the form of electrical activity (Seethaler 2006).

According to Ayurveda, marmas (similar to acupuncture points in Chinese Medicine) are vulnerable or sensitive spots that have a specific use in diagnosis and healing. They connect with nadis (energetic nerves) and chakras (energetic centers). They manage the interaction between the physical and the subtle bodies. They are like windows on the skin surface acting as junction points between body, mind, and spirit. I recall a teacher, who was training me on these points, saying to me, "Think of them as geysers where energy comes close to the surface and can be measured." The leaky gut syndrome was first described in Ayurveda. It arises from the presence of "ama," which is a toxic byproduct of poor digestion. One of the features of "ama" is that when it enters the "dhatu" (dhatu means tissue—plasma, blood, muscle, fat, bone marrow, reproductive tissue, etc.) cycle, it disrupts the nutrition and function of the tissues. It has an affinity for tissues that are weak and tends to accumulate there. Once lodged there, it causes increased congestion followed by inflammation and finally degeneration. Sushruta, one of the original Ayurvedic physicians, pioneered rhinoplasty and the surgeons of the East India Company learned the procedure from watching Ayurvedic surgeons. Dr. Peter Eckman's chapter talks about the differing approaches towards the definition of science between Eastern and Western Medicine. While Western Medicine is predominantly focused on the material aspect, Eastern Medicine also focuses on that which is nonmaterial. Dr. Marjorie Woollacott's research has shown that meditation affects our genetics and has proven neurobiological changes as well.

Dr. Valerie Hunt was a Professor Emeritus of Physiological Sciences at UCLA. She is best known for her pioneering research into vibrational medicine. She discovered that neuromuscular ennervation patterns were foundational to non-verbal communication. She proved that energy radiating from the body's atoms gives off frequencies 1000 times faster than the electrical activity of the body. Using fractal mathematics, her energy field data showed dramatic chaos patterns in human biological systems, and she showed that it did not take much beyond a homeopathic dose to convert the chaos into a beautiful, symmetrical pattern.

According to Deepak Chopra, M.D., "We can trace the physical structure of the body, down to the molecular level and still have no explanation for beliefs, desires, memory, and creativity."

The SQUID Magnetometer, Super Conducting Quantum Interference Device, can detect biomagnetic fields associated with physiological activities in the body. David Cohen of MIT used it to measure fields around the heart and the head in the 1970s. Dr. John Zimmerman studied therapeutic touch at The University of Colorado School of Medicine in the 1980s. He found pulsating biomagnetic fields emanating from the hands of healers with different healers having differing results. Cohen is currently on the faculty at Harvard Medical School and a mentor at MIT's Martinos Imaging Center (Wikipedia).

If we are to change course and have a balanced medical care system, then we need to extend our understanding to the so-called CAM modalities that have in actual fact existed for thousands of years before modern medicine and continue to exist. The ancient healing modalities are there, the cutting-edge research into nutrition, the microbiome, biophotons, epigenetics is all there, just not within the pages of our medical textbooks yet. We treat the mind as though the body does not

exist, and we treat the body as though the mind does not exist. The powerful effects of the mind on the body are dismissed as the placebo effect. It is as though we are missing the forest for the trees. The human body, capable of amazing feats of healing, is not a machine. All of us went into medical school with dreams of helping people, then the reality of the system hit, onerous burdensome regulations, up late at night, poor lifestyle, no time to eat well, to exercise. Who are we, as doctors, to tell people how to live, when our own lifestyles are not healthy? Doctors have a deep desire to heal others, they are intelligent, driven people. This book is an effort to bring another perspective that was perhaps not noticed, yet has much to offer.

Therefore, this book is offered to clinicians, their patients, families, and loved ones everywhere as a source of information and knowledge of a science-based understanding, regarding healing modalities that have much to offer humanity and to those that are the guardians of health.

Aruna Bakhru, MD, FACP

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Editor

Aruna Bakhru, MD, FACP, is Board Certified in Internal Medicine and a Fellow of The American College of Physicians. She graduated in Medicine and Surgery from Lady Hardinge Medical College, New Delhi, India and completed her residency in internal medicine at Prince George's Hospital and Medical Center in Maryland. She also conducted research with Valerie Johnson, MD, PhD, at New York Medical College, Lincoln Hospital and Medical Center. Currently, she is affiliated with Vassar Brothers Medical Center, Poughkeepsie, New York.

A respected and long-standing figure in her field, Dr. Bakhru currently serves as a physician with a focus on integrative and internal medicine at her private practice, which she has maintained for over 25 years.

Dr. Bakhru has held numerous appointments over the course of her career, serving as the Young Physician Section Representative of The Dutchess County Medical Society and as the Chair of the Integrative Medicine Subcommittee of The Dutchess County Medical Society. She has also served on the Ambulatory and Emergency Services Committee at Vassar Brothers Medical Center, the Medical Audit Committee of Vassar Brothers Medical Center, and the Complementary Care Committee at Vassar Brothers Medical Center, as well as on the Utilization Review and Quality Assurance Committee of Mohawk Valley Plan Health Plan.

Dr. Bakhru has over 20 years of experience and training in many other modalities such as nutrition, functional medicine, Ayurvedic medicine, herbal medicine, and bioenergetic medicine, as well as the efficacy of sound and light as healing modalities. She trained with The American Academy of Environmental Medicine, learning to treat twenty-first century problems caused by our lifestyle and environmental issues. She has also been involved with numerous community service activities, volunteering at the medical clinic for the indigent at Vassar Hospital and serving as a volunteer physician for the summer camp run by SVSC, a nonprofit group. She has also written for numerous publications, appeared on radio and television, and lectured on medically related topics.

Dr. Bakhru has been endorsed as a leader in the healthcare industry by *Marquis Who's Who*, the world's premier publisher of biographical profiles, and recently was named a Lifetime Achiever by that publisher. As in all *Who's Who* volumes, individuals profiled are selected based on current reference value. Factors such as position, noteworthy accomplishments, visibility, and prominence in a field are all considered during the selection process.

In addition to her status as Lifetime Achiever, Dr. Bakhru has previously received the Excellence in Integrative Medicine Award from Emord and Associates and was honored by The Holistic Doctors Recognition Board as one of the Top Ten doctors in New York State. Additionally, she received awards in Pathology and Forensic Medicine from the University of Delhi as well as the Certificate of Excellence from many insurance groups. Furthermore, Dr. Bakhru has been a featured listee in *Who's Who in America*, *Who's Who in Medicine and Healthcare*, *Who's Who in the World*, and *Who's Who in Science and Engineering*. She also volunteers on Cyber Safety India International Board of Advisors and is an Executive Committee member of the Dutchess County Regional Science Fair. She has also published various articles in her local newspapers as well as appeared on public television in White Plains, and radio talk shows for WKIP and WVKR 91.3 FM out of Vassar College.

Her website is www.centerforenergymedicine.com. She currently practices in New York and believes that treating the patient as a whole leads to better outcomes and satisfaction for both the physician and patient.

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Contributors

Shekhar Annambhotla, BAMS (Ayurved)
Director
Ojas, LLC—Ayurveda Wellness Center
and
President
Association of Ayurvedic Professionals of North America
Coopersburg, Pennsylvania

and

Director
Global Ayurveda Academy and Conferences
Pennsylvania

Peter A. Arhangelsky, Esq.
Principal Attorney
Emord & Associates, P.C.
Gilbert, Arizona

John Beaulieu, ND, PhD
Founder of BioSonic Enterprises, Ltd.
Stone Ridge, New York

and

Professor of Integrative Health
Zentrum für Inner Ökologie
Zürich, Switzerland

Stephen Harrod Buhner
Senior Researcher
Foundation for Gaian Studies
Silver City, New Mexico

and

Fellow
Schumacher College
Totnes, United Kingdom

Wesley Burwell, CBS, LHSC
PLT Coach and Instructor
Certified Stress Management–Polychromatic Light Therapy
Tillsonburg, Ontario, Canada

Yemeng Chen, PhD, LAc, FICAE
President
New York College of Traditional Chinese Medicine
Mineola, New York

Stevan Cordas, DO
Adjunct Assistant Professor
Texas College of Osteopathic Medicine
Fort Worth, Texas

Janice M. Dietert, MASS
Performance Plus Consulting
Lansing, New York

Rodney R. Dietert, PhD
Professor of Immunotoxicology
Department of Microbiology and Immunology
Cornell University
Ithaca, New York

Peter Eckman, MD, PhD
Private Practice
San Francisco, California

Dawn Ewing, RDH, PhD
International Academy of Biological Dentistry and Medicine (IABDM)
Spring, Texas

Magda Havas, PhD
Trent School of the Environment
Trent University
Peterborough, Ontario, Canada

Sayer Ji, BA
Director
GreenMedInfo.com
Naples, Florida

Scott Johnson, AMP, CEEOS, CCMA, CPC
Founder and President
Research and Development
at Zija International
and
Integrative Essential Oils
Certification Program
Orem, Utah

Harvey W. Kaufman, MD, MBA, FCAP
Senior Medical Director
Quest Diagnostics
Secaucus, New Jersey

Leslie Korn, PhD, MPH
Core Faculty
Capella University
Private Practice
Minneapolis, Minnesota

Vasant Lad, BAM&S, MASc
Director
The Ayurvedic Institute
Albuquerque, New Mexico

Ali Le Vere, BS (Human Biology), BS (Psychology)
Senior Researcher
GreenMedInfo
Naples, Florida

Michel Bouko Levy, MD
President and Founder
l'Institut d'Homeopathie de Provence
Marseille, France

and

Founder
Homeopathic Medical Association
of Canada
Ontario, Canada

Adonis Maiquez, MD, ABAARM
Medical Director
Carillon Miami Wellness Resort
Miami Beach, Florida

Miriam Maisel, MD
Family Practitioner
Nutrition and Lifestyle Intervention
Tel Aviv, Israel

and

General Practitioner
Dumfries and Galloway
Royal Infirmary
Scotland, United Kingdom

Anadi Martel, MSc
Physicist
Sensortech Inc.
Ste-Adele, Quebec, Canada

Darshan H. Mehta, MD, MPH
Medical Director
Benson-Henry Institute for Mind Body
Medicine
Massachusetts General Hospital
and
Associate Director of Education
Osher Center for Integrative
Medicine
Harvard Medical School and
Brigham and Women's Hospital
Boston, Massachusetts

Jeffrey Moss, DDS, CNS, DACBN
President
Moss Nutrition Products, Inc.
Hadley, Massachusetts

Arturo O'Byrne-De Valdenebro, MD
Biological Medicine Private Practice
and
Director
Academic Affairs at Sociedad
Argentina de Medicina
Biológica y Homotoxicología
(SAMByH)
Buenos Aires, Argentina

Arturo O'Byrne-Navia, MD
Medical Director
Centro de Medicina Biológica
and
Professor
Integrative Medicine Chair at Pontificia Universidad Javeriana
Cali, Colombia

Yoshiaki Omura, MD, ScD, FACA, FICAE, FAAIM, FRSM
Adjunct Professor
Department of Family and Community Medicine
New York Medical College
Valhalla, New York

and

President and Professor
International College of Acupuncture and Electro-Therapeutics
New York City, New York

and

Editor-in-Chief
Acupuncture and Electro-Therapeutics Research
International Journal of Integrated Medicine
Valhalla, New York

James L. Oschman, PhD
Nature's Own Research Association
Dover, New Hampshire

Mayoor Patel, DDS, MS
Private Practice
Craniofacial Pain and Dental Sleep Center of GA
Atlanta, Georgia

and

Adjunct Clinical Instructor
Dental College of Georgia
Augusta, Georgia

and

Tufts University
Boston, Massachusetts

David Perez-Martinez, MD
Founder of TuneUpRx
Faculty
Sound and Music Institute
New York Open Center
New York, New York

Joshua Plant, PhD
Chief Scientific Officer
Pharmatech Labs
Lindon, Utah

Gerald H. Pollack, PhD
Professor of Bioengineering
University of Washington
Seattle, Washington

Jacqueline Proszynski, BS
Clinical Research Program Coordinator
The Benson-Henry Institute for Mind Body Medicine
Massachusetts General Hospital
Boston, Massachusetts

Lisa Marie Samaha, DDS, FAGD
Private Practice Owner
Port Warwick Dental Arts
and
Founder, Researcher and Professor
Perio Arts Institute, PerioPassion Dental Seminars
and
International Academy for Ozone in Healthcare
Newport News, Virginia

Stephanie Seneff, PhD
Senior Research Scientist
MIT Computer Science and Artificial Intelligence Laboratory
Cambridge, Massachusetts

Alyse Shockey, RDH, CMT, CHHP
HH Wellness, LLC
Baltimore, Maryland

Virender Sodhi, MD (Ayur), ND
Ayurvedic & Naturopathic Physician
CEO, Ayush Herbs Inc.
Director, Ayurvedic and Naturopathic Medical Clinic
Bellevue, Washington

Miguel A. Toribio-Mateas, BSc (Hons), MSc
School of Health and Education
Middlesex University
London, United Kingdom

Marjorie H. Woollacott, PhD
Faculty
Institute of Neuroscience
and
Professor
Human Physiology
and
Director
Motor Control Laboratory
University of Oregon
Eugene, Oregon

Julia Worrall, RN
Certified Critical Care Nurse Specializing in Sleep and Craniofacial Growth and Development
Founder and Executive Director
The Foundation for Airway and Craniofacial Excellence (FACE)
Toronto, Ontario, Canada

Section I

Nutritional and Functional Medicine

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1 The Role of the Microbiome on Human Health

Rodney R. Dietert and Janice M. Dietert

CONTENTS

INTRODUCTION

Much of allopathic medicine today is based on a process for treating medically coded conditions with a specified regime of diagnostic tests, procedures, and the administration of pharmaceutical agents. Efficacy and safety of these agents is determined by a regulated procedure of phased evaluation, usually first in laboratory animal models and then, subsequently, in humans. Individual variation based on age, genetic background, sex, and existing diseases and conditions can influence efficacy and safety. However, the predictability of adverse outcomes among subpopulations has been highly imprecise if not largely unknown.

The assumption was that, with the advent of the human genome program and the complete sequencing of the human gene sequence, individual patient variation could be fully accounted for, and what has been envisioned as precision or individualized medicine would be the foundation for the future. However, the recent realization that the human patient is actually a majority microbial based on cell number and gene number, and that human metabolism and physiology reflects this chimeric reality, has changed how health and wellness is most effectively approached. No longer is it only the mammalian part of humans that can be medically treated with expectation that the overall health of the patient will be optimized. In fact, via both special issues and recognition of significant breakthroughs, *Science Magazine* has focused on the microbiome as a pivotal factor when considering human health versus disease (Pennisi and Mueller 2016).

This chapter describes a landscape in which integrative medicine can utilize the microbiome, the microbial part of humans, for more effective disease prevention, treatment, and care of patients. The foundational message is that species purity is unhealthy, and that it is not possible to have a truly healthy patient unless the microbiome is also well diversified and healthy. Early life attention to the microbiome is emphasized since we now know that our microbes developmentally program our physiological systems for later-life function. A dysfunctional microbiome in childhood has been connected to elevated risk of numerous serious childhood and adult diseases (Dietert 2016a). Both infectious and noncommunicable diseases (NCDs) are included in the discussion. However, given the fact that NCDs are the overwhelming majority killer globally, are stressing healthcare systems, and are more often managed across a lifetime rather than cured (Dietert 2016b), an emphasis is placed on them.

A DIFFERENT PATIENT

The human superorganism patient presents both challenges and new opportunities for both disease prevention and integrative therapies. Approximately 99% of the genes in humans are microbial. A recent cataloguing of all microbial genes in humans estimated that just under 10 million microbial genes exist (Li et al. 2014). By comparison, the human chromosomal genes are estimated to be in the range of 22,000–25,000 (International Human Genome Sequencing Consortium 2004).

In utero exposure of the fetus to microbes occurs via the placental microbiome (Aagaard et al. 2014). Interactions between the trophoblast layer, the outer layer of the blastocyst, and the microbiome (Mor and Kwon 2015) affect both fetal immune development and immunoregulation in the mother that is needed to maintain the pregnancy to term (Zheng et al. 2015). Management of the pregnancy needs to include management of the mother's microbiome including that of the placenta. Researchers have suggested that the placental microbiome profile is a driver of both pregnancy outcome and the future destiny for the fetus (Cao et al. 2014; Fox and Eichelberger 2015).

The primary microbial seeding event for the baby occurs at birth during vaginal delivery and via skin-to-skin contact (Mueller et al. 2015). However, Cesarean delivery interrupts the primary seeding event leaving the baby's microbial seeding to come largely from outside or beyond the mother. Antibiotics and other drugs given during pregnancy, as part of the C-section procedure, or immediately during infancy can also deplete the baby's microbiome and alter the course of infant microbial and physiological maturation (Bokulich et al. 2016; Stokholm et al. 2016; Yassour et al. 2016). When a newborn has a depleted microbiome, it has been represented as a type of birth defect in that there are known, predictable physiological alterations, anatomical changes (e.g., barrier function), and health risks associated with the continuation of this infant state (Dietert 2014). In fact, the early life events relative to the infant microbiome shape both subsequent immune and metabolic functions (Wang et al. 2016).

While attention to a healthy microbiome is beneficial at any age, there is particular benefit during pregnancy and early infant life. Attention to the microbiome during pregnancy has the potential to improve the health of both mother and baby (Isolauri et al. 2015). This affords a new, important opportunity for health professionals involved with pregnancy management. Likewise, attention to microbiome status of the newborn is critical, since the newborn's microbiome and physiological systems (e.g., the immune system and brain) co-mature together (Wopereis et al. 2014; Diaz Heijtz 2016). Breast feeding offers another window of opportunity both for microbiome seeding and for introduction of specific complex carbohydrates designed exclusively as an energy source for the microbiome (Bashiardes et al. 2016).

There is evidence that elements of modernization (urbanization, processed non-local food, elective C-sections), antibiotic overuse, and Westernized diets low in fiber have contributed to the degradation of the human microbiome and loss of diversity. Recent studies suggest that within-generation improvement of microbiome diversity is possible through rebiosis and dietary change. However, continued transmission of a degraded, unhealthy microbiome across multiple generations can blunt the capacity for us to use dietary changes as a strategy to correct problems with the microbiome

(Sonnenburg et al. 2016). For this reason, we may have little generational time to medically address microbial degradation in humans. The current generation of children is at risk from a deficient microbiome; but, based on the recent findings of Sonnenburg and colleagues (Sonnenburg et al. 2016), failure to act on the current generation of children could make microbiome corrections in future generations more difficult.

While the gastrointestinal microbiome has the most extensive research, it is important to recognize that many different tissues have their own microbiome and that these are distinct from that of the gut. Each body site such as the airways, skin, breast tissue, placenta, and urogenital tract has its own healthy and dysfunctional microbiome profiles. For example, Yu et al. (2016) recently described the human lung microbiome and reported that the lung microbiota are distinct from the microbial communities in oral, nasal, stool, vagina, and skin. In lung, Proteobacteria were the dominant phylum (60%).

THE NONCOMMUNICABLE DISEASE EPIDEMIC

Noncommunicable diseases (NCDs), also called chronic diseases, are the scourge of the twenty-first century. As recently as the early-mid twentieth century, infectious diseases were the primary concerns with first influenza and polio viruses as well as the tuberculosis-causing bacterium grabbing both medical and institutional public health focus. Asthma, type 1 and 2 diabetes, heart disease, obesity, cancer, autism spectrum disorders, Alzheimer's disease, Parkinson's disease, and the myriad of autoimmune and inflammatory conditions were but blips on the healthcare radar.

All that changed within mere decades and a couple of generations. In many ways, the battle against infectious diseases has been highly successful. New pandemics continue to emerge, and they present challenges; but their global impact pales in comparison to the toll of NCDs.

One of the challenges with NCDs is that few are actually cured. More often, the symptoms of these diseases and conditions are medically managed. In some cases, this can last for a lifetime resulting in decades of ever-increasing needs for prescriptions drugs. Such ongoing medical and drug dependency can take a toll not only on the patient but also on family members (Stuckey et al. 2016). Currently, the only exception to this trend of lifelong prescription drugs for certain NCDs is that drugs may be removed for patients near the end of life (Nishtala et al. 2016).

Another problem is that extensive co-morbidities exist for NCDs. The diagnosis of any one NCD automatically means that the individual is at an elevated risk of additional NCDs with aging (Dietert et al. 2010). With increased medical diagnoses, healthcare costs, and pharmaceutical burdens, and the likelihood of restrictions on function and/or activities, quality of life often degrades (De Maeseneer and Boeckxstaens 2011). Additionally, the risk of drug incompatibilities and problematic side effects increases, and the number of diseases and required medications increases accordingly.

Because of the importance of early life programming of later life NCDs, or what is known as the Barker Hypothesis, the earlier prevention and intervention measures can be taken, the greater the likelihood of reduced NCDs across an individual's life course. This was emphasized recently by Roura and Arulkumaran who stressed that to fully address the NCD epidemic, the frontline of the battle is *in utero* (Roura and Arulkumaran 2015) given the importance of fetal programming of later life disease (Morton et al. 2016).

THE PROBLEM WITH MANY EXISTING DRUGS

One problem with existing drugs and many of those about to be released is that the benefit-risk determination is likely to be flawed. Most of these drugs were never vetted for safety of the microbiome. In fact, they were vetted for safety under a rubric that was mammalian-centric and never considered whether the drugs could damage the microbiome or required specific microbes to work. This is likely part of the explanation for the frustratingly long list of side effects that are associated with many of today's drugs (see Table 1.1). However, beyond those known side effects (e.g., drug-induced

TABLE 1.1
Examples of Drugs Whose Efficacy and/or Safety Depend on Microbiome Status

Drug	Treatment Use	Reported Effect	References
Berberine	Metabolic disorders	Gut microbiota are required for drug absorption and microbiome status determines efficacy	Feng et al. (2015)
Amlodipine (a calcium channel blocker)	Hypertension	Therapeutic potency is affected by status of the gut microbiota	Yoo et al. (2016)
Cyclophosphamide	Cancer Autoimmune disease Transplantation	Requires specific microbes for efficacy, treatment alters the microbiome	Xu and Zhang (2015)
Digoxin	Cardiovascular disease	Both safety and efficacy depend upon the microbiome profile	Haiser et al. (2014)
Lovastatin (a statin)	Elevated cholesterol	Status of the gut microbiota affects the conversion of the prodrug lovastatin to the active form	Yoo et al. (2014), Klaassen and Cui (2015)
Metformin	Diabetes	Efficacy improved by co-administration of probiotic *Bifidobacterium animalis* ssp. *lactis* 420 in mice	Stenman et al. (2015)
Nitrazepam	A benzodiazepine used for anxiety and insomnia	Production of a teratogenic metabolite is affected by gut microbiota status	Klaassen and Cui (2015)
Non-steroidal anti-inflammatory drugs (NSAIDs)		Ibuprofen and naproxen both skew the gut microbiome vs. controls but they also enrich different families of bacteria	Rogers and Aronoff (2016)
Proton pump inhibitors	Excess gastric acid production, peptic ulcers, and gastro-esophageal reflux disease (GERD)	Long-term use produces a skewing in microbiome composition and an increased risk of *C. difficile* infection	Clooney et al. (2016), Imhann et al. (2016), Jackson et al. (2016)
Tempol	Anti-oxidant, prevention of weight gain	Tempol appears to require gut microbiota alterations for pharmacological activity	Cai et al. (2016)

gut symptoms or diarrhea), drug-induced microbial dysbiosis can eventually lead to other NCDs (e.g., inflammation-driven diseases) that are unlikely to be noted as a drug-induced "side effect."

In a recent comprehensive review of microbiome-associated drug and chemical metabolism, Klaassen and Cui (2015) describe how our microbes can drive numerous drug and chemical metabolic pathways. For example, bacteria can biotransform drugs and chemicals affecting the spectrum and relative amounts of metabolites that an individual produces and, thereby, affect drug efficacy and safety. This microbe-mediated transformation occurs through the following chemical reactions: acetylation, amine formation and hydrolysis of amide bond, azoreduction, deconjugation, deglycosylation, dehydroxylation, denitration, isoxazole scission, N-demethylation, N-oxide bond bond cleavage, proteolysis, reduction, hydrolysis, succinate group remover, and thiazole ring opening.

Additionally, our microbes can both produce and regulate the levels of certain super families of genes encoding inducible metabolic enzymes. One prominent family is the cytochrome P (CYP) 450 enzymes. CYP450 enzymes are so designated because 450 nm is the wavelength of light they maximally absorb when they are in a reduced state and complexed with carbon monoxide. By affecting CYP gene activity in the liver, the status of the microbiome can exert a significant influence on the metabolism of all xenobiotics. Among the most significant CYP450 for drug metabolism is the group known as 3A, which is prominent in the liver and intestines. CYP450 3A enzymes

metabolize most drugs and eventually help with detoxification of the body (Klaassen and Cui 2015; Selwyn et al. 2015, 2016).

Drugs are not the only chemicals metabolized by the microbiome. Health safety from environmental chemicals is also affected by microbiome status. As with drug metabolism pathways there are many ways that our microbes can affect the delivered internal dose of environmental chemicals (Dietert and Silbergeld 2015). Among these is the capacity of gut microbiota to activate a cell transcriptional factor known as the aryl hydrocarbon receptor (AHR). Microbes can do this through the metabolism of tryptophan (Zelante et al. 2013). AHRs are important because they bind flavonoids, polyphenolics and indoles, as well as synthetic polycyclic aromatic hydrocarbons and dioxin-like compounds. They are also important in the body's detoxification process, and the fact that microbes can control AHR expression as well as other biological processes determining our internal exposure to toxicants means that they play a significant role in our environmental health protection.

Susceptibility to toxic chemicals in the environment and food can be affected by microbiome status. For example, the status of the gut microbiota can affect the internal burden from oral exposure to heavy metals such as cadmium and lead (Breton et al. 2013). In the case of the toxic metal arsenic, gut microbes affect which of several different forms of arsenic will exist in the body. Some gut microbes have the capacity to produce the most toxic forms while others lack those genes. As a result, the specific profile of the microbiome can determine the risk to the individual from a given exposure to arsenic (e.g., via drinking water) (Dc-Rubin et al. 2014).

Finally, the industrial chemical melamine is a toxicological risk for both humans and animals. This was a recent problem when melamine contaminated both infant formula and pet food produced in China (Dalal and Goldfarb 2011; Wang et al. 2011). Melamine toxicity results in crystal formation in the kidneys. However, the extent of crystal formation after melamine exposure is affected by the presence of and levels of specific gut microbes (Zheng et al. 2013; Klaassen and Cui 2015). It is another example where the profile of gut microbes determines the actual individual health risk.

MANAGING THE MICROBIAL ECOLOGY OF THE PATIENT

A recent view of human biology is that we are a collection of thousands of different species that all fit together to the benefit of the whole. Our closest models for this are the living coral reef and tropical rainforests. Much is known about the ecological management of a coral reef or tropical rainforest, and they are appropriate models when it comes to the design of integrative health approaches for humans. The challenge will be to shift our basic thinking about the nature of the human patient.

As in the coral reef, risk to any of the species (mammalian and microbial) contributing to overall human integrity and health needs to be considered before pursuing treatment options. The benefit of the whole is the goal. In essence, the physician becomes a superhuman ecologist with the task of managing the microbial ecology of the patient so as to "do no harm." Either ignoring the status of a patient's microbiome or operating without a clear understanding of risk-benefit for all the patient's species can result in unintended adverse consequences.

Just as with the coral reef, the patient's total ancestral, environmental, and medical experiences play a role in the status of the microbiome. Modulators of the microbiome start with the chemicals and other environmental factors to which a human is exposed (e.g., diet, environmental pollutants, radiation, and drugs). Because the microbiome sits at our portals of exposure to the external environment (e.g., skin, gastrointestinal tract, airways, urogenital tract), the microbiome is exposed to, filters, deals with, and responds to these factors before our mammalian cells ever encounter them (Dietert and Silbergeld 2015). In effect, the internal exposure dose to a dietary component, environmental chemical, or drugs is heavily regulated by our microbiome. The particular composition and richness of an individual's microbiome can affect human health risk (Dietert and Silbergeld 2015).

Chemical factors are not the only considerations. Risk factors for the microbiome include physical and psycho-social factors as well. For example, undue stress is a known health risk. It is also a significant factor in microbiome balance. For example, maternal stress during pregnancy has been implicated in changes in the vaginal microbiome as well as vaginal protein profiles that are associated with the first wave of microbial colonization in the offspring and subsequent programming of both metabolism and neurological development (Jašarević et al. 2015). One of the ways that stress and other environmentally induced changes in the microbiome are thought to influence neurological development and behavior is through changes in epithelial barriers that separate the microbiome from immune cells. Increased permeability and loss of tight junction function among epithelial cells allow microbial signaling of immune cells that predispose for inflammation. John and colleagues (John et al. 2015) have suggested that the subsequent proinflammatory state that is created by the dysfunctional microbiome leads to brain alterations signaled though the vagus nerve such as cytokine-induced alterations of the HPA axis and shifts in tryptophan metabolism. One of the molecular pathways involved appears to be the inflammasome, which is a go-between for microbial disruption and immune establishment of a proinflammatory state (Wong et al. 2016).

Within the brain there are ultrastructural changes that reflect the state of the microbiome. For example, it appears that the level of myelination in the pre-frontal cortex region of the brain is directly related to the sufficiency of the microbiome (Hoban et al. 2016). Additionally, distinct gut-to-brain and brain-to-gut pathways linking anxiety/depression and irritable bowel syndrome (IBS) were recently described by researchers from Australia. In some cases, the neurologically related symptoms preceded the gastrointestinal distress and in many others, this relationship was reversed with IBS arising before anxiety or depression (Koloski et al. 2016). Recent studies of gut microbiota both in animal models as well as human patients have shown a link between gut microbiome status and the neuroinflammatory autoimmune disease, multiple sclerosis (Glenn and Mowry 2016). Similarly, gut microbiota dysbiosis has been demonstrated in patients with the debilitating condition myalgic encephalomyelitis (previously known as chronic fatigue syndrome) (Giloteaux et al. 2016). Finally, the outcome of ischemic stroke appears to be affected by the composition of the gut microbiota via their impact on immune regulatory cell activities (Benakis et al. 2016).

While more information on specific regulators of microbially driven, gut-brain alterations will be useful, it is increasingly clear that healthy neurological and psychiatric function is difficult if not impossible to maintain in the absence of a healthy microbiome. Additionally, there is a golden opportunity to use microbes and/or their metabolites as therapeutics for mood, depression, and psychological problems (Sherwin et al. 2016).

Recently, new adaptive tests to examine data sets for microbiome composition and physiological as well as health outcomes have provided new insights into the ecology of the human microbiome. For example, application of these multivariate data analyses has led to better insights into the role of gender in differences among specific bacterial families (Wu et al. 2016).

COMPLEMENTARY THERAPIES: REBIOSIS

Complementary strategies to achieve a better balance within the microbiome at various body sites involve the process known as rebiosis. This takes several forms: (1) consumption of fermented foods with active cultures, (2) consumption of or topical application of probiotic formulations containing missing or deficient microbes, (3) consumption of prebiotics (food/energy sources for specific microbes) often given with probiotics, and (4) the more comprehensive microbiota alteration called fecal microbiota transplantation (FMT). To facilitate the likelihood that the microorganism will take up residence in the patient, the nutrient tailored to support the growth of the probiotic microorganisms (called prebiotics) is often used either in the same formulation as the live microbial cultures or separately. Ideally, consumed probiotics can take up residence at the desired body site (part of the GI tract, skin, mouth, nose, urogenital tract). But even in cases where the microbes are only transient, there can be some metabolic benefit by the application and the presence of probiotic

metabolites (Guo et al. 2016). Table 1.2 illustrates some of the examples in which rebiosis has been used in the treatment of disease. Among the examples shown are allergic, inflammatory, behavioral, autoimmune, and infectious diseases and conditions.

Fecal microbiota transplantation involves a more comprehensive alteration of the gut microbiome than might be expected from consumption of probiotic-containing foods or probiotic formulations. Importantly, donor selection is important in FMT. As discussed by Fuentes and de Vos (2016) FMT is not really a radical idea. They argue that the most significant transplantation event is via natural childbirth when the mother donates her microbiota to seed the baby. FMT can lead to a complete change in the gastrointestinal microbiota such that it more closely resembles the donor profile than the recipient microbiome. However, while the impact on existing diseases such as *Clostridium difficile* infections can be prompt, complete changes in the microbiome profile may not be evident for months and could take years (Broecker et al. 2016).

In addition to the information in Table 1.2, many preventative and therapeutic applications involving probiotics and FMT are introduced in the following section.

Antibiotic Adjunct Therapies

Overuse of antibiotics is recognized as a major factor in the depletion of the human microbiome and even when they are needed, these drugs are likely to kill commensal bacteria along with the pathogen (Blaser 2016). Investigators have argued that it is time to consider probiotics as an adjunct therapy for antibiotic administration. In particular, this has been advocated in the treatment of *Clostridium difficile* infection (Spinler et al. 2016). However, given the impact of antibiotics on the microbiome, adjunct therapies could help avoid the destruction of the microbiome and subsequent altered physiology, barrier function, and risk of inflammatory-driven diseases. A recent trial in children looked at the adjunct administration of yogurt containing three probiotic bacteria versus control pasteurized yogurt for children receiving prescribed antibiotics. The study reported that the probiotics group had a lower and less severe incidence of antibiotic-associated diarrhea (Fox et al. 2015).

Postoperative Recovery

The postoperative phase of major surgical procedures is receiving additional attention as that can affect the subsequent health trajectory of patients (Fujikuni et al. 2016). There are opportunities for this to move beyond pain management to include attention to microbiome status, probiotics, and the use of prebiotics and functional foods. Mizuta et al. (2016) examined the effects of daily *Bifidobacterium longum* BB536 administration preoperatively (preoperatively for 7–14 days and then postoperatively for 14 days) among patients undergoing colorectal surgery. The clinical investigators found that probiotic supplementation resulted in both an improved balance of gut microbes following surgery and reduced levels of inflammatory biomarkers (e.g., C-reactive proteins).

Protection against Stress-Induced Dysbiosis

Preventative application of probiotics to avoid the damage of environmental changes can be beneficial. For example, Kato-Kataoka et al. (2016) reported that daily ingestion of milk-borne *Lactobacillus casei* strain Shirota by healthy medical students preparing for examinations led to an increased diversity of gut microbiota, reduced abdominal distress, reduced salivary cortisol levels, and reduced stress-induced changes in leukocytes in the probiotic-supplemented test group versus the placebo group. Early life stress can produce developmental impairment in learning. Researchers showed that a probiotic formulation of *Lactobacillus rhamnosus* and *L. helveticus* given to rat dams corrected maternal separation-induced developmental impairment of the pups (Cowan et al. 2016).

TABLE 1.2
Some Examples of Microbiome Rebiosis to Treat Diseases and Conditions

Medical Condition	Microbial Intervention	Reported Outcome	References
Atopy and food hypersensitivity	Meta-analysis of 17 human studies on consumption of probiotics during pregnancy and early childhood and risk of childhood atopy and food hypersensitivity	Probiotics administered both during pregnancy and early childhood could reduce the risk of childhood atopy and food hypersensitivity	Zhang et al. (2016)
Atopic dermatitis	Meta-analysis of 25 studies with 1599 participants concerning probiotics in the treatment for atopic dermatitis	Probiotics could be a useful treatment option for children and adults	Kim et al. (2014)
Bacterial vaginosis	In a multicenter study, 160 participants with at-risk vaginal environment profiles were randomly assigned to test and placebo groups. The test group was given a 7-day regimen of a probiotic mix with *Lactobacillus fermentum* 57A, *Lactobacillus plantarum* 57B, *and Lactobacillus gasseri* 57C	As a preventative measure for at-risk populations, probiotics restored the microbial profile and pH to normal ranges reducing the risk of bacterial vaginosis	Tomusiak et al. (2015)
Depression	*Supplementation with Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175	Decreased scores for anxiety and depression	Messaoudi et al. (2011)
Depression	Eight-week supplementation with *Lactobacillus acidophilus Lactobacillus casei* and *Bifidobacterium bifidum*	Beneficial effects on Beck Depression Inventory	Akkasheh et al. (2016)
Late-onset sepsis in preterm neonates	Meta-analysis of 17 trials with enteral probiotic supplementation examining risk of sepsis in neonates	Significant reduction in risk of any sepsis, bacterial sepsis and fungal sepsis that also included low birth weight babies	Zhang et al. (2016)
Gingivitis and peridontitis	Meta-analysis of 50 studies with 3247 participants involving use of probiotics in oral disease management	Treatment with probiotics bacteria such as lactibacili and bifidobacteria was effective in managing both gingivitis and peridotitis	Gruner et al. (2016)
Pathogenic bacterial biofilms	Probiotic bacteria (combinations of *Lactobacillus plantarum* SD5870, *Lactobacillus helveticus* CBS N116411 and *Streptococcus salivarius* DSM 14685) used to inhibit biofilm formation and disrupt existing biofilms	Overlay and co-culture experiments showed that the probiotics disrupted biofilm formation, disrupted existing biofilms and inhibited gene expression in *Candida albicans* that was required for the formation of biofilms by the opportunistic pathogen	James et al. (2016)
Recurrent *Clostridium difficile* infection	Fecal microbiota transplantation (FMT), including in the form of frozen preparations, has been shown to be effective at treating this condition at least in part by changing bile acid composition	FMT not only corrects this condition but also reduces the burden of antibiotic resistant genes in the microbiome of patients	Lee et al. (2016), Weingarden et al. (2016), Millan et al. (2016)
Rheumatoid arthritis	Sixty patients (30 test and 30 control) took probiotics (capsules of *Lactobacillus acidophilus, Lactobacillus casei* and *Bifidobacterium bifidum* for 8 weeks	Significant probiotic-associated clinical and metabolic improvement was found for the Disease Activity Score of 28 joints, as well as for metabolic and inflammatory biomarkers	Zamani et al. (2016)
Ulcerative colitis	Meta-analysis of 25 studies including 234 ulcerative colitis patients who received fecal microbiota transplantation (FMT)	Overall results were 41.6% with clinical remission and 65.3% with useful clinical outcomes	Shi et al. (2016)

Correction of Depression and Anxiety

Gut microbiota can communicate with the brain using immune, neuro, and endocrine pathways (Slyepchenko et al. 2014). Probiotics are becoming a useful tool in the treatment of depression and anxiety. Vlainić et al. (2016) described the value in probiotic adjunct therapy for treating major depressive disorder (MDD). Part of the basis for microbiome adjustments in MDD is the fact that the gut microbiome plays a major role both directly and indirectly in the production of neurotransmitters, neuroactive peptides, and glutamatergic and GABAergic transmission (e.g., GABA, serotonin, norepinephrine, dopamine) (Cryan and Dinan 2015). Additionally, the microbiome profile largely determines the balance of pro- and anti-inflammatory cytokines that play a role in MDD (Dinan and Cryan 2016). The control of mood and behavior is so extensive that researchers recently coined the term psychobiotics to refer to mind altering probiotics (Wall et al. 2014). Some gut microbes have the potential to regulate myelination in the prefrontal cortex via changes in gene expression (Hoban et al. 2016). Among the potential candidate probiotics to treat depression and anxiety are: *Bifidobacterium longum* (B.) 1714 and *B. breve* 1205 (Savignac et al. 2014).

Additionally, the immune system can be involved in the connection between social behavior and the microbiome. A recent study by Filiano et al. (2016) found that meningeal immunity, particularly interferon-gamma-driven signaling, is key to the level of GABAergic (γ-aminobutyric-acid) responses in neural circuits. Immune dysfunction can act as a pathway to social dysfunction.

Anti-Aging Effects

Oxidative damage in body sites such as the skin is a major part of the aging process (Poljšak et al. 2012; Rinnerthaler et al. 2015). Probiotics appear to offer promise in protecting the skin from both intrinsic and extrinsic aging (Sharma et al. 2016). Importantly, not only is oxidative stress attenuated, but barrier function can be improved via a microbial strategy. Among the probiotics that have shown promise for the skin are: *Lactobacillus plantarum*, *Lactobacillus paracasei*, and *Bifidobacterium breve*.

Protection against Recurrent *Clostridium difficile* Infection

Clostridium difficile infection presents a significant, largely hospital borne, health risk. One of the problems with antibiotic therapies is that while they may control the pre-existing infection, they invariably put the patient at an elevated risk for recurrent *C. difficile* infection. This appears to occur because of the existence of antibiotic-resistant *C. difficile* spores, which have an advantage to reinfect the patient due to the antibiotic-induced general disruption of the gut microbiota (Sbahi and Di Palma 2016). An effective tool against recurrent infection with *C. difficile* is FMT (Sbahi and Di Palma 2016). While this has been historically done by colonoscopy installed transplantation of fecal microbiota, more recent developments have allowed frozen oral capsules to be the route of administration (Youngster et al. 2014).

Protection against Environmental Toxicants

Because the microbiome resides largely at the site of the body's exposure to the external environment, the microbes receive the bolus of most drugs and environmental chemicals before the human mammalian cells. Risk of human toxicity is, therefore, affected by the diversity, richness, and composition of the microbiome in different sites (e.g., skin, GI tract). Heavy metals such as cadmium are neuro- and immuno-toxicants and have the capacity to disrupt barrier function at least in part via oxidative damage. A recent study in mice on cadmium exposure found that treatments with the probiotic *Lactobacillus plantarum* CCFM8610 increased excretion rather than absorption of cadmium, reduced disruption of intestinal barrier tight junctions, reduced inflammation, and decreased

the intestinal permeability of mice (Zhai et al. 2016). The discovery of the importance of certain probiotics on both barrier function and levels of inflammation is consistent with the recent focus on the microbiome, host defense barrier, and immune system complex termed the microimmunosome (Dietert 2016a).

Treating Metabolic Syndrome

Rebiosis approaches appear promising when it comes to treating metabolic syndrome. A course of *Bifidobacterium lactis* HN019 (in fermented milk) was administered to a subgroup of Met S patients for 45 days and lipid metabolism plus inflammatory biomarkers were evaluated in probiotic-administered versus control patients (Bernini et al. 2016). The investigators found that ingestion of the probiotics-laden milk resulted in a significant reduction in body mass index, total cholesterol, and low-density lipoprotein when compared with the baseline and control group results. Additionally, levels of two proinflammatory cytokines (tumor necrosis factor alpha and interleukin 6) were significantly decreased with the supplementation. Based on these results, the conclusion was that probiotic supplementation may reduce the risk of cardiovascular disease among MetS patients.

A key target in the treatment of metabolic syndrome via the microbiome involved the bacterial species *Akkermansia muciniphila*. *A. mucinphila* is a key bacterium involved with regulation of the mucus layer in the gut and, as a result, integrity of the gut barrier and protection against inappropriate and/or excessive inflammation. To date, prebiotics have been used to modulate the size of the *A. muciniphila* population in the patient's gut. However, next generation probiotic formulations including *A. muciniphila* are on the horizon pending safety evaluations, and these may be useful against metabolic syndrome linked conditions (Cani and Van Hul 2015; Gómez-Gallego et al. 2016).

Potential Help for Infantile Colic

A randomized double-blind study in Canada using *Lactobacillus reuteri* DSM 17938 found that daily administration of the probiotic to breastfed infants significantly reduced the crying time and fussiness in babies when compared to the placebo group (Chau et al. 2015).

BIOFILMS

Biofilms are community level organizations of microbial species that stick to each other, thereby forming a superstructure and usually also adhering to host tissue. The superstructure organization allows the microbes to change metabolism, producing an almost impenetrable matrix of extracellular polymeric substance (EPS) that protects this specialized microbial form from many traditional antimicrobial agents.

As a result, pathogenic biofilm can be comparatively resistant to both host defenses and normal medical treatments such as dosing with antibiotics. Some pathogens are more likely than others to form biofilms. Additionally, they can be associated with many different tissues including the oral and urogenital cavities and hair follicles. A further concern is the ability of biofilms to form on implanted medical devices.

Biofilm formation is affected by specific gene expression, which is affected by several factors including the surface to which bacteria attach (Watnick and Kolter 2000). It is also thought that biofilms are more likely to form in response to local ecological competition and changes such as cellular damage regardless of the instigating factor (e.g., bacterial-derived toxins such as pyocins as well as antibiotics) (Oliveira et al. 2015).

An example of biofilms is the three-dimensional biofilms formed by *Propionibacterium acnes* during acne vulgaris in sebaceous follicles (Jahns et al. 2012; Jahns and Alexeyev 2014). However, not every comedone contains *Propionibacterium acnes*, and some clinicians have suggested that inflammatory imbalances in the follicle may be the actual initiating factor for the condition (Shaheen

and Gonzalez 2013). Similarly, clinical presentation of Hidradenitis Suppurativa (HS) is also associated with bacterial biofilms potentially involving several different species. However, it is not clear whether the biofilms are involved with disease induction or reflect the disturbance of the local hair follicle environment once the condition has become established (Ring and Emtestam 2016).

While biofilms can prevent a significant health challenge in any tissue, their consideration is particularly important in managing oral hygiene and preventing oral disease. Biofilms are readily formed in the mouth as part of the regular community microbial structure (Arweiler and Netuschil 2016) However, if not managed, caries and oral disease can result. There is evidence that biofilm formation in the mouth can occur in stages during which facultative anaerobic bacteria can become replaced by gram-negative anaerobic bacteria (Wake et al. 2016).

Evidence suggests that probiotics can offer part of an integrative health strategy for prevention and reduction of biofilms. However, the specific selection of the probiotic bacteria, the genes they carry relative to the pathogens involved in the biofilm and the stage of development of the biofilm appear to be important considerations. Vuotto et al. (2014) recently reviewed the use of probiotics in the prevention and treatment of specific biofilms. Much of the most extensively studied examples involve *Bifidobacterium* spp.—and *Lactobacillus* spp.—containing probiotics. Combinations of *Lactobacillus plantarum* SD5870, *Lactobacillus helveticus* CBS N116411, and *Streptococcus salivarius* DSM 14685 bacteria or their supernatants have been found to significantly reduce oral biofilm formation by *Candida albicans* (James et al. 2016).

While biofilms are generally thought to be detrimental to the patient, there are several examples where biofilms involving keystone commensal species of bacteria are actually required to support fundamental human biological functions. Among these is the maintenance of the microimmunosome, the microbiome-host defense barrier-immune complex, and balanced physiology. For example, biofilm formation in the colon appears to be required to support normal mucus production. This is often disrupted with colitis. Restoration of the biofilm using a hydrogen sulfide donor chemical (diallyl disulfide) in experimental animals and in human *ex vivo* tissues can restore mucus production and reduce inflammation (Motta et al. 2015). This example of useful biofilm formation suggests that alterations of microbiota for improved health do not require elimination of all biofilms. Instead, changes in the microbial species composition of biofilms may be a more unifying strategy when patient barrier function is an issue.

CONCLUSIONS

Integrative medicine is likely to focus increasingly on the microbiome as biomarkers of future health risks, targets of therapeutic strategies, and indicators of the effectiveness of medical treatments. This is because the microbiome is a dominant and integral component of the newly envisioned human superorganism patient. Human mammalian-centric approaches treat only a portion of the patient and, while there is still much to be learned about the microbiome and microbiome-based medicine, it represents the path to truly holistic and integrative medicine.

The ongoing NCD epidemic is this century's health crisis and current approaches most often manage disease symptoms rather than provide cures. Microbiome profiling of patients is likely to become routine as physicians will need to know those parameters before determining the most useful therapeutic approaches. In fact, recent knowledge that some drug prescriptions pose an unacceptable risk for individuals with certain microbiome imbalances (e.g., digoxin) will drive the need to monitor a patient's microbiome profile (Haiser et al. 2014).

Rebiosis at any age can be a useful part of integrative therapies. But the range of effects is likely to be most significant during pregnancy (which can affect both the mother and child) and in the young. Changes in diet with the inclusion of prebiotics to feed desired microbes, consumption of fermented foods, use of probiotic supplements, and fecal microbiota transplantation are among the options currently available to shift the patient's microbiome profile. Finally, newly envisioned drugs are likely to work with and through the microbiome.

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2 Nutritional Approaches to Chronic Illness

Miriam Maisel

CONTENTS

Nutritional treatment of selected chronic conditions, emphasizing published research on interventions proven to prevent and reverse cardio-metabolic disease, and slow down progression and achieve remission in selected autoimmune conditions. Focusing on the efficacy of whole food plant-based nutrition, and water-fasting, as safe and effective therapeutic modalities. Ahead of the guidelines but not ahead of the evidence.

INTRODUCTION: PERSPECTIVES, PROBLEMS, PRIORITIES

As clinicians it is our duty to preserve human life and reduce human suffering. In good faith we commit years of our own lives to education and training, years when we are tasked with absorbing and integrating imponderable quantities of information. All this information should be the means by which the wish to make a difference matures into the power to do so. Our profession is privileged to live where the warmth of humanitarian values can meet the cool clarity of rigorous science. At least, in an ideal world this would be so. Regarding the science aspect, however, things may not be as clear as we would like to believe. On the whole, doctors are passive and very indirect consumers of science, and culturally indoctrinated simply to adhere to "best practice," defined by guidelines, produced by panels of experts, who rely on meta-analyses of the published peer-reviewed literature. This is very indirect indeed, and depends on implicit trust in the filtering process by which the guideline reaches the working doctor. Yet, how can working

doctors look at the staggering numbers of published papers and decode all the statistics about all the medical problems that we see every day? Guidelines are established, and then change, and even if our extensive medical training had really provided the tools to challenge any part of this process, where would we find the time? How many clinicians really read and understand medical research papers? How many of us even know what to read, or even how to choose what to read?

The area of nutrition is probably one of the most challenging. We all know that apart from the original zygote, formed from the union of sperm and egg, the mass of every human body is entirely formed from ingested and reassembled food. And this body is not just a static mass, but a highly complex and dynamic system where countless enzymatic reactions take place simultaneously, every millisecond. Food itself is not much less complex: even simple foods such as an apple or a lettuce leaf are virtual miracles of complexity, containing macronutrients, vitamins, minerals, fiber, and a huge variety of phytochemicals, many of which have yet to be defined. Having said that, how many physicians have learned during training and education that "most deaths in the United States are preventable" (Greger and Stone 2015, Lenders et al. 2013) or that "our diet is the number one cause of death and the number one cause of disability" (Greger and Stone 2015, Murray et al. 2013)?

In medical education and training we learn to target a single problem or aspect of a problem using a point to point approach. There is a pill for high blood pressure, a different pill for diabetes, a different pill for cholesterol, and a different pill for pain and inflammation, as if they were magic bullets. However, the term "magic bullet" comes from a different context. This term was first used by Nobel Prize winner Paul Ehrlich, at the end of the nineteenth century, and referred to the search for specific substances that would go straight to the major killers of the day, pathogens such as diphtheria and syphilis (Auterhoff 1967). The magic bullet approach is appropriate for acute infectious diseases, should prevention fail. But in the case of our modern Western chronic diseases, the equation changes. For chronic conditions, medications are prescribed long term and it is well known that the cholesterol lowering medications can promote diabetes, the various blood pressure medications can cause diabetes, gout, or depression, the anti-gout medications can damage the stomach and kidneys, and the antidepressants can cause weight gain and impair sexual functioning (British National Formulary 2016), although fortunately there are other pills to address the new problems. It is clear that whatever benefits conventional pharmacotherapy may have with respect to such chronic conditions, it does not provide magic bullet solutions. The situation may be more reminiscent of the mythical nine-headed hydra, a monstrous serpent. When one head was cut off, two would grow in its place.

The magic bullet idea seems also to exist with respect to the popular approach to nutritional supplements. U.S. law permits manufacturers to make health claims such as "supplement X will preserve heart health" as long as the claims are accompanied by a disclaimer, to the effect that the health claims have not been evaluated by the FDA (Cohen 2016). As there are now an estimated 55,000 supplements in the U.S. marketplace, and 52% of U.S. adults take supplements (Kantor 2016), one can probably assume that many people are convinced by these highly qualified health claims, at least sufficiently convinced to support a $32 billion industry (Cohen 2016).

The saving grace of the supplement phenomenon may be the public perception that such quasi-natural products are less dangerous than pharmaceuticals, an idea which speaks of an aspiration to attain health through more natural means. The popularity of supplements implies a deeply buried idea that nutrition, and perhaps even food, could be important for health. This phenomenon also demonstrates the willingness of a large proportion of the population to spend its own money on products of perceived benefit to health.

Certainly, no doctor could be expected to be fully conversant with the claims and effects (or lack thereof) of 55,000 different supplements, and it is indeed questionable how much a busy clinician should be interested in a manufacturer's claim on a little bottle which is followed by a disclaimer. But if patients show their doctor what supplements they are taking, and the doctor responds with

shrugged shoulders and a glazed expression, this may only reinforce the notion that doctors neither know nor care about "nutrition."

How can responsible clinicians find a way through this jungle of "too much information," or too much so-called information? Is it possible to come to a better and more useful understanding of the role of food, of nutrition, which will inform our clinical practice and which will be of significant benefit to our patients? In other words, what approach can we use to find information that is true and that matters (Campbell and Jacobson 2013)?

In this chapter, many studies will be presented, studies that demonstrate the potential of nutrition (food) as a therapeutic tool in some of the conditions that matter the most—major causes of death and disability in our society, now, at the beginning of the twenty-first century. A case could be made to say that awareness of at least some of these pioneering studies should be a cornerstone of medical education and should form part of the common knowledge base of clinicians, including not only physicians and surgeons, but also osteopaths, naturopaths, homeopaths, herbalists, practitioners of traditional Chinese medicine, Ayurvedic medicine, and so on. This is because the findings are so positive, and matter so much, that for clinicians not to share them with their patients is arguably unethical, since it constitutes a failure to inform patients of treatment choices that are highly effective and benign. If clinicians themselves are not exposed to these studies during their education and training, then a definite onus falls on the educating and training institutions and their standards. Hopefully, the findings presented in this chapter will inform the guidelines of the future. It is to be noted, however, that the landmark studies on cigarette smoking and carcinoma of the lung were first published in the 1950s (Hutchinson 2006). Yet it took a long time for perceptions to change and it required up to five decades for laws to be passed banning smoking in public places. A follow-up report by the original authors 50 years after the first evidence was presented concluded that prolonged smoking was likely to shorten life by a decade (Doll et al. 2004). Nowadays, it would be unthinkable not to address patients' smoking, since the research evidence has been incorporated into guidelines and has become part of accepted good practice. In the case of nutrition, as will be seen, much evidence exists in the literature but has not (yet) become part of standard guidelines. This should not prevent thoughtful and caring clinicians from applying safe and effective nutritional interventions that are not "ahead of the evidence" but only ahead of the guidelines.

THE HEART OF THE MATTER

Nutritional Intervention in Cardiovascular Disease

The CDC ranked "diseases of the heart" as the top leading cause of death in 2014, accounting for 23.4% of U.S. deaths, over 614,000 deaths in that year. Cerebrovascular disease is listed as the fifth leading cause of death, accounting for 5.1% of all U.S. deaths in 2014, over 131,000 deaths (Heron 2016). Considering these together would attribute 28.4% of all U.S. deaths in 2014 to diseases of heart and cerebrovascular disease combined, for a total of just over 747,000 deaths. Further, an earlier CDC analysis ascribes 10.9% of disability to these two entities, with 6.6% ascribed to "heart trouble," 2.4% to stroke, and 1.9% to high blood pressure, out of a total of 45 million adults reporting a disability in that year (Brault et al. 2009). This equates to upward of 4.9 million Americans living with disabilities broadly attributed to vascular or cardiovascular disease. In yet another analysis using data from the Global Burden of Disease 2010 Study, ischemic heart disease and stroke rank as the first and third causes of years of life lost to premature mortality, together accounting for 735,000 deaths deemed to be premature. These entities also contribute very significantly to the number of years lived with disability (Murray et al. 2013).

Any discussion of nutrition and coronary artery disease would be incomplete without including the pioneering clinical studies of Dr. Dean Ornish and Dr. Caldwell Esselstyn, which were published in the 1990s and which demonstrated symptomatic improvement of coronary artery disease,

improved heart function, and angiographic regression of severe stenoses. Both trials used a low-fat vegetarian diet.

Dr. Esselstyn's study aimed to reduce total cholesterol to below 3.88 mmol/L (150 mg/dl) and used a core diet based on whole grains, legumes, vegetables, and fruit, excluding meat, fish, fowl, added oils, excess salt, nuts, and avocados. Initially, non-fat milk and yoghurt were allowed in small amounts but these were later excluded along with caffeine and fructose. After 1987, lipid lowering medications were used to attain the desired cholesterol value if this had not been attained by diet alone (Esselstyn 1995, 2014).

Dr. Ornish's trial used a broadly similar diet but restricted salt only for hypertensive patients. Initially a small amount of egg white and a small amount of non-fat dairy were allowed, maintaining dietary cholesterol intake below 5 mg per day. The diet provided approximately 10% of calories from fat, 15%–20% from protein, and 70%–75% of calories from complex carbohydrates. Smoking cessation (for the one patient who smoked), stress management training, and moderate exercise were included. Vitamin B12 supplementation was used, but not lipid lowering medications (Ornish et al. 1990).

Dr. Ornish's study was randomized, and the control group followed "usual care" as provided by their own physicians. The recommendations current at the time were to consume "less red meat, more fish and chicken" aiming for a "low fat diet" in which 30% of dietary calories came from fat (Ornish 1990). In Dr. Ornish's study, The Lifestyle Heart Trial, in the experimental group, results at one year showed dramatic improvement (reduction) in angina frequency and duration, as well as an average change toward angiographic regression of coronary artery stenosis. In the control group, there was, on average, worsening of both symptoms and angiographic severity of lesions. The degree of improvement in the experimental group correlated with the degree of adherence to the diet and other components of the program. Dr. Ornish concluded that while his experimental diet was able to reverse coronary artery disease, the prevailing dietary recommendations current at the time (30% of calories from fat) did not go far enough to achieve reversal of disease (Ornish 1990).

Dr. Esselstyn's initial study followed a small group of cardiac patients from the Cleveland Clinic, all of whom had severe progressive triple vessel coronary artery disease, for a period of 5 years. The structure of the study did not involve a formal control group but patients who did not adhere to the dietary guidelines, or left the study, became a de facto control group. The 11 patients who completed the study had collectively experienced 37 cardiac events in the 8 years prior to the study. At the end of the 5 years of following the protocol, there were no new infarctions, and analyses of coronary lesions by percent stenosis showed that 100% of lesions had stabilized and 83% had regressed. Angina symptoms, present in 10 of the patients at the beginning of the study, decreased in all cases and were completely eliminated in 30% of cases. All five of the patients who dropped out of the study and resumed their former diet experienced new cardiac events, including worsening angina symptoms, disease progression requiring angioplasty or coronary artery bypass graft, ventricular tachycardia, and an arrhythmia related death (Esselstyn 1995). A larger study followed 198 patients for a mean of 3.7 years with the same dietary interventions, with the 21 patients who did not adhere to the program constituting a de facto control group, as in the earlier study. In the group of 177 patients who adhered to the dietary intervention, 81% improved and there were no cardiac deaths. Approximately 27 of these patients were able to avoid coronary artery stenting or bypass grafts that had previously been recommended. In the non-adherent group of 21 patients, 62% got worse, none experienced symptom reduction, and 2 died (Esselstyn 2014).

As previously noted, Dr. Ornish's study included formal stress reduction training and support groups. Dr. Esselstyn's study ostensibly included only a pure nutritional intervention (with some pharmacotherapy) to reduce total cholesterol to 3.88 mmol/L (150 mg/dL). However, in the original 5-year study, Dr. Esselstyn himself met with each participant twice a month to discuss the patient's food diary and blood test results. There were also gatherings of all the participants several times a

year. These meetings, as well as other intensive educational inputs, were broadly understood to have a positive effect on adherence of patients to the prescribed regime (Esselstyn 1995).

Dr. Esselstyn points out that myocardial reperfusion and reduction of angina symptoms was documented to occur sometimes after a matter of only weeks of adherence to the very low-fat plant-based diet. This is attributed to the restored ability of endothelial cells to produce the vasodilator nitric oxide, as well as a reduced production of endothelin, a vasoconstrictor produced by damaged endothelial cells (Esselstyn 2014). This and other mechanisms of interest will be discussed in a subsequent section.

There were other useful and positive findings in the studies described above, but the crucial take-home message is the answer to the question posed by Dr. Ornish: "Can lifestyle changes reverse coronary heart disease?" (Ornish 1990). The answer is a resounding yes. If this information alone were understood and internalized by doctors, and applied to patient care, a great many patients could benefit, since heart disease is a prime cause of death and disability (Brault et al. 2009, Heron 2016).

Nutritional Interventions in Diabetes

The CDC lists diabetes as the seventh leading cause of death, accounting for 2.9% of total U.S. deaths in 2014 (Heron 2016). This number does not consider the known contribution of diabetes to other leading causes of death such as heart disease, strokes, and end stage renal disease (CDC 2014). Diabetes also confers significantly higher risk for certain cancers including cancers of bowel, endometrium, and pancreas, and cancer mortality is also increased for diabetics. This implies that deaths due (or partly due) to diabetes are probably underestimated (Giovannucci et al. 2010). CDC statistics show an exponential rise in the number of diagnosed cases, from approximately 5 million in 1990, doubling to 10 million in 1999, and further doubling to 20 million cases in 2009 (CDC 2014).

A 22-week trial comparing a low-fat vegan diet (10% of energy from fat, 15% from protein, and 75% from carbohydrate) with the American Diabetes Association (ADA) diet (15%–20% calories from protein, <7% calories from saturated fat, and 60%–70% of calories from combined carbohydrate and monounsaturated fat) showed overall greater reduction of glycated hemoglobin (HbA1c) in the low-fat vegan group. The overall average drop in the vegan group was 1.0 percentage points compared with 0.6 percentage points in the ADA group. In participants who did not require medication adjustment during the study, the differences were greater, with a 1.23 percentage drop in HbA1c in the vegan group compared to a 0.38 percentage drop in the ADA group. The vegan group also experienced greater weight loss than the ADA group and also showed greater reductions in total and LDL cholesterol than the ADA group (Barnard et al. 2006).

A second study continued to follow the same group of participants for a total of 74 weeks. Here also the low-fat vegan diet improved glycemic and plasma lipid values more than the ADA diet, while weight loss did not vary significantly between the groups by the end of the 74-week study (Barnard et al. 2009).

The vegan group overall consumed 50% more fiber than the ADA group, and participants on average consumed 8.5 total servings of fruits and vegetables, compared to 5.6 servings for the ADA group.

The recommended macronutrient composition of the vegan diet was very similar to the diet in the Ornish and Esselstyn studies cited above, with 10% of overall calories from fat. However, analysis of the diet actually consumed by the vegan group Barnard study showed that approximately 22% of calories were derived from fat, with 5% of total calories from saturated fat. In the final analysis, these patients' total cholesterol dropped by 10.9%. In the ADA group, fat calories consumed slightly exceeded 30% of total dietary calories (similar to the recommendations followed by the control group in the Ornish study described above), and saturated fat consumed comprised 9.9% of calories consumed, and these patients' total cholesterol dropped only slightly (3.4%) (Barnard et al. 2009).

The lipid lowering effect of the vegan diet was noted to be particularly important, since cardiovascular complications are a primary cause of morbidity and mortality in diabetics.

The Ornish study, described in the previous section, demonstrated the superiority of the experimental (low-fat vegetarian) diet as compared to the standard recommendations at the time (reduction of red meat, consumption of 30% of dietary calories from fat) (Ornish et al. 1990). Not only did the experimental group in general reverse established coronary artery disease, the control group experienced progression of lesions and worsening of symptoms. Here, in the Barnard study, the experimental (low fat vegan) diet is shown to be superior to the ADA diet in terms of improvement in glycemic parameters and the "side effect" of improvement in serum lipids (Barnard 2009).

In support of the low-fat vegan diet, Dr. Barnard notes that intramyocellular lipid is associated with insulin resistance and that vegans have been found to have lower intramyocellular lipid than age and weight matched omnivores (Goff et al. 2005).

Nutritional Interventions in Hypertension

Salt and DASH

In a major analysis, high blood pressure appears as the third leading risk factor for death and the fourth leading risk factor for disability adjusted life years in the United States (Murray et al. 2013). Yet in a recent CDC document discussing the leading cause of death, "hypertension" as such is not listed among the top 10 causes. But, given that the first and fifth leading causes of death appear as heart disease and cerebrovascular disease (Heron 2016) and, worldwide, hypertension is responsible for at least 45% of heart disease deaths and 51% of stroke deaths (World Health Organization 2013), there can be no doubt that high blood pressure is a major killer. In addition, hypertension contributes to heart failure, aneurysms, renal failure, blindness, and cognitive impairment (World Health Organization 2013).

Mean blood pressure rises with age but it has long been known that this age-associated rise in blood pressure is not seen in societies where dietary consumption of salt is very low (Intersalt 1988). "Moderate" dietary sodium restriction is recommended by international (World Health Organization 2013) and national bodies, from 2.0 to 2.3 grams of sodium (5.1–6.0 grams of salt) for all individuals, down to 1.5 grams of sodium (3.8 grams of salt) for individuals who are black, over age 51, diabetic, or diagnosed as hypertensive (Kaplan 2015).

In most countries, average per capita daily salt intake, at 9–12 grams (World Health Organization 2013) is roughly double the general recommended intake and three times the more stringent recommended intake noted above. Multiple sources note that most dietary sodium is found in processed foods and therefore the approach of reducing the salt content of processed foods is regarded as a useful public health measure (Kaplan 2015, World Health Organization 2013). Another way, of course, would be for individuals to avoid processed food and limit the amount of salt which they themselves add to food to stay within the relevant daily guidelines ranging between 2300 mg sodium (6 grams or one teaspoon of salt) and 1500 mg of sodium (3.8 grams or 3/5 teaspoon of salt, just over half a teaspoon). This is a clear instruction that could be communicated easily by doctors to patients. For those choosing to consume processed foods, a helpful strategy for controlling sodium intake looks at "sodium density" favoring foods which contain no more than 1 milligram of sodium per calorie (Novick 2013), information which is readily available on food labels where the caloric and sodium content are both listed. In this way, a person eating 2000 calories per day would not consume more than 2000 mg of sodium (2 grams of sodium or 5.2 gram of salt, about 4/5 of a teaspoon) so that even if processed foods comprised the whole of their diet, they would remain within the general WHO guidance (World Health Organization 2013).

Salt restriction alone (to 2.4 grams of sodium or 6 grams of salt) is credited with producing an average 2–8 millimeters of mercury reduction in systolic blood pressure (NIH 2003). The Dietary Approaches to Stop Hypertension diet (DASH), in addition to limiting sodium, encourages a diet rich in fruit and vegetables (NIH 2003), which are good dietary sources of potassium (McGuire and Beerman 2013). Potassium deficiency can increase sensitivity to the blood pressure raising effect of dietary sodium, and correction of deficiency reduces this sodium sensitivity (Kaplan

2015). The DASH diet is credited with an average 8–14 millimeter of mercury reduction in systolic blood pressure (NIH 2003) and the increase of dietary potassium in this diet may account for the increased efficacy of the DASH diet over simple sodium restriction. More recent guidelines continue to support a combination of the DASH diet along with lowered sodium intake (Eckel et al. 2013).

Lifestyle management was at the top of the 7th JNC guideline but is preceded by the statement that most patients will require two medications to reach their blood pressure treatment goal (NIH 2003). In a similar vein, although the updated version of the JNC in 2014 places lifestyle interventions at the top of the treatment algorithm (with lifestyle interventions to be continued throughout management), the bulk of the guideline deals with pharmaceutical management of hypertension. This guideline is described as being based on an extensive evidence review by a panel of experts in hypertension, primary care, cardiology, pharmacology, epidemiology, and related fields. The evidence considered was initially restricted to randomized controlled trials (RCTs) and then further restricted to trials involving at least 2000 participants (James et al. 2014). Drawing conclusions from this evidence, it could seem that lifestyle measures have but a small part to play in the management of hypertension given the modest blood pressure lowering effect of the DASH. If one relies exclusively on the JNC 8 evidence, one is left with the impression that dietary intervention is relevant, but not powerful enough to achieve adequate change in blood pressure for patients who require lowering of systolic blood pressure by more than the 8–14 mm Hg expected from the DASH diet. One may be left with the implication or tacit assumption that before the advent of the anti-hypertensive medications, hypertension could not be effectively treated. The very fact of selection of only large RCTs as in the JNC 8 report (James et al. 2014) focuses attention on drug trials (for which RCTs are the agreed standard) but at the same time, as a result, focuses attention away from trials of nutritional interventions, which may be smaller or not randomly controlled, and yet, the excluded trials may well produce valid, beneficial, and even astonishing findings, like the studies of Drs. Ornish, Esselstyn, and Barnard cited above. These trials would have been automatically excluded from any meta-analysis which used the kind of criteria employed in the JNC 8, in effect throwing out the baby with the bath water.

Other Dietary Approaches to Hypertension

There are indeed trials involving nutrition, which have produced impressive blood pressure lowering results, but which would have been excluded from the JNC 8 analysis due to their size or design. Several of these trials provide evidence of more potent blood pressure lowering effect than simple sodium restriction or the DASH diet, using a variety of nutritional approaches.

Dr. Walter Kempner and the Rice Diet

The work of Dr. Walter Kempner is a case in point. Dr. Kempner, a physician and physiology researcher born and trained in Germany, took up a post at Duke University in North Carolina in 1934, when Hitler's anti-Jewish laws made it impossible for him to continue to be employed in the country of his birth (Newborg and Nash 2011). With his physiology background and after close observations of kidney tissue in vitro, Dr. Kempner reasoned that renal dysfunction could be ameliorated through reducing the workload of the kidneys, by reducing protein and fat in the diet, and that these interventions, along with reduction of sodium in the diet, would reduce edema, improve renal blood flow, and allow viable kidney tissue to heal. In 1939, he first used the later to be famous "rice and fruit diet" to treat patients hospitalized at Duke with severe kidney disease and edema. In the transcript of a lecture in which he described the logic that led him to this specific choice of diet, Dr. Kempner mentions as an aside that ideally one could substitute extracts of animal kidneys, or synthetic substances, for the "ferments" which had been destroyed in diseased kidneys. (This would have been, in effect, a magic bullet approach.) However, as such a solution was not yet available, he went on to his "less perfect approach," which he termed "the compensation of renal metabolic dysfunction with the rice diet" (Kempner 1946).

In an extensive report summarizing observations of 500 patients who were treated with the diet, Dr. Kempner describes the rice diet as containing 250–350 grams of white rice (uncooked weight), to be cooked in water or fruit juice. Fruits were allowed as well as fruit juice, but not vegetables, nuts, and so on. White sugar was allowed. Sodium intake was not greater than 150 mg per day (380 mg salt, about 1/16 tsp in kitchen terms), and this was mainly the sodium naturally present in foods. This was the whole of the diet. Many of the patients were suffering from severe hypertension with systolic pressures well over 200 mm Hg and diastolic pressures well over 100 mm Hg. Average blood pressure was 199/117 mm Hg. These 500 patients were described as seriously ill individuals who had not responded to other forms of treatment. Many had cardiac enlargement and EKG abnormalities such as T wave inversion and axis deviation. Retinal changes with papilledema, hemorrhages, and exudates were present in many of the patients (Kempner 1948). Such findings are characteristic of hypertension with multiple organ damage, or malignant hypertension (Cremer 2016), a condition which, in the 1950s, carried a very poor prognosis. How poor? One study of 211 British hypertensive patients who had diastolic blood pressures over 100 mm Hg (but who were considered unsuitable for sympathectomy) constituted a no-treatment group which was followed for 13 years. At the end of the 13 years, 106 patients (50%) were dead. Of the 106 patients who had died, 92 (87%) were under the age of 60. Of the 59 untreated patients with initial diastolic blood pressures above 130 mm Hg, 43 patients (72%) died. Within that group of 59, there were 21 patients with initial diastolic blood pressure over 150 mm Hg, all of whom died (100%). Of the 20 patients diagnosed with malignant hypertension, all died (100%). The deaths were recorded as due to cerebral hemorrhages, uremia, myocardial infarctions, aneurysms, and so on. Among the 105 survivors in the series of 211 patients, 37 (35%) had suffered strokes or myocardial infarctions, or were living with heart failure or angina. In a parallel series where 114 patients were treated with lumbodorsal sympathectomy, it was reported that 10 patients (9%) did not survive the operation itself. Of the 82 sympathectomy patients who met the criteria of diastolic blood pressure greater than 120 mm Hg prior to the operation, and who did not die from the procedure itself, 65 (80%) were judged to have been successfully treated with average reductions of 40 and 46 mm Hg for men and women, respectively. These 65 "successful" patients represent 57% of the original cohort of 114 patients (Leishman 1959).

The data presented above are meant to convey an impression of the seriousness of hypertension in Kempner's day, as well as the high risk of available treatment at the time. This should provide the context for understanding the ethical correctness of Dr. Kempner's decision not to have a control group in his rice diet studies (McDougall 2013). Untreated patients with severe hypertension, and, in addition, target organ damage, had little hope in those days.

In Kempner's study 500 patients were followed for an average of 85 days, or just under 3 months. In the original group of 500 patients, there were 26 patients (5%) who were critically ill at the onset of the diet, and who died within an average of 39 days. All but one of these had been deemed to have secondary renal involvement prior to commencing the diet. Kempner defined "improvement" in this study as a drop of 20 mm Hg in "mean arterial pressure" (MAP), the sum of systolic and diastolic pressures divided by 2. By these criteria, 311 (62%) of 500 patients improved, with average drops in MAP of 33 mm Hg and average drops in systolic pressure of 46 mm Hg. The "not improved" group included 163 (33%) patients who had a drop in MAP of "only" 11 mm Hg, and a drop in systolic blood pressure of "only" 17 mm Hg (Kempner 1948).

It is noteworthy that the "not improved" group in the rice diet experiment in the 1940s achieved a greater reduction of systolic blood pressure than is expected with the modern DASH diet where 8–14 mm Hg systolic blood pressure reduction is anticipated (NIH 2003). By current criteria, therefore, Kempner's "not improved" group would be deemed to have improved, meaning that out of the original patient group of 500, 474 (95%) experienced improvement.

In addition, dramatic improvements in retinopathy were seen, as well as resolution of EKG abnormalities including T wave inversion. Heart size, as measured by x-ray, was seen to be reduced in many cases. Glycemic control improved in diabetic patients with reduced need for insulin. Serum

cholesterol values also improved (Kempner 1948). Total cholesterol data from a prior series showed a reduction from an average of 6.28 mmol/l (243 mg/dl) to 4.7 mmol/l (183 mg/dl), a drop of 24% (Kempner 1946). Thus, while blood pressure was the main factor under consideration, other important parameters improved as well.

This diet required frequent checks of patients' blood and urine chemistry, and was recommended by Kempner for use in hypertensive vascular disease with cardiac, renal, and retinal involvement as well as in uncomplicated hypertension "when a more liberal regime has failed." Kempner recommended continuing the diet "without modification until the conditions which were the indication for its use have disappeared," at which point specific modifications could be made. Kempner did not oppose the use of lumbodorsal sympathectomy, but tactfully advised a trial of the rice diet before proceeding to a surgical option (Kempner 1948).

The Nutrient Dense Plant-Rich (Nutritarian) Dietary Protocol

The nutrient dense plant-rich (nutritarian) dietary pattern is similar in many ways to the research protocols of Ornish, Esselstyn, and Barnard described above. This diet is based on consumption of fresh and cooked vegetables, fruits, legumes, and whole grains, excluding dairy, refined oils, refined carbohydrates such as white flour, white rice, and sugar, and limiting salt to 1000 milligrams per day. It differs from the Ornish, Esselstyn, and Barnard vegan diets in encouraging the consumption of 30 grams (an ounce) of seeds or nuts daily and in permitting up to 240 grams (8 ounces) of animal products per week.

In one study (Fuhrman and Singer 2015), 2273 outpatients in a single-family practice were followed for an average of 3.8 years. There were 1759 patients (77%) who reported being at least 80% compliant with the nutritarian recommendations. Among 443 hypertensive patients, the average reduction in systolic blood pressure was 26.4 mm Hg and average reduction in diastolic blood pressure was 14.7 mm Hg. Of these 443 patients, 316 patients were on medication at the beginning of the study. Of these, 136 patients (43%) were able to discontinue their medication while still demonstrating an average reduction of systolic blood pressure of 28.6 mm Hg and an average reduction of diastolic blood pressure of 11.9 mm Hg. These improvements exceed those attributed to the DASH diet (NIH 2003) and compare favorably with results of the rice diet study described above (Kempner 1948).

Other parameters observed were weight and serum lipids. Within the group of 1759 adherent patients, 685 patients had a body mass index greater than 30 kg/m^2 at the beginning of the study. After one year of the nutritarian diet, average weight loss in this group was 22.3 kg (49 pounds). Large drops in serum lipids were also observed in this study. Thus, in this study, blood pressure was affected significantly and favorably, along with other important parameters.

Selected Special Foods

Linseeds (Flax Seed) The FLAX effects in Peripheral Arterial Disease (FLAX-PAD) study was a prospective double blinded placebo controlled randomized trial involving 110 patients with peripheral arterial disease and hypertension. The patients in the experimental group consumed 30 grams (1 ounce) of milled flaxseed daily over a period of 6 months. Alpha linoleic acid (ALA) and enterolignan levels in plasma were checked to evaluate compliance. Fish consumption was not allowed in either the treatment or placebo group for the duration of the study. In the treatment group, blood pressure declined throughout the 6-month study, and at the end of the 6-month study period, patients in the treatment group had an average reduction of 10 mm Hg in systolic blood pressure and 7 mm Hg in diastolic blood pressure. Patients whose initial systolic blood pressure exceeded 140 mm Hg experienced sustained reductions of 15 mm Hg in their systolic blood pressure. There was an overall absence of adverse effects in both the treatment and placebo group. There was 1 stroke in the treatment group compared with 2 strokes in the placebo group. There were 2 myocardial infarctions in the treatment group compared with 4 in the placebo group. Serum ALA levels correlated well with the blood pressure reductions noted above (Rodriguez-Leyva et al. 2013).

Hibiscus A 6-week double blind placebo controlled trial of hibiscus tea was carried out, in which the subjects were mildly hypertensive patients. The treatment group received 3 servings of hibiscus tea daily, while the placebo group drank a preparation with similar appearance and taste. In the treatment group, systolic blood pressure was reduced by 7.2 mm Hg and diastolic blood pressure was reduced by 3 mm Hg. In the placebo group, small reductions of 1.3 mm Hg and 0.5 mm Hg were seen, for systolic and diastolic blood pressure, respectively. Compared to the placebo beverage the hibiscus tea contained at least 10 times the amount of phenols, and had a 10 times greater oxygen radical absorbance capacity (ORAC) value. In addition, the hibiscus tea contained anthocyanins, which were not found in the placebo beverage. No adverse effects were reported. The authors propose that drinking a cup of hibiscus tea 3 times a day may be an intervention that would elicit better compliance than more comprehensive dietary interventions (McKay et al. 2009).

Medically Supervised Water-Only Fasting

A study of 174 consecutive patients with essential hypertension employed water-only fasting in a medically supervised environment. In this study "water-only fasting" is defined as "complete abstinence from…food, tea, juice, non-caloric beverages, etc., with the sole exception of distilled water ad libitum." Initial mean blood pressure was 159.1/89.2 mm Hg. Prior to the fasting period, participants were instructed to eat a diet consisting exclusively of steamed vegetables and fresh raw vegetables and fruits for at least two days. Participants fasted for an average of 10 to 11 days. The fasting period was followed by several days of supervised refeeding, initially with fresh raw fruit and vegetable juice, then with solid raw fruits and vegetables, after which a diet of whole natural foods was introduced. This diet consisted of fresh fruit, fresh, steamed, and baked vegetables, cooked whole grains and legumes, and small quantities of nuts and seeds. The whole natural food diet excluded meat, fish, fowl, eggs, and dairy as well as any added sugar, salt, or oil. The average length of the refeeding period was one half that of the fasting period. Participants were monitored with twice weekly blood and urine testing, and, where clinically indicated, EKG. Apart from mild nausea and orthostatic hypotension during the fasting period, no adverse effects were observed.

Blood pressures dropped during the pre-fasting and water-only fasting periods, and continued to drop during the refeeding period. The overall mean blood pressure drop was 37.1/13.3 mm Hg. Approximately 89% of subjects achieved normotensive status with a final mean blood pressure of 117.5/78.7. Patients with stage 3 hypertension (mean baseline blood pressure 193.8/96.4) achieved the greatest blood pressure reduction, with a mean drop in systolic blood pressure of 59.6 mm Hg and a mean drop in diastolic blood pressure of 16.9 mm Hg.

Given the continued drop in blood pressure during the refeeding period, the authors reasoned that the results might be sustainable with a low sodium vegan diet. In support of this, it was found that 42 of the original 174 hypertensive subjects, who were followed up after an average post-treatment period of 27 weeks, had a mean blood pressure of 123/77 at the time of follow-up (Goldhamer et al. 2001).

A further series of 68 patients with borderline hypertension was later studied, under the same conditions. Approximately 82% of patients achieved blood pressures under 120/80 mm Hg by the end of the supervised refeeding period (Goldhamer et al. 2002).

Natriuresis is cited as one of the likely mechanisms, but probably not the sole mechanism since the blood pressure reductions in the study were greater than those seen with salt restriction alone. Physiological changes during water-only fasting include natriuresis of 3.5–5.8 grams of sodium (9–15 grams of salt) per day, early in the fast (Goldhamer et al. 2013).

The authors point out that the water-only fasting period may provide an opportunity to resensitize the taste faculty in persons who had previously been accustomed to consuming a typical diet of high sodium and high fat foods, thus increasing the palatability of the low sodium, low fat, high potassium plant foods, which comprise the recommended follow-up diet.

SELECTED MECHANISMS UNDERLYING THE EFFECT OF FOOD ON CARDIO-METABOLIC PARAMETERS

Endothelial Function

The endothelium has several relevant functions, including regulation of vascular permeability and tone. It is described as the body's largest endocrine organ. It brings about short-term vasodilation through nitric oxide and other mediators, and vasoconstriction through thromboxane and other factors including oxygen-free radicals. There is an ongoing balance between vasoconstriction, which is pro-atherosclerotic, and vasodilation, which is anti-atherosclerotic. It has been asserted that "every risk factor that is associated with atherosclerosis also impairs endothelial function." These risk factors include, among others, cigarette smoking, hypertension, diabetes, and increased cholesterol (Vogel 1999). Endothelial injury is also one of the main microscopic pathological changes seen in malignant hypertension (Kitiyakara and Guzman 1998).

Endothelial function can be assessed clinically by measuring flow mediated dilation, using brachial artery ultrasound. The diameter of the brachial artery is measured by ultrasound at baseline, the artery is then occluded, and the diameter of the artery is measured again after occlusion is released. The percent difference in the two measurements is the flow mediated dilation, or FMD (Vogel 2000).

FMD has been used to study the post-prandial effects of different foods. In one study, comparing a high-fat meal to a low-fat meal, following a typical 900-calorie fast food meal composed of eggs, fried potatoes, and sausage, and containing 50 grams of fat and 225 mg of cholesterol, FMD was reduced by 50% at 3 hours and was still reduced by 25% at 6 hours. The 900-calorie low-fat meal of cereal with skimmed milk, juice and coffee, containing 0 grams of fat and 13 mg cholesterol, did not reduce FMD (Vogel et al. 1997).

Another study compared effects of ingesting 60 ml of different oils on FMD. The oils used were olive, soybean and palm oils, both fresh and at two different deep-frying levels. All meals showed acute endothelial impairment with FMD reduced by 32% at 3 hours, independently of the type of oil or deep-frying level (Rueda-Clausen et al. 2007).

Yet another study compared effects of three different 900-calorie 50-gram fat meals: olive oil and bread, canola oil and bread, and salmon and crackers. Contrary to the expectations of the researchers, FMD was reduced by 31% in the olive oil group, 10% in the canola oil group, and only minimally in the salmon group. Interestingly, the reduction in FMD in the olive oil and canola oil groups was significantly attenuated (but not abolished) when antioxidants in the form of salad and balsamic vinegar, or vitamins C and E, were consumed with the meal (Vogel et al. 2000). In the light of other studies showing benefits of a Mediterranean diet style on cardiovascular health, it had been broadly assumed that olive oil contributed to that benefit. The authors propose that the heart health benefits of a Mediterranean eating style are more likely due to consumption of anti-oxidant rich foods, such as fruits and vegetables, and omega-3 rich fish, noting as well that olive oil itself contains 17% saturated fat, and saturated fat consumption was shown to impair endothelial function in the earlier study (Vogel et al. 1997, 2000).

The Lifestyle Heart Trial (Ornish et al. 1990), described in a previous section, demonstrated improvement in angina symptoms, myocardial perfusion, functional status, and other parameters, with a very low fat vegetarian diet along with other lifestyle measures. In a small study aiming to elucidate mechanisms behind these improvements, participants in the experimental group adhered to the components of the lifestyle change program including vegetarian diet with fewer than 10% of calories from fat. FMD was observed to improve by 20%, and markers of inflammation and endothelial dysfunction, human high sensitivity CRP and human interleukin 6, were reduced at 3 months. The authors asserted that endothelial dysfunction constitutes an important factor in the pathogenesis of atherosclerosis, as it predisposes blood vessels to constriction and promotes inflammation and platelet activation (Harvinder et al. 2010). Dr. Esselstyn has repeatedly asserted that

when foods that cause endothelial dysfunction are avoided, the capacity of the endothelium to produce the vasodilator nitric oxide will be restored (Esselstyn et al. 2014). Given the duration of reduced FMD after a single high fat meal (Vogel et al. 1997), it is very plausible that with a diet where a high fat meal follows a high fat meal, the endothelium is continually assaulted and does not have the time to recover fully from each temporary impairment.

Modification of Trimethyl-n-Oxide Levels

Elevated plasma levels of trimethylamine-n-oxide (TMAO) are associated with atherosclerosis and cardiovascular adverse events. While the precise mechanism has not been fully elucidated, platelet activation is likely to be involved. In the human body, gut flora convert dietary choline, phosphatidyl choline (lecithin), and carnitine to TMAO. Dietary sources of these TMAO precursors include red meat, eggs, dairy, and salt water fish. The authors of a review article on TMAO note that altering the gut microbiome by antibiotic treatment has been shown to reduce TMAO during treatment, but do not regard this as a viable long-term approach. Instead, the authors propose reducing dietary intake of TMAO precursors (Velasquez et al. 2016).

NUTRITIONAL TREATMENT OF SELECTED INFLAMMATORY AND AUTO-IMMUNE CONDITIONS

Nutritional Treatment of Multiple Sclerosis (MS)

This debilitating progressive neurological disease is understood to be an immune condition, but little is understood about its causation and factors that may contribute to exacerbations or deterioration (Jelinek and Hassed 2009). Can food have a role to play?

Consulting the NICE guidelines, which provide the treatment standard for the United Kingdom, one finds no recommendations relating to food, and a brief statement saying that Vitamin D and omega-3 fatty acids should not be used to treat MS (NICE 2014). The Mayo Clinic succinctly denies that a special diet can treat MS, but gives a nod to a low fat and high fiber eating pattern, which is described as the recommended diet for the general population, and not specific for MS (Mayo Clinic 2016).

If one is satisfied with the views of these two authorities, one may be inadvertently doing a great disservice to one's patients.

The neurologist Dr. Roy Swank published a study in which 144 multiple sclerosis patients followed a "low fat" diet for 34 years. Patients were instructed to reduce dietary saturated fat to 15 g per day, mainly by cutting down on milk and fat from other animal sources. The diet included 5 g per day of cod liver oil. Unsaturated oils were used but hydrogenated and saturated plant oils (palm, coconut) were not (Swank and Duggan 1990). The full diet plan can be found in Swank's book (Swank and Duggan 1987). Patients were categorized at the outset of the study as having minimal, moderate, or severe disability, based on the standard grading correlated with the Kurtzke scale. Later, patients were categorized as "good dieters" or "poor dieters" based on self-reported consumption of less than, or more than, 20 grams of fat daily. At the end of 34 years, it could be seen that the patients classed as "good dieters" showed less neurological deterioration than the poor dieters. This was true at all three levels of initial disability, but the difference was most striking in the group that had minimal disability at the beginning of the study. At the end of 34 years, the surviving "poor dieters" were confined to bed and chair. Of the initial group of "poor dieters," 80% had died of MS related causes. By contrast, only 5% of the "good dieters" had died of MS related causes. The remaining "good dieters" in this group of survivors had an average Kurtzke grade of 1.1 at the end of the 34-year study. These patients were ambulatory and able to work, in contrast with the severely disabled "poor dieters" (Swank and Duggan 1990). This was a small but highly meaningful study, and as seen above, its results are not reflected or even mentioned in the MS guidelines.

In a discussion paper citing Swank's work, the point is made that there is presently enough evidence for lifestyle therapies to be a standard part of primary care management of MS. It is further stated that "many people are searching for the advice from complementary practitioners which they should possibly be receiving from their GPs" (Jelinek 2009). As seen above in the studies by Barnard, Fuhrman, and Kempner, lifestyle interventions may affect multiple health parameters in a positive manner. In citing Ornish's lifestyle approach to treating heart disease, which has also been shown to be associated with reduced progression of prostate cancer (Ornish 2005), it is affirmed that "the lifestyle approach in primary care, especially for chronic diseases, should be first line therapy and not an afterthought" (Jelinek 2009).

Inspired by Swank's work, a 1-year trial of a low-fat plant-based diet in multiple sclerosis studied a group of 61 participants diagnosed with relapsing remitting MS. There were 32 patients assigned to the diet group. Given the short duration of the study and the fact that most of the patients in both groups were taking disease modifying treatment (DMT), relapse rate was expected to be very low in both groups. This was in fact the case. At the end of one year, the two groups did not differ significantly in terms of new lesions on MRI. However, the treatment group experienced significant improvement in fatigue ratings, a meaningful benefit, since fatigue is one of the chief symptoms affecting quality of life in MS, even when DMT is used (Yadav et al. 2016). It is possible that given more time, outcomes in the two groups would diverge in other significant ways. Larger and longer-term outcome trials will be the final arbiter of effectiveness (Jelinek 2009), but while the results of such trials are awaited, there is Swank's study with outcomes showing that a dietary intervention sustained over decades was associated with the difference between nearly full functioning and severe disability or death (Swank 1990).

Nutritional Treatment of Rheumatoid Arthritis (RA)

A rheumatoid arthritis guideline by the Royal College of Physicians contains over 200 pages of evidence and recommendations, 5 pages of which are devoted to diet. While acknowledging evidence for various benefits from various diets, the guideline states that no modifications demonstrate global improvements in measures of disease activity and function, and that "there was no consistent evidence of benefit from any one particular diet" although research results showing some benefits from gluten free, elemental, and vegan diets were presented. It was further stated that some diets, such as vegetarian diets, might be unpopular with some patients. The ultimate recommendation was to encourage clinicians to advocate the principles of the Mediterranean diet for people with RA who "wish to experiment with their diet." Here the Mediterranean diet was described as having more bread, fruit, vegetables, and fish, and having less meat, and replacing butter and cheese with products based on vegetable and plant oils. This recommendation was made mainly based on the increased cardiovascular disease risk experienced by RA patients, and on the possibility that such a diet "might be beneficial to musculoskeletal symptoms." It was also asserted that the Mediterranean diet would more likely elicit better adherence than "more unpalatable alternatives" (National Collaborating Centre 2009). It should be noted that no evidence was presented for unpalatability of any specific eating pattern, or degree of patients' willingness or unwillingness to follow any particular diet, so that the remarks about potential compliance and palatability could be seen to reflect mere assumptions or prejudices of the guideline authors.

Published research on the treatment of rheumatoid arthritis with fasting followed by vegetarian diet is of interest in this context. This was a prospective single blind randomized trial with 53 subjects, of which 27 were randomized to the diet group. All subjects had rheumatoid arthritis with active disease, most were taking nonsteroidal anti-inflammatory drugs (NSAIDS), and many were taking corticosteroids, antimalarial drugs, gold, penicillamine, sulfasalazine, or cytostatic drugs. Only three patients in the treatment group were not on any medications at study entry. About half of patients reported specific food intolerances.

The regime for the treatment group was to a degree inspired by previously existing regimes at Scandinavian health farms (Kjeldsen-Kragh 1991). The initial fast of 7–10 days was not a water fast

as described above (Goldhamer et al. 2001, 2002), but a "subtotal fast" where intake was limited to herbal teas, garlic, vegetable broth, decocted potatoes and parsley, and juices of carrots, beets, and celery. Patients' medications were not altered. Following the sub-total fast, patients were fed with a basic diet which initially included only the elements listed above. On the principle used in elimination diets, a single new food item was introduced every second day. If symptoms worsened within the subsequent 2–48 hours, the item was excluded for that individual and only reintroduced one week later. If exacerbation occurred again, the food was not reintroduced. The first 3.5 months which followed the modified fast were defined as the "vegan phase." During this period, all dairy products and gluten were excluded along with meat, fish, eggs, refined sugar, citrus, salt, strong spices, preservatives, alcohol, coffee, and tea. Oils were permitted. The vegan phase was followed by a further 9 months where dairy and gluten were allowed; these were introduced one at a time and were not continued if they were seen to exacerbate arthritis symptoms (Kjeldsen-Kragh 1999).

Clinical indices such as pain, duration of morning stiffness, and joint swelling and tenderness improved markedly after only one month in the treatment group. At the end of 13 months, 12 of the 27 patients in the experimental group were categorized as "improvers" contrasted with only 2 of 26 patients in the control group. At the end of the 13-month trial, participants were free to change their diets. One year later, follow-up of 22 patients in the experimental group revealed that all the diet responders had continued the diet of their own accord. These responders continued to have reductions of clinical disease variables, as well as reduction of erythrocyte sedimentation rate (ESR) (Haugen 1999). Of note, about one-third of patients had reported exacerbations of symptoms with specific foods.

The authors credit the improvements among the responders to several characteristics of the diet, including immunosuppression due to decreased energy intake, identification and removal of individual aggravating elements of the diet through the protocol described above, differing proportions of fatty acids altering the inflammatory process, and changes in fecal flora (Kjelsden-Kragh 1999). Another factor of interest was the potentially protective role of natural antioxidants (Haugen et al. 1999).

The subtlety of a trial which individualizes dietary intervention while staying within the parameters of an overall vegan or vegetarian pattern is worth noting. Insisting on a totally uniform diet for all in the treatment group, or an immediate transition to a general vegan or vegetarian diet, might not have produced as much clinical improvement. This kind of individualized approach seems worthy of emulation both in research and clinically. However, the subtlety of the intervention in the study may have made it difficult to categorize and compare with other studies. While the above-mentioned guideline document did include this study in the evidence base, and even recognized the benefits in the treatment group, the experimental dietary pattern was merely described as "gluten free followed by vegetarian" (National Collaborating Centre 2009). This description clearly does not capture important features of the dietary intervention. The guideline had indeed stated that "there was no consistent evidence of benefit from any one particular diet" (National Collaborating Centre 2009), and in a sense that was not incorrect. However, the guideline did not mention the methodically individualized feature of the diet in this study. Guidelines purport to look for "best treatment," but in this case, if one were only to read the guideline and not the actual study, one could conclude that diet is not likely to be of much benefit for RA sufferers. This would be unfortunate, since patients in this particular study improved clinically and maintained the diet and improvements one year later, as described. The fact that patients continued the diet on their own also challenges the guideline assumptions of unpopularity and unpalatability which were, in any case, not supported by evidence. This is not to deny the usefulness of meta-analyses and guidelines, but such tools, in seeking the big picture (populations), may lose sight of the small picture (individuals and individual variation).

Remission of rheumatoid arthritis and other autoimmune conditions is described in a set of case reports where the therapeutic intervention was a combination of water-only fasting and diet. Brief case reports of three RA patients, one systemic lupus erythematosus patient and one patient with mixed connective tissue disease were provided, along with a case report from one fibromyalgia

patient. These patients each underwent a period of water-only fasting, preceded by a high nutrient density vegan diet (Fuhrman et al. 2002). Prior to the water-only fasting, patients had been weaned off their medications. The water-only fasting protocol with gradual refeeding was essentially the same as described in the blood pressure studies cited above (Goldhamer et al. 2001, 2002). The high nutrient density vegan diet was followed again after the refeeding period. These individuals were reported to have achieved remission from their autoimmune disease (or from fibromyalgia), and the remissions were reported to be maintained at follow-up months and even years later. In one case, when a flare of disease activity recurred, a second fast was able to produce remission again, and that remission was subsequently maintained (Fuhrman 2002). It should not be forgotten that a true remission of a painful and disabling autoimmune condition not only improves quality of life, but also spares the patient iatrogenic complications of the medical regimes which are usually used, regimes which carry significant toxicity.

Nutritional Treatment of Fibromyalgia Syndrome (FMS)

This condition produces chronic pain, but unlike known autoimmune diseases, lacks unique pathophysiological characteristics. A major clinical review describing a stepwise approach to FMS did not mention diet at all (Goldenberg et al. 2004). In the case report studies above (Fuhrman 2002), one of the patients had fibromyalgia, and obtained remission through the protocol of water-only fasting preceded and followed by a nutrient dense vegan diet. In a 3-month study of 30 fibromyalgia patients, a dietary intervention was used which consisted of a mostly raw vegan diet, which included flax seed and olive oils, but excluded alcohol, caffeine, refined sugar, refined and hydrogenated oils, dairy, eggs, and all meat. There were 19 of the 30 subjects who were classified as responders and had significant improvement in clinical measures of pain, fatigue, and quality of life (Donaldson et al. 2001).

A causative or contributory role in fibromyalgia pain symptoms has been hypothesized for dietary glutamate and aspartate, two non-essential amino acids which function as excitatory neurotransmitters. Bound forms of these exist in meat, whereas free forms of these amino acids are found in the diet as additives. Examples include monosodium glutamate (MSG), hydrolyzed protein, protein concentrate, aspartame, fish sauces, and aged cheeses. The author of a review of this subject advises using a whole food diet without additives, to adequately test for sensitivity to these agents (Holton 2016).

It should be noted that several of the regimes described in the preceding section would have also eliminated food additives, though this was not specifically addressed in the modified fast/vegetarian protocol (Kjelsden-Kragh 1999, Kjelsden-Kragh et al. 1991) or in the water-fasting/nutrient dense vegan protocol (Fuhrman 2002).

SUMMING UP: THE COMMON GROUND

With the exception of Dr. Kempner's rice diet and Dr. Swank's low-fat diet, all of the interventions described in this chapter utilized a broadly similar approach. They emphasized the consumption of cooked and raw vegetables, fruits, legumes, grains and seeds, while excluding meat, dairy, and eggs, and minimizing or excluding oils, sugar, and salt. All the regimes resulted in marked reduction of saturated fat (also a feature of the Kempner and Swank diets).

Calling these regimes "vegetarian" or "vegan" addresses only the exclusion aspect whereby meat, or all animal products, respectively, are excluded. Yet a vegan diet, thus defined, could be composed entirely of highly processed nutrient-poor elements such as sodas, candy, cakes, potato chips, doughnuts, and fake meats and cheeses laden with salt, oil, and additives. Without a fruit or vegetable in sight, it would still be, strictly speaking, a vegan diet (Maisel 2015b).

The term "whole food plant-based diet" has much to recommend it. This term, coined by the nutritional biochemist researcher and author of The China Study (Campbell and Campbell 2006),

refers to a diet composed of plant-based foods in forms as close to their natural state as possible, including vegetables, fruits, nuts, seeds, legumes, and whole grains, and avoiding heavily processed foods, animal products, salt, oil, and sugar (Campbell and Jacobson 2013, Maisel 2015a).

A look back at the various regimes cited in this chapter shows that they generally conform to this description. This is the essence of the regimes used to reverse atherosclerotic heart disease, improve diabetes, and reduce blood pressure, often extending beneficial influence on parameters other than the main target pathology. This is also the essence of the regime which brought about clinical improvement and even remission in rheumatoid arthritis and fibromyalgia. Further studies will better elucidate mechanisms behind the clinical improvements seen here and in the considerable body of evidence favoring a whole foods, plant-based diet (Campbell and Campbell 2012a,b).

In the real world, many smokers still opt to continue smoking. Similarly, many patients may not be interested in exploring dietary change. This should not prevent clinicians from recommending diet, and specifically, some form of a whole food plant-based diet, as first line treatment in many conditions, and as an adjunct to conventional therapy. Whether to follow such advice will, of course, be the patient's own responsibility.

For added reassurance, a recent position paper of the Academy of Nutrition and Dietetics asserts that appropriately planned vegetarian and vegan diets are healthful and nutritionally adequate (Academy of Nutrition and Dietetics 2016).

ETHICAL ASPECTS AND IATROGENICS

Earlier this year, the Centers for Disease Control (CDC) was challenged to list medical error as the third leading cause of death in the United States. A composite figure of 251,454 deaths per year was projected onto the total number of deaths in 2013 (2,596,993 deaths) which would mean that deaths due to medical error would account for 9.7% of all deaths. This composite figure was composed of a sum of deaths due to errors in judgment, skill, or coordination of care, diagnostic errors, system defects resulting in failure to rescue a patient from death, and preventable adverse events. The author therefore argues that medical error should be listed as the third leading cause of death, and further notes his view that the estimate derived from the literature represents an underestimate, since the studies did not include outpatient deaths or deaths at home due to medical error (Makary 2016).

This is not an entirely new observation. Nearly two decades ago, a figure of 225,000 iatrogenic deaths per year was quoted and similarly presented as the third leading cause of death. This figure was the sum of 12,000 deaths per year from unnecessary surgery, 7000 deaths per year from medication errors in hospitals, 20,000 deaths per year from other errors in hospitals, 80,000 deaths per year due to nosocomial infections in hospitals, and 106,000 deaths per year due to "non-error, adverse effects of medication." The author further stated that "how cause of death and outpatient diagnoses are coded does not facilitate an understanding of the extent to which iatrogenic cause of death and ill health are operative" (Starfield 2000).

The pursuit of benign and effective nutritional approaches takes on enhanced importance if it is recognized that "harmful effects of health care interventions likely…account for a substantial proportion of the excess deaths" in the United States (Starfield 2000).

Without complicated analysis, it should be clear that the deaths due to unnecessary surgery would not have happened if unnecessary surgery were avoided. Similarly, deaths due to adverse effects of medication would not occur if medication became unnecessary due to success of a benign dietary intervention.

For clinicians, who see patients one at a time, the huge numbers presented above may seem unreal and far away. But, recall that in Dr. Esselstyn's study, in the group of 177 patients who adhered to the dietary protocol, 27 patients were able to avoid coronary artery stenting or bypass grafts which had previously been recommended (Esselstyn 2014). They therefore also avoided the risk of dying due to unnecessary surgery. What degree of risk would they have been facing? In a series of over 500,000 percutaneous coronary interventions (PCI) the in-hospital mortality risk was

overall 1.27%, and ranged from 0.65% in elective PCI to 4.81% in ST-elevation myocardial infarction (Peterson et al. 2010). One may regard 0.65% as "low risk" equating to "only" a 1 in 154 risk of death for an elective PCI. At the lowest estimate, one in 154 patients undergoing elective PCI will die. If the elective surgery were avoided, that death would not occur. Since it has been shown that dietary intervention can make it possible for elective PCI to be avoided (Esselstyn 2014), it is truly imperative to present this option to patients.

The figure quoted above of 106,000 deaths due to "non-error adverse effects of medication" is a reminder that even the best intentioned and correctly prescribed medication may cause irreversible damage. Two of the studies cited in this chapter specifically address discontinuing of medication in the context of specific nutritional intervention for hypertension (Goldhamer et al. 2001, 2002). In Furhman's case series of autoimmune remissions, medications were discontinued (Fuhrman et al. 2002). Similarly, in the large outpatient series showing the effects of a plant-based, nutrient-dense diet on multiple parameters, many patients were able to discontinue prescribed medications (Fuhrman et al. 2015). Patients who take no medications are not exposed to the risks and adverse effects of medications, including death. Logically and ethically, if the use of diet can reduce or eliminate the need for medications, then diet should be offered and strongly encouraged as a first line treatment.

In Dr. Ornish's Lifestyle Heart Trial, patients in the control group were given treatment according to the prevailing "usual care," which offered the best standard of care at the time. That is, of course, the ethical way to do a randomized trial. The outcomes in the treatment group were significantly better than the outcomes of patients receiving "usual care." The results in Dr. Esselstyn's study similarly show that it is possible to achieve excellent results with dietary therapy. The same must be said of the work of Drs. Barnard, Kempner, Swank, Kjeldsden-Kragh, and Fuhrman, described in this chapter. And yet, the guidelines have not really changed.

Culturally and ethically, autonomy is a sacred right of patients. Patients depend on clinicians to inform them correctly so that they can make wise choices. While it may take time for official guidelines to change, the case can be made that conscientious clinicians have a duty to present dietary options to patients suffering from chronic diseases. Waiting for guidelines to catch up may be a case of "making the perfect into the enemy of the good," and while waiting, patients may be exposed to unnecessary iatrogenic harms.

CONCLUSION: "MIND THE GAP"

Nutrition is indeed a powerful force with respect to health, whether for the enhancement of health or its detriment. While most clinicians are aware of the causative role of nutrition with respect to chronic metabolic conditions such as coronary artery disease, hypertension, and diabetes, and many may acknowledge the possibility of prevention or attenuation of these conditions through a better diet, fewer are aware of the power of nutrition to reverse these conditions, and even fewer may be aware of the ability of nutrition to produce remission in inflammatory disease and reduce recurrence rates of malignancy.

Traditional medical education and many medical guidelines fail to consider the power of nutritional intervention. Some reasons for this have already been discussed in this chapter. There is a gap between the applied guidelines and published evidence which can be found in the medical literature. This phenomenon has been pointed out in several sections of this chapter.

A chapter of this length cannot pretend to treat in full such a vast subject as nutritional care of chronic diseases. It has been necessary to focus mainly on those conditions which cause the most morbidity and mortality, while presenting a sampling of other conditions which present clinical challenges, and for which drug toxicity is high.

It is hoped that, in addition to consulting relevant guidelines, conscientious clinicians will develop enough curiosity to search scientific databases such as PubMed for nutritional approaches to conditions that they treat, or at least read for themselves the main published studies presented here. It is hoped that clinicians will become more aware of the gap between guidelines and good

evidence and become aware that guidelines, due to their very nature, may exclude good evidence. It is to be hoped that conscientious clinicians will understand the potential of nutrition in a way that will lead to emphasizing diet much more, and first offering chronic disease patients a chance to try benign, effective, non-toxic, and potentially more economic options, before moving on to conventional drug treatment. This approach has the potential for being a winner on many levels, improving patient outcomes, reducing costs, and improving clinician satisfaction.

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3 Orthomolecular Parenteral Nutrition Therapy

Arturo O'Byrne-Navia and Arturo O'Byrne-De Valdenebro

CONTENTS

INTRODUCTION

Nutritional treatments by parenteral route can be considered as valuable tools in the integrative management when added to a conventional treatment set, both in acute and chronic diseases.

Its main objective is to recover quickly and regain stability in the internal environment (biological terrain). They are also directed to ensure the proper management of homeodynamic (Lloyd et al. 2001) mechanisms, and to maintain or recover the molecular chemical conditions that guarantee health. Their role is crucial in chronic degenerative diseases, which often oral supplementation of therapeutic nutrients does not elicit a proper response. One of the main limitations for the successful use of the oral route is the abnormal function of the gastrointestinal mucous membranes from toxic and proinflammatory dietary habits (Taira et al. 2015, Woting and Blaut 2016, Li et al. 2016). Along with the resulting disturbances of the microbiota, this usually causes abnormalities in the intestinal permeability and a compromised capacity in the absorption of nutrients, radically interfering factors involved in the absorption and utilization of nutrients.

During the last 30 years, orthomolecular nutrition has been developing a path in integrative medicine, based on the crucial role of basic nutrients in:

- The recovery of chronically ill patients,
- The optimization of therapeutic responses to conventional treatments,
- The strengthening of homeodynamic mechanisms (through the psycho-neuro-immuno-endocrine links).

All these possibilities allow the patients to return to normal daily life in a more physiological way, since many of the delays in the recovery processes are due to nutritional imbalances. Unfortunately, the lack of knowledge of many conventional colleagues regarding the therapeutic use of nutrients many times leads to criticism of a method of great value in daily clinical practice.

Nutritional Deficiencies/Insufficiencies that Support Intravenous Supplementation

Nutrition and orthomolecular supplements are optimal aid measures for most medical treatments. A patient recovers easier when the immune, endocrine, and neural systems (as master regulator systems for the rest of the body) are well nourished. On the other hand, the patient with nutritional imbalances will experience more difficulties overcoming the tendency to biological deregulation.

Unfortunately, in the modern world, many circumstances combine to create an increasingly poor state of nutrients, especially because it is not easy to find the right way to ensure the maintenance of health and structural/functional remodeling.

Understanding the concepts of deficiency and insufficiency plays a pivotal role in understanding the importance of intravenous nutritional therapy. This fully justifies the use of this type of orthomolecular practice, when facing serious nutritional issues in many patients. An historical misconception in the therapeutic use of nutrients has been limiting them to the critical patient, ignoring that for several nutrients, deficiencies/insufficiencies are widespread in the general population.

For some clinical settings, dietary amounts of many nutrients or oral supplementation based on the Recommended Daily Allowance (RDA) can be considered unable to attain clinical responses. In other cases, clinical improvement will take months to appear, thus making intravenous supplementation an interesting method of treatment.

Nutritional foodstuff values' tables of the commonly consumed foods serve only as reference values. Nonetheless, these tables do not reflect necessarily the actual state of the nutrient contents. This has been explained by many factors, for example, the lack or deficiency of a specific nutrient in the soil where these foods have been grown (Joy et al. 2016, Li et al. 2016). There are many other influencing factors, like agrochemical exposure of the crops, environmental toxicity, conservation, manipulation, and transport conditions, refinement of many foods, cooking techniques (peeling, high temperatures, cooking time), and so on, which may significantly impair the nutritional quality of the foods we consume every day (Teixeira et al. 2012, Gemenet et al. 2016, Poblaciones and Rengel 2016). A sustained consumption of nutritionally poor foods, slowly but inexorably leads to nutrient deficiencies among the population.

Some examples of specific nutrient deficiencies in foods/others are

- Preservation and storage processes make vitamins E, C, and/or B1 significantly dwindle its biological potential.
- The consumption of refined grains increases the needs of B complex vitamins and chromium to maintain the glucolipidic balance.
- Inclusion of "fake foods" (artificial flavoring and coloring of foods) compromise the availability of other nutritional factors.

- The little exposure to sunlight promotes global epidemic of hypovitaminosis D.
- Tobacco components (active or passive) affect epithelial barrier and mucosal systems, increasing the need of antioxidants (e.g., vitamins C and E).

Alcohol, a known liver toxin, reduces the absorption and bioavailability of many micronutrients, like vitamin C, vitamin E, B complex vitamins (thiamin, niacin, pyridoxine, folic acid, cyanocobalamin), calcium, magnesium, zinc, vitamin A/carotenoids, and SAMe (Lieber 1990, Ghorbani et al. 2016).

- Modern world stressful way of life increases the requirement of nutrients like glutamic acid, L-glutamine, L-arginine, antioxidants, and/or B complex vitamins.

Significant imbalance of essential fatty acids favors a trend toward persistent low-grade inflammation as a consequence of the distortion from modern habits and our Paleolithic genome (Ruiz-Núñez et al. 2016).

- Drug interactions with nutrients can affect their metabolism. This can be seen especially in polypharmacy patients due to chronic and/or multiple diseases. In some cases, specific medications alter the dynamics of the gastrointestinal system, affecting the absorption of nutrients (e.g., azathioprine, many of the chemotherapeutics, antibiotic related diarrhea, etc.).

Processing, storing, and heating/cooling of food may cause a loss of 40% of vitamin A, 100% of vitamin C, 80% B complex vitamins, and 55% of vitamin E (Harris and Karmas 1975).

Cutting or crushing food during preparation of meals starts enzymatic oxidation reactions that destroy important nutrients. The average loss of minerals and other nutrients from vegetables can reach more than 30% (Saxena et al. 2009).

All these factors lead us to understand that there is a considerable possibility of requiring parenteral nutritional replacement in patients with chronic or degenerative diseases. In this particular situation, the orthomolecular treatment has to ensure a quick and effective recovery of the deficient/insufficient nutritional components. There are other contexts like the acute patient. In that case, some of the nutritional circumstances may be similar, but the intravenous supplementation regimes are usually used for short periods of time. After the cause of the acute problem has been detected and corrected, it can be expected that any resulting nutritional deficiency does not prolong after a supplementation period limited in time.

Injectable Solutions in the Clinical Practice

As in any other pharmaceutical specialty, orthomolecular medicine requires the knowledge of the respective methodology of preparation of the nutritional therapeutic solutions to prevent any avoidable risk for the patient. When prepared under the proper manufacturing conditions, the orthomolecular intravenous solutions can be applied safely by trained personnel (both in the outpatient and in the inpatient setting).

The supplements suitable for nutritional therapy should have either pharmaceutical grade or should be manufactured by specialty compound pharmacies with experience in the preparation of injectable medications (Remington 1995). On the other hand, the attending physician practicing parenteral nutrition therapy should know the legislation and regulatory issues according to the country of practice. This must be taken into account especially for those regulations pertaining to the use of parenteral solutions in patients.

There are some fundamental conditions that the nutritional solutions should fulfill. All injectable nutritional/functional supplements must be sterile, pyrogen-free, and meet the stability and physicochemical conditions to assure the medical objective sought with this methodology treatment, while avoiding any complication arising from manufacturing issues (Lawrence 2007).

The use of the injectable route for orthomolecular supplementation becomes even more important in some specific situations related to the patient's condition:

- When the oral route is not possible, or when the conditions of the gastrointestinal tract do not guarantee the proper absorption of nutrients (from widespread intestinal dysbiosis to precise pathologies like short intestine syndrome);
- When the chemical nature or characteristics of the drug impede a satisfactory absorption by the oral route (e.g., Glutathione);
- When a quick correction fluid or circulating electrolytes is needed, or when a particular nutritional correction is mandatory (e.g., hypokalemia);
- When a faster therapeutic effect is required, due to the clinical condition or urgency;
- When the attending physician prefers direct control over the components and dosage of a nutritional mixture, according to the therapeutic objective.

Similarly, one might consider some specific situations in which the parenteral route can be recognized as the best way to ensure safety in the patient's treatment:

- When the pharmacological/clinical effect needs to be guaranteed, since the plasmatic levels obtained by the intravenous route do not depend on the process of intestinal absorption;
- When the treatment schedule must be correctly complied within the scope of inpatient institutions, as well as home care services;
- When the osmolarity, pH, or tonicity of the supplements are factors to be considered in the context of the patient (e.g., renal, cardiac, or hepatic disorders).

It is important that the health professional is trained specifically in the methodology of orthomolecular parenteral therapy. That allows a correct diagnosis of a particular medical condition, a determination of the type of orthomolecular treatment. It also allows the suitable preparation and administration of injectable components, as well as the recognition and prevention of any possible complications. Although not commonly seen in routine practice, some examples of these are: phlebitis, thrombosis, tissue damage, stroke, and local or systemic infection. As in any injectable therapy, when mistakes in dosage, volumes, and combinations are avoided, the risk of complications is clearly decreased.

The orthomolecular parenteral therapy comprises both intravenous and intramuscular administration. The best pharmaceutical presentations for these therapeutic routes available in the market are

- Ready to use pharmaceutical aqueous solutions,
- Dry soluble products with specific solvents, and/or
- Concentrated pharmaceutical solutions, which can be diluted prior to their use.

Application Routes in Parenteral Nutrition

Aqueous solutions are employed for the intravenous application. A peripheral vein (in most cases from the upper limbs) is chosen and varying volumes ranging from 0.5 to 1000 mL are dripped intravenously.

In some cases, there is also the possibility to apply "boluses" with volumes up to 10 mL. In other cases, intermittent solution applications can be performed over time (e.g., once a week), with volumes ranging from 100 to 500 mL. If total infusion volume exceeds 1000 mL or in some specific contexts like chelation therapy, it is recommended to have an infusion pump to perform a more controlled drip.

As it was mentioned before, the intravenous route has the advantage of not depending on the enteral absorption since the orthomolecular mixture is injected directly into the bloodstream and

from there to the interstitial compartment and to the cell. It must be taken into account that this is a faster route with more rapid clinical effects, but one should also be aware of possible dangers associated to this same reason. Adverse reactions may be related to:

- Inappropriate use of supplements (e.g., an excess of intravenous L-tryptophan or Zinc could cause headache in sensitive patients);
- Empirical or random combinations (e.g., including unbalanced proportions of antagonistic nutrients as copper/zinc or L-lysine/L-arginine in the same solution or mixes of multiple minerals with ascorbic acid);
- Negligence in preparing the mixture;
- Not considering physical parameters of the solutions, such as tonicity or pH.

All these previous factors can be clearly associated with the lack of knowledge regarding the proper methods of orthomolecular parenteral nutrition. In that sense, they can be prevented easily if simple measures are taken.

Nonetheless, there are some other plausible undesired effects related to idiosyncratic reactions, sometimes not adverted by the patient though his or her life. Some people can have individual sensitivity to any orthomolecular component, although some of them have produced this type of reaction more frequently than others (e.g., iodum, thiamine).

In their original presentation, most orthomolecular injectable solutions are hypertonic. If used in this form, they could generate hemolysis (Olszewer and Teruya 2009). Prior to the intravenous application, hypertonic presentations must be diluted in suitable physiological solutions, optimizing osmolarity. The final solution should be isotonic or slightly hypotonic, to be adequately tolerated by erythrocytes (Botella Dorta 2004).

Regarding the pH parameter, neutral solutions between pH 6 and 7.5 are recommended. It is important to mention that blood has a significant buffering capacity, mainly concerning acids.

The intramuscular route can also be considered for the supplementation of orthomolecular nutrients. In that case, liquid medications in aqueous solutions or aqueous/oily suspensions are preferred, with volumes ranging from 1 to 5 mL. For these applications, gluteal or deltoid muscles are ideal. Their striated muscle nature endows them with wide vascularity and few sensory innervations, allowing a better absorption accompanied with low pain (Botella Dorta 2011).

Intramuscular injection allows differential absorption times, depending on the nature of the applied solution. For aqueous solutions, rapid absorption will be seen, while oily solutions/suspensions can be considered a deposit form with slow absorption rates. The proportion between oil and water in these solutions will determine its absorption rate.

When the pH of intramuscularly injected products is close to the plasmatic one, the application shall be less painful. In another way, when the pH is too acidic or alkaline, this can generate secondary reactions. In most cases there could be a simple congestion, but in extreme cases there can be an inflammatory process and even tissue necrosis could occur (Lawrence 2007). A slight hypertonic solution could be more easily absorbed.

Some adverse reactions with intramuscular injection are related to the nature of the drug itself. It is widely known how vitamin B1 and B complex vitamins produce much more pain when injected through this route. This fact can be reduced in some degree when these types of orthomoleculars are injected deeply into the gluteal muscle.

Preparation of Mixtures for Parenteral Nutrition

Due to the practical importance of this aspect, it will be also mentioned in this chapter.

Health professionals, who include orthomolecular parenteral nutrition among their practices, should be trained particularly in the preparation of nutrient mixtures. The development of an institutional "procedures manual" is strongly suggested (Sobotka et al. 2009). This type of manual should

include: detailed instructions about all the processes related to the preparation of the mixtures (responsible personnel both for the preparation and application, proper facilities, available supplements, optimal quantities and number of supplements to be used, etc.).

The procedures manual is primarily a safety measure for the patient, the health staff, and the institution. It also plays an important role in the institutional qualification/habilitation processes with the local sanitary authorities granting the permissions required to perform such procedures.

The health personnel involved in parenteral orthomolecular therapy must include one coordinator (usually a registered nurse) skilled to conduct training to the rest of the team. This training should cover the following topics (Botella et al. 2002, World Health Organization 2003, Sobotka et al. 2009):

- Hygiene and aseptic techniques. This point is especially important due to the emergence of parenteral therapy-associated mycobacteriosis;
- Knowledge of possible physical or chemical incompatibilities between prescribed nutrients and/or between nutrients and diluents;
- Potential instability of intravenous mixture or nutrient diluent mixture;
- Hazards or risks of microbiological contamination during intravenous mixture preparation, during the time of peripheral access puncture, or during the mixture application;
- Restrictions on temperature, sunlight exposure, and other storage product requirements. Label-related issues (Kumar et al. 2013), such as passive errors due to lack of attention when reading the labels, poor quality labels (allowing deterioration of important data related to the supplement that makes them difficult to read), or even mislabel itself;
- Human errors like adding the same supplement more than once, or in excessive amounts;
- Lack of knowledge regarding a particular nutrient, particularly in the case of potential adverse reactions or adverse effect during its application.

Special Care in the Preparation of Orthomolecular Mixtures

Incompatibility

Incompatibility can result from physical or chemical interaction between components.

Attention must be called to the presence of physical incompatibility which is visually noticeable. It is characterized by a variety of possibilities as precipitation, clumping, cloudiness, frothiness, or changes in color of the mixture. Any of these abnormalities occurs when there is incompatibility between two or more components. Another option would be the incompatibility between any of the nutrients and the solvent vehicle. The physical changes can be evident in the solution bag even from the time of preparation of the mixture, but also during the application of it (Saldaña–Ambulódegui 2012).

Another potential incompatibility arises from the chemical interaction of orthomolecular mixture components. The possible responses to chemical incompatibilities include an affection of the purported therapeutic action of the supplementation (from partial to complete loss). It could also derive in the eventual augmentation of known potential toxicity of one component, or in the generation of toxic compounds with undesirable effects. The emergence of thrombophlebitis is not common but possible, mostly related to an incorrect management of the parenteral technique. As with any intravenous application, there exists the theoretical chance for developing embolisms, a rare complication not seen in more than 30 years of experience with orthomolecular injectable medications in our practice.

Usual potential factors affecting compatibility or stability of a parenteral nutrition solution are

- Problems with the pH of the mixture, which is considered the most critical factor (Olszewer and Teruya 2009).
  - Regarding the intravenous solutions, the closer the pH value is to 7, the less chance there is of having a painful or risky application. In physiologic conditions, blood has a pH of approximately 7.35, slightly alkaline. With the intramuscular injections, solutions with a pH between 4.4 and 8.5 are considered acceptable.

  - Some components are known because of their very low pH: Thiamine, N-acetylcysteine, L-leucine, or Cyanocobalamin. In turn, there are others like DMSO, which tend to have alkaline pH (around 10).
- The sequence in which the components are added.
- Modifications of components by exposure to light and/or inadequate temperatures (previous or during the application; e.g., alpha lipoic acid, ascorbic acid).
- Difficulties or problems with dilution of any component of the mixture.
- Significant changes secondary to the time elapsed between preparation and application.
- Complications arising from the type of diluent used.
- Improper conditions of packaging, transporting, and storing.

The institutional procedures manual serves as a useful method to minimize the risk of incompatibilities, therefore preserving the integrity of patient care during orthomolecular injectable therapy. There are some specific recommendations to observe in that regard:

- The solutions to be injected must be prepared and then injected in the shortest possible time. Avoiding the preparation of orthomolecular mixtures in advance should be the general rule. The concept of mixture stocking should not have any role in orthomolecular nor in integrative medicine.
- The number of components of a nutritional mixture should be kept to the lowest, and should follow rational protocols established previously, according the therapeutic target(s).
- If the mixture includes components with different pH, a previous check of this pH in their labels is recommended, to mix and add them in descending pH order (from alkalines to acidics).
- There exist several incompatibilities between some injectable orthomoleculars. For example, ascorbic acid plus minerals in the form of sulfate salts, due to the precipitation possibility of the last ones. Incompatible medications should never be mixed. They should be prepared in different solution bags and attention should be paid to the order of intravenous application of these solutions.
- Many practitioners of integrative medicine perform orthomolecular infusions along with other types of therapeutic approaches. When using medications with bio-regulatory properties (antihomotoxics and/or homeopathics) simultaneously during the orthomolecular mixture, the intravenous catheter should be used. Ideally, a washout of the intravenous line with 10 mL of sterile water solution should be performed before and after the injection of the bio-regulatory medication. When using two or more bio-regulatory medications, a minimum of 5 minutes should be left between their application.
- In case of having any doubt, a consult with the pharmacist of the institution is highly recommended.

Instability

Instability of some orthomolecular nutrients arises from chemical reactions considered undesirable and preventable, but in most cases irreversible. These reactions occur either because of mixing incompatible components in the same solution or external influences. The result could be in the form of toxic compounds or as a compromise in the therapeutic effectiveness of the nutrients. The most known of these influences are

- Oxidation of antioxidants after exposure to light and/or heat (especially alpha lipoic acid, but attention must be paid also with ascorbic acid, glutathione (Yamamoto and Ishihara 1994, Fleming 2016), and vitamin B5);

- Destruction by the action of ultraviolet light (B complex vitamins, particularly riboflavin, thiamine, pyridoxine, Cyanocobalamin, and folic acid (www.helapet.co.uk/downloads/lightaffectingdrugs.pdf));
- Hydrolysis of amino acid (polypeptidic) chains can result from their inclusion in acidic solutions.

Sterility and Modifications Due to Contamination

The sterility of an injectable nutritional solution is a mandatory condition. Microbiological controls of injectable drugs must be carefully fulfilled. When handling solution bags, intravenous application equipment, catheters, and so on, sufficient precautions have to be taken care of.

Beyond the required quality of the used materials, contamination can occur during the preparation and/or the application procedure itself. This phenomenon can be related to inadequate staff hygiene when preparing and administrating the solutions, and also to inappropriate infrastructure institutional conditions (Akers and Larrimore 2003, Williams 2005, http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/generalChapterInjections.pdf).

Apyrogenicity

Nutritional products intended for parenteral use must be free of pyrogens. Defensive reactions against a variety of microorganisms (Gram-negative or Gram-positive bacteria, viruses, and fungi), or its endotoxins (lipopolysaccharides, LPS from Gram-negative bacteria) can be found in parenteral pharmaceuticals and medical. Endotoxins are large molecular weight complexes (~106 Da) associated with and expressed in the outer membranes of Gram-negative bacteria (Kluger 1990, Hartung and Wendel 1995, Henderson et al. 1996, Rosimar et al. 2004). This is a reason of concern to the pharmaceutical industry, and as such, all the necessary means to avoid this situation must be present.

In our system, the endotoxin/LPS binds to the specific toll-like receptor 4 (TLR4) complex on the monocyte membrane (Lu et al. 2008) initiating the signaling and transduction inflammatory pathway. This pathway comprises several reactions leading to the induction of endogenous pyrogens such as Interleukin-1β (IL-1β), Interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α). The endogenous pyrogens then cause a change in the thermoregulation in the hypothalamus toward a higher body temperature in order to optimize all the immune system responses. In the case of exogenous pyrogens, the Interleukin-8 (IL-8) is induced in the monocyte. This chemokine by nature has different functions than the previously mentioned ones.

Pyrogens are hyperthermia inducing substances. They can come from intact, dead, or disintegrated microorganisms, whether they are pathogenic or not. In the case of intact (living) microorganisms, they often result from their metabolic products such as denatured proteins. Gram-negative bacteria are particularly known due to their capacity of pyrogen production. In comparison to other pyrogens, LPS are more resistant to heat (Hartung et al. 2001, Roth and Blatteis 2014) inducing higher febrile reactions. In this context, it is mandatory that the sterilization process is performed with the correct temperatures and controls.

From the clinical point of view, regarding other types of microorganisms, pyrogens from fungi are considered less important since they tend to produce only a slight temperature elevation. As demonstrated in experiments with rabbits, fungal mannans can be considered pyrogens by themselves (Nagase et al. 1984). Its effect is independent from the one of LPS, but has a weaker intensity.

In cases of contaminated orthomolecular therapeutic mixtures administrated intravenously, a febrile reaction occurs. This situation does not have any relationship with the nutritional agents included in the mixture, since none of the usual orthomoleculars is known to induce this type of reaction. This hyperthermical effect can go beyond 40°C (104°F) and have a duration ranging from 4 to 12 hours (Morimoto et al. 1988, Rosimar et al. 2004), if an antithermic measure is not taken. Other clinical features of the reaction against pyrogens include cold or chills, joint or lumbar pain, nausea and/or headache.

SPECIFIC PRODUCTS FOR USE IN ORTHOMOLECULAR INTRAVENOUS NUTRITIONAL THERAPY

Historical Considerations

The use of nutrition with therapeutic purposes has a long history in medicine, but it was only until the mid-twentieth century that the intravenous route was a feasible option. McCormick in Canada (McCormick 1959) was probably the first author to come up with the idea of the intravenous intervention in cancer, which according to his theories would arise from a defective collagen remodeling because of vitamin C deficiency.

During the 1970s, Linus Pauling and Ewan Cameron took back these interesting ideas (Cameron and Pauling 1973, 1974, Cameron et al. 1979). After encouraging clinical observations (Cameron et al. 1975), the group of Cameron later began their clinical research on terminal cancer patients, using high-dose intravenous Vitamin C. In their landmark publications (Cameron and Pauling 1976, 1978) they were able to show improvement in function and life expectancy in this oncologic group of patients. The patients receiving the high-dose vitamin C treatment had a median survival time of 300 days more compared to the non-treated patients (Cameron and Pauling 1978).

These claims were promptly scrutinized by researchers in the Mayo Clinic. They were not able to corroborate Pauling and Cameron's observations (Creagan et al. 1979, Moertel et al. 1985), thus disqualifying the treatment of oncologic disease with high-dose vitamin C. This publication closed the doors for the possibility of integrating vitamin C into conventional oncology treatment for many years.

It has already been clarified (González et al. 2005) that the trials from Pauling and Cameron and the ones from Moertel et al. are clearly different in their methodology. Pauling and Cameron used high-dose vitamin C delivered intravenously and the orally, in patients with moderately advanced disease. The Mayo Clinic trial used high-dose vitamin C delivered *only* orally in patients with severely advanced disease.

Additionally, at that time it was not known that the vitamin C pharmacokinetics differ clearly in the parenteral versus the oral use (Padayatty et al. 2004), rendering the studies by Cameron and Moertel incomparable. Prior observations of high-dose vitamin C researchers had already suggested such an effect, since the tumoral regression was possible only when the dose was maintained high enough (Cameron et al. 1975). Cameron did not have the pharmacokinetic data but emphasized the need of a continuous administration of high-dose vitamin C to achieve the expected results (Cameron 1991).

The following decades were characterized by the opposition of the two points of view. High-dose vitamin C advocates continued treating their patients with this approach, and conventional oncology continued rejecting this therapy. Hugh Riordan, MD in Wichita, Kansas contributed building a strong base of work from the practical therapeutic activity in complementary oncology. Dr. Riordan and his team have treated more than 40,000 cancer patients and have published research (Mikirova et al. 2008, 2016a,b, Riordan et al. 2005, Duconge et al. 2007, Padayatty et al. 2006) showing effectiveness for some cancers. The Riordan intravenous vitamin C (IVC) protocol for patients with oncologic disease (Riordan et al. 2003) involves the slow infusion of vitamin C at doses of 0.1–1.0 grams (g) of ascorbate per kilogram (kg) of body weight.

During the 1960s and the 1970s, John Myers, MD, an internist from Johns Hopkins Hospital in Baltimore, made particular remarks regarding the limitation of the oral route to provide an optimal nutrient intake (with therapeutic purposes). He concluded that since the average western world patient has a compromised capacity to absorb nutrients due to the lack of an optimal function of the digestive mucous membranes, the use of intravenous supplementation would be fully justified. Besides the absorptive limitation, there is also the inherent activity of detoxification systems (i.e., the "1st-pass effect"), turning the oral route into a suboptimal one. Hence, only a small fraction of the vitamins and minerals ingested by the average patient (either in food or in pills) are actually being successfully absorbed and then lead into the bloodstream. Dr. Myers started using a safe

mixture of key nutritional supplements which were administered in a single intravenous infusion (directly providing these nutrients to each cell in the body).

Although the pioneering work of Dr. Myers has always been recognized in the orthomolecular medical community, the exact composition of the so-called "Myers' cocktail" was not precisely known. The information related to Myers' patients was incomplete and there weren't any official publications available about this orthomolecular treatment, beyond anecdotic material. According to the review made by Dr. Alan R. Gaby, MD (Gaby 2002) who took over Dr. Myers' practice in Baltimore after his passing, it seems that Myers used a 10-mL syringe to administer a combination of magnesium chloride, calcium gluconate, thiamine, pyridoxine, cyanocobalamin, calcium pantothenate, and vitamin C. The exact amounts of the individual components were unknown, but Myers apparently used a 2% solution of magnesium chloride, rather than the more widely available preparations containing 20% magnesium chloride or 50% magnesium sulfate.

Based on the alleged "Myers' cocktail" composition by Gaby, he administered such a mixture of magnesium, calcium, B complex vitamins, and vitamin C. This author along with a group of collaborators report (Ali et al. 2009) satisfactory clinical results in patients with migraine, fatigue (including chronic fatigue syndrome), fibromyalgia, acute muscle spasm, upper respiratory tract infections, chronic sinusitis, seasonal allergic rhinitis, acute asthma attacks, and other disorders. According to these authors, through the years they have administered more than 1500 Myers' cocktails to patients with various clinical conditions.

Other orthomolecular nutrients like Glutathione have also been reported to be useful when administered together with Myers' cocktail, particularly in the context of cardiovascular disease (Forman et al. 2009).

According to our experience, since 1975 in the Academia de Medicina Biológica de Los Robles (Los Robles Biological Medicine Academy) in Popayan, Colombia, Dr. Germán Duque, MD initiated the intravenous administration of the so-called Moros' mineral constellations. This combination of oligo and macroelements was developed by Dr. Gustavo Moros, a Venezuelan cardiologist some years before. Dr. Moros used fixed doses of various minerals in different salt forms. This supplementation allows the complete reposition of the relative circulating pool from the most important minerals, providing a basic nutritional load for the extracellular matrix and subsequently for the cells. This type of intravenous orthomolecular compound has been the basis of the parenteral nutritional approach in our clinic for the last 35 years. There are several commercial presentations available in South America, for example, MM–16 Forte (18 minerals) from HeilPro DKN® (Cali, Colombia), MinTraz (19 minerals) from OrthomoLab® (Cali, Colombia), and Nutri-MINS (16 minerals) from BioMolec® (Quito, Ecuador). All these multimineral compounds conserve the Moros' concept of including a myriad of mineral salts as the nutritional orthomolecular supplementation method in both chronic and acute patients.

Theoretical Basis for the Therapeutic use of Intravenous (IV) Nutrients

Therapeutic intravenous administration of nutrients has some advantages over other routes, and of course like any therapeutic measure, is not free of some disadvantages.

Regarding the advantages, this route can achieve serum concentrations which are not obtainable with oral or even intramuscular (IM) administration.

For example, as the oral dose of vitamin C is increased progressively, the serum concentration of ascorbate tends to approach an upper limit, because of both saturation of gastrointestinal absorption and a sharp increase in renal clearance of the vitamin (Blanchard et al. 1997).

When the daily intake of vitamin C is increased by 12-fold, from 200 mg/day to 2500 mg/day, the plasma concentration increases by only 25% (from 1.2 to 1.5 mg/dL). The highest serum vitamin C level reported after oral administration of pharmacological doses of ascorbate is 9.3 mg/dL (Harakeh et al. 1990). In contrast, the IV administration of 50 g/day of vitamin C resulted in a mean peak plasma level of 80 mg/dL (about 12 times higher).

Similarly, oral supplementation with magnesium results in little or no change in serum magnesium concentrations, whereas its IV administration can double or triple the serum magnesium levels (Okayama et al. 1987, Sydow et al. 1993).

Many nutrients have been shown to exert pharmacological effects, which are in many cases dependent on the concentration of the nutrient (so as in most medicinal substances).

For example, an antiviral effect of vitamin C has been demonstrated at a concentration of 10–15 mg/dL, a level achievable with IV but not oral therapy. In another context, at a concentration of 88 mg/dL in vitro, vitamin C was able to destroy 72% of the histamine present in the medium (Uchida et al. 1989).

Lower concentrations were not tested, but it is possible that serum levels of vitamin C attainable by giving several grams in an IV push would produce an antihistaminic effect in vivo. Such an effect would have implications for the treatment of various allergic conditions.

Magnesium ions promote relaxation of both vascular (Iseri and French 1984) and bronchial (Brunner et al. 1985) smooth muscles, specifically with higher doses. This effect might be useful in the acute treatment of vasospastic angina and bronchial asthma, respectively.

These are only a couple of examples, but it is likely that these and other nutrients exert additional pharmacological effects (currently unidentified) when used in high concentrations.

In addition to having direct pharmacological effects, IV nutrient therapy may be more effective than oral or IM treatment for the correction of intracellular nutritional deficits. Some nutrients are present at much higher concentrations in the cells than in the serum. For example, the average magnesium concentration in myocardial cells is 10 times higher than the extracellular concentration (Frustaci et al. 1987).

This ratio is maintained in healthy cells by an active-transport system that continually pumps magnesium ions into cells against the concentration gradient. In certain disease states, the capacity of membrane pumps to maintain normal concentration gradients may be compromised. In one study, the mean myocardial magnesium concentration was 65% lower in patients with cardiomyopathy than in healthy controls (Frustaci et al. 1987), implying a reduction in the intracellular-to-extracellular ratio to less than 4-to-1. Considering that magnesium plays a key role in mitochondrial energy production, intracellular magnesium deficiency may exacerbate heart failure and lead to a vicious cycle of further intracellular magnesium loss and more severe heart failure with potentially disastrous consequences.

Intravenous administration of magnesium, by producing a marked, though transient, increase in the serum concentration, provides an opportunity for ailing cells to take up magnesium against a smaller concentration gradient. Since these cells belong to a pathological context, the nutrients taken up by them after an IV orthomolecular infusion may eventually leak out again. Nonetheless there is always the aim of inducing repair and healing phases from the replenishment of nutrients, even before the leak out happens again. With time, if cells are repeatedly "flooded" with nutrients, this improvement may be cumulative.

In the author's clinical observation, some patients who receive a series of orthomolecular IV injections become progressively healthier, not only from their main cause of consultation, but also from other minor complaints in their clinical history. In these patients, the interval between treatments can be gradually increased, and eventually the injections might be no longer necessary.

This can be considered as one of the disadvantages of the IV route, since not all the patients are willing to receive injections. Of course, this is not limited to orthomoleculars, but extends to any injectable product/medication.

Other patients require regular injections for an indefinite period of time in order to control their medical problems. This prolonged necessity of orthomolecular IV injections could conceivably result from any of the following:

1. Chronic disease states which are hardly reversible (e.g., many oncologic patients).
2. Advanced age, since it is characterized among others by a difficulty in the normal intestinal absorption of nutrients and the secondary deficits.

A genetically determined impairment in the capacity to maintain normal intracellular concentrations of a specific nutrient (Henrotte 1980).

An inborn error of metabolism that can be controlled only by maintaining a higher than normal concentration of a particular nutrient (Camp et al. 2013).

3. A persistent renal leak of a nutrient (Booth and Johanson 1974) or several nutrients, like in CKD (Merrill 1956).

Potential Side Effects Considerations

It is important to mention that the use of IV vitamin C must take into account a genetic defect called "Glucose-6-Phosphate Dehydrogenase Deficiency," or G6PD-deficiency, also known as "favism." This is a genetic mutation found in people of African or Mediterranean origin. If a patient with favism receives IV vitamin C, it can result in hemolysis (destruction of red blood cells, RBCs). This happens because without this critical enzyme, the RBC is not able to recycle Glutathione and thus is not able to handle oxidative stress/damage. Without Glutathione to protect it, the RBC will be destroyed, leading to anemia. This is a potentially very dangerous situation since it can end up in acute renal failure, and can even be fatal (although this is rare).

A genetic screening for G6PD-deficiency in patients programmed to receive IV vitamin C is thoroughly recommended. The practice of medicine and of orthomolecular supplementation is shaped by socioeconomical status. In that sense, we are aware of the screening being performed regularly in developed countries. On the other hand, in our experience in third world countries, where the test is expensive or simply not available, it is possible to begin IV vitamin C with low doses (e.g., 3–5 g) and tell the patient to pay attention to any change in the color of the first urination after the infusion. If there has been any low-level hemolysis (as evidenced by rose or light red color in the urine), the genetic test is indicated.

Although this genetic defect has been reported in the literature as a high incidence one (Minareci et al. 2006), in our particular Latin-American population we have not been able to see the first case in more than 30 years using low, medium, and high doses of IV vitamin C.

In any case, most patients with this mutation are already aware of their condition (given they were born with it) and the likelihood of red cell hemolysis/destruction with the ingestion of certain common foods, such as beans (especially fava beans). Any family history of favism reported by the patient obligates to the appropriate test before receiving IV vitamin C.

Another special group to consider is the chronic renal insufficiency (CKD) patient. In this case, some nutrients included in the orthomolecular infusions represent an increased risk of accumulation. This is due to the compromise in the blood filtering function of the kidneys, which helps maintain normal levels of fluid and ions in the bloodstream. If this process is impaired, receiving certain amounts of IV fluids possess an increased risk of "fluid overload" state. This applies also for patients with congestive heart failure and/or atrial fibrillation. Special precaution must be observed in patients taking Digoxin or other potassium-depleting drugs (e.g., some diuretics), since potential electrolyte imbalances in this group of patients can lead to heart arrhythmias in an easier way in comparison to the general population.

In any of these conditions, IV nutrients can be used but there are special cautions with volumes and duration of the infusions, to avoid a "fluid overload" state. Additionally, CKD can also impair the ability to filter and/or reabsorb specific minerals. Certain ions (K^+, Mg^+, Ca^{4+}) or mixes of them, with a higher osmolality, could eventually lead to accumulation of them and potential toxicity.

Intravenous magnesium is known to affect blood pressure (BP) and potentially lower its records. Magnesium influence in blood pressure is evident when it is used daily in hospitals around the world (particularly in the management of pregnancy-induced hypertension, or "toxemia gravidarum"). Patients with low blood pressure are advised to report any symptoms related to such conditions during and/or after an orthomolecular IV treatment. This phenomenon is usually counteracted

with the total volume of the infusion, but it could persist if the tendency to hypotension is notorious and/or if the dose of magnesium is high. Thus, caution is recommended in patients with low BP.

A similar caution must be mentioned in patients with tendency to hypoglycemia. Some orthomolecular nutrients have the capacity to influence the carbohydrate metabolism, such as chromium, zinc, manganese, vanadium, some B complex vitamins, among others (Sárközy et al. 2014). Glucose can bind to DMSO and be carried into cells. All these potential influences can lead to lower blood sugar levels. Patients with hypoglycemic tendencies are advised to report any symptom related to such condition during and/or after an orthomolecular IV treatment. In our institution, there is the universal recommendation of ingesting at least some food before any IV orthomolecular infusion.

Allergy is also a theoretical reason for concern, although the rarest of the potentially adverse reactions to occur. There is always of course the possibility of a patient with an unknown allergy. In that case, individual patients may have an allergy to a component of the IV combination and this can evoke an allergic response. Given the simple molecular characteristics of most of the orthomolecular nutrients used in IV infusions, it is not likely that an allergic reaction presents. Nonetheless, there are specific concerns about iodine, which in fact is recognized in medicine as a potentially strong allergen for some individuals. If there is any suspicion of a potential allergic sensitivity, the suspected substance should be avoided in the orthomolecular mixture. In the very infrequent case of an allergic reaction, the respective control treatment should be commenced quickly.

Intravenous (IV) Orthomolecular Therapeutic Agents

A wide range of substances that are part of the nutritional orthomolecular therapeutic approach can be injected through the veins into the bloodstream. Each nutrient has specific medical objectives, but since habitually a single nutrient is involved in several metabolic pathways and exerts actions in several tissues, it is common that the list of objectives/functions can rise to 5 or 6 per nutrient. When injected in conjunction with other nutrients with the same objective, a synergistic action can be expected, but this is more a theoretical concept given the difficulty to measure it. The nutrients in orthomolecular medicine can be grouped in several categories according either to their action or to their chemical structure. The most common ones will be reviewed in the next section of the chapter.

Antioxidant Agents

Vitamin C (Ascorbic Acid)

It is important to mention that vitamin C can act as an antioxidant or as a prooxidant depending on a variety of factors, like the dose administered and the physiologic or pathologic state of the recipient (Levine et al. 2011, Chakraborthy et al. 2014). Historically, lower doses up to 5 g have been considered as antioxidants (Traber and Stevens 2011), while the higher doses from 15 g and above have been recognized as prooxidant (Chen et al. 2008, Mendes-da-Silva 2014). Although this concept can prevail most of the time, there have also been publications (Hininger et al. 2005) which challenge this postulate. Of course, oxidative stress is a complex phenomenon to study and drawing conclusions only from basic studies can not necessarily be applied to the clinical reality. In the clinical and therapeutic contexts (where type III complexity is the rule rather than the exception and thus they are better understood with a systems biology approach (Welsby 1999)) the dose concept cannot be static, as in the case for the use of IV vitamin C.

Different studies have been published suggesting beneficial results in many clinical situations. One of the most prominent fields for the use of IV vitamin C is the modulation of the tissues, resulting in an aid to the healing process. This has been observed, for example, in a postsurgical setting, where the supraphysiologic supplementation of ascorbic acid resulted in improvements of the anastomosis healing. The authors attributed the effect to a better control of the local inflammatory process, and to a better quality and quantity of the collagen produced locally, resulting in a higher strength of the anastomosis (Cevikel et al. 2008).

Another possibility for the orthomolecular use of IV vitamin C is in the oncology field. In the clinical setting, doses of 10–75 g of vitamin C administered intravenously exhibited a cytotoxic effect upon entering cancer cells. According to their interesting results, the research team affiliated with the Bezmialem Vakif University Medical Faculty in Turkey encourages the use of IV vitamin C along with radiotherapy for the treatment of patients with bone metastases (Kiziltan et al. 2014).

The besought mechanism of action for the antitumoral effect of high dose IV vitamin C is the augmentation of hydrogen peroxide at the extracellular level (Riordan et al. 1995). Since the tumoral cells lack the proper antioxidative defenses (catalases, among others), they perish from the exposure to these type of doses (prooxidant) (Chen et al. 2007, Park 2013).

There are other possible additional mechanisms of action supporting the use of high dose IV vitamin C in cancer patients. In a basic study (Yeom et al. 2009) Korean authors found that the carcinostatic effect induced by high dose concentrations of ascorbic acid occurred through the inhibition of angiogenesis, according to several parameters of tumor evaluation (biopsy results, gene expression studies, and wound healing analysis, both in vivo and in vitro).

Several treatment protocols have been reported for high dose IV vitamin C as a therapeutic tool in patients with cancer. Most of them include the infusion of doses between 350 and 750 mg/kg every 3–5 days for a prolonged period of time. A thorough review of one of these protocols is provided by Mirikova et al from the Riordan clinic (Mikirova et al. 2013).

This, however, differs significantly from the original protocol used by Cameron et al. in the 1970s, and published in their landmark papers about the use of high dose IV vitamin C in cancer patients (Cameron and Campbell 1974, Cameron and Pauling 1976, 1978). In these observational studies, without the knowledge of vitamin C pharmacokinetics we have available nowadays, the most employed protocol combined the oral supplementation of several grams of vitamin C with daily IV infusions of 10 g of the agent for 10 days.

It is worth noting that despite the widespread use of high dose IV vitamin C in many integrative practices and clinics around the world, and of the interesting results that most of us constantly witness with the use of this measure in the oncologic patient, the available high-quality evidence on its effectiveness is still scant (Fritz et al. 2014). This precludes a definite and formal recommendation for this type of treatment, since to date there is only preliminary evidence which does not allow drawing strong conclusions about it. Nevertheless, according to this same evidence high dose IV vitamin C appears to have a good safety profile and a potential antitumor activity.

Regardless of the conceptual orientation of the consulted authors (Fritz et al. 2014, Jacobs et al. 2015), there seems to be much more agreement in the notion that high dose vitamin C infusions do play a role in the improvement of the quality of life and in the reduction of symptom severity in oncologic patients. We are optimistic that the years to come will bring substantial improvements in the quality of the evidence, through adequately designed and implemented controlled trials on the use of vitamin C in cancer treatment. This will be crucial not only for the growth and acceptance of the integrative oncology field, but also for the patients who will receive better medical care when infused with high dose vitamin C. Remaining questions dealing for instance with the most responsive tumors, or the optimal schemes of IV vitamin C (doses, rates of infusion, length of the treatment, etc.) still pose significant challenges even for the physician with years of experience in the field of orthomolecular medicine.

The clinical use of high dose IV vitamin C has another interesting chapter in the treatment of infectious diseases. Vitamin C has been used in many different aetiological contexts, but the viral infections are the ones that seem to exhibit a better response when this agent is utilized. Thanks to the laborious work of compilation of Robert McCracken (2004), it is possible to have access to many difficult to find publications in this area (e.g., articles from the 1930s to the 1970s, written by one of the most prominent pioneers in the clinical application of vitamin C, Dr. Fred R. Klenner).

In fact, many natural compounds have been tested in the search for the ability to suppress viral replication. IV vitamin C infusions produce a positive effect on disease duration and reduction of several viral antibody levels. Also from the group of the Riordan Clinic in Kansas (Mikirova

and Hunninghake 2014), the publication of a clinical study of ascorbic acid and EBV infection showed a reduction in antibody titers of EBV EA IgG and EBV VCA IgM during the IV vitamin C treatment.

There are some other observations from the medical literature that serum vitamin C concentrations at the millimolar levels are able to hinder viral infection and replication in vitro. For example, suspensions of herpes simplex virus (HSV) types 1 and 2, cytomegalovirus (CMV), and parainfluenzavirus type 2 were inactivated within 24 hours of having been treated at 37°C with 1 mg (5.05 mM) of copper-catalyzed sodium ascorbate per mL. Ascorbate concentrations as high as 10 mg/mL (50.5 mM) demonstrated only a minimum increase in effect on viral inactivation. The loss of infectivity did not alter either the hemagglutination or complement fixation qualities of the antigens (White et al. 1986).

Vitamin C exerts plenty of influences in the immune system function, both from the quantitative and qualitative points of view. As reported by Sorice et al. in their broad review from 2014 covering this topic (Sorice et al. 2014), vitamin C enhances the cytokine production and the synthesis of immunoglobulins in response to infection (Stephensen et al. 2006); up-regulates the activity of NK cells (Ichim et al. 2011); impacts the lymphocytes proliferation in a dose-dependent fashion, with physiological concentrations increasing it and supraphysiological concentrations inhibiting it (Bruunsgaard et al. 2003, Furuya et al. 2008, Calder et al. 2009); polarizes the differentiation toward type 1 response (leading Th0 subset to differentiate to Th1 subset) (Holmannová et al. 2012); and affects both antimicrobial and NK cell activities, lymphocytic proliferation, chemotaxis, and delayed-type hypersensitivity (Zhang and Farthing 2000).

In the same instance but from an opposite direction, inflammation represents an obstacle for the action of vitamin C on endothelilal cells, due to an inhibition of its uptake due to proinflammatory cytokines like tumor necrosis factor-alpha and interleukin-1 beta (Seno et al. 2004). Vitamin C itself has the possibility to modulate inflammatory processes and it consequences (Zhang et al. 2000). For example, high doses of vitamin C may attenuate exercise-induced inflammatory reactions.

Our clinical experience in the use of intravenous vitamin C in the treatment of infectious diseases has led us to observe that the everyday infections in immunocompetent patients (e.g., cases of common cold, mild gastroenteritis, uncomplicated bronchitis) evolve faster and with much less symptoms derived from the infection. This results after a comparison with previous similar infectious episodes referred by the patient or with household contacts or close relatives with the same disease but who did not receive the vitamin C treatment for any reason. In these types of infections one or two vitamin C infusions of 5–10 g have been very useful.

In cases of complex or chronic infections treated in our institution, vitamin C infusions also have an important role. An important difference with the acute but trivial infection, in the chronic ones or the complex acute ones, usually the patient must be injected in a series of occasions during a more prolonged time. Two to five vitamin C infusions of 15–20 g, given every 3–5 days is the customary treatment for an uncomplicated pneumonia (along with other measures from the biological medicine and the proper antibiotic scheme).

In chronic infections like hepatitis C (HCV), a long course of weekly vitamin C infusions of 15–25 g for 6 months, followed by every other week infusions with similar amounts of vitamin C, have been helpful to manage symptoms referred by the patients as infection related (e.g., fatigue, appetite alterations, sensation of dullness in the right upper quadrant of the abdomen). From a small number of patients with chronic HVC infection treated in our institution, in some of them the viral load has responded favorably descending, while in most of them it has stabilized at the previous count for long periods of time, and in some cases (the least) the viral load has ascended.

In other chronic but less complicated infections like the ones produced by herpes virus (herpes simplex virus type 1 and 2), frequent relapses often represent a high burden in patients' daily activities and tend to impact negatively in their quality of life. Our patients with HSV1 or HSV2 related symptoms have had noticeable reductions in the frequency, intensity, and length of the relapses within the first 6 months of treatment with 4–6 weekly vitamin C IV infusions followed by every

other week IV infusions for 2–4 months. The doses of vitamin C applied intravenously in these cases have been from 5 to 10 g per infusion.

Dengue fever is a relatively common reason of consultation in our area of Colombia, given the all-year-round warm weather (on average 26–33°C) with an altitude of 1000 m above sea level and the closeness to the Pacific shore where it is even hotter (on average 26–37°C), much more humid, and at the sea level. In addition to the occasional Dengue case from time to time as a routine scenario, during 2015 and 2016 in Colombia (as in most parts of the northern area of South America) there were pandemics of Chikungunya and Zika viral infections. Although our institution is not a reference center for the treatment of infectious diseases, some patients with these types of viral infections consulted, searching for additional measures others than the ones established by conventional physicians for symptom management. In Dengue, Chikungunya, or Zika cases (confirmed or clinically suspected) our typical IV vitamin C treatment included 2–5 every other day 15–20 g infusions followed by weekly applications for 4–8 weeks. As in other infections treated with biological medicine, patients referred an optimized and quicker evolution when compared to their same case before receiving the aforementioned scheme, or when compared to relatives, friends, or acquaintances of them who were not treated (for any reason).

At this point we consider of utmost importance to clarify that the practice of biological medicine goes far beyond the use of a single and isolated measure like IV vitamin C or even far beyond orthomolecular supplementation alone. In the biological medicine treatment of any viral infection, the vitamin C infusions are carried out in conjunction with other immune enhancing orthomolecular nutrients (for instance, oral vitamin C and oral/IV N-acetylcysteine, L-glutamine, and L-lysine) and also along with other measures from biological medicine like phytotherapeutics (Arena et al. 2008, Ciuman 2012, Lu et al. 2016), complex homeopathics to enhance Th1 antiviral response (Fimiani et al. 2000, Oberbaum et al. 2005, Enbergs 2006, Roeska and Seilheimer 2010), ozone therapy due to its immunostimulant and germicidal effects (Viebahn–Hänsler 2007), and/or neural therapy with procaine 0.5% both to ease the symptomatic burden and to modulate the inflammatory immune response.

In the story of vitamin C treatment in infectious disease, the episode of its use in the common cold is another one characterized by strong opinion struggles in the medical community. The current evidence regarding this issue points toward some already pretty well-established conclusions, but they are derived mostly from studies with oral vitamin C schemes.

According to the Cochrane review (Hemilä and Chalker 2013) on this issue (last updated by Hemilä and Chalker in 2013), there have been several clinical trials with different dosages of oral vitamin C which haven't been able to demonstrate a preventive/prophylactic effect of this supplement on the common cold. In that context 1 g per day of oral vitamin C was evaluated in several randomized and non-randomized trials, not resulting effective to reduce the incidence of the common cold when taken during the coldest months of winter. Although the general population may not achieve benefit from ingesting 1000 mg of vitamin C daily in terms of the common cold incidence reduction, specific populations subject to significant physical and/or thermal (cold) challenges (marathonists, skiers, and soldiers in six studies) may have an average of a 50% reduction in the incidence of this disease (Douglas and Hemilä 2005, Douglas et al. 2007).

Aside from the data on common cold incidence, a reduction of the intensity of symptoms and length of the infection has been seen consistently among those supplemented with oral vitamin C, both in therapeutic and prevention regimens. As a matter of fact, a 14% reduction in the length of colds was observed in children supplemented with vitamin C with a prophylactic intention, while the reduction in adults reached 8% (42). Larger doses have provided greater symptomatic benefit when compared to lower doses, when vitamin C was taken after the symptoms of the common cold had already started (Chambial et al. 2013, Hemilä and Chalker 2013).

In our clinical experience and taking into account the available information on vitamin C pharmacokinetics (Levine et al. 1996, Benke 1999, Levine et al. 1999, Duconge et al. 2008), small (in orthomolecular terms) but frequent doses of vitamin C have proved to be more useful in the case

of an acute infection. This is important since due to the dynamic flow phenomenon in vitamin C kinetics (Hickey and Roberts 2005, Hickey et al. 2005) this type of dose will produce (for a short period of time) peak blood plasma concentrations well above the ones achieved by a consumption of the RDA for vitamin C. Another factor to observe here is a difference in the turnover of vitamin C in healthy subjects versus patients with acute diseases including infection and myocardial infarction, as evidenced in several leukocyte lines (Hume et al. 1972, Bergsten et al. 1990, Chambial et al. 2013, Ferrón-Celma et al. 2009).

The usual scheme we have employed in our clinical practice is 500 mg of vitamin C taken every half hour for the first 2 hours, followed by every hour doses for the next 4 hours, and then every 2 hours for rest of the day. The patient is emphatically instructed to begin taking vitamin C as soon as the first symptoms of the common cold appear (even the prodromal ones). The following 3–5 days the patient takes an average 4–8 doses of 500 mg vitamin C each day, distributed throughout the day. The number of doses per day depends on the symptomatic evolution of the cold, and it is adjusted over time, according to close medical supervision. In patients whose respiratory disease seems to progress despite the described scheme or in those at higher risk (elderly, immunocompromised, or those with chronic respiratory diseases), we have applied a series of 1–3 IV vitamin C infusions from 5 to 25 g (separated by 2–3 days between them). The IV route can also be implemented from the beginning of the disease (usually along with the oral scheme) at the discretion of the attending physician.

Our regimen has been useful to diminish considerably the symptoms of the common cold as referred by the patients, and in some cases the cold has been aborted after the first day or two days of the regimen. Although the described method is not the exactly the same as the one reported by Anderson et al. in an old but well-designed randomized controlled trial (Anderson et al. 1974), it also supports the notion that larger doses are more effective in terms of symptom reduction during the common cold when the disease has already started.

Modern societies have been struggling with vascular disease (both cardiovascular and cerebrovascular) for many decades. Since cholesterol levels and metabolic syndrome were declared as risk factors for the development of atherosclerosis, most of the attention was strongly diverted to pharmacological measures to diminish blood lipids. As shown by Thomas Levy in his controversial but thoroughly researched work (Levy 2006), lipids are an undeniable actor in the movie of cardiovascular disease (CVD) and atherosclerosis, but it is also true that long standing vitamin C deficiency also plays a key role in the process. Structural and functional consequences of chronic low levels of vitamin C influence the quality of connective tissue and thus prepare an ideal terrain for the atheromatous plaque to develop (Levy 2006). Today, the concept of a relationship between this particular nutritional deficiency and CVD has been gaining terrain into the predominant paradigm of lipid as exclusive culprit factor in CVD (Moser and Chun 2016).

On the other hand, taking these concepts from the bench to bedside has not been easy task. Conflicting results from different intervention trials with vitamin C supplements (most of them through the oral route) are without a doubt a considerable obstacle, precluding a universal therapeutic recommendation for the use of vitamin C in primary or secondary prevention in CVD (at least with the currently available data) (Cook et al. 2007, Sesso et al. 2008, Myung et al. 2013).

Anyhow, as pointed out by Tveden-Nyborg and Lykkesfeldt in their interesting review with a section devoted to this issue (Tveden-Nyborg and Lykkesfeldt 2013), the negative results in these clinical trials evaluating vitamin C in CVD could be related to a variety of factors. The factors range from the design of the study (e.g., biased population selection when not using poor vitamin C status as an inclusion criterion), to the potential authors' unawareness of vitamin C nonlinear kinetics (different in many ways to the usual kinetics of medications subject of evaluation in clinical trials), to the concurrent use of several supplements in the population evaluated (prior or during the study itself, resulting in a confounding factor), among others. We share the opinion that this plethora of failed characteristics should be considered before drawing a definite conclusion on this matter, and paraphrasing these Danish authors, "there is a critical need for well-designed large RCTs that

select or offer the possibility to control for entry-level vitC status and also for the many potential co-deficiencies which may interfere with the interpretation of the results." The chapter of vitamin C in vascular disease is far from being closed.

In terms of mechanisms of action in vascular disease, it has long been recognized that due to the preponderant role of oxidative stress in endothelial dysfunction, the uptake of ascorbate and dehydroascorbate, so as the reduction of dehydroascorbate, and the release of ascorbate, may be of great importance in the regulation of local antioxidant capacity of the vascular bed, to preserve nitric oxide (NO) at physiological levels (Mendiratas et al. 1998). Vitamin C influences both on the NO synthase (eNOS) and on the cofactor tetrahydrobiopterin (BH4) are also significant in the NO activity and its potential impact on CVD and hypertension (61). Profound disturbances in NO bioavailability are a common feature observed in various cardiovascular pathologies including ischemic heart disease and hyperlipidemia (Mendiratas et al. 1998, Moser and Chun 2016).

Many other potential mechanisms of action have been put forward in the case of vitamin C in vascular disease according to results in experimental (animal and human) studies (Levy 2006, Tveden-Nyborg and Lykkesfeldt 2013, Moser and Chun 2016):

- Reduction in the monocyte adhesion to the endothelium;
- Limitation of the inflammation process, even at the intracellular signaling level due to reduction in the TNF-α-mediated NF-$\kappa\beta$ activation;
- Prevention of LDL oxidation; enhancement of the activity of lipoprotein lipase (LPL) as a clearing factor for oxidized lipids in the bloodstream;
- Enhancement of vascular smooth muscle cells conditions, resulting in a delayed rate of apoptosis and a controlled rate of proliferation (both important when atherosclerosis has already developed);
- Decrease in blood pressure values.

L-Glutathione (GSH)

Glutathione is probably the most important antioxidant at the cellular level and has a direct participation in multiple specific detoxification pathways, which are essential to protect our cells and tissues against potential damages inflicted by an enormous variety of harmful substances. This antioxidant is ubiquitous, being present to variable extent in all the cells and organs of the human body. Glutathione has a high capacity as an electron donor and a high negative redox potential. These factors, combined with intracellular concentration at the millimolar levels (from 0.1 to 10 mM (Bremer et al. 1981)), give GSH a very efficient antioxidant profile. The usual plasma concentrations, on the other hand, are on the micromolar level.

From the chemical point of view, Glutathione is a linear tripeptide formed in our cells by the amino acids L-cysteine, L-glutamic, and Glycine (denominated technically γ-L-Glutamyl-L-cysteinylglycine). The result is a water-soluble compound with antioxidant properties (Murray 1996). After Glutathione has yielded the electron of the cysteinil portion of the sulfhydryl group, reduced Glutathione (GSH) turns into oxidized Glutathione (GSSG) through its disulfide bridges. This is a reversible and dynamic process. As long as the rereduction of GSSG takes place, a dynamic balance can be established between the synthesis of GSH, its utilization as an antioxidant and/or detoxifying agent, and its recycling from GSSG (Lomaestro and Malone 1995). A tight homeodynamic control of the GSH availability is established both in the intracellular and extracellular compartments (Kidd 1997). In physiological but also in pathological conditions, GSH:GSSG ratio has been considered a major determinant of the global oxidative stress load (Birben et al. 2012). Most of the intracellular Glutathione (>98%) exists in the thiol-reduced form (GSH), the rest being comprised by the oxidized form glutathione disulfide (GSSG), and other several minoritarian glutathione S-conjugates like thioether, mercaptide, or other thioester forms (Ballatori et al. 2009).

Glutathione results particularly important in the liver, where it is highly concentrated in the hepatocytes (up to 10 mM). Other tissues with high concentrations of Glutathione are the spleen, the

kidneys, the crystalline, and blood cells like the erythrocytes and the leukocytes. Its conjugation is the primary mechanism to remove xenobiotics from the reactive oxygen species (ROS) type, some of which are carcinogens. Conjugation and reduction reactions require Glutathione as part of the process. The Glutathione S-transferase enzymes catalyze the metabolic pathways of Glutathione in the cytosol, microsomes, and mitochondria (Raza 2011). The family of glutathione S–transferase enzymes are responsible for quenching and detoxifying many environmental substances, including free radicals, peroxidized lipids, and xenobiotics (a wide variety of environmental toxins, but also medications like antibiotics, among others). The antioxidant responsive element (ARE) mediates the activation of many genes influenced by oxidative and chemical stress, whose promoter includes this particular element (Hayes and McLellan 1999).

GSH has also a role as "secondary antioxidant," given that it also interacts actively in the reduction of most antioxidants. GSH can turn these other antioxidants useful again after they had been oxidized, thus acting as a regeneration factor. Glutathione aids in the recycling of other antioxidants like ALA (Bast and Haenen 1988), and vitamins like ascorbic acid and alpha tocopherol (Birben et al. 2012). These antioxidants in turn help neutralize the free radical damage potentially inflicted to both cell organelles and also DNA.

Many chronic diseases have been linked to an augmented oxidative stress burden and to low glutathione levels (Ballatori et al. 2009). This includes neurodegenerative diseases (like, for instance, Amyotrophic Lateral Sclerosis, Parkinson's disease, Alzheimer's disease, Huntington's disease, and schizophrenia), also characterized by an affected GSH metabolism in the nervous system (Bains and Shaw 1997). Nonetheless, the ubiquity and pleiotropy of this tripeptide have made it difficult to establish strong links between its supplementation, a therapeutic potential, and specific diseases. From a theoretical perspective, neurodegenerative disease is one of the most prominent fields for GSH therapy (Bains and Shaw 1997, Zeevalk et al. 2008). A common feature in many of these ailments, including Alzheimer's disease and Parkinson's disease, is GSH deficiency at the neuronal and glial level. Neuronal survival depends on many factors, and GSH brain levels play a crucial role in the nervous system antioxidant defense. This has been postulated as the rationale for the development of therapeutic approaches using GSH replenishment in neurodegenerative diseases (Zeevalk et al. 2008).

The clinical studies about the efficacy of short experimental GSH IV supplementation schemes in Parkinson's disease patients have had mixed results. In 1996 Sechi et al. (1996) reported a 42% reduction in disability according to the modified Columbia University Rating Scale in their observational open-label study. The benefit lasted for 2–4 months, for the small sample ($n = 9$) of early stage, previously untreated Parkinson's disease patients, who received 600 mg of IV Glutathione twice daily for one month. Much closer to our days, a randomized placebo controlled trial was carried out in 2009 by Hauser and colleagues (Hauser et al. 2009) with 21 Parkinson's disease patients who were already in treatment. In this study, the treatment was well tolerated and consisted of 1400 mg IV Glutathion infusions, three times a week for a month. Also, there wasn't any difference in the unified Parkinson's disease rating scale (UPDRS) found between groups, but the authors make it clear that their main objective was not to assess the efficacy of the treatment but its tolerability and potential adverse effects.

As many other unconventional medical practices, IV Glutathione has also received strong criticism from the orthodox medical establishment. This was the type of reaction (Okun et al. 2010) after the publication of the trial from Hauser et al., with reasonable arguments dealing with discrepancies about the research methodology and the interpretation of the results. On the other hand, there were also very subjective arguments like considering the placement of an IV line as some kind of major challenge. It must be noted that thousands of IV lines are placed around the world every day to infuse all types of medications without any major complication. Even many complex conventional drugs can fill that category of "safe IV infusions" in the short term, regardless of their sometimes-disputable clinical effectiveness in the long term (Morgan et al. 2004). In fact, controversial facts and figures for effectiveness are far from being an unusual phenomenon, even for many of the most commonly used and prescribed medications (Leucht et al. 2015).

Also in this discussion (Okun et al. 2010), we consider some other arguments to be very debatable, like demonizing the fact of charging patients out of their own pocket for a medical practice (which in any case it was provided). This is an issue that usually will receive a more bitter criticism if the professional practices any form of unconventional medicine. On the other hand, regular critics of complementary medicine tend to ignore or understate the variety of scientific and medical behavior artifacts known for a long time in academic medicine. Prominent examples are: the influence of the pharmaceutical industry in the way research material is published as scientific articles in journals (Blumenthal et al. 1997, Bekelman et al. 2003, Landefeld and Steinman 2009, *PLoS Medicine* Editors 2009, Doshi et al. 2012); the ever-growing role of contract research organizations (CROs) and corporate sponsorship in clinical investigation (Davidoff et al. 2001, Smith 2005); the payments and fees made to doctors by the same pharmaceutical companies which economically support their research (McCarthy 2014); the overt or surreptitious commercial and economic ties established around the prescription of many conventional medications (Ornstein et al. 2017), a phenomenon not limited to high-cost drugs like biologics and oncologics, but it also includes many newly branded drugs in order to compete in crowded markets (Brodwin 2015).

It is true that most conventional colleagues will use a different mindset to judge the results from a clinical trial of any given medication, depending on the orientation it has (whether it comes from orthodox medicine or from complementary medicine). And so, the other reaction to Hauser and colleagues' study (Hauser et al. 2009) is a case report (Naito et al. 2010) of drug-induced hepatitis in a patient in Japan who received 1200 mg of IV Glutathione daily for 5 months. The alterations in transaminases remitted after 2 months of the suspension of IV Glutathione. Although it is very clear that this type of report is indeed important to construct a more complete safety profile of any medication, it must also be stressed that in our opinion, such an intensive scheme of IV Glutathione does not reflect the usual orthomolecular practice for this measure. The authors suggest that the doses of Hauser et al. study and the ones from their case report (16,800 mg vs. 24,000 mg IV Glutathione/month) are comparable. Not only do we not consider a 42% higher dose to be comparable, but we also emphasize that the length of the treatment in both scenarios is strikingly different: one month in the clinical trial versus 5 months in the case report. In any case, it turns very relevant to take additional control measures and foresights in any treatment scheme that could be considered experimental. If a patient would receive IV Glutathione for such a long period of time, it is strongly recommended to have a complete laboratory check up every month and any other evaluation pertinent to the liver function.

The arrival of a much clearer picture for the role of Glutathione in Parkinson's disease was only possible until recently, after new research was performed on this issue. The judicious work by Mischley and colleagues is proof that the constancy added to the proper conceptualization of a scientific investigation was able to yield interesting results in this matter (Mischley 2011, 31). The low molecular weight of Glutathione (around 307 Da) make this antioxidant an excellent candidate for the intranasal administration with therapeutic purposes (Mischley 2011).

Their first step was to investigate about any potential safety issues for the use of Glutathione in the intranasal presentation (Mischley et al. 2013). Among the thousands of registers in the database of the compound pharmacy which dispensed the intranasal Glutathione, 300 patients were randomly selected and the questionnaire was mailed to them. There were 70 respondents, whose majority had been prescribed intranasal Glutathione to treat three conditions: Multiple chemical sensitivity (MCS) ($n = 22$), chronic sinusitis/allergies ($n = 21$), or Parkinson's disease ($n = 7$). Adverse effects were common (with a lot of heterogeneity among groups), but all of them mild and mostly related to the route of administration of Glutathione (e.g., irritation of the nasal pathways, etc.). The authors highlight that most of the surveyed patients (78%) reported the overall experience with intranasal Glutathione as positive.

After this preliminary questionnaire-based evaluation of the safety of intranasal Glutathione, the next step by the group led by Mischley was to set up a double-blind, placebo controlled trial (Mischley et al. 2015) to gain further insight about the safety and tolerability of this measure in Parkinson's disease patients.

Thirty patients were unevenly allocated in 4 groups: two treatment groups with different intranasal Glutathione doses (300 and 600 mg/day) of 10 patients each, one placebo group (sterile saline was used) of 10 patients, and one watchful waiting group of 4 patients. The highest Glutathione dose of 4200 mg/week matched the one used in the study by Hauser et al. from 2009 (Hauser et al. 2009). During the 3 months of the intervention period, the patients were instructed to use the nasal spray with either Glutathione or placebo 3 times daily, and they should also keep a daily log of events in which they recorded a report on medication use and changes in symptoms (systemic and local) and general well-being according to validated scales (Monitoring of Side Effects Scale, MOSES and the SinoNasal Outcomes Test, SNOT-20). Laboratory evaluations including blood chemistry, complete blood count, and urianalysis were obtained at several points during and after the intervention (weeks 2, 4, 8, 12, 16). Besides the evaluation of the side effects (both positive and negative), the authors decided to include an assessment of the Parkinson's disease evolution during the study as well. For this purpose, UPDRS scores were used (also considered as a safety measure).

The treatment was well tolerated in both doses, without any statistically significant difference in comparison to the placebo group, both in the clinical and laboratory evaluations. This reflected the findings from previous studies (Hauser et al. 2009, Mischley et al. 2013) regarding the excellent profile of tolerability of Glutathione in Parkinson's disease patients. Aside from that, the authors report a slight clinical improvement according to the UPDRS symptoms scores in the two treatment groups over the placebo group. This trend persisted in the post hoc analysis of the results after the exclusion of the patients who changed medications throughout the study. According to their findings, which included a clinical response superior to placebo, without ignoring the fact of power limitations of this experimental design, Mischley et al. suggest the use of a delayed-start trial (or a similar) design in future investigations to determine a potential neuroprotective effect of intranasal Glutathione in Parkinson's disease. A compilation of the interesting works of Dr. Mischley can be found for further reading in her PhD thesis (Mischley et al. 2016).

Reproaches to the therapeutic use of Glutathione in the context of neurodegenerative diseases have been somehow repetitive (Schulz et al. 2000, Zeevalk et al. 2008, Okun et al. 2010). The controversy has revolved around the uncertainty about if the drug actually crosses the blood–brain barrier and if it does reach the central nervous system (CNS) in levels significant enough to generate any plausible biological or therapeutic activity. To address this problem, Mischley and colleagues carried out a proof-of-concept study using proton magnetic resonance spectroscopy (^{1}H-MRS) to measure the CNS uptake of Glutathione after intranasal delivery in a group of 15 mid-stage Parkinson's disease patients (Mischley et al. 2016). The results of this small pilot study consistently showed an augmentation of the GSH signal in ^{1}H-MRS brain after one single 200 mg intranasal dose. According to the authors, these preliminary findings warrant a more robust trial to evaluate the pharmacokinetic profile of intranasal Glutathione in a larger sample of patients with neurodegenerative diseases. Such a trial could provide information about the magnitude and duration of the increase of Glutathione in the CNS, and about the eventual repercussion of these variables in the efficacy of its use in Parkinson's disease. It could also allow optimizing Glutathione delivery techniques, dosing schedules, product stability, and intranasal formulations.

Glutathione supplementation has also been the subject of evaluation in other conditions outside the spectrum of the neurodegenerative diseases worsening with aging. In some clinical trials evaluating this antioxidant in chronic conditions characterized by a high load of oxidative stress (like cystic fibrosis, e.g. (Visca et al. 2015) or autism (Kern et al. 2011)), the use of oral Glutathione was able to induce changes in systemic oxidative stress biomarkers. It also showed benefits in particular aspects affected by the respective disease. Bear in mind that patients in these studies received Glutathione in oral high doses along with other routes of administration (e.g., intranasal or intradermal). Since there was a combined route of administration, the benefits observed cannot be attributed solely to oral Glutathione. In fact, given that the availability of GSH after the oral ingestion has produced conflicting results, and according to the aforementioned findings by Mischley and colleagues

(Mischley 2011, 2016, Mischley et al. 2013, 2015) about intranasal GSH, it is much more likely that the therapeutic action can be attributed to this way of administration.

Some important considerations must be noticed when supplementing Glutathione with a therapeutic perspective. First, many studies point out to the fact that achieving satisfactory blood levels after the ingestion of Glutathione is not reliable in the clinical practice (Witschi et al. 1992). Basic studies carried out in rodents in the early 1990s showed an increase in the concentrations of Glutathione after an oral load of the antioxidant, both in plasma (circulating free and protein-bound Glutathione) (Hagen et al. 1990) and in tissues (kidney, liver, brain, heart) (Aw et al. 1991).

In spite of these data, this situation does not seem to be replicable in humans and so it has long been known that Glutathione has a poor bioavailability after the oral supplementation (Hagen et al. 1990, Witschi et al. 1992), limiting its use as an oral therapeutic agent. The proteases in the small intestine carry out the protein digestion process, breaking down the Glutathione tripeptide into its basic constituents (just in the exact way it happens with all other peptide/protein chains). It has already been postulated that a possible explanation for the conflicting results about the eventual lack of effectiveness of GSH supplementation in clinical trials could rely on the lack of discrimination of individuals with high/poor antioxidant reserve among the sample of patients included in intervention studies to evaluate this measure.

In this regard, the limitation of an effective oral supplementation of GSH seems to be especially true for healthy adults. In this group, the alleged oxidative stress should not be high, at least from a theoretical point of view. For example, a 4-week protocol consisting of 500 mg of oral Glutathione taken twice a day, failed to induce any significant change in oxidative stress biomarkers in a randomized controlled trial including 40 healthy volunteers (Allen and Bradley 2011). In this study, the blood levels of GSH, GSSG, and the ratio of GSH to GSSG (as an indicator of oxidative stress) remained unchanged both in placebo of oral GSH group. In this same direction, Witschi and colleagues reported that during a 4.5-hour measurement period after the ingestion of a single high dose of Glutathione (3000 mg), it wasn't either capable of increasing blood concentration of glutathione, nor the one cysteine and glutamate as its primary constituents (Witschi et al. 1992).

The results of both these trials, however, have been found debatable by Richie Jr. and colleagues (Richie et al. 2013, 2015). Regarding Allen and Bradley clinical trial (Allen and Bradley 2011), they call the attention on how potential variations in red blood cells' volume and number can impact GSH levels. Furthermore, there is a disagreement in methodological aspects related to the moment of acidification of erythrocytes, which would eventually compromise the stability of both GSH and GSSG and thus could lead to erroneous measurements (Mills et al. 1994). Regarding Witschi and colleagues' publication (Witschi et al. 1992), they call on the attention about the short half-life of Glutathione (only 1–2 minutes), which makes it practically impossible to find an increase in its blood levels after a single oral dose (Kleinman and Richie 2000). Studying the pharmacokinetics of GSH (Aebi et al. 1991), other authors found a longer half-life for its high-dose IV infusion in healthy volunteers. Despite not having the enteric absorption as hindrance, and thus going directly through the blood stream and from there to the cells, IV high-dose Glutathione half-life remains always within the minutes' range (14.1 ± 9.2 min).

In contrast to these results there have been indeed some studies demonstrating an elevation of GSH levels after its oral supplementation. One example is the recent publication by the group of Richie Jr and colleagues (Richie et al. 2015) in which a much longer period of oral Glutathione supplementation (6 months) was able to demonstrate a significant rise in its plasmatic levels compared to placebo. In this clinical trial, 54 healthy adults were randomly divided into three groups: two treatment arms with differential doses of 250 mg/day and 1000 mg/day of Glutathione, and a placebo group. GSH was measured in several compartments and cell types at baseline and at 1, 3, 6, and 7 months (after 1 month of washout). Measurements included GSH in plasma and whole blood, lymphocytes, erythrocytes, and exfoliated buccal mucosal cells. Also, different immune response tests were performed. Phagocytosis and respiratory burst were assessed in neutrophils at baseline and at 3 and 6 months; NK cell cytotoxicity and lymphocyte proliferation was evaluated at baseline and at 3 months.

Both GSH doses produced changes in some of the parameters tested. For instance, regarding GSH levels in whole blood, low-dose and high-dose participants exhibited an increase at 1, 3, and 6 months of GSH supplementation. In other compartments (erythrocytes, plasma, and lymphocytes) mean GSH levels significantly augmented 30%–35% after 6 months of 1000 mg/day GSH. In exfoliated buccal mucosal cells obtained after a mouth rinse with distilled water and brushing of the cheeks and gums with a soft tooth brush, a significant 260% increase was present in the high-dose group. For the low-dose group (250 mg/day of oral GSH), whole blood GSH levels increased significantly (17%), a situation that was also evident in erythrocytes (29%). The authors also report a decrease in the oxidative stress of the supplemented participants, due to the significant reduction in the GSSG/GSH ratio induced in both low- and high-dose GSH dose groups. Moreover, after 3 months of oral GSH supplementation NK cell cytotoxicity increased in both dose groups, but only the high-dose GSH group reached a significant level of increase. In this immune parameter, the authors declare that larger sample sizes and longer evaluation times are necessary to generalize these findings. Except for the patients in the high-dose group, whose GSH levels remained significantly greater than baseline after the washout period, most of the evaluated parameters after GSH oral ingestion returned back toward baseline levels at the 7th month measurements. This would suggest the need for a permanent GSH supplementation if therapeutic/antioxidative action is desired.

In our experience, the use of IV Glutathione in the context of diseases characterized by an elevated oxidative stress burden has provided an interesting tool to enhance the potential antioxidant effects of IV infusions. This concept is applicable (at least from a theoretical perspective) when GSH is injected along with other orthomolecular medications sharing this profile, like vitamin C, ALA or Coenzyme Q10. In our patients, the doses have ranged from 200 mg to 1 g of IV Glutathione, 600 mg being the most common one. GSH is infused through a peripheral vein, diluted in saline solution (volumes of 200–400 mL), using a slow to moderate drip (40–60 drops per minute), and according to the individual tolerance (more on that below). Such antioxidant IV drips have resulted in faster recoveries from day to day infections. In other clinical situations, like chronic diseases, after the regular antioxidant drips including GSH some patients have referred a transient subjective sensation of better overall performance for their daily activities. This energy boost was felt both in the mental and the physical domains and lasts 2–5 days on average.

Although the concomitant use of vitamin C with GSH can be recommended in many pathological states, it has been discussed if this notion can be considered universal. Oncologic disease is one of the areas where this postulate has been put to debate. The Glutathione paradox in cancer has been exemplary described by Traverso and colleagues in their 2013 paper: "While GSH deficiency, or a decrease in the GSH/glutathione disulphide (GSSG) ratio, leads to an increased susceptibility to oxidative stress implicated in the progression of cancer, elevated GSH levels increase the antioxidant capacity and the resistance to oxidative stress as observed in many cancer cells" (Traverso et al. 2013). This poses interesting questionings about the role of GSH either as a potential treatment against cancer or as a cancer cell protector.

Based on years of clinical practice Dr. Harald Krebs, an experienced author from the field of complementary medicine, published protocols (Krebs 2010) using high-dose IV vitamin C (intended as a pro-oxidant) along with IV Glutathione, doses ranging from 1200 to 2400 mg (intended as an anti-oxidant). Even coming from the conventional medicine, there are several reports about the use of IV GSH for the enhancement of chemotherapy tolerability (Smyth et al. 1997). The concept of GSH as a protective agent against chemotherapy adverse effects in ovarian cancer patients treated with Cisplatin had already been propounded more than a decade before (Zunino et al. 1983, 1989, Oriana et al. 1987, Aebi et al. 1991). Initially GSH was conceptualized as a renal protective measure in tumoral rodent models (Zunino et al. 1983, Tedeschi et al. 1990), but the protection it provides against chemotherapy related neurotoxicity and ototoxicity was found out and investigated in the years afterward (Cascinu et al. 1995).

Intravenous GSH can also provide protection against damage inflicted by therapeutic radiation. This was assessed in a randomized pilot trial of patients who had been operated of endometrial