The Disease Delusion

CONQUERING THE CAUSES OF CHRONIC ILLNESS FOR A HEALTHIER, LONGER, AND HAPPIER LIFE

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To Susan Bland, who has lovingly held
me to the highest standards of dedication to
excellence, and to my family, which has supported
me in what it takes to make this happen

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FOREWORD

Imagine a time when people died or suffered from incurable acute infections. Imagine a time before antibiotics when women died of simple childbirth fever, when a bad chest infection could lead to death, when a strep throat caused heart failure, when limbs were amputated because of an infected wound. Those commonplace occurrences seem unimaginable now.

Yet that is the exactly the state of medicine today as we face the tsunami of chronic diseases that will cost our global economy $47 trillion over the next twenty years and kill twice as many people around the world as infectious disease.

As we spend more and more for health care, we get less and less. The United States has worse health-care outcomes and lower life expectancy than almost every other developed nation. Heart disease, diabetes, cancer, autoimmune diseases, digestive disorders, dementia, allergies, asthma, arthritis, depression, attention deficit disorder, autism, Parkinson's disease, hormonal problems like early puberty and infertility—these and more cause endless suffering and drain our financial resources. Chronic diseases now affect one in two Americans and account for 80 percent of our health-care costs. Yet despite a host of new drugs and procedures, the incidence of chronic disease continues to rise, not only in the United States but around the globe as developing countries adopt the worst of our food and culture.

The answer to this paradox should be obvious to all of us: what we are doing is not working. Our current medical model was constructed

to treat acute disease, which we have mostly vanquished. We identified a single agent for illness—a microbe—and a single agent to treat it: antibiotics. Since then, medicine has pursued a quest: to find a pill for every ill. This quest has failed. We need a different paradigm, a different model for diagnosing and treating this new epidemic of chronic disease.

The Disease Delusion dissects the failure of medicine to solve our health crisis and lays out a new map for understanding and treating illness based on functional medicine, a fundamental paradigm shift from medicine by symptom to medicine by cause, from medicine by disease to medicine by system, from medicine by organ to medicine by organism. It is an ecological view of the body where all the networks of our biology intersect and interact in a dynamic process that creates disease when out of balance and creates health when in balance. It takes all the component parts of science, all the puzzle pieces, all the data about how we get sick and what makes us well, and reorganizes them into a narrative that makes sense, one that has the capacity to fix our health-care crisis nearly overnight if it was applied widely.

Medicine is the youngest science. There is no theory of medicine. There are no organizing principles that help us navigate the territory of chronic disease. Functional medicine is that breakthrough theory, the biggest breakthrough idea in medicine since the discovery of the microbe and antibiotics.

It is a cataclysmic shift in our view of biology. There are moments of awakening in science that are not incremental but transformational—Columbus proving the earth was round, not flat, Galileo showing us the earth was not the center of the universe, Darwin explaining that species evolved and didn't arise fixed in their current form, and Einstein shattering our notions of time and space. Functional medicine is a paradigm shift of equal magnitude and significance.

Disease appears real and fixed, just as the earth seems flat and time and space seem linear and solid. In *The Disease Delusion*, the father of functional medicine, Dr. Jeffrey Bland, the man who has synthesized more medical science from more fields of study than any other

human in the past thirty years, shatters our notion of disease. Disease as we think about it is a false idol. It does not exist in the way we think about it. The names we give diseases are useful for finding the right medication but not for truly getting to the cause or creating a healing response.

When we tell a patient who has symptoms of sadness and hopelessness, who can't sleep, who lacks interest in daily activities, food, or sex that he has depression, this is not helpful. Depression is not the *cause* of his misery; it is merely the name we give to this constellation of symptoms. We then treat these symptoms with an antidepressant, which works only a little better than chance.

The actual cause of the depression may vary greatly from patient to patient. It may be a leaky gut caused by gluten that activates the immune system to produce antibodies against the thyroid, leading to low thyroid function and depression. It may be a vitamin B12 deficiency resulting from long-term use of an acid-blocking drug for reflux, or a folate deficiency caused by a gene called MTFHR, or a vitamin D deficiency resulting from inadequate sunlight. It may be a mercury toxicity from a diet too high in tuna, or an omega-3 deficiency from a diet too low in fatty fish, or prediabetes brought on by a diet high in sugar. The symptoms may arise from changes in brain chemistry brought on by life trauma or stress, or even by alterations in the gut flora resulting from antibiotic use. Each of these factors—dietary, environmental, lifestyle—creates a different imbalance, yet all cause depression. Knowing the name of a disease tells us nothing about its true cause; nor does it lead us to the right treatment. This is the disease delusion.

As a student of functional medicine for twenty years, and as a practitioner who daily faces the failures of our current medical model and witnesses the miracles of treating illness using this new medical paradigm, I feel strongly that we are on the verge of a true transformation in medicine.

Functional medicine is not simply about improving diet or getting more exercise or managing stress or reducing exposure to environmental toxins, all of which are critical foundations for creating

a healthy human. Above all, functional medicine is the science of creating health. Disease goes away as a side effect.

Functional medicine is a personalized method for getting to the root of symptoms and restoring balance. It is the story of a little girl, Elise, who had suffered from intractable psoriasis, with red, weeping, raw skin from head to toe, since she was six months old. Her parents had taken her to the top medical schools, and she had been given the most advanced drugs, including powerful immune suppressants and chemotherapy to shut off inflammation. When I first saw Elise she was four years old. She had just emerged from a month in the intensive care unit after fighting a life-threatening staphylococcus infection triggered by her medication, Enbrel, which suppressed her immune system. Rather than inquiring about the root cause of her inflamed skin, doctors used medication to suppress symptoms. Still she was no better. No one asked about her diet or thought about how her history of antibiotics as a baby affected her delicate gut flora, thus setting up the conditions for inflammation.

Functional medicine led me to a different set of questions. Rather than asking what drug I should use to treat the symptoms, I asked what caused the inflammation in the first place—a simple idea that is foreign to our medical training. The causes of inflammation are few—microbes, allergens, toxins, poor diet, stress. And I asked what her immune system needed to regain balance. Then I applied these principles to her by removing a common cause of inflammation in our diet—gluten, known to be linked to psoriasis—and cleared out bad microbes (yeast) in her gut that resulted from years of antibiotics and steroids. I also added a few ingredients needed to support proper immune function—omega-3 fats, zinc, vitamin D, and probiotics to help balance her gut flora.

Within two weeks her skin, red and raw for over three years, was clear. Not a miracle, but a repeatable result that is a natural outcome of breaking our disease delusion and employing a new framework for solving our chronic disease epidemic.

Paradigm shifts are hard, detractors abound, yet the evidence is in and the failure of our current approach is evident to any student

of health care. The time is ripe for a radical transformation in health care with the power to end needless suffering for millions of people. *The Disease Delusion* is the manifesto for the new medicine. Every medical student, every stakeholder in health care, and every government leader involved in health policy should read it. For the rest of us, it is our road map to true health and healing.

Mark Hyman, MD
Chairman, Institute for Functional Medicine
November 19, 2013
West Stockbridge, Massachusetts

CHAPTER 9

Energy

1. Do you routinely feel a fatigue you can't explain or justify?
2. Are eight hours of sleep not enough for you?
3. Do you get muscle pain after even moderate exercise or activity?
4. Ever feel brain fog? Feel it often?
5. Do you have trouble walking comfortably up a flight of stairs? Are you excessively winded when doing so?
6. Do you lack ambition? Is your energy level low?
7. Ever find that you just can't tolerate disturbances around you that you used to be able to ignore or dismiss or manage?
8. Do you worry about undertaking an activity that incorporates exercise because you know you won't feel good afterward?
9. Are you ever bone-weary? Often?
10. Do you feel you just don't have the energy to cope with the issues of daily living?
11. Do you frequently get headaches for no known reason?
12. Have your senses of smell and taste gotten worse?
13. Are you forgetting things you shouldn't be forgetting?
14. Do you feel older than your age?
15. Does a regular old cold wipe you out for a prolonged period of time?

John just turned sixty. It has brought him up short; he finds himself thinking about his life and his health in ways he never has before.

One reason may have been his birthday celebration. Not the main one—that was at home with his wife, plus the kids and their spouses showing up via Skype with their good wishes. No, the birthday party that really got to him was the morning golf game and lunch at the club with The Guys, the group of eight good friends who have been golfing and lunching together since they were all in their thirties. Back then, the conversation had been about work and sports and politics. Lately, and especially at the birthday celebration, talk focused mostly on how they felt they were "getting on," their aches and pains, the discomforts and growing list of limitations that everyone knows are just part of the aging process.

Not that any of The Guys are sick. All are blessedly free of the serious diseases that many of them watched their parents suffer through, and some of their contemporaries as well—arthritis, heart problems, diabetes, cancer. It's just that most of them feel that they simply don't have the energy they once used to count on. Like John, they're tired but can't seem to get a really good night's sleep. Once, they woke up every morning feeling rested, refreshed, ready to go go go. Not anymore. "It's just part of getting old," said one of them, resigned. The others nodded.

Well, Philip didn't nod, and neither did Larry. But then, those guys always looked and acted younger than the other six—more vital, with much more energy, and with a kind of zest John doesn't think he can manage anymore. His only explanation is that it's the luck of the genetic draw. He said as much to Philip as they were packing up their clubs and heading out—something about how Philip had been "dealt a better hand when they were passing out the energy genes."

Phil chuckled, then slapped John on the back. "Don't you believe it, Birthday Boy. I created this energy. You could even say I work at it. I'm aging, all right. But it's healthy aging."

John thought about that all the way home. Healthy aging sounded a lot better than his own lackluster progression toward more aches and pains, more limitations, and way less energy for life.

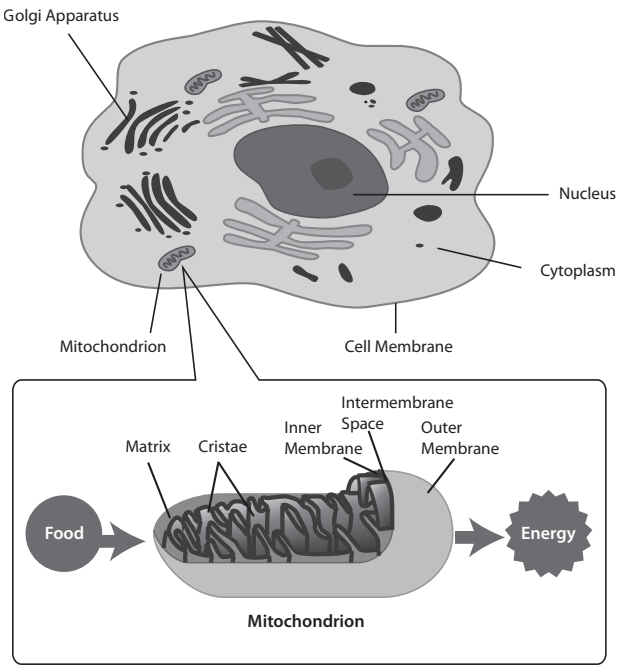
We all know what energy is. It's the strength and vitality that are just there—available to power us through our daily activities of work

and play. It's mental as well as physical, and it's typically something we feel we can recharge with physical rest or through some mental or even emotional agitation.

"Bioenergetics" is the scientific term for the constellation of cellular processes that keeps our physiological energy flowing; it's the way the energy to power a living organism is harnessed, made available, used, transformed to support our physiological processes. It's how our personal energy works.

Energy is produced inside us in the mitochondrion of the cell. Check it out in Figure 6. As we learned in Chapter 2, the mitochondrion is an organelle in the cell; that is, it serves a specific purpose in the cell just as organs serve specific purposes in the body. The mitochondrion's specific purpose is to convert the fat, protein, and carbohydrate from the food we eat into energy. It does this through

FIGURE 6: CELL MITOCHONDRION AND ENERGY PROCESS



the highly sophisticated, highly complicated process known as metabolism. As we age, this mitochondrial bioenergetics—the transformative process that creates energy in the mitochondria—diminishes, which is why six of The Guys, including John, feel they have a lot less energy and grow more tired more quickly than they used to. The question is why our bioenergetics diminishes.

Let's start with how the energy gets produced. Again, that process takes place in the mitochondria and is called metabolism—specifically, aerobic metabolism. Simply put, the food matter you have ingested is burned—that is, combined with oxygen. This particular act of burning isn't like throwing a log on the fire, however. On the contrary. The combustion process in the mitochondria is controlled very carefully so that the energy from the food does not wholly burn away like the heat from a wood fire in your fireplace. Instead, the process of mitochondrial bioenergetics captures the energy liberated during metabolism and stores it in the form of three specific chemical compounds—adenosine triphosphate, or ATP; nicotinamide dinucleotide, NADH; and flavin adenine dinucleotide, or FADH. These storage chemicals then allow the energy to be transferred to other sites within the tissue where the energy powers up the cells to do the work that cells do—contracting muscles, transporting signals, keeping the brain moving, repairing tissue, and everything else that supports the body's core physiological processes. ATP, NADH, and FADH are our cells' energy fuels. In essence, everything we do depends on the production and management of these cellular energy fuels that in turn rely on proper mitochondrial function.

If that's the case, what's the secret to ensuring proper mitochondrial function? Remember back in Chapter 2 when we talked about how some of the genetic information in our mitochondria comes exclusively from our mother—our maternal DNA? That means that our mitochondrial bioenergetics is to some extent inherited, but only just. In reality, mitochondrial function is regulated by thousands of genes, the vast majority of which are influenced in their expression by our lifestyle, environment, and diet. That also means that most of our energy as we age is controlled by the interaction of our genes with environmental

and lifestyle factors. Our surroundings, what we eat, how and how much we exercise: all these factors influence our energy level because all send messages to the genes that regulate our mitochondrial function. So the secret to ensuring mitochondrial function is, once again, what happens at that intersection between environment and our genes.

Yes, the core physiological process of mitochondrial bioenergetics diminishes as we grow older, but by adjusting our environment, lifestyle behaviors, and diet, we clearly have a shot at making our bioenergetics more efficient, thereby retarding that diminution or keeping it at bay a lot longer. What should we know, therefore, especially as we age, about the particular factors that can influence the genetic expression regulating our mitochondrial function? That's what this chapter is all about.

MITOCHONDRIA AND BIOLOGICAL AGING

Our physiological ability to metabolize food with oxygen in the mitochondria gives us an energy advantage over organisms that do not use oxygen for their energy production. Organisms that can't use oxygen can't really squeeze all the energy out of the food as we can, breaking it down completely into carbon dioxide and water, urea, and inorganic salts. In a competition for energy in the world, those that use oxygen more efficiently win.

The problem is that the use of oxygen is a double-edged sword. One edge gives us the energy advantage; the other edge is corrosive. Just as oxygen can rust iron, so too can it "rust," or oxidize, cells. The resulting damage accelerates biological aging and therefore advances the progression of many chronic illnesses—heart disease, diabetes, kidney disease, arthritis, dementia and such other degenerative neurological diseases as Parkinson's disease, and loss of muscle.

In the 1950s, a medical scientist at the University of Nebraska College of Medicine, Denham Harman, proposed an interesting and at the time controversial theory on aging. He likened the corrosive effects of oxygen in the mitochondria to a kind of chemical reaction called free radical chemistry. Free radicals are highly

reactive—indeed, explosive; in fact, the phrase originally was coined for fireworks. Harman called oxygen's damaging effect on mitochondria "free radical pathology," characterizing it as an explosive increase in corrosive activity over time.

The analogy is what happens if you leave a stick of butter out on the kitchen counter. For the first few days, the butter looks and smells like butter. Then all of a sudden it has turned into a glob of goo that smells and tastes rancid. Rancidity is the result of free radical chemistry; once all the antioxidants in the butter have been used up defusing harmful oxygen, the next corrosive reactions meet no defensive action; the butter just goes off and becomes rank. Dr. Harman suggested that aging and the diseases of age were to some degree a form of biological rancidity related to free radical pathology.

I remember sharing the lecture stage with Denham Harman at a medical conference in Germany in 1983, when we both wondered how long it might take the scientific establishment to recognize his hypothesis as an important contribution to the science of disease. Now we know: After more than fifty years of research by thousands of investigators, the first decade of the twenty-first century finally saw the medical community accept the theory, while the pharmaceutical industry has embraced it, developing several successful drugs that treat diseases associated with free radical pathology.

Not that the mitochondria don't have their own protections against the corrosive effects of oxygen. Over tens of millions of years of evolution, the mitochondria have developed numerous protections so they can keep on converting food to energy—even if they must constantly defend themselves against the damaging effects of oxygen as they do so.

Some of these antioxidants, as the protections are called, are vitamins—vitamins C and E, for example. Others are enzymes produced within the mitochondrial cell specifically to defuse damaging forms of oxygen before they can cause injury; among these are superoxide dismutase (SOD), catalase, and glutathione peroxidase.

Glutathione is the most important of these protectors. You may remember that in Chapter 5, it played a key role as a conjugase in

the detoxification process against toxins. Here in Chapter 9, it also provides protection against mitochondrial injury from oxygen. To carry out these important and varied roles, glutathione is made up of three amino acids: glutamic acid, cysteine, and glycine. Cysteine is a sulfur-containing amino acid, and we need a sufficient supply of it to produce glutathione. We get our cysteine supply from high-quality protein. So an individual on a low-protein diet or consuming protein that does not contain enough sulfur-containing amino acids is probably compromising his or her ability to produce enough glutathione to meet the body's needs. Poor-quality diet in general, as well as heavy alcohol use and exposure to chemicals, can overload the glutathione protection system and render the mitochondria susceptible to damage from oxidation.

But glutathione is not the only defense against mitochondrial injury. An entire antioxidant team works cooperatively to defuse corrosive forms of oxygen. We've already noted vitamins C and E—the latter best consumed in its natural form containing not just the collection of tocopherols that typically constitute this vitamin, but also super antioxidants called tocotrienols. (The best sources of both are brown rice, whole grains, and soy.) Also on the antioxidant team are such members of the B-complex vitamin family as thiamine (vitamin B1), riboflavin (vitamin B2), and niacin (vitamin B3). Mitochondrial defense also depends on minerals like selenium and magnesium to activate specific antioxidant enzymes in the mitochondria—among them superoxide dismutase (SOD), catalase, glutathione reductase, and glutathione oxidase.

But the big news is the ongoing research into the many phytonutrients that also selectively activate the antioxidant enzyme system by turning on the expression of genes that control its activity. Phytonutrients from berries, green tea, grape and peanut skins, and such fragrant spices as rosemary, thyme, basil, and turmeric have all been found to regulate genetic expression in ways that control oxidation damage to the mitochondria.

So does exercise. And with exercise, it's all relative. A well-trained athlete has more than twice the metabolic capacity in her

muscle mitochondria as a sedentary person. One reason is that exercise actually stimulates the production of more mitochondria in the cells. It's called mitochondrial biogenesis, and it literally multiplies the number of mitochondria.

What we have now learned is that some forms of exercise are more effective in stimulating mitochondrial biogenesis than others—specifically, cross-training between aerobic cardiovascular conditioning and anaerobic strength conditioning. Practically speaking, that means that the most highly recommended form of exercise is to alternate moderate-intensity aerobic exercise—jogging, bicycling, swimming, stair-climbing, rowing, dancing—with such anaerobic activities as weight training, isometrics, heavy calisthenics, or any resistance exercise done at high intensity for shorter periods of time. The objective is to build oxygen-using capacity by conditioning the lungs and heart while at the same time stimulating mitochondrial biogenesis by creating oxygen debt in the muscles—that is, by stressing the mitochondria and sending a message to the genes to increase the number of mitochondria in response.

It is fascinating to compare the microscope images of the muscle tissue of people who do this kind of cross-training regularly with images of people who are engaged only in aerobics or people who are sedentary. You can actually see that the people on the cross-training program have the most mitochondria in each cell; the aerobic-trained folks have slightly fewer mitochondria; and the sedentary group have far fewer than either of the other two. Clearly, exercise speaks to the genes; the louder it speaks, the more cellular bioenergetics is increased.

What we also understand is that exercise should be regularly performed, part of the normal routine of life. John thought about that as he drove away from the club after his birthday golf outing and his chat with Philip. He hadn't played a round of golf in some time, and he was feeling it in his arms and across his back. Both Philip and Larry, he knew, were gym rats; they belonged to health clubs and attended regularly, and Philip, he also knew, did yoga, which The Guys used to kid him about. John himself had never bothered with a regular exercise routine; his travel-heavy job as head of sales made it

difficult, and his own fitness made it unnecessary, or so he thought. He could put in a week of sixteen-hour days on the road, going to meetings, hosting rich lunches and richer dinners for clients, sleeping five hours a night in a different time zone each night, and barely feel it. He'd still come home on the weekend and think nothing of playing a full eighteen holes. Now, after nine holes, his muscles ached.

The reason is simple. John's unconditioned body had exceeded the capacity of his mitochondria to provide the energy needed to fuel his body's activity, so every swing of the club after that point started producing waste called lactic acid. It happens in your body as well. When the buildup of lactic acid hits a certain level in the tissues, that stimulates the nerves to send a pain message to your brain. And while any form of vigorous activity will signal the genome to increase mitochondrial function, a once-in-a-while golf game is nowhere near enough to extend the point at which the tissues start accumulating lactic acid—and keep that threshold out there. It is only through regular conditioning, particularly the cross-training kind, that you can do more and more activity before your body gets to the point where it starts producing lactic acid and you feel pain. Such conditioning builds the increased capacity, and the regularity of an exercise routine sustains it.

Sustained exercise is not only great for muscular stamina and endurance; it also affects pain conditions throughout the body. Did you know that a common form of headache is associated with mitochondrial insufficiency? Like a muscle accumulating too much lactic acid, the mitochondrial reserve in the neurons of the brain can also exceed its capacity. The same regular cross-training routine that conditions muscles can also condition the neurons of the brain. It means exercise is a pain antidote from head to toe.

GOOD OXIDANTS

So if oxidants can be damaging, does that mean that the absence of oxidants is good? As you will have guessed by this point in this book, the answer is no. Our physiology is never all or nothing; too little of

something is as upsetting to the balance as too much. And it is the balance that counts. It is that often complex, sometimes very delicate equilibrium within and among all the processes that keeps us ticking over and in health.

In fact, of course, the body uses oxidants for a number of important functions, one of which is immunity. One of the ways a white blood cell "kills" a foreign invading cell is through the release of a caustic form of oxygen known as hypochlorite. You probably have some in the house; it's bleaching agent. Hypochlorite is produced by the T cells; when the cells come into contact with a foreign invading organism, they send out the hypochlorite literally to bleach the invader to death. Too much bleach, however, can cause collateral damage to the adjacent healthy cells and injure their energy-producing mitochondria.

The bottom line? We need enough oxidation to produce energy and defend ourselves from invaders and the harm they can do, but not so much that the defensive action injures the mitochondria and other components of the cell.

And the best way to maintain the balance of our energy process, maintain efficiency in our bioenergetics, and keep biological aging at bay is with a substantially plant-based diet rich in phytonutrients—a glass of fresh-squeezed vegetable juice daily would help—and a regular program of cross-training exercise.

But what happens when the process goes out of balance and our bioenergetics is affected? Let's turn to that next.

CAUSTIC OXIDATION

It is in the mitochondria that the greatest number of caustic forms of oxygen are produced, and they are produced, paradoxically, by a lack of oxygen. I think of it as the dialectic of mitochondria—thesis and antithesis together, each mitochondrion creating the seeds of its own destruction. We see this condition in high-altitude climbers—you've heard of the Death Zone on Mount Everest?—or among extreme athletes who push themselves beyond their aerobic limit for

prolonged periods, or in people who are deprived of oxygen because of an injury or problem with circulation of the blood carrying oxygen, or even in people with severe anemia. When the tissues are starved for oxygen—it's called hypoxia—the mitochondria begin producing caustic oxygen substances that injure the tissue or organ that is the site of the deprivation. Most of the time, the caustic oxygen substances are trapped and decontaminated by the antioxidant protection systems in the cell, but when the production of toxins exceeds the ability of the system to manage them, injury results, and the consequence is a diminution of bioenergetics.

It's why even a regular exercise program should not push too hard. While regular conditioning extends the pain threshold, extensive exercise to the point of exhaustion can increase the risk of mitochondrial injury. In a number of extreme adventure racing and ultra-marathon events, post-event blood tests have shown that some individuals are indeed damaging themselves. Even worse, we've seen some who go beyond their aerobic limit for so long that their bodies shut down and they collapse on the event course.

We've also learned, through the extraordinary work of Dr. Bruce Ames, professor emeritus in biochemistry at the University of California at Berkeley, that the process of caustic oxidation can deface and eventually damage the book of life itself. That's tough to do because the DNA in our genome is locked in a vault that is far more secure than Fort Knox. Still, excessive exposure to caustic forms of oxygen produced in the cell can breach that security and damage the DNA—and with it the clarity of the genetic message in the genome.

The consequences for our health range from adverse to catastrophic, depending on where the injury to the DNA occurs and how well it can be recognized and repaired by the cell. But cancer, arthritis, heart disease, and degeneration of the nervous system and brain can all be triggered by such injury. The brain is particularly vulnerable because, oddly, it has a very poor antioxidant defense system.

I learned of the connection between caustic oxidants and such diseases of the brain as Alzheimer's, Parkinson's, and Lou Gehrig's disease back in 1990, when I first met Drs. Wayne Matson, of the

Massachusetts Institute of Technology, and Flint Beal, at the time a research neurologist at Harvard Medical School and the Brigham and Women's Hospital in Boston. They had spent the late 1980s exploring whether Denham Harman's theory of free radical pathology could in some way explain the injury to the brain that characterizes so many neurodegenerative diseases. Specifically, Matson and Beal wanted to know what caused the production of the caustic oxidation substances. They found that the brain cells themselves produce caustic forms of oxygen. They do so when they receive a message of alarm from their environment—maybe a toxic chemical, a stress reaction, or an inflammatory message from the immune system. Any and all of these can trigger mitochondrial dysfunction in the brain cells.

To the extent that substances in the diet contribute to the inflammatory response, this alarm reaction can be transferred to specific cells in the brain and, potentially, to such genetic susceptibility factors as the ApoE4 gene. This is the gene identified over the past two decades as occurring in people showing a much higher incidence of both Alzheimer's and heart disease than the population at large. Further exploration of the ApoE4 gene revealed that this gene made the people who carried it more susceptible to the production of caustic oxidation and to its effects and more sensitive to the adverse effects of saturated fats in their diet.

This was actually good news for carriers of the ApoE4 genetic marker. It told them that the gene does not doom them to Alzheimer's or heart disease; rather, it's a signal to them to personalize their lifestyle, environment, and diet to mitigate their susceptibility to both. Clearly, people who carry the ApoE4 genetic marker should, for starters, minimize their intake of saturated fat and maximize their intake of protective antioxidants and phytonutrients.

Ongoing research confirms these conclusions, as we find that the risk of neurodegenerative disease is greater in people with insulin resistance and type 2 diabetes, two other conditions influenced by the same dietary issues. Remember the work directed by Dr. Suzanne Craft about a type 3 diabetes—diabetes of the brain? Craft's "discovery" of this was based on conclusive evidence that as type 2 diabetics

age, their risk of dementia increases. The correlation between diet and disease is too potent to ignore.

Too potent by far: additional research has found that people who do not smoke, whose diet is plant-based, who consume minimal sugar and saturated fat, and who exercise regularly show a greater than 50 percent reduction in the incidence of Alzheimer's disease versus those who follow none of those habits. I don't know about you, but my guess is that if the pharmaceutical industry came up with a drug that cut in half the incidence of Alzheimer's disease, we would all want it—no matter the price. Yet here it is: At the rather low cost of making some changes in diet and lifestyle, we can protect the body and brain against injury to the mitochondria and against the effects that the release of caustic forms of oxygen have on brain health and function. That's a big reward at a cheap price.

CHRONIC FATIGUE SYNDROME AND MITOCHONDRIAL ENERGY

The southwestern United States seems an odd place to find chronic fatigue syndrome, yet that's exactly where the first cases of the syndrome were discovered and reported in the 1980s. The physician credited with analyzing the condition as a syndrome is Paul Cheney, both an MD and a PhD, who at the time was working as an internist in Incline Village, Nevada.

Cheney described the syndrome as characterized by bone-weary fatigue, muscle weakness, swollen glands, brain fog, intolerance of exercise that was previously well tolerated, and the desire to sleep through the day. At first there was just a small cluster of patients, but reports on the syndrome grew rapidly until it had become a recognized global health problem. Originally given a number of different names—one was myalgic encephalitis, meaning sore muscles associated with an inflammation of the brain—it was eventually universally known as chronic fatigue syndrome, or CFS.

Medical investigators around the world searched for the cause of the syndrome. Most leaned toward the theory that it originated in

a chronic viral infection, but the world's foremost virologists were unable to find a specific virus that could be the source. Over time, it became clear that the condition had multiple causes that worked together to alter the function of the immune system.

I first met Paul Cheney through my good friend Scott Rigden, a talented family doctor in Scottsdale, Arizona, and in the late 1980s, our research group at the center joined with both physicians in trying to identify biomarkers of the syndrome that would help define its cause with more precision. By 1990, our data suggested that CFS was an issue of reduced mitochondrial bioenergetics as a consequence of something "poisoning" the mitochondria. We initiated a small clinical research study in a group of thirty CFS patients and found exceptionally high incidence of biomarkers signaling caustic forms of oxygen as a result of mitochondrial dysfunction. In particular, the biomarkers measured serum lipid peroxides, providing a measurement of rancidity in the blood, and damage to DNA from caustic oxygen substances called 8-hydroxydeoxyguanosine, or 8-OHdG.

The thirty patients were then put on a twelve-week program aimed at improving their mitochondrial bioenergetics and reducing the effects of the caustic forms of oxygen. The program required them to consume a low-allergy diet enriched with rice protein and to supplement with high levels of nutrients necessary to support mitochondrial function—zinc, coenzyme Q10, lipoic acid, and vitamin E, for example. At the end of the twelve weeks, the biomarkers of mitochondrial dysfunction had improved markedly; so had the patients' CFS symptoms.

The published results of our study evoked a response from Dr. Martin Pall, a biochemistry professor at Washington State University. He introduced himself as a former CFS patient. Because Dr. Pall felt the initial symptoms of fatigue and brain fog following a flight back to the United States from Europe, he originally attributed his illness to jet lag. But as the symptoms worsened, and as his once sharp memory began to fade, he realized that he needed to take a leave of absence from his academic position and focus on getting well. Pall's way of doing that was to use all his remaining energy—and all his

biochemistry training and experience—to understand his condition and find a solution for it.

It took two years of full-time work. Pall culled all the research he could find, including our work and that of others looking at dysfunctional mitochondrial bioenergetics, and leveraged it with his understanding of mitochondrial function.

A key source was the work done at the Center for Molecular Medicine at Emory University School of Medicine in Atlanta—specifically, research exploring how to manage children born with genetic imperfections in their mitochondrial function. The center's researchers had found that the nutritionally related substances N-acetyl carnitine, coenzyme Q10, lipoic acid, and N-acetylcysteine could mitigate the symptoms of mitochondrial dysfunction in these children.

Putting it all together, Pall developed the working hypothesis that the mitochondria of CFS patients are injured by activation of the immune system. He then came up with a treatment plan consisting of high doses of the nutritional substances that support mitochondria in their job of producing ATP and fueling metabolism. Pall himself became the first test patient for his plan, and a year later, he was well.

His plan has since been taken up by numerous other physicians in treating their own CFS patients. But it was Paul Cheney himself who gave the approach its name; he calls it mitochondrial resuscitation.

Martin Pall's hypothesis that activation of the immune system injures the mitochondria in CFS patients throws into sharp relief the kind of adverse influence stress can have on mitochondrial health and our bioenergetics. It is one of the loudest signals our lifestyle and environment can give to the genes regulating our mitochondrial function. Simply put, if there is too much stress for too long a time, the stress hormone adrenaline can cause the mitochondria to commit suicide.

I suppose that's one reason I find it so interesting that in blue zones like Ikaria, where people live longer and healthier lives, one of the characteristics that define their lifestyle is the sense of community, and another is the preservation of downtime. The sense of community means that even the most do-it-yourself loner knows that help

is available if needed and that others are looking out for him. The preservation of downtime means that everyone is expected to spend a prescribed amount of time restoring his or her body, mind, and soul; it's considered an integral and essential part of life, and again, everyone knows it and counts on it. Both of these certain expectations, which seem a far cry from lives spent in isolated, 24/7 interaction with the Internet, are associated with a reduced allostatic load and decreased levels of stress hormones. The mitochondria in blue zoners don't have to self-destruct; they're not damaged by lifestyle behavior or poisoned by caustic oxidants. The result? Blue zoners preserve their cellular energy reserves and show a lower biological age than the rest of us. They live longer, healthier lives.

SPECIAL NUTRIENTS FOR MITOCHONDRIAL PROTECTION

Regular exercise and a healthy, plant-based diet can keep our mitochondrial function healthy and efficient. But when damage occurs, something more may be needed. The role of phytonutrients not just as protectors of mitochondrial function but as treatment mechanisms for mitochondrial damage is an emerging science, and it has prompted important discoveries in the way these plant-derived compounds can influence health.

A good framework for understanding this influence is the concept of hormesis, a term revived precisely in this context around the turn of the millennium by Dr. Edward Calabrese, a professor at the School of Public Health at the University of Massachusetts. The term refers to an unexpectedly large biological effect from a very low level of exposure to a particular treatment. Instead of the effect of the treatment increasing as the dosage is increased, hormetic substances realize a bigger impact at a lower dose.

When it comes to mitochondrial protection, we've learned that specific phytonutrients at very low levels of exposure can influence genetic expression at precisely the right control points for regulating

the complex process of mitochondrial function.* What this means is that even a small amount of the right phytonutrient taken at the right time can influence health much more than would have been expected from the amount consumed and absorbed.

It's a little bit like acupuncture—that is, a small influence at just the right point on the body can effect significant change. At issue here, however, are metabolic control points—the specific regulation points in our complex network of genes where a small influence can promote a substantive shift in genetic expression. One example is the positive clinical effect on health outcome in CFS patients with very low doses of specific types of omega-3 fatty acids and phospholipids derived from marine sources. Dr. Garth Nicolson, director of the Institute for Molecular Medicine, administered as little as 3 grams per day of these substances to his CFS patients. Given that the body contains more than 15,000 grams of fat, it would be logical to expect that 3 grams of specific fats would soon be diluted by all the other fats in the body. In this case, however, as Nicolson concluded, the influence is hormetic: although the dosage was minimal, the impact of the specific substances regulated the genes that control signal transduction in the cell, which in turn influenced genetic expression affecting the patients' symptoms.

Which phytonutrients are known to have hormetic influences on mitochondrial function? Resveratrol from grape skins and peanuts, epigallocatechin gallate (EGCG) from green tea, curcumin from turmeric, isohumulones from hops, quercetin from buckwheat, watercress, and dill all work—optimally, when found in whole, minimally processed foods and supplements.

* From the work of Dr. Mark Mattson and his research team at the Laboratory for Neurosciences at the National Institute on Aging. The work examined the hormesis mechanism with phytonutrients shown to have a positive effect on mitochondrial function.

CALORIE RESTRICTION

Here's another of the characteristics associated with blue zoners: not only is their food minimally processed and plant-based, it's also relatively lower in calories. Despite all the lovely fresh fruit, wine, and olive oil of Ikaria, for example, by comparison with most developed-economy cultures, Ikarians live on a calorie-restricted diet.

This is not a particularly revolutionary concept, and the impact of partial calorie restriction on mitochondrial bioenergetics has been the focus of considerable research for some time. That calorie restriction could be a way to preserve health and extend the life span was first observed in a laboratory setting by Professor Clive McCay at Cornell University in the 1950s, when he and his students recorded an increase in life expectancy of nearly 35 percent in rats fed a diet of 25 percent fewer calories than the control group. Similar results have been found in many other species of animals from flatworms to monkeys: calorie restriction results in a lower incidence of disease and a longer life.

The research with monkeys has been particularly important—especially the twenty-year study carried out at the University of Wisconsin that is the longest controlled study of calorie restriction in a primate model thus far. The animals in both the control group and the calorie-restricted group were all about the same age at the start of the study; by the end of it, the results were obvious—and remarkable. The control monkeys looked like geriatric cases. They were stooped over; their fur's texture was poor and its color faded; and they had limited mobility. The control group also suffered many more deaths than the calorie-restricted group of monkeys, which not only looked and acted much younger than the control group but also recorded far healthier blood biomarkers. The conclusion was again evident; calorie restriction was shown to improve health and life expectancy over the long term.

The question is why. The answer in large part seems to be found in the difference in the number and type of genes that are expressed in the calorie-restricted group of animals versus those that are eating ad lib. The genetic expression of the calorie-restricted group effected

low stress response and increased maintenance of mitochondrial function over time.

From this evidence, we conclude that too many calories over too long a time results in a kind of mitochondrial burnout—particularly if the calories come from such fast-acting energy sources as sugars, processed flour products, concentrated fats and oils, and excessive animal protein.

An added point of interest to the calorie restriction effect is the recent finding that many of the phytonutrients that have hormetic effects on mitochondrial function mimic the influence on genetic expression that is seen with calorie restriction. This means that a diet centered on plant foods along with a modest calorie reduction, which often accompanies the switch to a plant-based diet, can produce a double-whammy impact on the genes that regulate mitochondrial bioenergetics, supporting mitochondrial function while also reducing the potential for adverse effects of the caustic effects of oxidation.

Denham Harman was right back in the 1950s when he predicted that the next century would teach us much more about the effect of diet on free radical pathology and its influence on health, disease, and aging. We're learning new lessons every day.

Yet so much of what we're learning is not being applied. I am reminded of the senior residence where my mother lives—a community of about a hundred retired seniors with an average age in the eighties. Many of the residents have one or more of three main health problems—type 2 diabetes, dementia, and macular degeneration with impending blindness. The same is true in other senior residence facilities across the nation and the world. But the tragic circumstance of these facilities is not that the residents are old and need assistance in their daily lives. No, the real tragedy is in the kitchen.

It is as if the foods being served are intentionally designed to increase the production of caustic oxygen substances and send residents' mitochondria on a path to suicide. Meals consist of high-glycemic-load foods, are filled with sugars and saturated fats, and are virtually devoid of any fresh food at all except a salad of store-sourced lettuce

covered in a dressing with sufficient fat and sugar to rob it of any positive nutritional value. I find this criminal as well as tragic.

Yes, meals are important for more reasons than food. These are the times of day when residents get together, socialize, engage in conversation. And certainly, the food that is served should support residents' comfort and, to be sure, their enjoyment. But those aims can be achieved with just a little creative menu planning; such planning should be based on a commitment to the importance of nutrition in preventing the diseases of aging that result from mitochondrial catastrophe.

I've seen other places too—enlightened senior living facilities where low-glycemic-load menus are offered, sugars are minimized, and nutrient-rich foods are plentiful. In such facilities, I see fewer people who are losing their memory, walking with a walker or motorized scooter, or losing their eyesight.

But I am not surprised to hear my mother's co-residents complaining of fatigue, low energy, forgetfulness, and weakness—all symptomatic of mitochondrial impairment, all serious issues that rob quality of life from people *and* propel them to the use of expensive medical services. It's a real-world example of what the loss of mitochondrial bioenergetics means in the reality of people's lives. And in a world where we are all living longer, it's an object lesson in how not to ensure healthy aging.

Okay, I've said my piece.

JOHN AND THE GUYS

By the time he got home, John had remembered that both Philip and Larry had had one beer each in contrast to the two or three drinks the rest of them downed during lunch. He also seemed to recall that the two younger-looking, more vital-seeming guys had said no to the dessert even though both of them had eaten only a salad for their main course. There was a pattern here, a method to the madness Philip and Larry seemed to represent, and John began to wonder whether doing as they did might help him regain the energy he lost.

I know the rest of this story because John called Philip and

asked for a referral to his doctor, a functional medicine practitioner who told me what happened. John made some changes in his life; they amounted to his taking charge of his own bioenergetics and health.

No, he did not join the health club—not his thing. But he set himself a regular program of walking and stuck to it. His wife soon joined him, and lately, they've both taken up cycling as well. They also changed their diet; John described it as "switching places," meaning that meat became a side dish—and a less and less frequent occurrence—and vegetables became the center of the meal. Sweets and processed food pretty much went away and, to John's surprise, were not missed.

It did not take long for John to become an energy gainer instead of an energy loser. In addition, his body has taken on a new shape and form, one consistent with the genetic expression of his vitality genes and not his aging genes. To me, the change in John is a classic example of Linus Pauling's axiom that if you get the structure right, the function will follow.

The truth is that structure can tell you a lot about function, which is why we'll turn to structure next.

CHAPTER 9 TAKEAWAY

1. Our energy is produced by the mitochondria in cells; it is in the mitochondria that carbohydrate, protein, and fat are metabolized, producing cellular energy.
2. This energy-producing process is dependent upon proper intake of vitamins, minerals, omega-3 fatty acids, and phytonutrients.
3. Altered mitochondrial function can result in cellular damage associated with accelerated biological aging and chronic disease.
4. Specific antioxidants such as vitamin E, selenium, vitamin C, coenzyme Q10, lipoic acid, and N-acetylcysteine can protect against mitochondrial damage.
5. Cross-training exercise that alternates aerobic and anaerobic conditioning helps to strengthen mitochondrial function and improve cellular energy production.

6. Chronic fatigue syndrome is related to altered mitochondrial function.
7. Insulin resistance and its related condition, type 2 diabetes, can reduce the mitochondrial function in the brain and contribute to dementia.
8. A mitochondrial resuscitation program can improve cellular energy production.