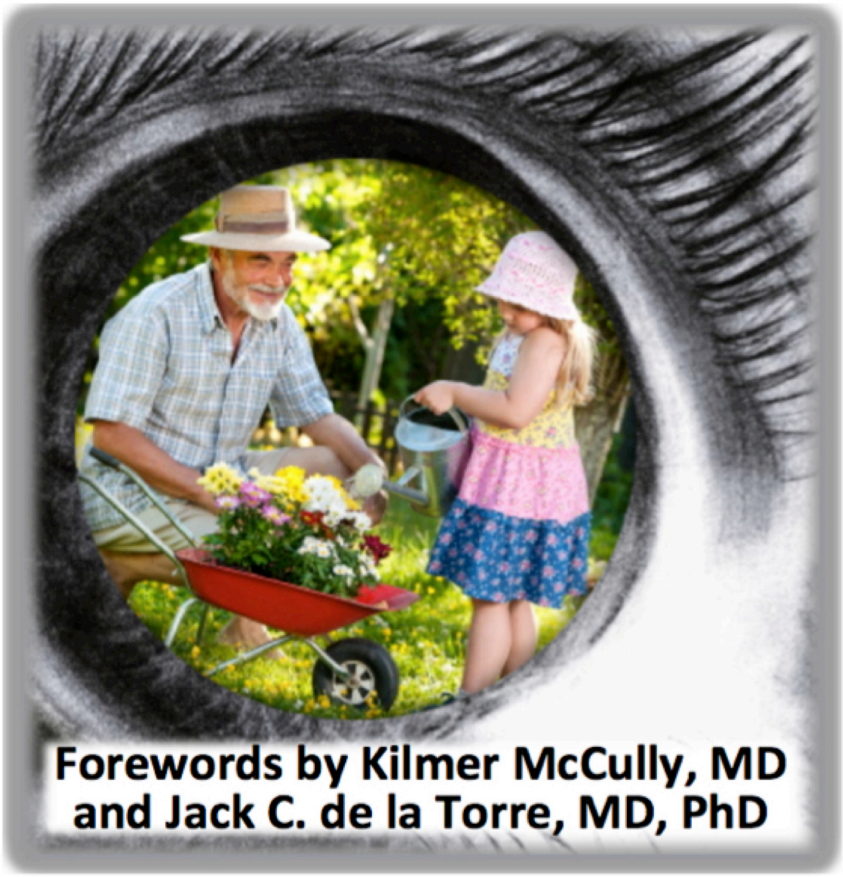
The End of Alzheimer's



A Differential Diagnosis Toward a Cure

Thomas J. Lewis, PhD and Clement L. Trempe, MD

The End of Alzheimer's

A Differential Diagnosis Toward a Cure

The Truth about Alzheimer's, Dementias, and other Neurodegenerative Diseases Revealed.

Includes a Multi-Stage Process of Screening, Early Diagnosis, Root-Cause Diagnosis, and Disease Process Reversal.

Thomas J. Lewis, PhD and

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Dedication

This work is dedicated to my (tjl) father, "Papa," who passed from Alzheimer's disease a decade ago. It is also dedicated to my mother, Cecelia (Neema, Momalou).

My mother is very "old school," having lived through the Great Depression and WWII. She married my father at the age of 24 and was completely committed to family. She never could envision abandoning him to someone else as he slipped into dementia. My mother so completely and selflessly managed my father and the home, that my siblings and I were insulated from his true condition. We did learn later that his behavior was somewhat typical of Alzheimer's patients in that during his severe episodes, he would lash out and become violent. She often explained bruises as being caused by her clumsiness.

Regardless of my father's behavior and the prompting of his doctors, my mother disregarded any suggestions to place him in full-time care. She had vowed, at the time of their wedding, to be there for him for better and for worse and in sickness and in health. She was not one to compromise on her promise. What I neglected to consider was that, since his fate was sealed, my efforts were not for my father but rather to help my mother. She was always so strong and capable, so I assumed that she could and would handle anything.

Ten years after the passing of my dad, my mom, at the age of 91, is doing heroically well. Thanks be to God.

- Thomas J. Lewis, Ph.D.

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Modern civilization depends on science … knowledge should not be viewed as existing in isolated parts, but as a whole, each portion of which throws light on all the other, and that the tendency of all is to improve the human mind, and give it new sources of power and enjoyment … narrow minds think nothing of importance but their own favorite pursuit, but liberal views exclude no branch of science or literature, for they all contribute to sweeten, to adorn, and to embellish life … science is the pursuit above all which impresses us with the capacity of man for intellectual and moral progress and awakens the human intellect to aspiration for a higher condition of humanity.

- Joseph Henry

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Foreword

By Jack C. de la Torre, MD, PhD.

It's time to face facts. Suppose Dr. Alois Alzheimer came back from his grave to see how the disease that bears his name has progressed in the last 100 years since its discovery in 1907. He would be amazed to learn how much innovative research has been done to uncover the cellular, molecular and biochemical mechanisms of the disease but only where animals and test tubes are concerned. It is my guess that Dr. Alzheimer would also be totally perplexed and disheartened at the fact that after a century of research and over 100,000 scientific papers written on the subject, patients presently diagnosed with Alzheimer's disease are no better off now than they were in 1907. This fact alone invites the troubling question, are we on the right track to finding a way to help Alzheimer patients?

To search for an answer to this consequential question, one needs to read "The End of Alzheimer's" by Dr. Thomas Lewis and Dr. Clement Trempe who write about this disqueting problem and possible ways to solve it.

It is important to recall how research works, both at the basic and clinical levels. Clinical research is generally an off-shoot of basic research. Basic research to a problem usually involves a hypothesis, experimentation and evidence to prove or disprove the hypothesis. If experimentation repeatedly fails to support a hypothesis, scientists usually move on to seek another hypothesis. This is not the case with the Abeta hypothesis, the reigning paradigm of Alzheimer's disease whose concept of clearing amyloid plaques from the brains of Alzheimer victims has entirely failed to help them in reported clinical trials held so far. Common sense dictates that when you discover you are riding a dead horse, the best stratetgy is to dismount.

Having said that, one assumes that although many basic researchers are quite smart, they are also totally dependent on funding to do their research. No funding, no research. Even the most brilliant hypothesis can lay in the corner of the laboratory gathering dust if funding is not obtained. Who provides the funding? The main funders are the pharmaceutical industry, the government (NIH) and private foundations, mostly in that order of money-giving generosity.

Government and private foundations rely on a panel of 'experts' to advise the bureaucrats whether a research project is worthy of funding. Often, a conflict of interest arises from these supposedly impartial advisors who more often than not, opt to fund their friends or research projects close to their hearts. They are in essence, the keepers of the gate. Pharmaceutical-derived funding is more businesslike. They prefer to fund research projects that will bring them money by the truckload. Alzheimer's disease is a disorder that affects over 5 million people in the U.S. and 36 million worldwide so it has become an excellent target of investment.

To find even a negligible benefit to Alzheimer patients, a patented drug sponsored by pharmaceutical money, can mean, as Drs. Lewis and Trempe correctly point out in their book, the mother lode of return investment reaching billions of dollars annually. This is

what Dr. Alzheimer would find callous and mean-spirited, should he return from the grave.

Since it is axiomatic that most scientists with an intellectual or financial stake in a theory tend to ignore the facts that may undercut their views, it is not surprising that the Abeta hypothesis has survived this long. To survive, the Abeta hypothesis has creatively morphed into a 9-headed Hydra whose heads, like the mythical monster, can regrow after being cut-off. Thus, each time sharp evidence cuts off one of its heads, the monster hypothesis survives by quickly growing another head. In this fashion, each clinical trial failure greeted by jury of vested scientists whose chorus is, "it didn't work, BUT…" and thus, another head on the Hydra is regrown to fight another day. Consequently, the continued re-invention of these anti-Abeta compounds continue to be retested on Alzheimer in multi-million dollar clinical trials.

Why do these pharmaceuticals persist in clinically re-testing the same failed concept over and over again and expecting a different result? In the case of the Abeta hypothesis, the answer is, money. This point is fluently discussed by Drs. Lewis and Trempe. They offer a compelling argument that while the Abeta hypothesis is dying from an absence of supporting clinical evidence, millions of dollars continue to be poured into these single-minded Abeta projects by the greedy pharmaceutical companies. They hope to tap into this billion dollar industry if one of their drugs is approved for any positive action on Alzheimer's disease, no matter how clinically inconseqeuntial.

Tragically, research avenues not dealing with anti-Abeta therapy are ignored by these same pharmaceuticals who have decided, at least for the moment, not to hedge their bets with several promising concepts that may help prevent or control Alzheimer onset.

Drs. Lewis and Trempe also discuss the important issue concerning how the start of Alzheimer's disease can be significantly prevented or controlled by early identification and detection of offending risk factors in both healthy and mildly symptomatic individuals. Such a strategy involves treating the modifiable precursors to Alzheimer dementia will also ensure their control and prevention. This approach will not only result in a better mental health outlook for the patient but also will significantly lower the exponentially growing incidence of this devastating dementia and the explosive impact from its socio-economic consequences.

Drs. Lewis and Trempe have written a mind-opening, well-informed and intelligent account of the history, present and future interventions and distillation of keen thinking on the subject of Alzheimer's disease. This book will be the focus of many prospective and pivotal discussions on how medical research will eventually govern this mind-shattering disorder.

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By Kilmer S. McCully, MD

In their brilliant and comprehensive analysis of Alzheimer's disease, Drs. Lewis and Trempe present an innovative strategy for prevention and treatment of this devastating disease. By understanding the underlying cause of the disease, rational measures are used to arrive at the correct diagnosis, which is the key to successful management of the disease. In this analysis, ophthalmological observation and thorough determination of general health are used to assess the potential for the development of dementia in the individual patient. By using the results of medical research available on the internet, a successful strategy can be developed from the "Trillion Dollar Conundrum" as published in scientific articles world-wide. The Trillion Dollar Conundrum refers to the two million research studies of Alzheimer's disease and other diseases, funded to the extent of $500,000 each that are published in the medical literature each year. In the conventional wisdom of the cause of Alzheimer's disease, the medical establishment, and more importantly, the pharmaceutical industry commit immense sums of money to development of drugs to counteract the amyloid cascade hypothesis. In their analysis, most of these efforts have proven to be fruitless, and the new approach of Drs. Lewis and Trempe, based on scientific understanding, is presented to guide therapy and prevention.

In the years since 1906, when neuropathologist Alois Alzheimer introduced the concept of tangles and plaques in the brain as a cause of early-onset dementia, the disease has been found to be closely related to vascular disease in arteries of all organs of the body. The conclusion of a century of medical research is that vascular dementia and dementia associated with tangles and plaques in the brain are closely related to and associated with aging, declining oxidative metabolism, and infections. A further conclusion is that inflammation and the immune system are participants in the initiation and progression of dementia observed in Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and other neurodegenerative diseases. These diseases are associated with inflammation of the brain, and two molecular markers of inflammation in the blood, homocysteine and C-reactive protein, are especially useful in following the inception, progress, and treatment of these diseases.

Homocysteine is a four carbon amino acid containing sulfur in the form of a sulfhydryl group. Homocysteine was discovered in 1932 by the eminent American chemist Vincent DuVigneaud by heating the amino acid methionine in concentrated sulfuric acid. In contrast to methionine, homocysteine does not occur in the peptide linkages of proteins, even though the molecule differs from methionine, an important sulfur amino acid of proteins, only by a methyl group. The importance of the methyl group and its relation to the biochemistry of sulfur were explored in animals by DuVigneaud and many other investigators in the 1930s and 1940s. However, the importance of homocysteine in human disease was totally unknown until 1962, when cases of the disease homocystinuria were discovered in children with arterial and venous thrombosis, mental retardation and other disturbances of the central nervous system. Analysis of vascular disease occurring in cases of homocystinuria caused by different inherited enzymatic abnormalities of methionine metabolism, revealed the atherogenic effect of homocysteine in causing arteriosclerotic arterial plaques. This concept is termed the homocysteine theory of arteriosclerosis, since many important aspects of

atherogenesis occurring in the general population are attributed to the effect of homocysteine on the cells and tissues of the arteries.

Homocysteine became an important factor in understanding the cause and treatment of Alzheimer's dementia in 2002, when investigators at the Framingham Heart Study demonstrated that participants with elevated blood homocysteine levels are at greatly increased risk of developing Alzheimer's dementia when followed for a decade. This observation corroborated the hundreds of published studies documenting elevation of blood homocysteine as an independent, potent risk factor for atherosclerosis in the general population.

A further development in understanding the origin of atherosclerosis and dementia occurred when investigators demonstrated remnants of micro-organisms in arterial plaques in subjects with atherosclerosis and in the brains of subjects with Alzheimer's disease. The pathogenesis of vulnerable atherosclerotic plaques was attributed to obstruction of vasa vasorum of artery walls, where inflammation and deposition of lipids is first observed in atherosclerosis, by aggregates of lipoproteins, micro-organisms, and homocysteinylated lipoproteins. These aggregates become trapped in vasa vasorum because of high tissue pressure of artery walls and because elevated blood homocysteine causes endothelial dysfunction, narrowing the lumens of capillaries and arterioles. Obstruction of vasa vasorum by these aggregates causes ischemia, death of arterial wall cells, hemorrhage, and rupture into the intima creating a micro-abscess, the vulnerable plaque.

In a similar process in the brain, spirochetes from the oral cavity invade the nerves of the nasopharynx and olfactory tract, spreading to the brain, where inflammatory reaction and deposition of A-beta amyloid creates the plaques and tangles of Alzheimer's disease, as shown by the eminent Swiss neuropathologist, Judith Miklossy. The analysis of Drs. Lewis and Trempe takes advantage of these observations by showing that treatment of chronic intracellular infections by organisms such as Chlamydia pneumoniae, Mycoplasma pneumoniae, Helicobacter pylori, Rickettsiae, Borrelia burgdorferi (of Lyme disease), and Archaea has the potential for arresting the pathogenesis of dementia by enhancement of immune system function through optimal nutrition and nutritional supplements and by elimination of sources of further infection by meticulous oral hygiene.

As the pathophysiological processes of aging, atherosclerosis, and dementia are characterized by elevation of blood homocysteine, an explanation of the origin of these systemic processes is related to biosynthesis and metabolism of homocysteine. Two decades ago a new theory of oxidative metabolism was introduced to explain the observations of oxidative stress and aerobic glycolysis in atherosclerosis, cancer, autoimmune diseases, and other degenerative diseases of aging. According to this theory, oxidative phosphorylation is dependent upon thioretinaco ozonide, the complex formed from retinoic acid, homocysteine thiolactone, cobalamin, ozone and oxygen. This theory also explains the coordination of reduction of oxygen by electrons from electron transport particles of mitochondria with the polymerization of phosphate with a precursor of adenosine diphosphate (ADP) to produce adenosine triphosphate (ATP) and the proton gradient across mitochondrial membranes.

A recent development of this theory implicates nicotinamide adenine dinucleotide (NAD+) as a precursor of ADP, leading to the active site of oxidative phosphorylation, thioretinaco ozonide oxygen NAD+ phosphate. This theory explains the origin of elevated blood homocysteine in aging, atherosclerosis, and dementia, because this active site complex is consumed by micro-organisms occurring in vulnerable plaques of the arteries and plaques and tangles of the brain in Alzheimer's disease. This active site of ATP synthesis is also the precursor of the important co-enzyme adenosyl methionine, the precursor of methylation reactions and the allosteric regulator of the enzymes of homocysteine metabolism. Adenosyl methionine and NAD+ within cells both decline in aging, and nicotinamide riboside, a precursor of NAD+, activates sirtuins which regulate mitochondrial function in aging. The anti-aging properties of nicotinamide riboside are attributed to increased synthesis of NAD+ and thioretinaco ozonide, molecules which both decline in aging.

The brilliant strategy by Drs. Lewis and Trempe takes advantage of revolutionary new concepts for guiding enhancement of immune function and treatment of chronic infections in prevention and treatment of Alzheimer's disease. The diagnosis of mild cognitive impairment by psychological testing, combined with assessment of ophthalmological abnormalities and determination of health status through thorough testing of biochemical markers related to infection and inflammation, are necessary for improving the prognosis and reducing the risk of dementia. The implications of this strategy for the individual and for the population are enormous. Control of dementia, atherosclerosis, and degenerative diseases of aging by the insights of Drs. Lewis and Trempe has the potential for revolutionizing management of chronic disease in the general population.

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November 24, 2014

Preface

"The seeds of great discovery are constantly floating around us, but they only take root in minds well prepared to receive them."

- Joseph Henry

Globally, almost one trillion dollars ($1,000,000,000,000—one million times one million dollars) is spent annually on medical and related research. Are we getting what we pay for? Yes and no.

When you search through and read the medical literature, the depth and breadth of the information is almost beyond comprehension. I use http://www.scholar.google.com for most searches, and this engine allows for a fair number of inputs including searching for key words in the body or the title of articles. The amount of research in the area of Alzheimer's is mind-boggling. If you want to know the association between Vitamin D and Alzheimer's, at least 20,000 titles are found. The number drops to 20 when the search is "title only." A search for "amyloid and Alzheimer's" yields over 123,000 records. Beta-amyloid is considered one of the two most important biological "hallmarks" of Alzheimer's disease (AD).

Pick an association you might think is important about Alzheimer's disease and to be sure, a search will yield many articles. A rule of thumb is that each article costs approximately $500,000 to produce considering researchers, their time, laboratories involved, meetings, and all ancillary items associated with performing research and creating a finished technical document, complete with a novel thesis. Thus there are about two million research articles published each year, give or take.

Translation of pure research into clinical practice is a big problem and rears many ugly heads. From a patient's perspective, it simply takes too long for the information obtained by researchers to reach the clinic. Some may estimate that the time lag between discovery and clinical application is ten years but I believe it is at least, on average, twenty years. Compare this to other industries such as information technology. The time from discovery to the shelf is often less than one year and we, the consumers, demand that new technologies are at our fingertips immediately. It is likely that the lag time between discovery and clinic will only lengthen. This is in complete contradiction to essentially every other enterprise.

Consider the book *The Singularity Is Near: When Humans Transcend Biology* by Dr. Raymond Kurzweil. Four central postulates of the book are as follows:

1. A technological-evolutionary point known as "the singularity" exists as an achievable goal for humanity.
2. Through a law of accelerating returns, technology is progressing toward the singularity at an exponential rate.
3. The functionality of the human brain is quantifiable in terms of technology that we can build in the near future.

4. Medical advancements make it possible for a significant number of this generation (Baby Boomers) to live long enough for the exponential growth of technology to intersect and surpass the processing of the human brain.

Do you see any signs of #4 emerging anywhere? Medicine appears to be stagnant or even going backward compared to other "technologies." We are holding even on cancer and heart disease and losing ground in diabetes, Alzheimer's, and other neurodegenerative diseases.

What is the problem and solution? It is actually quite simple: **"translational medicine."** Consider this simple example: according to *U.S. News* in 2010, Harvard Medical School was ranked *first* in medical research globally. That same year, Massachusetts General Hospital, a Harvard Medical School teaching hospital, was ranked 57th. Yet these two institutions are connected. Mass General is part of Partners Health Care, and Partners is affiliated with Harvard Medical School. Most of the doctors at the hospital hold Harvard Medical School appointments. Why is there such a large discrepancy, first in research yet 57th in clinical delivery? There is an apparent lack of translation between research and patient care even within the same organization! Researchers perform research (mainly on animals that have artificially induced disease, thus have little correlation to actual disease in humans) and clinicians treat humans, and the two groups do not talk (and experimental ideas must pass over ten years of FDA muster).

The entire medical industry is incredibly segmented into tight verticals, and there is little cross-pollination. Shrinking research dollars leads to research groups being very protective of their novel ideas, which exacerbates this. Also, doctors are busier than ever trying to care for patients while earning a decent wage as both Medicare and commercial insurance reimbursement are diminished. Are you aware that major hospitals are training their doctors to make a ten-minute visit feel like thirty minutes? [1] Yes, medicine has decayed to that point, far away from the house call.

I work with a very fine doctor, Dr. Clement Trempe, who, now in his seventies, should be retired. However, his love of patient care and medicine keeps him in the office daily. And, he has a slight financial issue. He frequently spends hours (two to five) with patients and follow-up tests, recommendations, phone calls, entry of electronic medical records, and a myriad of other new requirements. He often is only reimbursed $65 for an office visit under Medicare, for patients over 65 years of age. So, if he spends three hours with a patient and is reimbursed only $65, isn't he better off working his way up the ladder at Dunkin' Donuts?

I first learned from him what the "Trillion Dollar Conundrum" (as I now call it) is all about. It is illustrated by way of a simple story. He frequently goes to Avenue Louis Pasteur (to the Harvard Medical School auditorium) to attend lectures by prominent researchers. He told me, "I know I'm the only clinician who attends these lectures because I'm the only one wearing a tie. All the other attendees are in sneakers and jeans. They are all Ph.Ds. When the lecture is over, they go back to their lab. I go back and see patients."

My father taught me long ago that, when something doesn't make sense, money is involved. I believe the same holds true in modern medicine. There are plenty of

medications and even supplements that work to prevent and/or treat Alzheimer's disease, but they never get notoriety. Why? Who is going to spend the money to test and promote generic drugs or even vitamins for this purpose? Yes, there is some degree of testing, but marketing drives our world, and drugs or products without a strong potential for financial reward have no backers. The drugs that are pushed are those that are "on patent" because the drug companies and their tremendous marketing machines have the financial impetus to drive these to the doctor's office. Many good drugs that are or become generic (and no longer have patent protection) just fade away from use in clinical practice because young medical students are not taught about them. Why? These medications do not make drug companies money thus young doctors are not taught about their value. To exacerbate this problem, since about 1980, drug companies have been allowed to sponsor medical school curriculum, and that "education" focuses on new "on patent" drugs, which are controlled and marketed by the pharmaceutical companies. [2]

The point is a simple one. There is more than enough research, even for a disease like Alzheimer's. There are a myriad of options for both early detection and treatment of patients who already have Alzheimer's disease, contrary to what the Alzheimer's Association and other pundits continue to say. These organizations constantly send the message that there is no cure or even a way to slow the progression of Alzheimer's, thus more research money is needed.

This book provides a thorough review of the trillion dollars of annual medical and scientific literature. Based on that review, a case is made for a differential diagnosis process for Alzheimer's and related disorders. We believe you will arrive at the conclusion that there **is** a way to slow the progression of, or even reverse, Alzheimer's disease based on a proper and thorough diagnosis that goes well beyond Alzheimer's.

What does a differential diagnosis of Alzheimer's do for you? Again, a short story provides an ample illustration. When I talk to doctors about Alzheimer's and infer that there are ways to prevent, slow the progression, and even reverse the course of the disease, one hundred percent of the time the doctor will ask, "What is the treatment?" I always provide a terse answer, "The question should not be: 'what is the treatment?' The question should be: 'what is the diagnosis?'" It may seem like a diagnosis of Alzheimer's is a death sentence. However, a differential diagnosis that delves deeply and broadly into the patient, their environment, physiology, and all the things that makes a person a person, may arrive at a diagnosis that has bona fide treatment options.

Consider this description for the disease Typhus:

> "Typhus is any of several similar diseases caused by Rickettsia bacteria. The name comes from the Greek typhos (τῦφος) meaning smoky or hazy, describing the state of mind of those affected with typhus."

Do Alzheimer's patients sometimes have a "smoky or hazy" state of mind? Yes. Could Rickettsia bacteria be the cause? Maybe. Has your neurologist tested for Rickettsia? No. Is Rickettsia disease, misdiagnosed as Alzheimer's disease, potentially treatable? Yes.

Stop hoping for modern medicine to save you. It could if it were not for the way the industry is constructed, based on verticals, profit motives, and general lack of translation from research into the clinic where the information can benefit you. The good news is that you can save yourself. The Internet is not structured into verticals. It costs nothing except for a monthly subscription to get online, and you can translate the information for your own health and well-being. This book offers a detailed translation for you.

I hope you find the information I've translated for you compelling.

Good luck.

You can beat Alzheimer's disease.

Be well,

Thomas J. Lewis, Ph.D. 2014

First, I want to thank Dr. Lewis for putting together this book that explains what I have been doing for years. Yes, there are more comprehensive diagnosis and treatment for Alzheimer's disease and other neurodegenerative diseases related to aging that is provided in clinical practice today. I am a clinician and have never taken any money from any drug companies. The point is that, I am free from bias that financial influences inevitably control.

I did not begin my career in medicine with the goal of helping people with Alzheimer's. However I have been blessed with the opportunity to learn about disease from something far greater than a test tube in some laboratory. I learned from my patients. They dictated my career path. I am an Ophthalmologist and am also very curious. I also believe in the Hippocratic Oath and am true to its pledge, to do no harm and to help the body health itself.

In the 1980s I gave up a lucrative practice of treating eye diseases as diseases isolated to the eye only. Back then, surgery and laser treatment was the way to go. I soon realized that my patients with eye diseases were always sick in many ways. I'm a doctor so how could I ignore this fact? Can treating the eye with a laser or surgery "cure" the reason why my patients had the eye problems and were otherwise ill? Of course not. And, by reading the medical literature it was becoming clear at that time, that the eye disease was the symptom of a broader condition of poor general health.

My practice changed 30 years ago to be one where I used the eye and eye diseases as a biomarker for broader systemic (whole body) disease. The eye is quite unique for detecting disease. Using simple ophthalmic tools, eye doctors are able to perform disease "biopsy" simply by looking into the eye. Our tools magnify the tissue in the eye and some more advanced tools are able to map tissue very precisely. We are able to "see" disease happening at its earliest stages. I know your cardiologist would benefit greatly in their diagnosis by opening up your chest and peering in at the tissue. Clearly you would not approve of that just for the purpose of diagnosis. However, optometrists and ophthalmologist can do the same thing, but non-invasively. The eye contains both blood vessels and nervous system tissue. We can "open" a window into your health by simply having you, our patients, open your eyes. We all have one circulatory system and one nervous system. What is happening in your eyes is, for the most part, the same thing that is happening in your heart and your brain. This is a much underappreciated and under utilized part of medicine.

Modern medicine is seeking the holy grail of early detection through biomarkers and billions of research dollars are being spent to find biomarkers and develop expensive drugs to treat disease. They are looking for the one thing (it is never one thing) that causes the major disease of our society; cardiovascular disease, diabetes, Alzheimer's, and cancer. The answer to their quest is staring them right in the eye.

I am not aware that a simple eye examination was included in any of the more than 200 failed prospective drug studies done by pharmacological companies in their quest for a new Alzheimer's treatment. During my more than 40 years of practice on the Harvard University staff I had the opportunity to see patients that were in many such studies. On many occasions patients with memory disorders participating in those studies had no evidence of neurodegenerative changes in their eye and their memory problem were

due to other causes such as severe B12 vitamin deficiency, drug induced transient memory loss, or other causes not related to AD. Many of the memory problems related to aging are not related to AD and this could contribute failure of those 200+ studies. The early neurodegenerative changes in the eye are related to the future possibility of AD and not to other multiple causes of memory problems.

After more than 200 failed studies we have to change things. You know what they say about people that keep doing the same thing over and over yet expect different results. (Do not forget that the people involved in those studies are among the smartest in the country).

In future AD studies patients should be recruited based on evidence of finding early ocular neurodegenerative diseases changes related to possible future development of AD.

A sick eye is, for the most part, in a sick body. Treat the causes of the sick body and the health of the eye will also improve. I'm one of very few Ophthalmologists who takes this approach. Why? Because eye doctors treat eye diseases, cardiologists treat heart diseases, neurologist treat brain diseases, and so on. These specialties seldom collaborate. Each medical discipline has its own set of diagnostics and drugs for their special ailments. But it should not be that way. We should all work together and face the facts that diseases overlap and are often connected.

When I started diagnosing and treating eye patients for systemic (whole body)diseases, back in the 1980s, their eyes did indeed get better. In fact they got much better and stayed much better compared to people who were treated as if their eyes existed in isolation from the rest of the body. Most importantly, many patients with serious disease beyond the eye reported back to me that these other conditions improved upon with whole body treatments. One of those conditions that improved was Alzheimer's disease.

I also learned from my patients what does not work. I never use my patients as a laboratory but medicine, as a science, is constantly evolving and new ideas are the norm. One such ideas was the value of antioxidants. Major National Institutes of Health studies promoted the use of antioxidants. However, when I suggested patient take, for example, vitamin E, they reported back to me that their eye got worse. Sure enough, when I examined these patients, they did show more bleeding, swelling, and scarring. When I removed them from the vitamin, their eye problem resolved. We can learn so much from patients. Dr. Alzheimer for whom Alzheimer's disease is named taught us that medical development should start with patients in the clinic, followed by laboratory research to understand why. Today we have it backwards as drug companies start in the test tube and hope their results will extrapolate into humans. Few, if any, major advances in medicine have occurred using this method.

Medical researcher have unequivocally proven that glaucoma, like Alzheimer's, is a neurodegenerative disease. The eye is an extension of the brain and the death of retinal ganglion cells in the back of the eye leads to glaucoma. The same or similar process happens in the brain of Alzheimer's patients where neurons die. It makes sense that these diseases are connected because we have one circulatory system, one central nervous system, and one lymphatic system. All these systems are interconnected. It is

almost physiologically impossible for a disease, especially a slowly incubating chronic disease, to live in complete isolation from the whole body.

It is time for a new model for disease management. Two-thirds of disease is chronic in nature and accounts for almost $2 trillion dollars of healthcare spending annually in the U.S. alone. How does healthcare currently manage these diseases? By reacting to them once they are already impacting the patients health. This is wrong and does not abide by the Hippocratic Oath. These diseases do not just suddenly strike a patient. Even cardiovascular diseases including heart attacks do not just suddenly happen without warning signs. A person who experiences a heart attack has a sick heart that got there through a slowly progressive decay over years or even decades. This is true for all the chronic diseases. It is time to institute new measures to evaluate the so-called "well person" before they have clinical symptoms of disease. Don't be fooled, just because you do not have symptoms does not mean you are illness free. Our bodies are both resilient and redundant and is often able to function well even when our health is partially compromised. It is at this stage patients are most receptive to treatments. But how do we inform people about their chronic subclinical disease?

The eye provides the answer for people interested in learning about their current and future potential for chronic disease. The beautiful part of the eye is that those most at risk already had the tests. That is, the answers to your current and future health condition is already done and it's free. How so? If you had an eye examination then your eye doctor has the information you need to appreciate your health condition and risks. There are 50,000 eye doctors in the U.S. and each sees roughly 1000 patients each year. Thus eye doctors are examining and evaluating 50,000,000 U.S. patient each year. What if each of those patients were informed of their results as it related to chronic disease? You can be sure chronic disease would not be epidemic in American and the world as it is today. Here is a short list of eye diseases and their relationship to chronic diseases:

Nuclear cataract: Associated with increased risk of cardiovascular disease.
Cortical cataract: Associated with Alzheimer's disease.
Glaucoma: Now considered Alzheimer's disease of the eye.
Macular degeneration: Those with this disease are at increased risk of both cardiovascular disease and Alzheimer's.
Loss of visual acuity: Sudden or steady vision loss is associated with increased risk of all cause mortality.

The issue you still have is finding someone willing to explain the meaning of the results. This is a big challenge we face in medicine today. The eye doctors, for the most part, understand the results and your risks but they are unwilling to share the information with you because it is "not their job." The fracturing of medicine has caused this. Doctors "pass the buck" from one specialist to the next and no one really takes charge of the information. Dr. Charles Mayo, the founder of the Mayo Clinic, used the concept of "Grand Rounds" to bring all the specialists together to confer on clinical cases. It worked and made Mayo famous. Today, the modern Mayo Clinic no longer uses this technique, it is too expensive. Instead, the patient is shuttled to each specialist who works in apparent isolation.

At your last routine eye examination did your eye doctor tell you that you have evidence of an early neurodegenerative disease process going on in your eyes? If you have a certain type of cataract, early evidence of macular degeneration, or glaucoma you have evidence of an early neurodegenerative process related to the possible future development of AD? This is if you survive another 10 to 15 years. All those eye diseases are associated with significant increase mortality and only the lucky survive long enough to have a chance of developing AD. I know this sounds counterintuitive but the average lifespan of Americans is less than 80 years yet many Alzheimer's patients are in their 80s and 90s. They somehow outlived the average, albeit with a serious degenerative disease.

Sadly I am not aware of a single eye doctor that discussed the overall health consequences of eye diseases with their patients. I have trained over 200 fellows of ophthalmology and none of them have the courage to go beyond a diagnosis of an eye disease with their patients. You have to ask your eye doctor if you have early evidence of any of those diseases after every eye examination and ask what should be done to control the chronic systemic inflammatory process related to those diseases.

As a doctor who always put my patients first, I find the big medical industrial complex aligned against the patient. The Alzheimer's Association, for example, proves to me that they are not interested in a cure for the disease. They continue to support researchers pursuing a failed approach to the disease (Chapter 2). And big pharma will never produce a pill that will "cure" Alzheimer's and other major chronic diseases. The human body is too complex for that "monotherapy" approach. Pills make money and treat symptoms, but seldom cure disease. People cure disease by taking good care of their health and seeking treatments as a last resort. Their eyes are important because it exposes diseases early. The instruments used to measure disease in the eye are very accurate and precise so I am able to show my patients how their lifestyle changes, and in some case medications, have improved their eyes and their overall health. This is motivating to most of my patients.

I hope you read, understand, and enjoy this book. It explains the pitfalls of modern medicine but it also shows you the bright side as well. There are researchers from all over the globe doing interesting and beneficial work to show why disease happens. These researchers paint a very clear picture that diseases like Alzheimer's do have treatments that work. That is, there are ways to prevent, slow, and reverse Alzheimer's. The key is to detect the disease early. This is where the eye comes in because the tests are quick, simple, non-invasive, low (or no) cost and provide a great deal about your current and future health.

As I come closer to retirement I hope I can leave a legacy of ways to improve my patient's and your health. I have worked with other doctors but with limited success. They are too busy keeping their heads about water. However, the people with the most to gain are people like you. Maybe if more people like you become informed about ways to protect your health you will demand this type of approach from medicine. You are our hope for what I consider the right and proper change to medicine.

Be Well, Sincerely,

Clement Trempe, M.D. 2014

10
Alzheimer's Disease Prevention

"America's health care system is in crisis precisely because we systematically neglect wellness and prevention."

- Tom Harkin (U.S. Senator, IA)

Why is the illustration above appropriate? Alzheimer's will be eliminated, one person at a time, through developing good habits in our youth and not by treating the elderly with severe disease. Did your grandmother force you to take cod liver oil? If you are now elderly and free from dementia or other chronic diseases, say a prayer of thanks to her.

People with Alzheimer's disease have a serious health problem that is not hopeless. This concept is contrary to the establishment that says there is no way to slow or reverse this disease. This book illustrates that science and medicine does have a solid understanding of many of the aspects of the disease. With this knowledge, a differential diagnosis and targeted treatments can attack the disease at its root. Even under these circumstances, reversal of Alzheimer's is challenging at best. **What is the real solution to Alzheimer's? Prevention!**

The places to start investigating prevention strategies are the written works of Paul Clayton and by taking a history lesson on Claude Bernard. Both of these scientists offer real and practical solutions to Alzheimer's disease prevention.

Prevention strategies are best designed on the foundation of knowledge about what causes Alzheimer's disease. Can you base your strategy on the potential formation of beta-amyloid? This concept is difficult to understand, let alone use to devise an avoidance strategy. And, as explained in Chapter 2, the best and brightest minds in research and medicine have failed to help Alzheimer's sufferers with any type of beta-amyloid approach. Evading disease caused by inflammation and/or infection is a much more manageable approach.

Remember, if Alzheimer's disease onset is pushed back by a mere five years, the number of afflicted will be reduced by about half. Those are good odds, and there are ways to hold AD at bay, as opposed to what we hear in the news about this disease. What is the approach to preventing, or at least pushing Alzheimer's way into our future? The answer is to understand and address the true causes of the disease and enhance the health of your immune system. Both of these approaches will reduce inflammation, chronic diseases in general, and Alzheimer's disease.

In this chapter we do not focus on prevention strategies published by the major thought leaders including the Alzheimer's Association, WebMD, and the Mayo Clinic. Please browse through those sites as they speak to general measures such as exercising more, curbing smoking, and taking care of your mental health. Here we mainly focus on factors that have a profound impact on immune system function including vital micronutrients that are often deficient or in excess and cause immune system dysfunction due to their discordant balance.

In their Alzheimer's prevention section the Mayo Clinic states:

"According to a statement from the National Institutes of Health (NIH), a number of factors could play a role in whether you develop Alzheimer's disease. However, more research is needed before modification of any of these factors can be proved to prevent Alzheimer's disease." [3]

The Mayo Clinic and the other pundits are raising the white flag over Alzheimer's disease. This is a major disservice to you and your family because they are ignoring bona fide research in favor of promoting a cry for more research funding. For example, as you will read in this chapter, the Framingham Study shows conclusively that fish oil consumption reduces the future risk of Alzheimer's by as much as 75%. Why is that not a headline on every AD website? Some do state the value of omega-3s but only in very guarded terms.

Prevention Through Internal Balance

Most of this book has been a projection of researchers' voices from around the globe and through time. This section on prevention is no exception as the Trillion Dollar Conundrum—that is, the wealth of research available on science and medicine, holds the answers. Start with a keyword search on "Alzheimer's" and "prevention." A title search returns over 700 articles that is equal to a lot of nighttime reading. Now focus on those that you, with a little personal responsibility, are able to incorporate into your

life. For now, limit your reading to those that include immune health and inflammation control in some form.

An article by a group of Australians titled, "*The molecular basis of the prevention of Alzheimer's disease through healthy nutrition*," pops up as interesting. [4] The abstract to their paper is included here. Read it with caution because, as discussed in Chapter 7, inflammation is a treasure and is there to protect us.

> "The Alzheimer's disease (AD) brain shows numerous pathological phenomena, including amyloid plaques, neurofibrillary tangles, elevated levels of advanced glycation end products and their receptor, oxidative damage and inflammation, all of which contribute to neurodegeneration. In this review, we consider these neuropathologies associated with AD and propose that inflammation and oxidative stress play major pathogenic roles throughout disease progression. **It is believed that oxidative stress and inflammation not only play major roles early in the disease, but that they act in a reinforcing cycle, amplifying their damaging effects.** Therefore, epidemiological studies indicate that **anti-inflammatory, and neuroprotective agents** including those from medicinal plants and health promoting foods may protect against AD. This concept is further supported by evidence that certain diets (such as a Mediterranean diet) have been associated with a lower incidence of AD. This review highlights specific foods and diets thought to lower the risk of developing AD and discusses the potential of healthy nutrition in disease prevention."

What is an anti-inflammation strategy?

1. Anti-inflammation is a strategy to build immune health so when our immune system acts on our behalf, it does so decisively and then quickly settles back down to normal levels.
    a. Anti-inflammation is a strategy to create an internal balance that then suppresses the growth of otherwise opportunistic pathogens or other "insults" that impact our health.
    b. Anti-inflammation is **not** a strategy to suppress inflammation (with NSAIDs and other immune system depressants). This may be a proper strategy to quell short-term inflammation that causes pain but, it is inappropriate for the management of chronic inflammation.

Be careful not to confuse the terms antioxidant and anti-inflammation. They are not the same. In fact, they may be diametrically in opposition. The innate immune system is primarily an oxidative process, with white blood cells as our first line of defense. They identify invaders then kill them with peroxide—a highly oxidizing substance. Oxidative stress is frequently cited as a cause of Alzheimer's and other inflammatory diseases, but this is likely from downstream effects of the inflammatory process and is not primary. David Sinclair from Harvard Medical School was a founder of Sirtris Pharmaceuticals, the science of which was based on the super antioxidant resveratrol. After the sale of Sirtris, Sinclair stated during an NPR interview, "Antioxidants have shown disappointing results in the area of anti-aging medicine."

The Australians are on the right track because they are not proponents of supplements; rather, they endorse whole foods. This is the right approach to building a healthy immune system and avoiding chronic disease. No single diet type provides the balance upon which our physiology is based. The concept of a "diet" infers a restriction of some type. The mid-Victorians did not "diet" per se; they struggled to take in sufficient calories to compensate for their toils and labors. Fortunately for them, their foods were natural and unprocessed. That is the key. The best diets, from an anti-inflammation perspective, appear to be the Paleo and Mediterranean. Both these nutritional concepts steer clear of processed foods and excessive carbohydrate consumption.

Past experience does tell us what to avoid, or at least control, in our quest for proper internal balance. "*High carbohydrate diets and Alzheimer's disease*," a scientific article produced by the University of Colorado, does well explaining the current surge in Alzheimer's and other inflammatory diseases. [5] "**Evolutionarily discordant high carbohydrate diets are proposed to be the primary cause of AD by two general mechanisms**. (1) Disturbances in lipid metabolism within the central nervous system inhibit the function of membrane proteins such as glucose transporters and the amyloid precursor protein. (2) Prolonged excessive insulin/IGF signaling accelerates cellular damage in cerebral neurons. **These two factors ultimately lead to the clinical and pathological course of AD**. This hypothesis also suggests several preventative and treatment strategies. **A change in diet emphasizing decreasing dietary carbohydrates and increasing essential fatty acids (EFA) may effectively prevent AD**." "Effectively prevent" may be language that is too strong. However, this advice about carbohydrates and essential fatty acids may certainly play a role in the prevention of Alzheimer's disease.

This study poses a conundrum almost as big as the previously discussed Trillion Dollar Conundrum. Specifically, if carbohydrates are limited, what is the replacement source of calories? Madison Avenue has brainwashed the U.S. and the world into believing that high fat intake equals obesity. Yet our store shelves are filled with low fat (high carbohydrate) alternatives that are making us fat. The answer to the carbohydrate/fat conundrum is to increase the intake of healthy fats that maintain a longer feeling satiation and quell inflammation. The book "*Eat Fat Lose Fat*" by Dr. Mary Enig and Sally Fallon explains how to reduce carbohydrates, increase healthy fat intake, and improve overall health. [6] A simple strategy to employ that helps avoid carbohydrate overload is to 1. Cook and eat a home, and 2. Grocery shop along the outside isle of the store but avoid the deli counter. By skipping the inner isles, your cart will contain significantly fewer carbohydrates and processed foods.

Foods today are somewhat stripped of their nutritional value due to over farming of land, processing, genetic modifications, and a host of other reasons. The elderly are particularly at risk of deficiencies because they do not absorb minerals well, compared to younger people. Many people do supplement in an attempt to be healthy, and this is probably important for both the active and the sedentary because even those with sedentary bodies have metabolically active and hungry brains. Some vitamins, nutrients, and supplements may be harmful in excess and should be purchased and taken based on knowledge, not just based on the latest headline in *Self*, by that "Oz" headline machine, or *Men's Health*. Calcium, which will be discussed in great detail later

in this chapter, is a mineral that is the poster child for a well-intended message that may have gone terribly wrong. There are extensive research compilations on the "calcium hypothesis of dementia." Therefore, don't assume that if it is good for one specific thing that it is healthy for you long-term or is essential, as a supplement, for your good health. The Harvard School of Public Health teaches, "The dose makes the poison." Both oxygen and water are toxic at either extremes of dose.

Inflammation Starts in the Gut

The Microbiome may be the hottest topic in medicine today, particularly with progressive practitioners. Microbiome refers generally to the gut and specifically to the beneficial microorganisms that work symbiotically with our bodies to produce immunity, provide nutrients, and manage waste. Dysbiosis refers to a condition with microbial imbalances on or within our bodies. Bysbiosis is most prominent in the digestive tract or on the skin, but can also occur on any exposed surface or mucous membrane such as the vagina, lungs, mouth, mose, sinuses, ears, nails, or eyes.

Researchers are discovering a causal relationship between an imbalanced gut microbiome (gut dysbiosis) and a growing number of conditions and diseases – for example, acne, allergies, asthma, celiac disease, chronic Lyme disease, Crohn's disease, diabetes, Graves disease, gum and tooth disease, irritable bowel, lichen planus, lupus, multiple sclerosis, psoriasis, rheumatoid arthritis, UTIs, all the other 80-100 autoimmune diseases, and some cancers. See Autoimmune Disorders for more information.

Serious memory loss, as with Alzheimer's, has also been found to be related to gut bacterial imbalances. How does this happen? When the micro-organisms living in the gut become out of balance, inflammation develops – and chronic inflammation is the hallmark of chronic diseases including AD. We now appreciate that chronic inflammation is our leads to opportunistic pathogen proliferation. Apparently in dysbiosis, when beneficial bacteria are lost, antagonistic pathogens are able to grow. And their development leads to a general decline in immunity so other latent and harmful species can also thrive, leading to inflammation, neuroinflammation, and Alzheimer's disease.

Here is the conclusion from an article titled, "Obesity and Gut's Dsbiosis Promote Neuroinflammation, Cognitive Impairment, and Vulnerability to Alzheimer's disease: New Directions and Therapeutic Implications." [7]

> "Systemic inflammation occurs due to LPS (bacterial remnants) efflux from the gut; this up-regulates neuroinflammation including that in the hippocampus and cerebellum. Brain pro-inflammatory cytokine generation and synthesis, i.e. neuroinflammation promotes amyloid deposition and tau hyperphosphorylation that enhance hypofunction/dysfunction in key brain regions, including the hippocampus and cerebellum. This cascade of events promotes neuronal injury/apoptosis and degeneration, leading to cognitive impairment and vulnerability to Alzheimer's dementia."

Your solution to prevention of this significant problem is actually quite simple but you have to start young, in fact very young. However, it is never too late to protect your health.

1. Expecting mothers need to develop good gut health following some of the suggestions below.
2. Have a natural birth and dretch your newborn in all your beneficial bacteria. This is their first and vital exposure.
3. Allow your 0-3 year old to play on clear dirt. Soil is the earth's gut and is full of beneficial microbes and minerals. Why do our very young always tough things and reach for their mouths? In nature, very few things are toxic so this is action is not due to a death wish. They are naturally building their immunity.
4. Avoid GMO and processed food from very early in life (pre-birth for mothers) until your last days.
5. Take a multimineral supplement. This supports the function of our enzymes. And healthy bacteria have enzymes too. This will promote gut health.
6. Eat fermented foods as they contain beneficial food-processing microbes.
7. Take broad-spectrum probiotics and, more importantly take prebiotics. Too much of a good thing is also bad so be careful when chosing a probiotic. Another approach is to switch brands frequently.
8. Read what follows as there are many more suggestions to create good health and prevent Alzheimer's disease.

Magnesium

Do you know that wheat has three times as many genes as a human? How is this relevant to Alzheimer's disease you might ask? Wheat has many more genes compared to us because it does not have the capacity to move to find proper nutrition to grow. It must have, within its gene pool, adequate diversity to accommodate life and growth regardless of the quality of soil upon which its seeds fall. Crafty humans are aware of this and are able to modify the genes of wheat and other plants so they can grow in nutrient deficient soil. **It is less expensive to produce seeds that can grow in magnesium deficient soils than it is to fertilize the fields with magnesium**. The consumer thus loses a source of valuable nutrients. This is one significant concern regarding GMO seeds, crops and our good health.

Magnesium is a special, necessary, yet all-to-often overlooked mineral. Sixty percent of the body's magnesium is found in bone yet our focus is only calcium intake. The majority of magnesium in muscle is found in the mitochondria, where it plays a key role in metabolism and is believed to be involved in the permeability of the outer membrane. [8]

Dietary intake of magnesium has gone down dramatically over the past 100 years. It is estimated that 68 to 80 percent of Americans are magnesium deficient. [9,10,11] In places

where water is harder, levels of magnesium are higher, and the incidence of coronary artery disease is lower. Magnesium deficiency apparently leads to early and sudden mortality by cardiovascular diseases. Almost 8 million deaths from sudden cardiac failure occurred in the U.S. between 1940 and 1994 that were largely attributed to magnesium deficiency. [12,13,14,15]

Evaluation of your homeostasis for magnesium is not straight forward, as serum levels (in the blood) are a poor indicator of magnesium status. Most of the magnesium in our bodies resides inside of cells contrary to calcium that resides outside of cell membranes. Heart muscle levels are almost 20 times higher than serum levels. It turns out that measuring white blood cell levels is a more sensitive test. The best test is ionic magnesium measurement or elemental X-ray analysis. However, none of these methods is definitive. [16,17] Many factors regulate magnesium absorption, including vitamin D levels. [18] As calcium levels go down, magnesium absorption increases. High intakes of calcium, protein, vitamin D, and alcohol all increase magnesium requirements. Without adequate magnesium, bones will be dense, but some will have poor integrity. Northern European countries, where the calcium to magnesium ratio is 4:1, have the highest rates of osteoporosis. [19]

In lieu of tests, the best way to insure adequate magnesium is simply through supplementation or, preferably, through dietary modifications, as magnesium has a very favorable safety profile. Abundant magnesium leads to a loose stool and then to diarrhea. The best dietary sources of magnesium are whole grains, nuts, and fruits. These include buckwheat flour, tofu, figs, cashews, avocado, millet, and brewer's yeast. All green plants contain magnesium, as this metal is at the center of the chlorophyll molecule.

Magnesium has an effect of relaxing smooth muscle and is therefore useful in conditions such as hypertension, dysmenorrhea, constipation, asthma, angina, stroke, heart attack, and Alzheimer's disease. It decreases coagulation and acts as a calcium channel blocker, helping the heart to pump more effectively and regulating blood pressure. [20,21,22] Magnesium is involved in the function of more than 300 enzymes, as well as in regulating muscle contractility and nerve impulses. Virtually all body systems also rely on magnesium for at least some of their metabolic functions. [23,24,25] Do you find it interesting that drug companies invest billions of dollars in drugs that are involved in the action of a couple of enzymes yet we take their drugs while being magnesium deficient? This is quite a paradox.

Magnesium deficiency is insidious because it can mimic many other disorders. These include fatigue, poor nail growth, irritability, weakness, dysmenorrhea, muscle spasms or tightness, cardiomyopathy, anorexia, sugar cravings, hypertension, and anxiety. [26,27,28,29,30] Does magnesium deficiency mimic these diseases or is the deficiency the disease? Deficiency can result from kidney disease and intake of diuretics, and it can cause depletion of potassium intracellularly and affect muscles and bones. Magnesium deficiency can be caused by poor absorption or high metabolic use, as is likely the case for hyperthyroidism, kwashiorkor, diabetes mellitus, alcoholism, pancreatitis, parathyroid disorders, high dietary phytic acid, and diarrhea. [31,32,33,34]

The clinical use of magnesium can be applied to a variety of conditions. These include constipation, muscle cramping, torticollis, acute angina following a myocardial infarct or stroke, asthma, kidney stone prevention (especially when given with vitamin B6), and dysmenorrhea. Other candidates for magnesium supplementation are GI spasms or cramping, eclampsia, heart disease (especially cardiomyopathy), [35,36] diabetes mellitus, nocturnal muscle cramps, mitral valve prolapse, toxemia of pregnancy, fibromyalgia, migraine headaches, lead toxicity, general fatigue, anxiety, and irritability. Isn't it interesting to see the interconnectedness of many of these diseases as shown simply and elegantly through magnesium deficiency?

General dosing of daily magnesium should be approximately 450 mg, considering all sources. However, for GI cramping, asthma, constipation, and heart disease, it is recommended to take magnesium to improve bowel tolerance (until the bowel movements become "loose"). Fortunately the toxicity of magnesium is fairly low, with diarrhea being the biggest problem. Reduce the dose until bowel movements return to normal to prevent other possible symptoms of magnesium toxicity, such as calcium deficiency, hypotension, depletion of potassium, and respiratory depression. [37]

Magnesium and Inflammation

In two large observation studies (the Women's Health Initiative [38] and Nurses Health Study [39]) greater magnesium (Mg) intake was associated with lower levels of inflammation as measured by CRP, IL-6, and TNF-α receptor, a measure of TNF-α activity. Data from the Multi-Ethnic Study of Atherosclerosis (MESA) failed to find significant differences in IL-6 or CRP levels between individuals with the highest and lowest magnesium intakes, but did find a significant association between greater dietary magnesium and the lower levels of the inflammation-associated proteins homocysteine and fibrinogen. [40] **Magnesium was rated as the most anti-inflammatory dietary factor in the Dietary Inflammatory Index, which rated 42 common dietary constituents on their ability to reduce CRP levels based on human and animal experimental data**. This did not include foods that are often mistaken as supplements. For example, fish oil has a more profound impact on lowering CRP compared to magnesium.

"Memory functions decline with age, and severely deteriorate during Alzheimer's disease. Several studies suggest that dietary/environmental factors can reduce the prevalence of AD in humans. Magnesium is essential for maintaining normal body and brain functions." This is according to Chinese researchers as presented at a Shanghai conference in 2012. [41] Magnesium deficiency is common in the elderly and is an important factor to consider in the prevention and management of dementias including Alzheimer's.

Magnesium and Alzheimer's

Stepping back to 1990, "*Magnesium depletion and pathogenesis of Alzheimer's disease,"* by a French researcher, presented evidence indicating dementias are associated with a relative insufficiency of magnesium (Mg) in the brain. [42] Such insufficiency may be attributable to low intake or retention of Mg; high intake of a neurotoxic metal, such as

aluminum (Al), which inhibits activity of Mg-requiring enzymes; or impaired transport of Mg and/or enhanced transport of the neurotoxic metal into brain tissue.

Finally, a recent paper portends what may be an important part of the future of Alzheimer's treatment. [43] This paper was written by German researchers and has a clear thesis and conclusion. Part of the abstract is reproduced here:

> "The cholinergic deficit in Alzheimer's disease (AD) remains the cornerstone for the understanding of chemical signal transfer. Hypofunctions of cholinergic systems are significantly involved in the signs and symptoms of senile dementia of the Alzheimer type… Magnesium is directly involved in numerous important biochemical reactions and is particularly a necessary cofactor in more than 300 enzymatic reactions and specifically in all those processes involving the utilization and transfer of adenosine triphosphate. A study in patients with different diagnoses showed low enzyme activity of choline esterase in erythrocytes (red blood cells). Administration of magnesium resulted in normal catalytic activity of choline esterase. The measurement of the enzyme activity of choline esterase is a possibility to prove magnesium deficiency and to verify the efficacy of magnesium administration. **Magnesium deficiency, resulting from low magnesium dietary intake, is more common and may be corrected by magnesium supplementation**."

Take your magnesium—it is such a simple health enhancement measure—and discard your calcium.

Calcium

With our newly found understanding about the connection between Alzheimer's and cardiovascular diseases, let's look at the impact of calcium supplementation on the latter. The medical literature is full of research on this topic as a scholar.google search yields 285 articles, just between 2010 and 2013, using the keywords "calcium" and "cardiovascular" in a title-only search. The first one that comes up paints a vivid picture. The title is, "*Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis.*" [44] This team from New Zealand and the U.S. conclude:

> "Calcium supplements (without co-administered vitamin D) are associated with an increased risk of myocardial infarction (heart attack). As calcium supplements are widely used these modest increases in risk of cardiovascular disease might translate into a large burden of disease in the population. **A reassessment of the role of calcium supplements in the management of osteoporosis is warranted**."

A reassessment of the role of calcium supplement indeed! The National Osteoporosis Foundation, on their website states, under "Debunking the Myths,"

> "Myth #9: Taking extra calcium supplements can help prevent osteoporosis.

"Taking more calcium than you need does not provide any extra benefits. Estimate the amount of calcium you get from foods on a typical day to determine whether a supplement is right for you."

You probably get enough calcium in your foods to prevent osteoporosis and supplementation is not worth the risk. What you **do not** have at sufficient levels are vitamin D and magnesium. There are no appreciable side effects from taking these essential components compared to calcium.

"Evidence from limited data suggests that vitamin D supplements at moderate to high doses may reduce CVD risk, whereas calcium supplements seem to have minimal to doubtful cardiovascular effects. Further research is needed to elucidate the role of these supplements in CVD prevention." This is the conclusion by another set of researchers. [45] Although the researchers did not find any negative contribution from calcium (or did they, but the vitamin D was protective?), they showed the importance of vitamin D. Based on current data, treating 1,000 people with calcium supplements for five years would prevent only 26 fractures but would cause an additional 14 heart attacks. Both these numbers would most likely decrease if the 1,000 people had sufficient vitamin D and magnesium in their systems.

The New York Academy of Sciences assembled a book titled, *The Calcium Hypothesis of Dementia*, in early 1990s based on a summit on the topic. A classic paper included in the books is titled, "*The calcium rationale in aging and Alzheimer's disease*." [46] The full original article is available in electronic form on the Internet. Some key points from this article are reproduced here:

- Calcium is required for the function of all cells in the body, including neurons.
- Calcium is intimately involved in a variety of 'plastic' changes in the brain.
- Calcium thus is likely to have key roles in the cellular processes underlying aging-related changes in the brain, including normal age-associated memory impairments as well as more severe dementias, including Alzheimer's disease.
- The pivotal role of calcium in so many neuronal processes dictates the need for precise regulation of its intracellular levels. **Any dysregulation, however subtle, could lead to dramatic changes in normal neuronal function**.
- The calcium hypothesis, which posits that in the aging brain, transient or sustained increases in the average concentration of intracellular free calcium contribute to impaired function, eventually leading to cell death.
- The hypothesis suggests that the final common pathway that may contribute to cognitive deterioration of aging vertebrates, including persons with Alzheimer's disease or other aging-related dementias, is increased free calcium within neurons. The functional impairment that characterizes a patient at a particular time in the aging-related disease process may be relieved by reducing excessive calcium influx."

There are plenty of updates to this important research. A google.scholar search over a four year period starting in 2009 yields 20 articles with Alzheimer's and calcium in the title. The key term appears to be "dysregulation" of calcium. Whatever the scientific jargon, please consider taking the advice already provided, and do not upset your calcium balance with supplements.

Vitamin D

"*The Miracle Vitamin*," by Paula Dranov, states, "new evidence shows that getting enough D may be the most important thing you can do for your health." [47] This is a true statement, and the preferred way to get vitamin D is through sun exposure and by taking cod liver oil. Cod liver oil contains the key fat-soluble vitamins A and D. Most importantly, this natural source contains all the variations (isomers) of the vitamins.

The health benefits of vitamin D are prominently highlighted in the New York Well Blog. Key recent headlines concerning vitamin D include:

- *Low Vitamin D Levels Linked to Disease in Two Big Studies*. [48]
- *What Do You Lack? Probably Vitamin D*. [49]
- *Low Vitamin D Tied to Premature Death*. [50]
- *Vitamin D May Lower Cholesterol*. [51]
- *Low Vitamin D Tied to a Pregnancy Risk*. [52]
- *Low Vitamin D Tied to Aging Problems*. [53]

Clearly, insufficient vitamin D impacts our health from birth to death.

But it turns out that the term "vitamin" is a misnomer for vitamin D. It is really a hormone. The word "vitamin" means something our body needs that it can't make, so must be obtained from food. "D hormone" (vitamin D) is instead an essential substance that we make on our skin from sun exposure. It is a hormone like thyroid, estrogen, or testosterone. Using the proper word "hormone" reminds us that it affects multiple parts of the body and that it is essential to every cell in the body.

From what molecule does vitamin D come when light hits our skin? Cholesterol. [54] Yes, that same "evil" substance that the drug companies claims causes so much harm. Maybe we are learning that cholesterol is not so evil and even important for our protection against Alzheimer's disease.

Vitamin D, the fat-soluble hormone is naturally present in very few foods, added to others, and available as a dietary supplement. It is also produced when ultraviolet rays from sunlight strike the cholesterol in the skin and trigger vitamin D synthesis. Vitamin D obtained from sun exposure, food, and supplements is biologically inert and must undergo a chemical reaction (hydroxylation) in the body for activation. One reaction occurs in the liver and converts vitamin D to 25-hydroxy vitamin D, also known as 25 vitamin D, vitamin D3, or simply vitamin D. Under normal conditions, another reaction occurs primarily in the kidney to form the physiologically active 1,25-dihydroxyvitamin D, also known as calcitriol.

Importantly, activation of 25-hydroxy vitamin D to the 1,25-dihydroxyvitamin D occurs in inflamed tissue. Here, the activated form of vitamin D is working in concert with our immune system to deal with the inflammation. This "activation" process is often the cause for the failure of ingested vitamin D supplements to raise the serum vitamin D levels in patients. In this capacity, a measurement of blood vitamin D levels, for those under supplementation, may reveal a disease process in progress. Those patients with low vitamin D levels, but who appear to have adequate intakes of the substance should be tested for the activated (1,25-dihydroxy) form of vitamin D.

The activated form of vitamin D may positively impact Alzheimer's disease. A Canadian group carried out long-term treatment of mice with activated 1,25-dihydroxy vitamin D reduced beta-amyloid plaque formation, importantly of both the soluble and insoluble type. Of particular importance, the amyloid reduction occurred in the hippocampus region of the brain. This led to improvement in conditioned fear memory. The data suggest that the vitamin D receptor and treatment with vitamin D or its activated form is important therapeutically for the prevention and treatment of Alzheimer's disease. [55]

Vitamin D promotes calcium absorption in the gut and maintains adequate (and balanced) serum calcium and phosphate concentrations to enable normal mineralization of bone and to prevent low calcium concentrations. It is also needed for bone growth and bone remodeling by osteoblasts and osteoclasts. Without sufficient vitamin D, bones can become thin, brittle, or misshapen. Vitamin D sufficiency prevents rickets in children and osteomalacia in adults. Vitamin D also helps protect older adults from osteoporosis.

Vitamin D has other roles in the body, including modulation of cell growth, neuromuscular and immune function, and reduction of inflammation. Many genes encoding proteins that regulate cell proliferation, differentiation, and apoptosis are modulated in part by vitamin D. Many cells have vitamin D receptors, and some convert the diol to the triol of vitamin D. Serum concentration of the diol of vitamin D is the best indicator of vitamin D status. It reflects vitamin D produced by sunlight and that obtained from food and supplements and has a fairly long circulating half-life of 15 days. Vitamin D functions as a biomarker of exposure, but it is not clear to what extent vitamin D levels also serve as a biomarker of effect. Serum vitamin D levels do not indicate the amount of vitamin D stored in body tissues. Vitamin D, although not synthesized by sunlight in the winter in the northern hemisphere, is available to the body by storage in fat throughout the year, assuming adequate exposure to sunlight during summer months.

There is considerable discussion about the serum concentrations of vitamin D associated with deficiency (e.g., rickets and other degenerative diseases), a scientific consensus process has not developed adequacy for bone health and optimal overall health. Based on its review of data of vitamin D needs, a committee of the Institute of Medicine concluded that persons are at risk of vitamin D deficiency at serum vitamin D concentrations <30 nmol/L. Some are potentially at risk for inadequacy at levels ranging from 30–50 nmol/L. Practically all people are sufficient at levels ≥50 nmol/L; the committee stated that 50 nmol/L is the serum vitamin D level that covers the needs of 97.5% of the population. Serum concentrations >150 nmol/L are associated with potential adverse effects. These adverse affects, however, are relatively mild. There has never been an incident of serum concentration >125nmol/L from sun exposure alone. It is nearly impossible to achieve a level of 150 nmol/L through supplementation.

According to research from the U.K. and Canada, "Vitamin D was initially thought to play a restricted role in calcium homeostasis, but the pleiotropic (multi-factorial) actions of vitamin D in biology and their clinical significance are only now becoming apparent." [56] In their publication, the researchers found 2,776 binding sites for the vitamin D receptor along the length of the genome. These were unusually concentrated near a number of genes associated with susceptibility to autoimmune conditions such

as MS, Crohn's disease, systemic lupus erythematosus (or 'lupus'), rheumatoid arthritis, and to cancers such as chronic lymphocytic leukemia and colorectal cancer. They also showed that **vitamin D had a significant effect on the activity of 229 genes**. "Vitamin D status is potentially one of the most powerful selective pressures on the genome in relatively recent times." As with magnesium, the action of vitamin D is the envy of the drug companies.

Vitamin D appears to exert anti-inflammatory activity by the suppression of pro-inflammatory prostaglandins and inhibition of the inflammatory mediator NF-κβ. [57] Although intervention studies of its anti-inflammatory activity in humans are lacking, **several observational studies suggest vitamin D deficiency may promote inflammation**. Vitamin D deficiencies are more common among patients with inflammatory diseases (including rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, Alzheimer's disease, and diabetes) than in healthy individuals. [58,59,60,61,62,63,64,65] They also occur more frequently in populations that are prone to low-level inflammation, such as obese individuals and the elderly. Vitamin D levels can drop following surgery (a condition associated with acute inflammation), with a concomitant rise in CRP. Low vitamin D status was associated with elevated CRP in a study of 548 heart failure patients and with increases in IL-6 and NF-κβ in a group of 46 middle-aged men with endothelial dysfunction. [66]

Vitamin D and Alzheimer's

Elizabeth Pogge from the Midwestern University College of Pharmacy crafted a paper titled, "*Vitamin D and Alzheimer's Disease: Is there a Link?*" [67] Dr. Pogge wrote, "The current observational studies seem to identify a link between vitamin D and dementia, particularly AD. Before this evidence can be used to make a recommendation for routine supplementation in elderly patients to prevent AD, more prospective trials with a longer follow-up period are needed to show a causality relationship."

The following is a recommended rewrite to the conclusion above, replacing the "need more research," with something helpful to humanity. "The link between Alzheimer's and vitamin D is very interesting especially considering that most of modern society is deficient in vitamin D. We therefore recommend that all people consider having vitamin D levels measured and supplement as necessary to ensure everyone have levels widely considered sufficient. In lieu of measurement, consider supplementing with vitamin D because this vitamin has been proven safe, even at high levels, over years of study and clinical experience." Which recommendation will save more lives and reduce human suffering?

Let's circle back to that statement about vitamin D being the most important thing you can do for your health. Here is part of an abstract from a U.K. and Canadian 2013 research article: [68]

> "This review highlights the epidemiological, neuropathological, experimental, and molecular genetic evidence implicating **vitamin D as a candidate in influencing susceptibility to a number of psychiatric and neurological diseases**. The strength of evidence varies for schizophrenia, autism, Parkinson's disease, amyotrophic lateral sclerosis, and Alzheimer's disease, and is especially strong for multiple sclerosis."

Vitamin D was discovered as the cure for rickets, and those on vitamin D therapy were found to have lower incidences of infectious diseases such as Tuberculosis. The 1903 Nobel Prize in Medicine or Physiology was awarded to Professor Niels Finsen in recognition of his work on the treatment of diseases, and in particular the treatment of lupus vulgaris by means of concentrated light. Lupus vulgaris is, as we now know, a form of tuberculosis, with localized lesions on the skin, especially that of the face, such as the nose, eyelids, lips, and cheeks. What do you suppose the light therapy produced on the exposed skin—vitamin D maybe?

Modern research shows that high doses of vitamin D help tuberculosis patients recover more quickly. Vitamin D, given in addition to antibiotic treatment, appears to help patients through likely antibiotic action of its own, by dampening down the body's inflammatory response to infection, and enabling tissue to recover more quickly and with less damage. "**We found that a large number of these inflammatory markers fell further and faster in patients receiving vitamin D**," according to researchers of a paper titled, "*Vitamin D accelerates resolution of inflammatory responses during tuberculosis treatment.*" [69]

A large group of researchers from across the pond and the U.S. combined to determine whether low vitamin D concentrations are associated with an increased risk of incident all-cause dementia and Alzheimer disease. [70] In this study they evaluated 1,658 ambulatory adults free from dementia including Alzheimer's disease. Vitamin D levels were measured, and the patients were tested subsequently for an average of 5.6 years. Dementia occurred in 171 participants including 102 cases of AD. Individuals considered deficient in vitamin D were 2.25 times more susceptible to dementia and AD; those considered insufficient in vitamin D were more than 1.5 times more susceptible compared to those who were at sufficient levels of vitamin D. The 14 MDs and Ph.Ds. concluded:

"Our results confirm that vitamin D deficiency is associated with a substantially increased risk of all-cause dementia and Alzheimer's disease. This adds to the ongoing debate about the role of vitamin D in non-skeletal conditions."

These researchers are not alone in their claims about the value of vitamin D and Alzheimer's. Just within the past year the titles listed below provide further validity to this important relationship.

- *Vitamin D, cognition, and dementia: a systematic review and meta-analysis*. [71]
- *Low serum vitamin D concentrations in Alzheimer's disease: a systematic review and meta-analysis*. [72]
- *Meta-analysis of memory and executive dysfunctions in relation to vitamin D*. [73]

One little vitamin (hormone) yet so much power to promote good health, and you can obtain it naturally, at no cost, through some prudent exposure to the sun.

Vitamin E

The jury has cast a unanimous verdict against antioxidants in diseases of inflammation. Our own clinical experience, particularly with advanced macular degeneration, has been negative. That is, patients report an increase in symptoms, especially bleeding in

the wet form of AMD, when on vitamin E supplementation. However, popular wisdom is that gobbling up free radicals is critical to maintaining health. Proceed with caution. A Cambridge-based biotech company sold a resveratrol concept (a powerful antioxidant that you no doubt have seen make its way onto drug store shelves recently) to GSK pharma for $728,000,000 on the premise that mice fed their antioxidant compound(s) lived twice as long. GSK abandoned the project after they couldn't reproduce the results. We have yet to learn from Ponce de Leon. Antioxidants are not turning out to be the fountain of youth.

A U.K. groups wrote, "*Vitamin E for Alzheimer's disease and mild cognitive impairment*," in 2008. [74] The authors stated that vitamin E is a dietary compound with antioxidant properties involved in scavenging free radicals. Laboratory and animal studies have pointed towards a possible role for vitamin E in the prevention and management of cognitive impairment. To date, only one randomized controlled trial has assessed the efficacy of vitamin E in the treatment of AD patients and only one assessed the role of vitamin E in patients with mild cognitive impairment (MCI). In the vitamin E study for moderately severe AD patients, a lower number of those taking vitamin E declined to incapacity over a two-year period compared with the placebo group. However, AD patients taking vitamin E experienced a greater number of falls. In the MCI study, vitamin E 2000 IU daily produced no significant difference in the rate of progression to AD compared to the placebo group.

What is your call to action? Be careful about supplementing with vitamin E until further notice. Also, not all supplements are created equally. There are several forms (isomers) of the basic compound of vitamin E. Any supplementation should include that blend of isomers in their naturally occurring ratios. In a 2008 study, the authors said, "the combination of [alpha-tocopherol] and [gamma-tocopherol] supplementation appears to be superior to either supplementation alone on biomarkers of oxidative stress and inflammation and needs to be tested in prospective clinical trials." [75]

Iron

Clearly we need iron in our bodies to survive, and plenty of it. Iron is at the center of the heme molecule of hemoglobin that is responsible for the uptake and transport of oxygen to tissue in need, through our circulatory system. However, iron dysregulation is receiving substantial consideration as a factor contributing to AD. The critical question, which is yet to be fully answered, is: can limiting or removing "excess" iron prevent or curtail Alzheimer's?

Researchers at UCLA provide some clarity about iron, iron metabolism, and the potential for excess iron to cause or exacerbate AD. "It is difficult to measure iron in tissue when the tissue is already damaged. But the MRI technology we used in this study allowed us to determine that the increase in iron is occurring together with the tissue damage (of Alzheimer's). We found that the amount of iron is increased in the hippocampus and is associated with tissue damage in patients with Alzheimer's but not in the healthy older individuals—or in the thalamus. So the results suggest that iron accumulation may indeed contribute to the cause of Alzheimer's disease." [76,77]

The researchers indicate that the findings are not all bad news. "The accumulation of iron in the brain may be influenced by modifying environmental factors, such as how

much red meat and iron dietary supplements we consume and, in women, having hysterectomies before menopause." [76]

Most of the basic building blocks in our bodies can be deleterious when deficient or in excess. This is true for some of the most fundamental substances like water and salt. This issue to be solved, always, is the root cause. The solution for dehydration is obvious, take in water. An iron dysregulation in part of the brain impacted by Alzheimer's may not have such an obvious answer. Controlling your iron intake, especially by limiting iron supplementation that is not recommended by a doctor you trust, may be prudent based on the UCLA and other studies. Women clearly have less of a need to reduce iron intake. Several male doctors we know, who are aware of the general oxidative stress that excess iron can create, give blood at least once each year.

Zinc

Yes there are many magnificent papers on zinc and Alzheimer's disease including one by Brits in 2010 titled, "*The Role of Zinc in Alzheimer's Disease*." [78] The authors inform us that zinc, the most abundant trace metal in the brain, has numerous functions, both in health and in disease. "Zinc has multifactorial functions in Alzheimer's disease (AD). Zinc is critical in the enzymatic non-amyloidogenic processing of the amyloid precursor protein (APP) and in the enzymatic degradation of the amyloid-β (Aβ) peptide. Zinc binds to beta-amyloid promoting its aggregation into neurotoxic species, and disruption of zinc homeostasis in the brain results in synaptic and memory deficits. Thus, zinc dyshomeostasis (variable concentrations) may have a critical role to play in the pathogenesis of AD."

From the perspective of inflammation, zinc-containing antioxidant proteins reduce reactive oxygen species (free radicals), which indirectly inhibits nuclear factor kappa beta (NF-κβ) [1] activity and prevents the production of several inflammatory enzymes and cytokines. Zinc can also inhibit nuclear factor kappa beta NF-κβ in a more direct manner. Zinc supplementation is associated with decreases in inflammation in populations that are prone to zinc deficiency, such as children and the elderly. Low level inflammation and circulating pro-inflammatory factors (CRP, TNF-α, IL-6, and IL-8) were reduced in elderly subjects by moderate zinc supplementation in several studies. Like zinc, selenium deficiencies are common in chronic inflammatory states associated with disease, where selenium supplementation has been associated with reductions in inflammation and better patient outcomes.

Mass General researchers reviewed zinc through an article titled, "*Zinc takes the center stage: its paradoxical role in Alzheimer's disease*." [79] They indicated, "Zinc in human nutrition is undoubtedly essential," and "… the protective effect of zinc against beta-amyloid cytotoxicity, coupled with anecdotal results from a few zinc supplementation studies warrant further research."

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[1] NFkB is a protein that acts as a switch to turn inflammation on and off in the body. It is sometimes described as a "smoke sensor" that detects dangerous threats like free radicals and infectious agents. In response to these threats, NFkB "turns on" the genes that produce inflammation. As we age, NFkB expression in the body increases, as does chronic inflammation sets the stage for aging body's defense against diseases ranging from atherosclerosis and diabetes to Alzheimer's.

The Age-Related Eye Disease Study (AREDS), explored in Chapter 6, set out to investigate if vitamins and/or minerals could slow the progression of age-related macular degeneration. A conclusion from one of the many AREDS-generated research articles reads, "The AREDS trial results suggest that antioxidants and zinc, either alone or in combination, were modestly effective for category 3 and 4 patients with AMD. The trials leaves unanswered the question of supplementation for category 1 and 2 patients as well as the long-term safety of the agents. Due to the morbidity of the visual loss associated with AMD and the lack of treatments, it may be reasonable to use supplementation in the selected high-risk group." [80] These results do not marginalize the value of zinc but suggest that the high doses used in the study do not significantly alter the impact that the proper physiological levels of zinc already exert.

What should you do regarding zinc? Stay tuned as more information about its connection to Alzheimer's disease emerges. Identify foods high in zinc that are found on the outer isle of your grocer's shelves including: liver, certain mushrooms, asparagus, chard, scallops, lamb, beef, maple syrup, shrimp, green peas, yogurt, oats, pumpkin seeds, sesame seeds, turkey, miso, and spelt. Consider taking zinc supplementation up to daily recommendations by the USDA. Never take high doses of any supplement, as this is not natural to our history, with few exceptions. Vitamin D is a notable exception where we store the vitamin in our adipose tissue for consumption in the winter as few foods provide it naturally.

Vitamin K

Vitamin K is a fat-soluble vitamin. The "K" is derived from the German word "koagulation." Coagulation refers to the process of blood clot formation. Vitamin K is essential for the functioning of several proteins involved in blood clotting. There are two naturally occurring forms of vitamin K. Vitamin K_1 also known as phylloquinone, is synthesized by plants and is the predominant form in the diet. Vitamin K_{12}comes from animal sources and synthesis by intestinal bacteria.

In the Rotterdam Heart Study, people eating lots of Edam and Gouda cheese had higher levels of vitamin K_2 and less artery calcification. [81] Higher levels of Vitamin K_2 are also associated with lower risk of prostate cancer. By keeping calcium out of the brain, K_2 may also help prevent Alzheimer's Disease. There is a clear pattern: too much calcium in the wrong places cause trouble. Calcium in the right place (ie bone) is a good thing. Vitamin K_2 appears to make sure calcium goes into the right places in the right amounts.

A relative deficiency of vitamin K is common in aging men and women. The concentration of vitamin K is lower in the circulating blood of APOE4 carriers, the gene that, to some degree, predisposes a person to Alzheimer's disease. Evidence is accumulating that vitamin K has important functions in the brain. It is now proposed that vitamin K deficiency contributes to the process of AD and that its supplementation may have a beneficial effect in preventing or treating the disease. Vitamin K may also reduce neuronal damage associated with cardiovascular disease.

Curcumin

Extensive in vitro (outside the body) and animal studies have examined the effects of curcumin on experimentally induced inflammatory diseases (atherosclerosis, arthritis, diabetes, liver disease, gastrointestinal disorders, and cancers) and disease markers (lipoxygenase, cyclooxygenase, TNF-α, IL-1β, NF-κβ, and others). Fewer human studies have examined curcumin's effects on patient-oriented outcomes in inflammatory diseases, but most of the small, randomized controlled trials of curcumin have consistently shown patient improvements in several inflammatory diseases, including psoriasis, irritable bowel syndrome, rheumatoid arthritis, and inflammatory eye disease.

Curcumin is undergoing studies in Alzheimer's disease, and initial results show no benefit from the compound. A combined Japanese and German team wrote, "*Curcumin and Alzheimer's Disease,*" and reported a lack of effect. [82] Their abstract is provided here because it is very educational. Curcumin is involved in the inhibition of so many mechanisms thought to be important to Alzheimer's disease; yet early results are disappointing.

> "Curcumin has a long history of use as a traditional remedy and food in Asia. Many studies have reported that curcumin has various beneficial properties, such as antioxidant, anti-inflammatory, and antitumor. Because of the reported effects of curcumin on tumors, many clinical trials have been performed to elucidate curcumin's effects on cancers. Recent reports have suggested therapeutic potential of curcumin in the pathophysiology of Alzheimer's disease (AD). In in vitro studies, curcumin has been reported to inhibit amyloid-β-protein (Aβ) aggregation and Aβ-induced inflammation, as well as the activities of β-secretase and acetylcholinesterase.
>
> In in-vivo studies, oral administration of curcumin has resulted in the inhibition of Aβ deposition, Aβ oligomerization, and tau phosphorylation in the brains of AD animal models, and improvements in behavioral impairment in animal models. These findings suggest that curcumin might be one of the most promising compounds for the development of AD therapies.
>
> At present, four clinical trials concerning the effects of curcumin on AD have been conducted. Two of them that were performed in China and USA have reported no significant differences in changes in cognitive function between placebo and curcumin groups, and no results have been reported from two other clinical studies. Additional trials are necessary to determine the clinical usefulness of curcumin in the prevention and treatment of AD."

Rule of thumb: If you are studying the literature for information about disease, completely ignore "animal only" studies. They are probably right 50% of the time when translated to humans, so consider flipping a coin instead. The lack of detailed studies with curcumin and its antioxidant properties suggests that you should enjoy curry, but avoid supplementation.

For those of you hungry for more information, there is plenty on curcumin and Alzheimer's disease, provided by UCLA at the following web address:

http://Alzheimer.neurology.ucla.edu/Curcumin.html

DHEA

DHEA is a hormone that is naturally made by the human body. DHEA is an adrenal steroid hormone, the precursor to the sex steroids testosterone and estrogen. DHEA is abundant in youth, but steady declines with advancing age and may be partially responsible for age-related decreases in sex steroids. In cell culture and animal models, DHEA can suppress inflammatory cytokine activity, in some cases more effectively than either testosterone or estrogen. Chronic inflammation itself may reduce DHEA levels. DHEA supplementation in elderly volunteers (50 mg/day for two years) significantly decreased TNF-α and IL-6 levels, as well as lowered visceral fat mass and improved glucose tolerance (both associated with inflammation) in a small study. [83] Remember from the previous chapter that blocking IL-6 restores the production of neurons.

In a sample of newly diagnosed Alzheimer's patients, researchers did not find significant association between presence of Alzheimer's or impairment in cognitive domains and DHEA levels. This result was confirmed by scientists from Oregon who also explain the pitfalls of rodent models for measuring specific effects of DHEA relevant to humans. [84]

Estrogen (and other Hormones)

Estrogen is important to the building and maintenance of nerve networks in the brain from early on in life. Several studies are now pointing to the fact that estrogen may offer protection against Alzheimer's disease in postmenopausal women. One study conducted on almost 90,000 postmenopausal women found that those taking estrogen had a significantly longer life, and by the time of their deaths, the women on estrogen had a 40% lower incidence of Alzheimer's disease. [85]

Estrogen docking sites are present in several regions of the brain, including those involved in memory (such as the hippocampus). When activated by estrogen, these sites, in turn, activate processes that are beneficial to the brain. In addition, estrogen may in effect raise levels of certain brain chemicals (neurotransmitters). These include the neurotransmitters acetylcholine (implicated in memory), serotonin (implicated in mood), noradrenaline (implicated in mood and other autonomic functions), and dopamine (implicated in motor coordination). Thus, estrogen facilitates networking between nerve cells, promoting their ability to "talk to" one another.

The medical literature is full of articles discussing (mainly) the benefits of estrogen towards Alzheimer's disease. A "title only" search of scholar.google returns 350 articles! The first of these articles was published in 1986. [86] The abstract from a 1994 paper from the USC School of Medicine provides a very nice summary of the cause/effect of estrogen replacement therapy. [87]

> "The authors explored the possibility that estrogen loss associated with menopause may contribute to the development of Alzheimer's disease by using a case-control study nested within a prospective cohort study. The Leisure World Cohort includes 8,877 female residents of Leisure World Laguna Hills, a retirement community in southern California, who were first mailed a health survey in 1981. From the 2,529 female cohort members who died between 1981 and 1992, the authors identified 138 with Alzheimer's disease or other dementia

> diagnoses likely to represent Alzheimer's disease (senile dementia, dementia, or senility) mentioned on the death certificate. Four controls were individually matched by birth date (±1 year) and death date (+1 year) to each case. **The risk of Alzheimer's disease and related dementia was less in estrogen users relative to nonusers** (odds ratio = 0.69, 95%; confidence interval 0.46=1.03). **The risk decreased significantly with increasing estrogen dose and with increasing duration of estrogen use.** Risk was also associated with variables related to endogenous estrogen levels, it increased with increasing age at menarche and (although not statistically significant) decreased with increasing weight. **This study suggests that the increased incidence of Alzheimer's disease in older women may be due to estrogen deficiency and that estrogen replacement therapy may be useful for preventing or delaying the onset of this dementia."**

Do not forget that women account for two-thirds of all Alzheimer's cases.

Another 1994 paper and one from 2010 provide hope to Alzheimer's sufferers in that "estrogen replacement may improve cognitive performance of women with this (AD) illness." [88,89] Recent studies are helping us fine-tune what constitutes most beneficial estrogen replacement therapy.

> "Previous studies in postmenopausal women have reported that estrogen treatment (ET) modulates the risk for developing Alzheimer's disease (AD). It has recently been hypothesized that there may be a 'critical period' around the time of menopause during which the prescription of ET may reduce the risk of developing AD in later life. This effect may be most significant in women under 49 years old. Furthermore, prescription of ET after this point may have a neutral or negative effect, particularly when initiated in women over 60–65 years old. In this paper, we review recent studies that use in vivo techniques to analyze the neurobiological mechanisms that might underpin estrogen's effects on the brain post menopause. **Consistent with the 'critical period' hypothesis, these studies suggest that the positive effects of estrogen are most robust in young women and in older women who had initiated ET around the time of menopause**."

Fish Oil in Cardiovascular Diseases

Eat plenty of fish, especially cold-water fish. Supplement with fish oil or, preferably, cod liver oil. Do not make any excuses or be influenced by media. Fish oil is not a vitamin, mineral, or other supplement; it is simply a food that is deficient in the diet of many of those with chronic diseases. Along with vitamin D, fish oil has a panoply of benefits to health including those suffering with Alzheimer's disease. Fish oil is the best source of the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) that can only be synthesized to a limited extent in humans. These fatty acids are essential constituent of the membranes of neurons. Thus fish oil supplementation, or consuming fish, is critical. Omega-3 fatty acids have been well studied for their prevention of cardiovascular disease and mortality in tens of thousands of patients. The anti-inflammatory effects of omega-3s contribute to this activity. They have also proven successful at improving patient outcomes in scores of studies of inflammatory diseases,

particularly asthma, inflammatory bowel disease, cardiovascular diseases, Alzheimer's disease, and rheumatoid arthritis. Emerging studies show fish oil conferring a wealth of benefits in guarding against depression, cancer, osteoporosis, and other crippling diseases of aging.

Fish oil lowers triglycerides. Dangerously high levels of triglycerides have become more common as Americans develop metabolic syndrome, cardiovascular disease, and other nutrition-related illnesses. Elevated triglycerides greatly increase risk for heart disease. The right dose of omega-3s can significantly reduce triglyceride levels and help correct other cardiac risk factors that accompany metabolic syndrome. [90,87,91] In fact, omega-3 fatty acids derived from fish oils are now available in the form of a prescription drug called Omacor, which has been approved specifically for the treatment of elevated triglycerides. [92] Do not get in the habit of succumbing to the prescription pad. Instead, eat plenty of fish and take fish oil or cod liver oil in large amounts to compensate for a sub-optimal diet.

Silent inflammation triggers a chain of events leading to heart disease and other illnesses. Omega-3 fatty acids suppress multiple steps in this inflammatory process, inhibiting the production of inflammatory cytokines and prostaglandins probably through a variety of mechanisms that includes immune system augmentation. Furthermore, omega-3 fats boost production of anti-inflammatory compounds. These anti-inflammatory effects may have important implications for fighting heart disease and numerous other disease processes associated with excessive inflammation. [93,94,95,96,97,98,99] People who consume a greater amount of omega-3 fatty acids demonstrate lower levels of C-reactive protein, a cardiovascular risk factor, suggesting that omega-3 supplementation might help prevent cardiovascular disease by, for example, reducing infectious burden, thus lowering inflammation. [100] Omega-3s from fish oil may help to modify the structure of atherosclerotic plaque in ways that make it less dangerous. In fact, studies show that omega-3s can slow the rate of atherosclerotic plaque growth. Fish oil rich in omega-3 fatty acids contributes to healthy vascular function by increasing the production of an important blood vessel-dilating substance in the endothelial cells. [101,102]

Omega-3 supplementation actually changed the composition of unstable atherosclerotic plaque, making it less likely to rupture and thus less dangerous. Subjects who had severe carotid plaque and were scheduled to have it surgically removed received either fish oil or sunflower oil prior to surgery. When the plaque was removed at surgery and examined, researchers found that those who took fish oil had less plaque inflammation as well as more stable plaque. By contrast, those who took sunflower oil had more unstable, rupture-prone plaque. [103] Fish oil also helps reduce certain proteins that promote abnormal blood clotting and inhibit platelet aggregation, two effects that reduce the likelihood of clot formation on active, ruptured coronary plaque that could result in a heart attack. [104] One of the most dramatic benefits of fish oil is its ability to prevent sudden death, particularly sudden cardiac death. Scientists believe that omega-3 fatty acids from cold-water fish may help prevent these sudden deaths by reducing potentially fatal abnormal heart rhythms, or arrhythmias.

Australian and Chinese scientists studied the results of 11 trials and uncovered a significant reduction in plasma homocysteine in association with greater intake of

omega-3 polyunsaturated fatty acids. [105] Treatment periods ranged from 6 to 48 weeks, and doses varied between 0.2 and 6 grams per day. The analysis confirmed a reduction in plasma homocysteine levels in association with omega-3 fatty acid supplementation, with an average decrease of 1.59 micromoles per liter experienced by those who supplemented compared to those who received a placebo. "Our systematic review provides, to our knowledge, the most comprehensive assessment to date of the effects of omega-3 polyunsaturated fatty acids on plasma homocysteine," the authors announced.

Dr. Kilmer McCully, the pioneer of the homocysteine theory showed, way back in 1993, that fish oil lowered plasma homocysteine in subjects with elevated cholesterol (hyperlipidemia). [106]

Fish Oils in Alzheimer's and Dementia

Since vascular diseases are tied to Alzheimer's and other dementias, there should be no surprise that fish oils are helpful for Alzheimer's sufferers and also play a key role in prevention. The literature on this topic is rich and extends back into the 90s. The Japanese took the early lead through publications and patents. One such patent from 1994 is titled," *Brain function ameliorant composition, learning capacity enhancer, mnemonic agent, dementia preventive, dementia curative, or functional food with brain function ameliorant effect*." [107] Here is a part of the abstract from that patent:

> "The invention aims at ameliorating brain functions to thereby effect learning capacity enhancement, memory enhancement, and prevention and cure of senile dementia, and to provide a functional food having a brain function ameliorant effect. The invention composition comprises at least one member selected from among n-3 unsaturated fatty acids, i.e., docosahexaenoic acid, eicosapentaenoic acid…"

Two articles that bracket 16 years of research from 1997 to 2013 are examined here. The earlier one is titled, "*Polyunsaturated Fatty Acids, Antioxidants, and Cognitive Function in Very Old Men,*" (it sounds more like a new sitcom). [108] This team from the Netherlands says, "This study raises the possibility that high linoleic acid intake is positively associated with cognitive impairment and high fish consumption inversely associated with cognitive impairment." The 2013 article was likely chosen from the most conservative group, the Alzheimer's Drug Discovery Foundation. [109] Polyunsaturated fatty acids (fish oil) are not really drug candidates; they are foods, although there are a couple on the market. The title of their article includes the key word "prevention." They state, "Of particular relevance, epidemiology indicates a higher risk of cognitive decline in people in the lower quartile of n-3 LC-PUFA intake or blood levels."

Higher blood levels of eicosapentaenoic acid (EPA) are associated with a lower risk of dementia and depression in elderly persons in a French study. [110] EPA is an omega-3 polyunsaturated fatty acid found in certain fish that may decrease the risk of dementia and Alzheimer's disease. The study included 1,214 French persons aged 65 or older who were examined for dementia and blood levels of fatty acids over four years. Depression was also assessed because it has been related to both low EPA and dementia. By four years, 65 patients had developed dementia. A higher level of EPA was

associated with a lower likelihood of dementia, even after accounting for depression and other patient characteristics. An association between depression and dementia was also confirmed. The authors concluded, "**Because depression and dementia share common vascular risk factors, the vascular properties of EPA could contribute to decrease depression and dementia risk simultaneously**."

Researchers at the Rush Institute of Healthy Aging conducted a study to see if consuming fish and different omega-3 fatty acids protect against Alzheimer's. [111] Over 800 participants unaffected by Alzheimer's disease (between the ages of 65 and 94) were monitored from 1993 to 2000 and then followed-up for a four year period to see if they developed Alzheimer's. Researchers discovered patients who ate fish once or more per week or increased the amount of omega-3 fatty acids in their diet had a **60% lower risk of developing Alzheimer's disease**. While these are only the results of one single study, they are encouraging.

Mentally return to Chapter 2 for a moment to put this "60% lower risk" into perspective based on the new efforts of big pharma and those who live and die with the Amyloid Cascade Hypothesis. All therapeutics lowering beta-amyloid failed to improve cognitive functioning and other aspects of Alzheimer's disease. In fact, many of the patients enrolled in these trials got worse compared to a sugar pill. Desperate for these drugs to work, spokespeople for big pharma say that they will "soldier on" and test their drugs on people who do not have Alzheimer's or mild cognitive impairment. They argue that in patients with symptoms, the disease has progressed too far, and the therapy did not stand a chance (this is not correct, their therapy is based on bad science). Basically, they will reproduce the study by the researchers at Rush Institute. What chance does their beta-amyloid therapy have at outperforming omega-3 fatty acids? How likely is it that the FDA will ask big pharma to compare their results to omega-3 fatty acids rather than a sugar pill?

Omega-3s may reduce symptoms in mild Alzheimer's disease. A study published in the October 2006 issue of the *Archives of Neurology* suggests fish oil supplements may slow cognitive decline in patients with very mild Alzheimer's. [112] This double-blind, placebo-controlled study had 174 Alzheimer's patients receive either a placebo or 430 mg. of DHA along with 150 mg. EPA, four times a day. The randomized treatment lasted for six months, and then all subjects received the fish oil supplements for another six months. Patients who took omega-3 fatty acids experienced less change in their rate of cognitive decline compared to those who took the placebo. A smaller group of 32 patients with mild Alzheimer's disease experienced a significant reduction in their rate of cognitive decline compared to the placebo group. And surprisingly enough, **when the placebo-group patients took the omega-3 supplements for six months post-placebo trial, they also experienced the same reduction in mental decline**.

PUFA 3, PUFA 6, and PUFA 6/3 Ratio

Omega-3 fats are also known as PUFA 3 (polyunsaturated fatty acids). The key clinical omega-3 fats are EPA and DHA, which are found largely in cold-water fish. The PUFA 6/3 ratio is also important as PUFA 6 tends to promote pro-inflammatory molecules while PUFA 3 does just the opposite. High ratios (more PUFA 6) (>5) are associated with chronic silent inflammation. The following is a very concise abstract that discusses

the history of our diets with respect to PUFAs in general and provides information on diseases impacted by an "imbalance" of PUFAs. The paper was written by Artemis P. Simopoulos from The Center for Genetics, Nutrition and Health, Washington, DC, and is titled, "*The Importance of the Omega-6/Omega-3 Fatty Acid Ratio in Cardiovascular Disease and Other Chronic Diseases.*" [113]

> "Several sources of information suggest that human beings evolved on a diet with a ratio of omega-6 to omega-3 essential fatty acids (EFA) of ~1 whereas in Western diets the ratio is 15/1–16.7/1. Western diets are deficient in omega-3 fatty acids, and have excessive amounts of omega-6 fatty acids compared with the diet on which human beings evolved and their genetic patterns were established. Excessive amounts of omega-6 polyunsaturated fatty acids (PUFA) and a very high omega-6/omega-3 ratio, as is found in today's **Western diets, promote the pathogenesis of many diseases, including cardiovascular disease, cancer, and inflammatory and autoimmune diseases, whereas increased levels of omega-3 PUFA (a lower omega-6/omega-3 ratio), exert suppressive effects.**
>
> In the secondary prevention of cardiovascular disease, a ratio of 4/1 was associated with a 70% decrease in total mortality. A ratio of 2.5/1 reduced rectal cell proliferation in patients with colorectal cancer, whereas a ratio of 4/1 with the same amount of omega-3 PUFA had no effect. The lower omega-6/omega-3 ratio in women with breast cancer was associated with decreased risk. A ratio of 2–3/1 suppressed inflammation in patients with rheumatoid arthritis, and **a ratio of 5/1 had a beneficial effect on patients with asthma, whereas a ratio of 10/1 had adverse consequences**."

These studies indicate that the optimal ratio may vary with the disease under consideration. This is consistent with the fact that chronic diseases are multigenic and multifactorial. Therefore, it is quite possible that the therapeutic dose of omega-3 fatty acids will depend on the degree of severity of disease resulting from the genetic predisposition. A lower ratio of omega-6/omega-3 fatty acids is more desirable in reducing the risk of many of the chronic diseases of high prevalence in Western societies, as well as in the developing countries. Thankfully, the solution to your good health is simple—eat more fish and supplement with fish oils. And you can improve your chances of good health by decreasing your intake of the inflammation-creating omega-6 (PUFA-6) fats. The books by Barry Sears on the "Zone" diet provide what you need to know about avoidance of omega-6s. [114,115]

Excess PUFA 6 interferes with the health benefits of PUFA 3, in part because they compete for the same rate-limiting enzymes. A high proportion of 6/3 fat in the diet shifts the physiological state in the tissues toward many diseases that involve blood clotting, inflammation, and vessel constriction. Chronic excessive production of n−6 eicosanoids derived from PUFA 6 is associated with heart attacks, thrombotic stroke, arrhythmia, arthritis, osteoporosis, inflammation, mood disorders, obesity, and cancer. Medications used to treat and manage these conditions work by blocking the effects of the PUFA 6 known as arachidonic acid. Many steps in formation and action of n-6 hormones from n-6 arachidonic acid proceed more vigorously than the corresponding competitive steps in formation and action of n-3 hormones from n-3 compounds.

The PUFA 6:3 ratio plays a role in dementia and Alzheimer's, too. A 2013 German review article delved into the science behind the PUFA ratio and dementia. [116] The abstract is reproduced here:

> "It has been suggested that the intake of certain fatty acids may influence the risk of dementia. However, current reviews have focused only on the therapeutic effects of omega-3 fatty acids, mostly as supplements. To date, the evidence for the relevance of the omega-6/omega-3 ratio has been neglected. Therefore, we searched the databases Alois, Medline, Biosis, Embase, Cochrane Central Register of Controlled Trials, and The Cochrane Database of Systematic Reviews for 'essential fatty acids' and 'dementia' and aimed to conduct a comprehensive review across study types."
>
> "All studies that reported on the association between the n-6/n-3 ratio and dementia or cognitive decline were selected. In the 13 animal studies we examined, the dietary n-6/n-3 ratio was shown to affect brain composition, Alzheimer's disease pathology, and behavior. Our review of the 14 studies in humans that fulfilled the selection criteria (7 prospective studies, 3 cross-sectional studies, 1 controlled trial, 3 case-control studies) provided evidence, albeit limited, supporting an association between the n-6/n-3 ratio, cognitive decline, and incidence of dementia. **This review supports growing evidence of a positive association between the dietary n-6/n-3 ratio and the risk of Alzheimer's disease**."

Berberine

Berberine, an isoquinoline alkaloid isolated from medicinal herbs frequently used in traditional Eastern medicine, has multiple therapeutic effects for metabolic disorders, microbial infection, neoplasms and inflammation. [117] Increasing interest has focused on its anti-inflammatory effects. In microglia, the main immune system of the brain, berberine suppresses neuroinflammatory responses and attenuates the production of inflammatory mediators. Substantial evidence also shows that berberine exerts neuroprotection in cerebral ischemia (blood flow loss to regions of the brain) and Alzheimer's disease. [118]

There are a variety of other supplements and food intake modifications that can impact your likelihood of developing chronic diseases like Alzheimer's. Google David Wheldon of England to see his list of recommendations for multiple sclerosis, as MS and AD are both neurodegenerative processes, and there is logical overlap.

Prevention – In Your Control

Alzheimer's disease is preventable. Claude Bernard, Alois Alzheimer's, and other doctors and scientists of history who documented the dearth of "Alzheimer's" disease even 100 years ago present that proof. Paul Clayton, a modern man, indicates that chronic degenerative diseases were 10% of what we experience today, during the mid-Victorian era (1870). What is this pall that has overcome our people and inflicted us with rampant and expanding poor health? I think we all know the answers.

The comforts, convenience, and economics of modern society have superseded our good sense. Everything we do on a day-by-day and minute-by-minute basis perpetuates

poor health. It starts with a bowl of sugar-laden cereal with fat-free milk, after a restless night's sleep. Next we jump into an automobile and struggle through a commute to get to a climate-controlled office. We rush through lunch prepared of more processed foods that our bodies rapidly convert to sugars and fats. Now back to our climate-controlled bubble. We are rewarded at the end of the workday with a ride in our well-deserved luxury car that doesn't even require a finger to open the trunk. We settle into a nice Stouffer's dinner, because our spouse worked to afford his or her car, too. Finally, some free quality time with the boob tube, some carbonated beverage, coffee, dessert, a cigar, and a nightcap. Off we go for another restless night's sleep.

Surprise…

You know what to do (sort of—except you think low fat is good—it's just the opposite, especially for your brain). But you don't do it anyway because the circle of life doesn't provide the luxury of time to truly care for yourself.

In the spirit of keeping it simple, focus on increasing your intake of vitamin D, fish oils, magnesium, and zinc while avoiding calcium and omega-6s. A key issue is dose. Most of the time, when researchers find that these supplements are ineffectual, the reason is likely the low dosing level. The PUFA 6/3 ratio helps us understand this conundrum. If your PUFA ratio is >15/1 (plenty of Americans have a 40/1 ratio or higher), then supplementing with 500 mg/day of PUFA 3 is like giving someone who is dying of thirst a shot glass of water. The amount is insufficient, and the impact on chronic health will not be measurable. USRDAs are established to be very conservative numbers and are not appropriate guidelines for people who are significantly out of balance.

Look upon foods differently compared to supplements. Fish oil (and cod liver oil (CLO)) is food, not a supplement. Our family takes 15 grams of cod liver oil daily! Come on, it's not that bad. It is not the same thing your grandmother gave you. Here is how we take cod liver oil. We take a shot glass and fill it half full (half empty if you prefer) with CLO. Drink some orange juice, then shoot the CLO to the back of your throat and quickly swallow. Next, drink some more orange juice. You won't know what hit you, in a good way. Do this in the evening just prior to bed, as this will reduce or eliminate any upset caused by the CLO. Also, if you are new to this, start with one-eighth of a shot glass and work your way up.

Focus on preventative measures, and you will have no need to read Chapter 11.

"The doctor of the future will give no medicine, but will instruct his patient in the care of the human frame, in diet and in the cause and prevention of disease."

– Thomas Alva Edison.

Take your cod liver oil.

Here's to your health!

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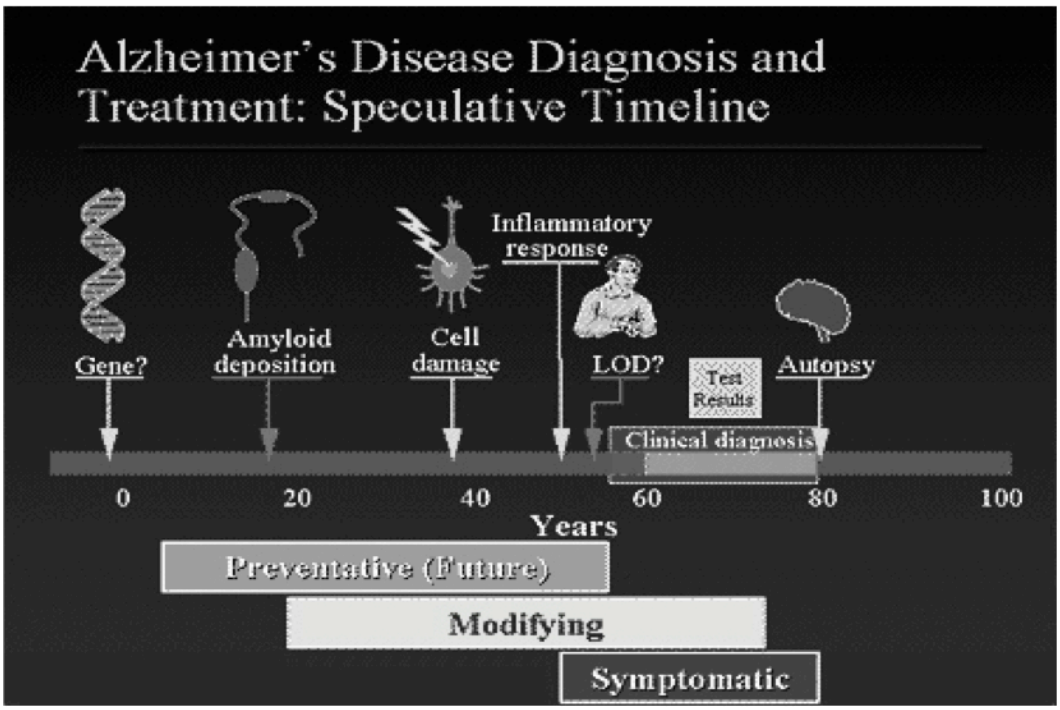
11
Differential Diagnosis Toward a Cure for Alzheimer's



"It must be remembered that physicians of today are trained to treat the sick, and they must learn how to examine so-called well persons to prevent them from getting sick."

- Dr. Charles Mayo

A New Diagnostic Language – Risks and Causes

As stated by Dr. Joseph Martin (former Dean of the Harvard Medical School), "There is a great need to find a way to prevent Alzheimer's disease, delay its onset, or retard its progress; an effective treatment that delayed its onset by an average of five years would reduce the cost to society by nearly 50% which adds up to hundreds of billions annually and save untold human suffering. [1]

Because AD has such a long asymptomatic phase, people must be treated when they have mild symptoms of early dementia or even before symptoms appear. Medicine now has inexpensive technologies to diagnose the early signs of AD 20 years before a patient

becomes aware of any cognitive problems. This is the best time to treat Alzheimer's. Dr. Charles Mayo (the founder of the world famous Mayo Clinic) told us 100 years ago that: "It must be remembered that physicians of today are trained to treat the sick, and they must learn how to examine so-called well persons to prevent them from getting sick." [2]

Modern medicine cannot accurately diagnose Alzheimer's disease, even in those who have severe dementia. This is the consensus of essentially every Alzheimer's pundit. It is generally agreed that definite specific confirmation of Alzheimer's disease requires autopsy. Here pathologists are able to differentiate Alzheimer's from other types of dementia. However, in general, there is rather poor correlation between the degree of brain atrophy, including Alzheimer's hallmarks, and the functionality of the patient. If medicine admits they cannot diagnose advanced Alzheimer's, what can standard-of-care medicine do for the early (asymptomatic) diagnosis?

If we admit that diagnosis is difficult or impossible then what? Is it truly important to you, a patient, whether you have any of the many types of dementia or Alzheimer's type dementia? Will treatment vary if you have Lewy Body Dementia, vascular dementia, or AD? No! The treatments are all the same within the standard of care. All these diseases are treated essentially in the same way.

Why then is there such a focus on diagnosing Alzheimer's type dementia with great accuracy? The answer lies in the treatments targeted for AD, that is anti-amyloid therapy. However, as Chapter 2 clearly demonstrates, anti-amyloid therapies of all types fail to change the course of Alzheimer's and more than likely make the disease worse.

You as the "Alzheimer's" patient or an individual concerned about your potential to develop Alzheimer's are best served by focusing on your risk for the disease or its acceleration. Assessing risk is best achieved through a differential diagnosis. The concept of a differential diagnosis is really the evaluation of multiple measures across multiple medical disciplines some of which indicate disease risks while others indicate disease causes. When you establish your specific risk factors and causes, now you have something actionable. That is, now you have targets that may change the course of the disease in your favor.

We state that there are two parts to a differential diagnosis, namely risks and causes. This is very empowering to you, a person concerned about or afflicted with a neurodegenerative process like Alzheimer's. With a good understanding of risks, you will be able to "diagnose" Alzheimer's yourself and work with your healthcare professionals to help you stop or minimize the impact of these diseases.

You might ask, is it worth worrying about my risks because there is no (reported) cure for Alzheimer's disease? This is a valid question, and the answer is: indeed it is worth worrying about risks because these risks are not Alzheimer's, per se. The risks are associated with causes that manifest in a disease that medicine happens to name Alzheimer's, for example. Causes are preventable or "curable" and when you attack causes, that will help you prevent or stop Alzheimer's.

A recent medical research paper concluded that around half of the AD cases may be attributable to potentially modifiable factors. And that number is based on a short set of

risk factors including: diabetes, midlife hypertension, midlife obesity, physical inactivity, smoking, depression, and educational attainment. [3] Here we discuss many more risk factors, some of which are modifiable and others that are not. However, all tolled, the number of AD cases we believe are attributable to potentially modifiable risk factors far exceeds 50%. This means controlling or preventing Alzheimer's disease is substantially in your own hands. †

Let's review what we have learned from Chapters 1-10 that will help you understand your Alzheimer's risk and guide you on a path of either prevention or effective treatments.

Keep Asking Your Doctor "Why," not "What"

Do not allow your doctor to give you "ten-cent-word" diagnoses. Many are meaningless and simply mask a lack of understanding as to the cause of your ailment. A classic example is "Essential Hypertension." It is a fancy word that means elevated blood pressure of unknown cause. But you, when you receive such an elegant diagnosis, are convinced your doctor is on top of your condition, after all, you were prescribed a drug. But why is your blood pressure elevated? Is lowering it indiscriminately the right thing to do?

The problem of diagnostic nomenclature extends back probably since medicine was first practiced. Consider this excerpt from a 1908 Journal of the American Medical Association article By Dr. Wiel. [4] We pick up the dialog after the author discusses a variety of meaningless diagnoses:

> "There are many more meaningless diagnoses than these, and it may be that each section of the country has its own particular foibles of this nature, but should not all conscientious physicians discard the use of these terms, and if there are none better to be found in the present terminology, why use terminology at all? It is self-evident that the expression "I don't know" is better than "biliousness" and the rest of the category, and brings some comfort that there is after all much doubt left, in the clearing of which we can find use for our years."
>
> Our distance from Utopia in medicine, as in all things, is vast, and though we shall never attain the ideal, we make one step towards it when we face our ignorance when we find it, and we make still another when we try to overcome it. Rather than call things by false names or meaningless names, let us call them by no names at all, and so, for the love of Æsculapius and Hippocrates, let us hear little more of "biliousness," "ptomain poisoning" and the like."

Patients in the 21st Century seeking medical treatment frequently insist on or even demand a diagnosis to explain their set of symptoms. Once a name has been provided, they can direct their energy to potential treatment to resolve, relieve, or at least lessen their symptoms. Dr. Wiel eloquently stated in 1908, "the indispensible and essential action predicating rational treatment of disease is establishing a diagnosis." He goes on

† Genetic factors play a minimal role in the great majority of Alzheimer's cases. Your internal environment Is the most important determinant of your potential for AD.

to say some diagnoses are used to "cover our ignorance and to pander to the desire of the patient" seeking an answer.

Today, although technology and diagnostic testing are vastly improved, different factors now affect the diagnostic capabilities of the physician. Busy lifestyles, high patient volumes, hypochondriacal patients, and office schedules which allot a fixed amount of time per patient tempt even the most ethical practitioner to provide a diagnosis not on evidence-based medicine, but rather a non-verifiable opinion designed to pacify a patient desperately seeking an answer.

Physicians have now coined such scientific sounding names such as fibromyalgia, chronic fatigue syndrome, sick building syndrome, repetitive strain injury, multiple chemical sensistivity, and myofascial pain. Patients desperate for a diagnostic explanation frequently glom onto these names, feel relieved when provided, and seem anxious to share their new "diagnosis" with friends and family. Support groups now are fashionable which reinforce their belief of an unproven diagnosis and give the new "name" further credibility. These groups provide enormous comfort, empathy, reassurance, and embellishment as our patient shares symptoms and stories with similarly affected individuals.

Our current insurance and billing system mandates a diagnosis, even one that is fabricated, to allow appropriate reimbursement for the provider. In the slotted area on the insurance form, the "new diagnosis" is entered and a properly assigned diagnostic code now confirms and validates the diagnosis. No diagnostic code has been yet established to reimburse the physician who writes, "I don't know," or "aches and pains" in the diagnostic slot.

Alzheimer's Risks – Conventional Wisdom

Organizations like the Mayo Clinic, WebMD, and the Alzheimer's Association publish risk factors for Alzheimer's. These conservative organizations rely on medical research studies that show bona fide cause/effect relationships. Many of these risk factors may seem obvious and may not be critically important because they are mostly based on common sense, yet AD rates are increasing exponentially. However, if you truly work to avoid these risks, you will absolutely be less likely to progress to the clinical stage of the disease. Here is a basic list of risk factors:

Age: Okay, this risk factor doesn't help you much. However, many Alzheimer's sufferers outlive the national average, so in some ways, these people were able to maintain good health before AD took over. However, in essentially all cases these older sufferers had sub-clinical systemic inflammation for years before being afflicted with AD. The way their health decayed prior to the onset of AD is often obvious but is not recognized as a disease or important. For example, sudden weight loss, balance issues, and deterioration in strength is a clear sign of accelerated aging and possibly Alzheimer's. Many of our "pre-Alzheimer's" patients report losing significant distance off their golf drive. Indeed this can be part of normal aging, but when the change is abrupt, it usually is indicative of disease.

Family History: This is often lumped in with genetics. Clearly people in the same family have similar genes, so if family members have the disease, then you may assume that

you, too, are predisposed. However, the medical research asserts that the common "environment" among family members is a much stronger influence on your future potential for AD compared to common genes. If you have family members with AD, evaluate their environment (nutrition, exercise, chemical exposure) in comparison to yours and make changes based on consideration of risk factors. In my family (TJL), my dad came down with Alzheimer's at the age of 82. When I review the family environment, fish was clearly missing from our diet. My father all but refused to eat fish except during Lent. All my family members have modified our "environment" to include frequent meals featuring oily, cold-water fishes.

Sex: Women are substantially more likely than men to develop Alzheimer's disease. Indeed women live longer, but there is something more profound than just longer life. Hormones and low-fat diets are likely contributions to the difference in AD rates for men and women.

Mild cognitive impairment: People with mild cognitive impairment (MCI) have memory problems or other symptoms of cognitive decline that are worse than might be expected for their age, but not severe enough to be diagnosed as dementia. Those with MCI have an increased risk—but not a certainty—of later developing dementia. Also, people with accelerated memory decay are systemically sick, and many die before the disease progresses into dementia. Taking action to ameliorate risk factors at this stage may help delay or prevent the progression to dementia.

Head trauma: People who've had a severe head trauma or repeated head trauma appear to have a greater risk of Alzheimer's disease. What do you do if you have had concussions in the past? Understand and control all the other risks that are within your control.

Heart health: Do you find it interesting that all the Alzheimer's pundits consider heart health a very important risk factor yet modern medicine only focuses on the brain? If you have Alzheimer's, you will only have a neurologist who pays little attention to the condition of your heart. Many of the items listed by the major medical websites give a list of heart health risk factors that are critical to you controlling or preventing Alzheimer's. One of the most important is homocysteine levels. High homocysteine is highly correlated to Alzheimer's risk. However, the homocysteine-lowering strategy can profoundly impact your outcome. As discussed in Chapter 7, simply lowering homocysteine levels with B-vitamins does not work. Challenge your doctors to find the cause of the elevated homocysteine (do not accept B vitamin deficiency as the answer). The doctor who knows how to modulate your physiology to lower homocysteine will go a long way toward preventing or abating Alzheimer's disease. Again, do not disregard the connectivity of diseases. When you take healthy measures that result homocysteine levels going down, many chronic diseases may be avoided.

Heart health warning: Cardiovascular disease management is becoming a very controversial area, particularly for the elderly. How you treat a 55-year-old male with severe cardiovascular disease is quite different compared to a 75-year-old woman with high blood pressure. Clearly exercise, good nutrition, and ceasing smoking will benefit the heart and reduce your odds of AD regardless of your age or sex. However, the Mayo site states high blood pressure, high blood cholesterol, and poorly controlled diabetes

as risk factors for Alzheimer's. Remember a very simple truism, your brain is the control center for your body.

Blood pressure: It is often elevated in the elderly due to calcified and stiff vessels. The brain, being up hill from the heart, suffers when arteries can deliver less blood. What does the brain do? It signals for more blood flow the only way it can, by increasing blood pressure. Many studies point to the need for elderly patients to have higher blood pressure compared to healthy middle-aged people. A blood pressure of 150/95 is not a risk for Alzheimer's and instead is probably protective. However, many seniors on blood pressure lowering medications have blood pressure that are too low for the health of their kidneys and brain. Often seniors will take their blood pressure medication at night because it makes them light headed if they take it in the morning. This is a dangerous practice, especially for seniors inclined to make a bathroom run during the night.

Cholesterol: About 25% of all the cholesterol in your body is in your brain. Since the brain is only 2-3% of the mass of your body, the brain has 10 times as much cholesterol compared to other bodily tissues. Study after study shows that there is essentially no correlation between cholesterol intake and blood cholesterol levels. The liver produces cholesterol in response to signals by the brain. People, especially women, with low cholesterol levels after the age of 70 have much higher mortality rates and more AD. The low-fat, anti-cholesterol campaign has failed as illustrated by the massive increases in obesity and chronic degenerative diseases prevalent in our society today.

Poorly controlled diabetes (part 1): This piece of conventional wisdom is **dangerously wrong**. "Controlled" diabetes generally implies keeping blood glucose levels below 170 mg/dL. The ACCORD (Action to Control Cardiovascular Risk in Diabetes)‡ clearly shows that diabetics on "tight" glucose control have significantly higher death rates compared to those not "tightly" controlled. Why? The brain, again, tells the story. The brain consumes 20-25% of all the oxygen we inhale. The brain is 10 times more metabolically active compared to the average tissue in the body. Under tight glucose control, there is less glucose available as an energy supply. Adding to the problem is that diabetics are insulin resistant, meaning their bodies cannot make efficient use of the available glucose and it has difficulty entering the brain. Because the brain is so highly metabolic, it must be allowed to control the output of glucose from the liver so it can obtain the energy it requires to function.

Poorly controlled diabetes (part 2): The ACCORD MIND study is looking at the impact of glucose control on cognitive function. University of Edinburgh researchers wanted to know why type 2 diabetes patients are at increased risk of cognitive decline. [5] They suspected hypoglycemia (most likely caused by insulin administration [6]) as a "candidate risk factor." They concluded, "The relationship between cognitive impairment and hypoglycemia appeared complex, with **severe hypoglycemia**

‡ The ACCORD study is the largest multi-centered randomized study ever done on diabetes. Contrary to what was expected and what we have been told for over half a century, tight control of blood glucose is deadly in diabetics.

associated with both poorer initial cognitive ability and accelerated cognitive decline." Here is our request to medicine: Stop killing people (cardiovascular deaths) and destroying their brains. Find the cause of insulin resistance and treat it. §

Type 2 diabetes is an inflammatory disease that results in elevation of the blood glucose in response to the inflammation. With inflammation, even increased serum insulin levels is not able to overcome the insulin resistance. Higher than normal levels of glucose in the circulatory system is a "last ditch" effort of the brain to protect itself from an energy crisis.

Lifelong learning and social engagement: Studies have found an association between lifelong involvement in mentally and socially stimulating activities and reduced risk of Alzheimer's disease. Factors that may reduce your risk of Alzheimer's include:

- Higher levels of formal education;
- A stimulating job;
- Mentally challenging leisure activities, such as reading, playing games or playing a musical instrument; and
- Frequent social interactions.

Alzheimer's Risks That You Can Determine

We believe that Alzheimer's disease can be prevented or reversed if the disease is recognized early and proper treatment is started. You personally hold the key to early recognition of Alzheimer's and other dementias in yourself and in those whom you love. Medicine is too hung up on the nuance of diagnoses between pure Alzheimer's and other types of dementias. That differentiation will not help you, but understanding and acting upon Alzheimer's risks that are gaining new appreciation will help you keep Alzheimer's at bay.

Many of the emerging risks associated with Alzheimer's disease are actually diseases themselves. Others are biomarkers for degenerative processes associated with diseases. Here is a listing and explanation of some of the most important "risks" associated with the current or future development of Alzheimer's disease. After you understand these risk factors, you will be in a position to determine your risk for Alzheimer's more accurately than Alzheimer's specialists who languish in mostly brain-only studies.

Diet

Shockingly, neither the Mayo Clinic nor the Alzheimer's Association list diet as a risk factor for Alzheimer's disease. Diet and exercise have the most profound impact on our bodies' immune system. When our bodies are under attack, the immune system is

§ The various medical websites provided very different information on a "hypoglycemia" search. The Mayo Clinic boldly states, "Hypoglycemia is most common among people who take insulin, but it can also occur if you are taking oral diabetes medications." The American Diabetes Association did not make any reference to the connection between taking insulin and hypoglycemia. Why? Do they have your best health interests in mind? A search of "ACCORD" on their site brings you to a page titled, "Mixed Results From ACCORD." Deeply imbedded in the article is how tight control of blood sugar increases mortality. Shouldn't "tight control with insulin kills you faster" be the headline on the American Diabetes Association home page?

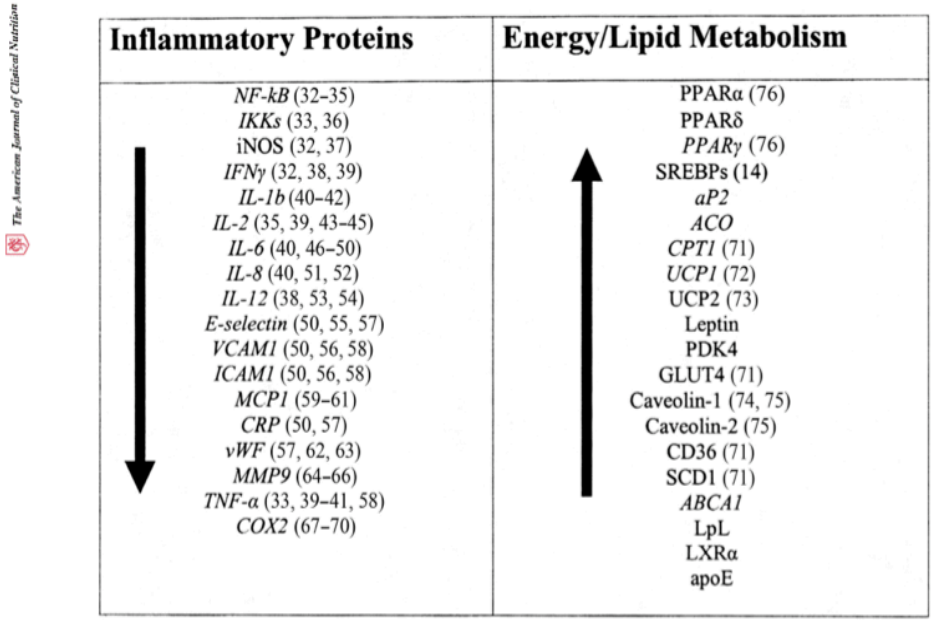
activated, and we note inflammation—the consequence of an activated immune system. Most Alzheimer's experts agree that inflammation is a major part of the disease, yet they are not bridging the gap between nutrition, inflammation, and Alzheimer's.

Fortunately many studies show the connection between AD and diet. A very significant finding comes from the famous Framingham Heart Study. This is a longest ongoing study of human health extending back to 1948 and is a cooperative project between the National Heart, Lung, and Blood Institute and Boston University. The study has looked beyond the heart because they have gathered systemic data on patients for over 60 years. Here is a significant finding of the Framingham Heart Study regarding Alzheimer's disease:

> "A recent report from the Framingham Heart Study showed that persons with plasma phosphatidylcholine DHA in the top quartile of values had a significantly (47%) lower risk of developing all-cause dementia than did those in the bottom quartile. [7] Significantly (P = 0.04) greater protection was obtained from consuming 2.9 fish meals per week than from consuming 1.3 fish meals per week." [8]

Why does eating fish curb cardiovascular disease and Alzheimer's? The following figure from the American Journal of Clinical Nutrition sheds light on the matter. [9]

Genes influenced by n−3 fatty acids and by glitazones.



American Society for Nutrition Am J Clin Nutr 2006;84:949

The authors of the study on the benefits of fish oils (n-3 fatty acids) state, "Accumulating evidence in both humans and animal models clearly indicates that a

group of very-long-chain polyunsaturated fatty acids, the n−3 fatty acids (or omega-3), have distinct and important bioactive properties compared with other groups of fatty acids. n−3 Fatty acids are known to reduce many risk factors associated with several diseases, such as cardiovascular diseases, diabetes, and cancer. Modulation of specific genes by n−3 fatty acids and cross-talk between these genes are responsible for many effects of n−3 fatty acids."

Fish oils have strong anti-inflammatory properties for many reasons including boosting your immune system function.** Alzheimer's and the other major chronic diseases that plague us are diseases of inflammation. We discussed nutrition and supplements as part of Chapter 10. However, it is worth reviewing the key points that are provided here as action steps.

Step 1. Evaluate your diet and replace empty calories with inflammation-suppressing foods like fish.

Step 2. Reduce intake of sugary foods and other foods that contribute to diabetes. The book *Grain Brain* by Dr. David Perlmutter provides appropriate guidance. [10] A simple actionable step is to avoid foods and soft drinks that contain fructose, particularly corn syrup.

Step 3. Avoid low-fat diets. Higher fat diets have more calories per gram but also contain a much higher nutrient content, especially for the brain. Fats that contain more omega-3s and fewer omega-6s are better for brain health. This includes fish of all type and nuts. Certain nuts, like walnuts, have much more favorable ratios of omega-3s compared to almonds, for example. A simple Google search will give you the nutritional data you need to make healthy decisions. Trans fats should be completely removed from your diet.

Step 4. Follow a diet that is akin to the Paleo or Mediterranean diets.

Step 5. Supplement with Vitamin D and magnesium but do not supplement with calcium. In fact, work to reduce your calcium intake. Your bones will be just fine with the available calcium in your diet and the extra vitamin D and magnesium.

Glaucoma

This "eye" disease is a neurodegenerative disorder. The optic nerve in the back of the eye (retina) sustains the same type of atrophy as is seen for neurons of the brain in AD. "We've seen for the first time that there is a clear link between what causes Alzheimer's disease and one of the basic mechanisms behind glaucoma," says Dr. Francesca Cordeiro from University College London. [11] A scholar.google.com search of "Alzheimer's" and "Glaucoma" appearing together in the medical journal articles yields 26,600 individual research papers. Here are a couple of titles:

- *Glaucoma: ocular Alzheimer's disease*? [12]

** If you are interested to learn more about the role of fish oil on inflammation perform a scholar.google.com search for Neuroprotectin D1 and Resolvin. They are a few of the break down products of fish oil that play important roles in the protection of the brain and the eye and in helping to terminate (resolve) the inflammatory process.

- *High frequency of open-angle glaucoma in Japanese patients with Alzheimer's disease*. [13]
- *Glaucoma and Alzheimer's Disease: Age-Related Neurodegenerative Diseases with Shared Mechanisms*? [14]

Glaucoma is clearly more than a disease the eye and brain. The medical review article titled, "*A sick eye in a sick body? Systemic findings in patients with primary open-angle glaucoma*" demonstrates that glaucoma is a whole-body disease. [15] Eye diseases seldom occur in isolation from the rest of the body. If the body is sick in glaucoma and glaucoma and Alzheimer's have overlapping causes, then it only makes sense that Alzheimer's is a disease of the whole body that manifests in the brain.

Glaucoma is an early warning sign for future Alzheimer's disease. There may be cases in which Alzheimer's precedes glaucoma, the diseases occur at the same time, or AD occurs after glaucoma develops. However, an optometrist or ophthalmologist can look for glaucoma routinely, non-invasively, and at a low cost. Even if glaucoma and Alzheimer's develop at the same time, you cannot "see" Alzheimer's in the brain but you can see glaucoma in the eye. Recall from previous chapters that Alzheimer's incubates and develops over decades. By the time Alzheimer's is clinically noticeable in a patient, their brain has suffered significant atrophy. Watching out for the earliest stages of glaucoma is a very good way to evaluate your risk for Alzheimer's in the future. What do you do if you are diagnosed with glaucoma and are concerned about the future possibility of Alzheimer's

> Step 1. Reread Chapters 6-10 and continue reading this chapter so you have the power of knowledge to help you find (and guide) a doctor who can help you.
>
> Step 2. Find that doctor who regards glaucoma as a systemic disorder and not an eye-only disease.
>
> Step 3. Institute measures outlined throughout this book to support immune system health and carefully follow the treatment regiment prescribed by your (new?) doctor who understands the root causes of glaucoma (and Alzheimer's).
>
> "If your doctor investigates and treats glaucoma properly, as a systemic inflammatory disorder, you are on the right path to either prevent or treat Alzheimer's."
>
> - Clement L. Trempe, MD

Macular Degeneration

This eye disease is also a systemic chronic inflammatory neurodegenerative disease related to aging that is proceeded by 10 to 20 years by mild elevation of blood markers of inflammation. The causes of inflammation and disease are the exact same factors that lead to Alzheimer's, cardiovascular disease and type 2 diabetes. Thus macular degeneration is, and a biomarker of, both neurodegeneration and cardiovascular disease. Dr. Don Anderson of the University of California has spent the better part of 25 years characterizing deposits in the retina called drusen that often form early in macular disease. These deposits contain the same misfolded protein associated with Alzheimer's disease. His work culminated in many research papers and this press

release from UC Santa Barbara, "Scientists at the Center for the Study of Macular Degeneration at the Neuroscience Research Institute of the University of California, Santa Barbara have found a link between the brain plaques that form in Alzheimer's disease and the deposits in the retina that are associated with age-related macular degeneration (AMD)." [16]

Recently the work of Frost has confirmed and extended the work of Dr. Anderson. [17] Frost has developed a method to highlight the amyloid deposits in drusen and make detection of these formations in the eye clearer. However, any eye doctor with standard optometric equipment is capable of detecting drusen formations very early along the disease process. Identifying the earliest stages of macular degeneration, by way of drusen, is arguably the earliest way to assess future risk of AD.

As with glaucoma, macular degeneration is not an "eye-only" disease. Your steps to protect yourself from Alzheimer's using macular degeneration as a biomarker/diagnostic are the same as for glaucoma.

Step 1. Find a doctor who treats macular degeneration as a systemic disorder. The current eye injections of inhibitors of the vascular endothelial growth factor will not help with Alzheimer's. In fact they are much more likely to accelerate and worsen the condition because it is known that these eye injections cause patients to have serious systemic "adverse events" in up to 40% of patients treated within two years. "Adverse events" is a convenient medical term that means more heart attacks and stroke.††

Step 2. Reread chapters 6-10 to gain a better understanding of the causes of drusen formation, macular degeneration, and Alzheimer's disease. Armed with this information, you may be able to find a doctor willing and able to help you prevent and battle Alzheimer's disease.

Step 3. Institute measures outlined throughout this book to support immune system health and carefully follow the treatment regiment prescribed by your doctor who understands the root causes of macular degeneration (and Alzheimer's).

Cortical Cataract

Harvard Medical School elegantly showed that deceased Alzheimer's patients they studied had beta-amyloid plaques in their brains. [18] They also showed that these same patients had "supranuclear" cataracts—also known as cortical cataracts. Their work showed that the amount of beta-amyloid in the brain corresponded with the amount found in the eye, in the cortical cataract. These cortical cataracts generally form long before a patient has clinical AD. In medicine today, cortical cataract are not removed at early stages and usually just observed. The reason is these structures form on the edge of the lens where lens stem cells are most prevalent, and have very little impact on

†† The intraocular injection of VEGF inhibiting drugs (the drugs for macular degeneration and some other eye diseases of the retina) cause a significant decrease in the circulating level of VEGF for up to one month. VEGF is essential for the rejuvenation of all the vascular endothelium (blood vessel linings) in the body.

vision for years. Few doctors recognize these formations for their rich diagnostic information.

Cortical cataracts are also an early warning sign for Alzheimer's, but what is an early warning sign for cataracts? They do not just suddenly appear but rather form over time. The process looks something like this:

First the top cortical layer of the lens periphery starts on increase in thickness before any of the beta amyloid fibrils (the actual cataract) becomes visible. This swelling produces accurately measurable optical changes, an effect known as coma aberration. At this stage the cortex (edge) of the lens has a milky appearance probably caused by accumulation of beta amyloid precursor (monomers and oligomers). Eventually the milky deposit coalesces and form clearly visible fibrils called cortical cataracts that Harvard Medical School showed contains the same beta amyloid as is found in Alzheimer's brains.

Drusen found in the retina is a very early indicator of Alzheimer's disease. However, coma aberration attributable to lens swelling may appear even earlier. The challenge for you, the patient, is to find an optometrist or ophthalmologist willing to investigate you, who most likely is otherwise healthy, for these Alzheimer's biomarkers. And, once identified, the greater challenge is to find a doctor who understands the fundamental processes that lead to the deposition of these misfolded proteins (cortical cataracts and their precursors).

Step 1. Find an optometrist who specialized in "pathology." Many optometrists will claim they understand eye pathology and indeed they do. However, few include looking at eye pathology in their routine practice. These eye doctors and their technicians are skilled at measuring pathologies like cataract, glaucoma, macular degeneration, dry eye, and retinal nerve physiology.

Step 2. If you have evidence of early cortical cataract formation or any evidence of early age related macular degeneration or glaucoma you must find a doctor who appreciates that those eye diseases are early visual biomarkers for chronic systemic inflammatory disease process related to accelerated aging. They are not simply eye diseases as the great majority of eye doctor view and treat these conditions. The doctor you find must interested and willing to do a thorough appropriate medical history and appropriate blood tests to get at the root of your disease.

Step 3. Appreciate and try to institute measures outlined throughout this book to support immune system health and carefully follow the treatment regiment prescribed by your doctor who understands the root causes of cortical cataracts (and Alzheimer's).

All chronic diseases, including cortical cataract formation and the diseases with which it is associated are multifactorial. That is, more than one thing is contributing to the over activation of the normal chronic systemic inflammatory process associated with aging. The tricky part of managing chronic diseases properly is that inflammation is part of the normal aging process. As our immune system slowly deteriorates (Immunosenescence) our body need to adapt by using the inflammatory process to

protect us from disease. Your goal is to locate a doctor who will take the time to find out if your have an over activated immune system and work with you to control the contributing factors. Those factors that contribute to disease are usually different from one person to another and the way that patients adhere to and respond to treatment is also very different from one person to another. The modern 10 minute office visit of the standard-of-care does not provide adequate time for your doctor to personalize your diagnosis and treatment.

Retinal Nerve Fiber Layer Thinning

RNFL thinning is early concrete evidence that you could have glaucoma especially if the trend continues. Measurement of RNFL thinning is mainly used to study the progression of glaucoma. Multiple sclerosis is another neurodegenerative disease, usually diagnosed in younger individuals, which is often correlated to RNFL thinning . Chapter 6 delved into the RNFL thinning / Alzheimer's connection. Many studies show a strong correlation between RNFL thinning/atrophy (glaucoma) and brain atrophy as measured using MRI. Measuring RNFL thickness is an important way to measure and study a person's neurodegenerative disease process. The equipment used to measure this parameter, Optical Coherence Tomography (OCT) is an instruments similar to a CAT scan except that a weak beam of light is use instead of an X-ray beam. These instruments are extremely accurate and precise. Thus, while the eye diseases discussed above are excellent ways to evaluate your AD risk, OCT measurements of the RNFL provide a more objective way to follow the course of the disease. A recent research article corroborated this statement as follows, "In our study, the thickness of RNFL in patient with AD was lower than that of controls. This suggests that OCT has the potential to be used in the early diagnosis of AD as well as in the study of therapeutic agents." [19]

How do you go about determining your retinal nerve fiber layer thickness and if a degenerative disease process impacts it?

Step 1. Find an optometrist or ophthalmologist who specialized in "pathology." Many optometrists will claim they understand eye pathology and indeed they do. However, few include looking at eye pathology in their routine practice. These eye doctors and their technicians are skilled at measuring pathologies like cataract, glaucoma, macular degeneration, dry eye, and retinal nerve physiology.

Step 2. If you have retinal nerve fiber layer thinning or atrophy you must find a doctor who appreciates that this is a systemic disorder and is willing to do appropriate system-wide tests (blood tests for example) to get at the root of your disease.

Step 3. Institute measures outlined throughout this book to support immune system health and carefully follow the treatment regiment prescribed by your (new?) doctor who understands the root causes of retinal nerve fiber layer thinning and/or atrophy (and Alzheimer's).

Cardiovascular Disease

A recent article in the top medical journal, the New England Journal of Medicine confirms 25 years of effort by Jack C. de la Torre. Dr. de la Torre's work was highlighted

in Chapter 8. The New England Journal of Medicine article is titled, "Proteotoxicity and cardiac dysfunction – Alzheimer's disease of the heart?" [20] There is sufficient evidence linking Alzheimer's and other dementias to inflammation and vascular problems. The challenge you will have, if you want to effectively be treated for cardiovascular disease to prevent future Alzheimer's, is that the current cardiovascular treatments do not delve into true root causes. In fact, some of the major treatments for cardiovascular disease including statins and blood pressure lowering drugs may actually exacerbate Alzheimer's disease and other dementias.

Alzheimer's disease desperately needs new science and new approaches to control and reverse the disease. Unfortunately, cardiovascular disease also needs new approaches. The cholesterol management approach is not working. Statins are presumed to be miracle drugs, but other cardiovascular drugs are actually much more important for controlling (not curing) the disease. These include beta blockers, ACE inhibitors, and Angiotensin receptor blockers. These latter drugs do appear to have positive impacts on Alzheimer's while statins do not (despite desperate attempts by that industry to prove otherwise).

Here is an action plan for those of you with diagnosed cardiovascular disease who are now concerned about your potential to develop AD.

Step 1. Reread Chapter 8 to fully understand the AD/cardiovascular disease connection.

Step 2. Find a doctor who will measure you inflammation burden and will also check for intracellular infection and other causes of elevated inflammation.

Step 3. Find a doctor who knows how to treat the causes of inflammation from the root. Remember, inflammation is (generally) a treasure. It is your immune system working on behalf of your good health. Appropriate diagnostics delve into the causes of inflammation, and appropriate treatment attacks these causes.

Diabetes

We need to go no further than the article titled, "*Alzheimer's Disease is Type 3 Diabetes – Evidence Reviewed.*" [21] The authors emphatically conclude, "the term 'type 3 diabetes' accurately reflects the fact that AD represents a form of diabetes that selectively involves the brain and has molecular and biochemical features that overlap with both type 1 diabetes mellitus and type 2 diabetes mellitus." A study on type 2 diabetes as a risk factor for Alzheimer's suggests the process is connected to "cerebrovascular pathology." That is, the vascular disease caused by diabetes is a major contributor to AD. [22] This makes sense because diabetes and vascular disease are interwoven as is AD and vascular disease. The take-home lesson for you, concerned about future Alzheimer's, is that systemic sugar metabolism dysfunction is a severe risk factor for Alzheimer's.

The good news is that you now know that managing diabetes will help curb Alzheimer's. However we already cited the ACCORD study that showed how tight control of sugar worsens outcomes. People on tight glucose control are sicker and die sooner. Also, the ACCORD MIND study shows that hypoglycemia (mostly caused by

insulin treatment in diabetics) contributes to and accelerates cognitive decline. What are your action items for preventing or treating Alzheimer's if you have diabetes?

Step 1. Recognize the link between diabetes and cardiovascular disease. The point of intersection is inflammation; therefore review Chapter 7 on inflammation.

Step 2. Locate a doctor who does not use the old, tired, and deadly way for managing diabetes—that is, controlling glucose levels with insulin injections. This method treats symptoms, not causes. The causes of type 2 diabetes (and that of cardiovascular and Alzheimer's diseases) are those factors that increase your inflammation burden. The key is your environment, particularly your diet that can either promote or mitigate inflammation. The second is infection that increases the inflammatory burden associated with aging above normal levels. Pathogens proliferate opportunistically when our immune system weakens. A good way to assess your susceptibility is to monitor your baseline inflammation. You will achieve better health if your baseline levels are lowered consistently, over time.

Periodontal Disease

Bruce Paster is the Senior Member of the Staff and Chair of the Department of Microbiology at the Forsyth Institute, part of the Harvard Medical School. [23] He told us unequivocally that everyone who is 55 years or older has some level of periodontal infection. What about a connection between gum disease and Alzheimer's? The medical literature is loaded with research confirming the connection. Here is one of thousands, "*Emerging evidence for associations between periodontitis and the development of Alzheimer's disease*" [24] The root of the AD/gum disease connection is inflammation as discussed in detail in the following journal article, "*The Microbiome and Disease: Reviewing the Links between the Oral Microbiome, Aging, and Alzheimer's Disease*." [25]

There is more to oral health than just brushing and flossing regularly. Cosmetic and functional surgery and implants that consider only the health of the mouth often have severe system-wide health consequences.

Root Canals: Each of your teeth is a vital (living) organ. Like your liver, lungs, kidneys, and other organs, teeth sometimes become diseased and fail. In that case, a dentist may recommend root canal treatment, which starts with removing the dentinal pulpal complex—the tooth's "guts," so to speak, which are rich in nerves, blood vessels, and delicate connective tissue. After cleaning the chamber, the dentist fills it with rubbery putty and caps the remaining tooth structure with a restoration. Establishment dentists call this "saving" the tooth, which is odd since, by definition, a root canal tooth is a dead tooth. All the living stuff – what once kept it alive – is gone. But this doesn't mean that nothing is happening inside. The absence of the pulp has major consequences. Because there is no blood supply, pathogenic bacteria that were formerly held in check by your immune system multiply. Due to the oral cavities' proximity to the blood supply and the central nervous system, the bacteria can invade both systems, with health damaging consequences. For a comprehensive yet understandable explanation of the impact of oral bacteria, please read "*Scientific American Presents: Oral and Whole Body Health*." [26]

Dental Implants: Implants are a foreign body in your mouth, despite the best efforts of the dental community to use substances that the body accepts. Also, as in the case of root canals, the implant is not living and thus is not graced with blood flow and protective immunity the blood supplies. These foreign bodies harbor bacteria and proliferate inflammation. If you are not a believer, try this simple experiment. Place a small splinter under your skin. You will undoubtedly note that the area will soon become inflamed. Why? It is becoming infected, and your body's immune system is going to work for you. Your immune system will likely lose the battle unless the splinter is removed. Even antibiotics will not permanently relieve your symptoms of inflammation, unless the source (the splinter) is removed.

Proper oral hygiene is much more than preventative dentistry—it is preventative disease! One of the diseases that proper dental care can help prevent is Alzheimer's. Here are the steps:

Step 1. Brush after every meal.

Step 2. Floss after every meal.

Step 3. See your dentist at least two times each year but preferably four times, regardless of your age.

Step 4. Do not obtain root canals or dental implants.

Step 5. If you have periodontal disease, have it treated aggressively.

Step 6. Remove teeth that are infected immediately.

Step 7. Remove dental implants and teeth subject to root canal surgery.

An article in *Business Insider* states, "We've mentioned before that not flossing daily can shave years off your lifespan. Here's more proof that poor dental hygiene—which allows harmful bacteria to enter the bloodstream—leads to a host of medical problems, including heart disease, respiratory problems, and diabetes." [27] They are missing the connection to Alzheimer's, but diabetes and heart disease should be all the motivation you need to take action.

The connection between oral hygiene, periodontal disease, and chronic disease is not new. The doctor who tried to bring this concept to prominence was Charles Mayo, the founder of the Mayo Clinic. Here is an excerpt about Dr. Mayo's concept on oral and whole body disease. [28]

> "Dr. Charles Mayo, founder of the famous Mayo Clinic, believed in the 'focal infection' theory of disease, something so archaic that today almost no one has heard of it. The theory basically states that an oral infection can influence the health of the entire body. Addressing the Chicago Dental Society in 1913, Mayo said, 'The next great step in preventative medicine must come from the dentists.'
>
> Mayo appointed Dr. Edward C. Rosenhow to head a team of researchers dedicated to focal infection theory. From 1902 to 1958, Rosenhow conducted experiments and published more than 300 papers, 38 of which appeared in the *Journal of the American Medical Association*. During the same period, Weston A. Price, founder of the research institute of the National Dental Association,

published his findings indicating that dental and oral infections were often the primary cause of disease.

These two medical pioneers established a simple but profound fact. If you pull an infected tooth, the patient will often recover from disease—serious disease, from chronic fatigue to cancer, from dermatitis to diabetes, from hemorrhoids to heart disease. Drs. Rosenhow and Price theorized that disease often originated from infections in the mouth that entered the bloodstream and eventually caused major problems in some part of the body. The evidence they amassed and published is staggering, yet the next great step Dr. Mayo hoped for did not come, and their work is largely forgotten today."

Dr. Mayo brought a couple of brilliant ideas to light, none of which are currently being practiced by the clinic that bears his name, or any other major medical institution for that matter. One of those ideas is the concept of focal infection discussed above and the other is "grand rounds." In grand rounds, all the specialists in medicine come together to evaluate the patient and bounce ideas off each other. Today, specialists see patients in isolation of other specialists. Your PCP, who is supposedly managing your care, has neither the time nor expertise to supplant the diagnostic and treatment power of the grand rounds concept. Why have grand rounds gone out of favor? If we had to guess, it is the influence of the drug companies who have developed specific drugs for each of the myriad of medical specialties. Many of these drugs would fall into obscurity in the grand rounds environment.

The concept of grand rounds was discussed in a recent *Medpage Today* article. [29] The topic was not Alzheimer's; however, the findings about the need for grand rounds to help avert serious disease hold true for all the major chronic diseases. The authors provide the following insights. "It takes a village to successfully treat and manage patients… but those villages are few and far between." "About 84% of doctors believe that coordinated care among healthcare professionals is important but only 33% believe that coordinated care is currently adequate in their respective countries." About 60% of the doctors in France said there were adequate professionals outside the hospital setting to help coordinate care. Among physicians in other countries, however, only about 30% to 40% said coordinated outpatient care was feasible. The U.S. came in at the low end, with about 27% of the surveyed doctors indicating there were adequate settings for coordinated care in their country."

Other Alzheimer's Predetermining Factors

The items above provide you with a guide to evaluate your future risk of Alzheimer's disease. There is vast and compelling evidence to support a strong link between any of those items and Alzheimer's. The items listed here are also important for your Alzheimer's risk self-diagnosis but probably have many confounding health elements compared to those discussed above.

Chronic stomach problems: Any stomach problems or family history of stomach problems could imply helicobacter pylori infection. This bacterium is considered both synergistic and pathogenic and, the latter "condition" is linked to Alzheimer's disease. Helicobacter pylori infection is a cause of stomach ulcers, and the doctors who made that discovery were awarded the Nobel Prize in

Medicine in 2005.

History of positive TB skin test or night sweats: Tuberculosis is making a comeback and people positive for TB have more Alzheimer's disease. It may not be the TB itself that is causing AD, but active TB is an indication that your immune system may be failing.

History of or current Lyme disease: This is very similar to TB. It may not be a cause but an indication of your immune system health.

History of leg cramps: This may infer a magnesium deficiency.

Raw or very rare meat: Toxoplasmosis is an infectious species obtained from undercooked meat. Toxo is a cause of a number of neuropsychiatric disorders and may be a contributor to AD.

Weight loss: If you are a senior, have you experienced sudden weight loss not attributable to a diet program? "Epidemiologic studies have shown that weight loss is commonly associated with Alzheimer disease (AD) and is a manifestation of the disease itself. The etiology of weight loss in AD appears multifactorial. Hypotheses to explain the weight loss have been suggested (e.g., atrophy of the mesial temporal cortex, biological disturbances, and higher energy expenditure); however, none have been proven." [30]

Trips and falls: According to a WebMD article, "Falls may be an early sign of Alzheimer's disease, researchers report. In a study of 125 older adults who appeared physically and cognitively healthy, two-thirds of those with large deposits of Alzheimer's-associated plaque in their brains suffered falls. In contrast, only one-third of those with little or no plaque experienced falls." [31]

Function: Changes in memory and general functioning is a late sign of pending and advancing dementia. The specific issue for which to watch include: forgetfulness; challenges in planning or solving problems; difficulty completing familiar tasks at home; confusion about time and/or place; being challenged by special relationships; language problems; impaired decision making, withdrawal from social activities; and mood and personality changes.

Sudden loss of physical strength. This condition may be a result of lost brain control or due to an overlapping disease called Inclusion Body Myositis that could be considered Alzheimer's disease of the muscle.

Diagnosing and Treating the "Well" to Prevent Disease

Dr. Mayo commented over 100 years ago about the need to treat the "well" to prevent them from becoming ill. Little has changed in the investigation and treatment of so-called well persons to prevent them from getting sick. This is true for all the chronic inflammatory diseases related to aging including Alzheimer's. The statistics bear out the need for "well person" treatment as these chronic diseases are increasing exponentially. If you wait for your doctor to make a diagnosis of (chronic) disease, it will be far more advanced and much more difficult, if not impossible, to control.

The problem a doctor faces in treating the "well" is he or she needs a diagnosis to get paid and be justified to order blood tests. Let's consider the case of a homocysteine test. You read, in Chapter 7, that elevated homocysteine is highly correlated to the future risk of Alzheimer's. The Mayo Clinic website states that "Elevated Homocysteine" is an Alzheimer's risk factor. [32] Please let us know what happens if you are a "well person" and you go to the Mayo Clinic and ask for a homocysteine blood test because of your concern about future Alzheimer's. Even if you already have a diagnosis for a disease that predisposes you to develop AD in the next 10 years such as age-related macular degeneration, glaucoma, type 2 diabetes, or cardiovascular disease, your doctor is often not permitted (or at least, you will not be reimbursed for the test) by these diagnoses to order blood tests or other diagnostic procedures such as MRI or special tests of the eye to document the early changes related to AD. You may get these tests if you insist and are willing to pay cash.

Many articles are written about unnecessary tests and costs associated with diagnosing and treating "healthy" people. But our society is overwhelmed with slowly developing chronic diseases. We must find cost-effective ways to examine the so-called "well person." Proof of the need to better manage the health of the well comes from the medical literature and is summarized in the *New York Times*. [33]

> "After a routine test of her blood sugar eight years ago, Randi Sue Baker, a seriously overweight 64-year-old, learned that type 2 diabetes was bearing down.
>
> With that test result, she joined the 79 million Americans over the age of 20 who have prediabetes. Up to 70 percent of them will go on to develop diabetes, but 90 percent don't even know they are at risk. In fact, as many as 28 percent of adults with full-blown diabetes don't know they have it, according to Edward W. Gregg, a senior epidemiologist at the Centers for Disease Control and Prevention."

In this *New York Times* article, the author Jane Brody goes on to explain that diabetes accounted for $245 billion in health care expenses in 2012, about one in six health care dollars. You now know that people with this condition often progress into Alzheimer's, if they survive diabetes.

The main goal of the examination of an apparently well person is to eliminate the probability of future chronic diseases. This patient is in good health with no complaints (no diagnosis). The very early diagnosis of AD is often very simple. Hundreds of millions of research dollars are spent to find early biomarker AD before it becomes symptomatic and very challenging to treat. And, as Chapter 2 illuminated, more than 200 studies have been performed on early dementia and have failed miserably.

Does it make more sense to spend that research money in the real world—that is, on people like you? Wouldn't we curb much more disease by screening our population based on known risk factors, biomarkers, and overlapping disease? A homocysteine test is relatively inexpensive and, as explained in Chapter 7, may be the single most important measure of your future chronic disease health. What would the return on investment be for a homocysteine test (in combination with other simple and highly correlated tests that are already known)? Compare this to the Pittsburgh dye [34] that is toxic, followed by an expensive and nerve-racking PET scan? **Priceless**.

Differential Diagnosis for the Well and the Afflicted

"You never change things by fighting the existing reality. To change something, build a new model that makes the existing model obsolete."

— Richard Buckminster Fuller

The steps to brain health, Alzheimer's prevention, and an understanding of the cause(s) of Alzheimer's disease for the purposes of effective treatment include six components:

1. Screening
2. Baseline measurement
3. Comprehensive assessment
4. In depth root cause(s) analysis
5. Intervention(s)
6. Repeat steps 1-5 periodically to optimize

In dentistry, these same steps are followed. The dentist and hygienist screen your oral health with simple methods (visually). They acquire baseline information with X-rays and closely note recession, gum pockets, and other markers of oral health and disease. A comprehensive assessment is conducted, which may involve a specialist looking at cavities and extraction needs. Occasionally, your dentist may look into a more in-depth root cause analysis, in the case of, for example, periodontal disease, and refer you to a specialist for evaluation and treatment. Interventions include action items determined from the previous steps. Of course, we all understand the concept of preventative dentistry, and many of us return to the dentist on a regular basis to keep ahead of oral disease and decay.

The steps 1-5 are a logical progression of activities that one should consider, regardless of health or age. A baseline assessment is a fairly broad evaluation. However, for Alzheimer's disease, what is proposed here is far different compared to a routine physical performed within the standard-of-care. The eye-screening portion of this diagnostic protocol is far more predictive of your future chance of having a serious health problem than what any doctor can determine through a routine physical examination. Chapter 6 contains the evidence. Why our major health pundits, including the National Institutes of Health (who funded some of the research on the eye) are keeping this information from doctors and the public is only a guess.

Before embarking on the journey through the subsequent pages on a differential diagnosis toward a treatment let's briefly consider what tests provide the earliest diagnosis of a person with Alzheimer's or other chronic diseases. First, no single test or single measurement of that test is every truly adequate to characterize disease. Medicine tries to accommodate our busy lifestyles and the need for profit by creating science around a single test like cholesterol. If you ignore the hype, that type of approach is an abject failure. Thus how can one be sure of a diagnosis? We discussed this in Chapter 3 and summarize the ideas here.

Demonstrated reproducibility or trends: Repeat tests at defined intervals. The rule of thumb scientists use in evaluating lab data is obtain three tests and then use the

standard deviation to determine the statistically significant value. In medicine, tests are expensive, and often blood needs to be drawn. Thus it would be impractical to draw three vials of blood at the same time and send the samples to three different laboratories.

Since we are mainly concerned with chronic diseases with long incubation times, it makes sense to get the "key" tests done regularly, or at least annually. Increase the frequency to quarterly for any tests that show slightly abnormal values. Certain tests for chronic diseases also are markers for acute events such as trauma. An example is C-reactive protein. If your C-reactive protein is high, it does not infer chronic disease. However, if you retest in one to three months and it is still high, then there may be something brewing in your body. A third test in another one to three months will provide the certainty needed to determine if you are "silently" ill.

Get a range of tests: Alzheimer's researchers are desperately seeking the definitive test for beta-amyloid plaques in sufferer's brain. However, science we presented in Chapter 2 shows that some Alzheimer's patients are free of beta-amyloid while some healthy people have burdens of amyloid that researchers thought were sufficient for the subjects to have disease. Having a single test, like cholesterol, is expedient and profitable, but it does not weave a story about your health. Alzheimer's is a story, not a moment in time.

Which tests provide early disease detection? The tests that provide the earliest indication of disease generally go in the following order, from earliest to latest.

1. Blood Tests: When we are sick, our immune system reacts almost immediately. The adaptive immune system is slow, taking about five days to respond to new threats. In acute (immediate) disease, blood markers of immune activity relax back to normal levels once the illness passes. In chronic disease, inflammatory markers elevate and, although they may fluctuate, they tend to stay higher than normal baseline levels.
2. Eye Tests: The eye is a tremendous biomarker for diseases of itself but also for diseases of the whole body. Our bodies are robust and often overcome illnesses, particularly low-grade illnesses. When left unchecked, the causes of these diseases can proliferate, leading to slow degradation of tissue. The eye is an early biomarker for a couple of reasons. First, it is transparent, and disease development at its earliest stages is seen optically. The lens at the front of the eye is a magnifying "glass" that helps doctors see disease markers developing in the back of the eye. Second, the eye is less prone to develop an autoimmune reaction to mild antigenic stimulation. ⌗⌗ The eye is "immune privileged" and a outstanding witness to what is happening in the rest of our body.
3. Brain Test: We are blessed with brains that build significant redundancies as we develop and grow. Noticeable or even measureable loss of brain function occurs only after significant disease and atrophy. Another exacerbating feature of brain

⌗⌗ Antigenic stimulation is anything that stimulates a response from the immune system.

measurement is the integrity of the protective skull and blood/brain barrier that somewhat isolates the brain.

Summary: Although the eye is a fantastic marker for Alzheimer's and neurodegenerative diseases in general, if you want to be diagnosed as early as possible, when you have the best chance of preventing or stopping the disease, obtain blood tests. Some of the right tests are listed in the section titled, "Baseline Screening" (below).

1. Routine Screening

Routine screening, by definition, should be conducted at regular intervals to look for initial signs and symptoms of disease, preferably before clinical symptoms start to appear. This screening involves the evaluation of possible and absolute biomarkers that are either known or thought to precede disease that we have already covered in this chapter. By design, routine screening is as non-invasive, cost-effective, and expedient as possible. Medical technicians and other lower-level healthcare members may conduct routine screening. Modern standard-of-care does **not** perform routine screening despite claims to the contrary. The physical exam is an outdated test still used by modern medicine, and does little to diagnose chronic diseases like Alzheimer's disease at their early stages.

The standard physical exam has hardly changed during the past 100 years. It is not the process of a preventative check-up that is failing us; rather, it is the tests that are offered. These tests are oblivious to important targets for disease. And the real problem is that only the limited tests offered are covered by health insurance.

"The experimenter who does not know what he is looking for will not understand what he finds."

- Claude Bernard

A strong case exists for the connection between the eye, the brain, the body, morbidity (disease), and mortality (early death). This is very true for biomarkers and other indicators of Alzheimer's disease. A routine screening, which is very efficient, cost-effective, and non-invasive, may therefore start and end with a comprehensive eye exam as discussed in Chapter 6. The exam must focus on: specific markers for general systemic diseases; specific markers for cardiovascular diseases; formations associated with neurodegeneration; and the hallmarks of Alzheimer's disease including beta-amyloid formations and neurofibrillary tangles.

With the eye exam, doctors are able to search for the two major hallmarks of Alzheimer's disease and indicators of other "co-morbid" diseases such as cardiovascular disease and diabetes. The key tests are:

- Slit lamp microscopy for lens evaluation,
- Fundus camera for retina evaluation,
- Optical coherence tomography (OCT) to analyze the retinal nerve fiber layer,
- Scanning Laser Polarimeter (SLP) to measure the retinal nerve fiber layer and microtubule health, and
- VER/VEP to measure brain signal strength and response.

What we are recommending here and what you will get from a routine exam with your eye doctor are not quite the same. As part of every routine eye examination your eye doctor will measure your visual acuity, test your eye movements, and measure your eye pressure. He or she will likely use the following optical instrument to examine your eyes, but only for eye evaluation purpose and not for preventative screening:

Slit Lamp Microscope: This device looks at the front part (anterior segment) of the eye, particularly the lens and the cornea to detect chronic and aging changes. Nuclear cataracts are readily seen and are known to correlate with the presence of cardiovascular disease. Chapter 6 discusses the Age-Related Eye Disease Study that shows how visual impairment, caused by cataract formation, is a predictor or early mortality due to some type of vascular disease. Cortical cataracts are also easily detected and are highly correlated to Alzheimer's disease. Evidence of this is provided by a Harvard Medical School study. Pseudo-exfoliation is believed to be the early formations of cortical cataracts, thus the earliest potential indicator for future AD. Pseudo-exfoliation has been considered an "amyloid" material since 1973.

The American Optometric Association (and others) publishes a grading scale for cataracts that correlates with disease. A slit lamp with an attached camera can be employed to accurately track the progression or regression of cataract. The Oculus Pentacam, a tomography instrument, can be used to augment the slit lamp information as it performs very precise and accurate measurements of lens structures. However, most optometric and ophthalmic offices do not have this device. The slit lamp microscope is adequate for the initial screening phase.

Fundus Camera and Ophthalmoscope: These are used to examine the back of the eye (posterior chamber or "Fundus"). The Fundus camera is capable of recording detailed photographs of the retina, the retinal blood vessels, the retinal pigment epithelium under the transparent retina, and the optic nerve. Neurodegenerative disease is inferred by a pale or cupping optic nerve. Drusen is an amyloid formation and is indicative of a latent systemic and neurodegenerative disease process. In addition, the Fundus enables the observation of the integrity of the microvessels in the back of the eye. Quantifiable irregularities noted are indicative of local and systemic inflammation and cardiovascular disease. This system is also useful for the detection and the measurement of diabetic retinopathy. The Optos version of the fundus camera obtains a wide angle photo of the entire posterior and mid periphery of the eye in a single photo. This instrument allows the biomarkers and eye features to be qualified and quantified to accurately follow disease. Finally, glaucoma is observed via the fundus camera and other means. Many recent studies indicate that glaucoma is Alzheimer's disease of the eye and that Alzheimer's disease is glaucoma of the brain.

Other instruments that should be used for preventative health screening purposes, but are seldom part of a routine eye examination include:

Optical Coherence Tomography (OCT): This instrument is used to measure macular edema and macular volume, which is related to brain volume and thus brain neurons, and provides information similar to a brain MRI. Critical is the measurement of the nerve fiber layer. The layers in the retinal nerve fiber layer (RNFL) connect and correspond to different areas in the brain. There is a strong correlation between the

RNFL and glia, the white matter in the brain that is a measure of neurotangle density (intelligence). There is also a strong correlation between reduced macula volume and Multiple Sclerosis in young people and Alzheimer's disease in older people. A weaker but emerging connection exists between Parkinson's disease and the RNFL. Macular degeneration is also observed with OCT. OCT is useful for the detection and measurement of diabetic retinopathy. It provides an objective digital measure of many parameters that can be quantified and tracked to evaluate patient whole-body health and changes to their health status.

Scanning Laser Polarimeter (SLP): The SLP looks beyond thickness and density of the retinal nerve fiber layer (measured by OCT) to underlying structural organization that is key to RNFL Integrity. This system studies microtubules of the axons by measuring the polarization of light. A decrease in polarization infers unhealthy axons, thus a neurodegenerative process. Recent studies suggest that RNFL microstructures undergo changes in orientation and density before RNFL anatomical thickness changes become apparent. The SLP measurement depends on both RNFL thickness and the cumulative level of organization of its microstructures. Alteration of these microstructures is potentially tied to the two hallmarks of Alzheimer's disease, beta-amyloid and neurofibrillary tangles. The latter is caused by phosphorylation of tau protein. This is quickly becoming the "new" therapeutic target for Alzheimer's disease within pharmaceutical companies.

These tests require approximately 10 minutes of clinic time each. Some of these tests require eye dilation. All these tests produce digital data that can be compared against data obtained at each subsequent visit. Thus, any changes in underlying health status may be accurately tracked. Also, standards are well-known, so these tests provide a good assessment of the type and the extent of any deterioration or disease as compared to a large population of age-mates.

For the purposes of routine screening, a cognitive functioning test (the MMSE or equivalent, see Chapter 3) should be recorded to establish a baseline for an individual. These tests, although reported by some researcher as useful for early detection, are clearly late-stage tests. They need to be performed because they have become somewhat of a standard for assessing the degree of existing (symptomatic) disease. Neurological function does not "fall off a cliff." The inflammatory degradation associated with dementias is a slow and progressive process. Therefore, it is critical to establish "ground level" functioning for perfectly healthy people. A one-time test (one data point) may be corrupted by any number of factors including sleep, medications, and stress. Similar to high blood pressure, the cognitive tests should be recorded regularly, taking into consideration that a high frequency may lead to false readings as the person taking the test "learns" the expectations.

The Mini-Mental State Exam (MMSE): This test is a widely used test for cognitive function among the elderly; it includes tests of orientation, attention, memory, language, and visual-spatial skills. In general, participants scoring below education-adjusted cut-off scores on the MMSE may be cognitively impaired. There are arguably many more, better tests for cognitive impairment that can be used in a screening mode. Many of these are mentioned in Chapter 3.

When should you have your first routine screening? Immediately. How often should you have a routine screening? For many of us, these tests are already done if you have seen you optometrist of ophthalmogist recently. However, there a few, if any, eye doctors willing to share with their patients the association between eye pathology and diseases like Alzheimer's. Your doctor can best determine when your next screening should be conducted. As a rule-of-thumb, screening should be performed starting at age 40 then every five years thereafter until the age of 60 when the frequency should be every two years.

2. Baseline Determination

We are all unique individuals. You want to be compared to yourself, not some amorphous statistic, don't you? So often in medicine, the patient is judged "by the numbers," rather than by looking at the person. This "baseline" step can be comprehensive or limited based on the judgment of your doctor and particularly on his or her evaluation of your phenotype. Age may determine the depth and breadth of this assessment. In baseline determination, a patient will go through a wide range of tests to establish the base or current status with regard to brain health, cognitive function, and the factors that may impact brain health. Baseline tests include ocular tests, blood testing, and neurological and psychological assessment. Baseline testing also includes any or all of the tests in "Routine Screening."

Advanced Ocular Tests

These tests are in addition to those in routine screening. Some of these tests are very obscure while others do not have adequate reimbursement for doctors to even consider doing. However, they all provide valuable information about your health status, particularly with regard to neurodegenerative disease. Many of these tests are potentially useful to drug development companies who are looking for that next blockbuster drug to defeat AD.

Optical Path Deviation (OPD): This is a research and clinical tool used in refractive surgery that very accurately measures the optical path aberration in the cornea and the lens (Cataract). In the case of refractive surgery the corneal aberration can be corrected based on those measurements (Lasik surgery). The same instrument can also accurately measure changes in the lens before the cataract is visible. Often this lens swelling is due to the accumulation of a misfolded protein precursors associated with Alzheimer's. Slight changes in the accumulation and coalescing of these proteins in the eye can cause a significant change in aberration, thus this tool can be used very early on to potentially diagnose disease and measure treatment efficacy. The OPD produces a quantifiable digital report that can be used in a health report card and also facilitates tracking of patient progress.

Visual Evoked Response (VER): This simple device measures the transmission of signals from the retina to the back of the brain across four synapses and between five neurons. The signal generated is highly correlated to acute and chronic neurodegenerative processes, and it is highly reproducible, quantifiable, and very useful in tracking progression/regression of brain response.

Micro Perimeter Assessment: This device has both an infrared and a color fundus camera, and a real-time tracking system that allows for a full automatic assessment of the eye's fixation stability. It measures the stability of the eye fixation that is controlled by the six muscles surrounding each eye. The extent that a subject cannot focus, or maintain a stable focus, is indicative of a neurodegenerative process. This device offers a simple, yet semi-objective and quantifiable way to characterize the extent of disease and evaluate treatments. This instrument also measures visual fields.

Visual Field: Our peripheral visual fields (peripheral vision) gradually constricts as a normal process of aging. More rapid or advanced visual field contraction indicates accelerated aging. This device also allows the study of side vision. Inflammation leading to tissue disease is a potential cause of peripheral visual field changes as are brain tumors. The typical system provides both qualitative and quantitative results that can be used in a health report card and to track patient progress.

Pentacam Scheimpflug (Imaging of the cornea and the crystalline lens): This instrument takes over 25,000 very accurate measurements in less than one second of the anterior (front) structures of the eye. This camera has five difference functions; hence its name "penta" (five) camera. Two of those functions are useful to study the changes in the eye associated with AD and aging seen in the lens and the cornea.

- Lens Tomography: The Pentacam performs very precise and reproducible measurements of the lens. Information obtained includes; precise measurements of cataracts including density, and average lens opacity (related to cataracts and inflammation).

The accurate lens measurement could be useful to follow the changes caused by the accumulation of beta amyloid protein (one AD hallmark biomarker) in the lens.

- Corneal thickness and volume: Like skin thickness, corneal thickness diminishes with age. Premature thinning is a sign of accelerated aging. This instrument imparts more objectivity compared to the slit lamp microscope and provides information about the cornea and the lens not obtained in a slit-lamp measurement. The data obtained is very objective and classifiable, and thus is useful in a health report card and for monitoring patient progress with respect to both neurodegenerative and cardiovascular diseases. Formations like nuclear and cortical cataracts are accurately mapped through tomography.

Retinal Laser Doppler Instrument: Laser Doppler systems provide imaging to measure blood vessel size and speed of blood flow. Patients with Alzheimer's and other diseases of inflammation show a significant narrowing of the venous blood column diameter compared with the control subjects and a significantly reduced venous blood flow rate compared with the control subjects. This test saw considerable buzz as an Alzheimer's "diagnostic" technique at the International Alzheimer's Association meeting in Paris, 2011. However, this is a rather non-specific test that is worth recording as part of a differential diagnosis.

Blood Tests

Alzheimer's disease is now recognized as a disease of the brain and of the general cardiovascular system. Markers in the system-wide (systemic) blood may give clues as

to the origin and progression of the disease. During baseline testing, some key blood tests should be considered. They are listed in order from most-to-least important based on the author's judgment, evaluation of the literature, and relevant clinical experience. Some consideration in placement was given to the ability of the patient to modify that risk factor in a favorable way and thus to prevent or slow Alzheimer's disease.

Homocysteine: This is a metabolic by-product of methionine metabolism. Progressively elevated blood levels of homocysteine are a documented risk marker for cardiovascular events, age-related macular degeneration, glaucoma, and Alzheimer's disease.

C-reactive protein: CRP is the single best measure of your "chronic disease temperature." CRP is one of a number of acute phase reactant proteins that increases in response to inflammatory stimuli. In large epidemiologic studies, elevated levels of CRP have been shown to be a strong indicator of CVD. The plasma cytokine interleukin-6 (IL-6) plays an important role in mediating inflammation and is a central stimulus for the acute-phase response. In particular, IL-6 induces the hepatic (liver) synthesis of CRP. IL-6 is implicated as one of the important inflammatory substance that halts generation of new neurons (neurogenesis). In fact, IL-6 is the only known cytokine capable of inducing all acute-phase proteins involved in the inflammatory response. [35] For more information read "Hope for the Afflicted" later in this chapter.

Complete Blood Count with Differential (CBC): Parameters obtained in this test tell a lot about the level of immune system activity by measuring white blood cell counts and other factors that help determine why the immune system is active. The most useful data obtained from the CBC with differential includes:

- White blood cell (WBC, leukocyte) count: White blood cells are part of your immune system. They protect the body against infection. If an infection develops, white blood cells attack and destroy the bacteria, virus, or other organisms causing it. White blood cells are bigger than red blood cells but fewer in number. When a person has a bacterial infection, the number of white cells rises very quickly. The number of white blood cells is routinely used to determine if our body is responding to infection, to see how the body is dealing with cancer treatment, or if an immune system disorder exists.
    - Neutrophil granulocytes are generally referred to as either neutrophils or polymorphonuclear neutrophils (or PMNs) and are subdivided into segmented neutrophils (or segs) and banded neutrophils (or bands). Neutrophils are the most abundant type of white blood cells in mammals and form an essential part of the innate immune system. Neutrophils are recruited to the site of injury within minutes following trauma and are the hallmark of acute inflammation. These cells also protect the body against infection by destroying bacteria.
    - Eosinophil granulocytes, usually called eosinophils or eosinophiles (or, less commonly, acidophils), are white blood cells that are one of the immune system components responsible for combating multicellular parasites and certain infections. Along with mast cells, they also control mechanisms

associated with allergy and asthma. They are granulocytes that develop during hematopoiesis in the bone marrow before migrating into blood.

- Lymphocytes and Natural Killer Cells: NK cells are a part of innate immune system and play a major role in defending the body from both tumors and virally infected cells. NK cells distinguish infected cells and tumors from normal and uninfected cells by recognizing changes of a surface. NK cells are activated in response to a family of cytokines called interferons. Activated NK cells release cytotoxic (cell-killing) granules that then destroy the altered cells. They were named "natural killer cells" because of the initial notion that they do not require prior activation in order to kill cells.
- Basophils appear in many specific kinds of inflammatory reactions, particularly those that cause allergic symptoms. Basophils contain anticoagulant heparin, which prevents blood from clotting too quickly. They also contain the vasodilator histamine, which promotes blood flow to tissues. They can be found in unusually high numbers at sites of ectoparasite infection (e.g., ticks). Like eosinophils, basophils play a role in both parasitic infections and allergies.

Vitamin D: This hormone is a "neurosteroids hormone" as as such is a potential biomarker of AD. [36] Patients with Alzheimer's disease have a lower serum vitamin D compared to matched controls. In a prospective (forward looking) study it has been demonstrated that low levels of vitamin were associated with substantial cognitive decline in the elderly population. [37] In fact, it has been shown that supplementation with vitamin D improves cognition in patients with Alzheimer's disease. More commonly vitamin D is known to promote calcium absorption in the gut and maintains adequate serum calcium and phosphate concentrations to enable normal mineralization of bone Vitamin D has other roles in the body, including modulation of cell growth, neuromuscular and immune function, and reduction of inflammation. Many genes encoding proteins that regulate cell proliferation, differentiation, and apoptosis are modulated in part by vitamin D. Vitamin D3 is neuroprotective and therapeutic in attenuating iron-induced neurotoxicity in the central nervous system. The toxic effects of iron on the brain is important in AD and it is even more important in Parkinson's disease. [§§] Iron is now added to the flour and as we get older we all accumulate iron that is stored as ferritin in our body. If your serum ferritin is high you should give blood on a regular basis and make sure that your serum vitamin D level is optimal.

Please take your vitamin D supplements, get sensible sun and have your vitamin D level check annually. Be aware that if you take vitamin D (25-hydroxy vitamin D) and your serum level does not go up to the optimal level of 40 to 80 you should see a doctor and have your 1,25 dihydroxy vitamin D measured. If it is elevated you have and inflammatory disease process that is causing your 25-hydroxy vitamin D to be activated. Do not take higher amount of vitamin D if your 1,25 dihydroxy vitamin D is elevated. See a doctor familiar with the causes of vitamin D activation and is willing to

[§§] See discussion on Iron and Ferritin in Chapter 10.

perform root-cause tests. In Dr. Trempe's experience only a very few doctors measure 1,25 dihydroy vitamin D.

Omege-3 Fatty Acids: These critical substances are also known as polyunsaturated fatty acids or PUFAs, particularly PUFA 3s. The key clinical omega-3 fats are EPA and DHA, which are found largely in cold-water fish. It is well established in current literature that a higher blood level of these important fats may help to reduce the risk of Alzheimer's disease, heart disease, and stroke.

PUFA 6/3 Ratio: High levels (>5) are associated with chronic silent inflammation.

Glucose: It is a type of sugar that the body uses for energy. An abnormal glucose level in your blood may be a sign of diabetes. For some blood glucose tests, you have to fast before your blood is drawn. Other blood glucose tests are done after a meal or at any time with no preparation. Hemoglobin A1c (HbA1c, A1c) is a more dependable way to determine your average blood glucose level. The red blood cells that circulate in the body live for about three months before they die. When sugar sticks to these cells, it gives us an idea of how much sugar has been around for the preceding three months. In most labs, the normal range is considered 4-5.9%. In diabetes, it's 7.5% or above, and in pre-diabetics it's around 7.0%. The benefits of measuring A1c is that is gives a more reasonable view of what's happening over the course of time (three months), and the value does not bounce as much as finger stick blood sugar measurements.

Insulin: This hormone is associated with the characterization of the Atherogenic Lipid Profile and Metabolic Syndrome. Abnormal fasting insulin, especially when combined with other risk factors, identifies patients at significantly higher risk for CVD and Alzheimer's.

Tumor necrosis factor alpha (TNF-α): TNF-α is a growth factor for immune cells and osteoclasts, the cells that break down bone. It has well-known pro-inflammatory functions and may be elevated in chronic infections, certain cancers, and hepatitis C. TNF-α is being (incorrectly, we believe) considered a direct therapeutic target for Alzheimer's disease. [38] Indeed, anti-inflammatory strategies may have short-term benefits of relieving symptoms, but long term, suppressing immune function (inflammation) always fails. Thus TNF-α is another important marker of inflammation, and elevated levels should be used for diagnostic purposes and a reason to dig deeper and find a cause for its elevation. The section in this chapter titled, "Hope for the Afflicted" should shed light on the shortcoming of just suppressing inflammation.

Fibrinogen: This is a plasma glycoprotein that can be transformed by thrombin into a fibrin clot in response to injury. The combination of elevated fibrinogen with other CVD risk factors can substantially increase disease potential. "Fibrinogen is normally found circulating in blood, but in AD it deposits with Aβ in the brain parenchyma and the cerebral blood vessels. We found that Aβ and fibrin(ogen) interact, and their binding leads to increased fibrinogen aggregation, Aβ fibrillization, and the formation of degradation-resistant fibrin clots. Decreasing fibrinogen levels not only lessens cerebral amyloid angiopathy and BBB permeability, but it also reduces microglial activation and improves cognitive performance in AD mouse models." [39] As with elevated tumor necrosis factor alpha, this does not imply that fibrinogen is a

therapeutic target. That will be determined through more research. However, fibrinogen is a bona fide diagnostic parameter for AD.

Interleukin-6 (IL-6): Elevated levels may occur in different conditions including chronic infections, autoimmune disorders, certain cancers, and Alzheimer's disease. This test may be redundant because of the connection between IL 6 and CRP.

Ceramides: "Serum ceramides increase the risk of Alzheimer's disease," according to a Mayo Clinic group. [40] They may not increase the risk on their own, but their presence at a high level surely is an indicator of increased risk. "Compared to the lowest tertile, the middle and highest tertiles of ceramide were associated with a 10-fold and 7.6-fold increased risk of AD respectively. Total and high-density lipoprotein cholesterol and triglycerides were not associated with dementia or AD." "Results from this preliminary study suggest that particular species of serum ceramides are associated with incident AD." A routine blood test for ceramides is not available in the standard-of-care, but the technology is available for such tests.

Sex Hormones:

- Testosterone is a hormone made by your body and is responsible for the normal growth and development of the male sex organs and for maintenance of other sexual characteristics. In men, testosterone is produced in the testes, the reproductive glands that also produce sperm. The amount of testosterone produced by the testes is regulated by the hypothalamus and the pituitary gland. Testosterone deficiency can also lead to a number of disturbing symptoms, including loss of stamina and lean muscle mass, reduced libido, anxiety, depression, and cognitive decline.
- Estrogen is probably the most widely known and discussed of all hormones. The term "estrogen" actually refers to any of a group of chemically similar hormones; estrogenic hormones are sometimes mistakenly referred to as exclusively female hormones when in fact both men and women produce them. Estrogens act on the central nervous system (CNS) through genomic mechanisms, modulating synthesis, release and metabolism of neurotransmitters, neuropeptides and neurosteroids, and non-genomic mechanisms, influencing electrical excitability, synaptic function, and morphological features. Therefore, estrogen's neuroactive effects are multifaceted and encompass a system that ranges from the chemical to the biochemical to the genomic mechanisms, protecting against a wide range of neurotoxic insults. Many biological mechanisms support the hypothesis that estrogens might protect against Alzheimer's disease by influencing neurotransmission, increasing cerebral blood flow, modulating growth proteins associated with axonal elongation, and blunting the neurotoxic effects of β-amyloid.
- Pregnenolone, testosterone, estrogen, cortisol, and DHEA are members of a family of natural hormones that are essential for human survival. Scientists have discovered that pregnenolone also can be manufactured in the brain from cholesterol instead of being transported through the blood-brain barrier from other parts of the body. This supports recent findings showing that pregnenolone

is involved in a variety of brain-related functions such as memory, concentration, and mood. [41]

Apolipoprotein E (apoE): This is an inherited trait. The apoE genotype predicts lipid abnormalities and responsiveness to different dietary fat intake. The e4 version of the apoE gene indicates an individual's increased risk for developing late-onset Alzheimer disease. People who inherit one copy of the APOE e4 allele have an increased chance of developing the disease; those who inherit two copies of the allele are at even greater risk. The apoE e4 allele may also be associated with an earlier onset of memory loss and other symptoms.

Magnesium: This mineral plays many vital roles in preventing heart disease, controlling blood pressure, and maintaining healthy cholesterol levels. This test is placed low on the list because serum levels probably do not accurately portray the true balance of magnesium. Are you taking magnesium supplements?

Adiponectin: This substance is a protein hormone that modulates a number of metabolic processes, including glucose regulation and fatty acid catabolism. Adiponectin is exclusively secreted from adipose tissue into the bloodstream and is very abundant in plasma relative to many hormones. Korean researchers studied the literature and concluded that there is a correlation between adiponectin and AD. "Adiponectin is an adipocytokine released by the adipose tissue and has multiple roles in the immune system and in the metabolic syndromes such as cardiovascular disease, type 2 diabetes, obesity, and also in the neurodegenerative disorders including Alzheimer's disease. Adiponectin regulates the sensitivity of insulin, fatty acid catabolism, glucose homeostasis and anti-inflammatory system through various mechanisms. Previous studies demonstrated that adiponectin modulates memory and cognitive impairment and contributes to the deregulated glucose metabolism and mitochondrial dysfunction observed in Alzheimer's disease. Here, we aim to summarize recent studies that suggest the potential correlation between adiponectin and Alzheimer's disease." [42]

Cholesterol/HDL ratio: Many studies have sought to show the benefit of high HDL levels and the results remain mixed. However, the ratio of total cholesterol to HDL is physiologically important. A ratio of <4 is preferred.

Calcium: This mineral is an important mineral in the body. Abnormal calcium levels in the blood may be a sign of kidney problems, bone disease, thyroid disease, cancer, malnutrition, or another disorder. Excess calcium is connected with hardening of the arteries and dementia. The "calcium hypothesis of dementia" is an emerging theory on one of the potential root causes of accelerated brain aging.

β2 microglobulin: This is a measure of the activity of the acquired immune system and can provide information about infection and inflammation. Tests for β2 microglobulin are being evaluated for Alzheimer's with favorable results. [43] A *Daily Mail* article discusses this test as viable for AD, however a spinal tap is required. [44]

Urinary Albumin: Studies have shown that elevated levels of urinary albumin in people with diabetes or hypertension are associated with increased risk of developing cardiovascular disease (CVD).

Kidneys: Blood tests for kidney function measure levels of blood urea nitrogen (BUN) and creatinine. Both of these are waste products that the kidneys filter out of the body. Abnormal BUN and creatinine levels may be signs of a kidney disease or other disorders.

Myeloperoxidase: Recent studies have reported an association between myeloperoxidase levels and the severity of coronary artery disease. It has been suggested that myeloperoxidase plays a significant role in the development of the atherosclerotic lesion and rendering plaques unstable. Researchers continue to link cardiovascular and Alzheimer's disease, and the marker myeloperoxidase (MPO) is not providing exception to this emerging rule. Research led scientists to make the following statement: "AD patients showed significantly increased plasma levels of MPO, which could be an important molecular link between atherosclerosis and AD." [45]

NT-proBNP: This is a progressive CVD risk marker with powerful, independent prognostic value for detection of clinical and subclinical cardiac dysfunction. [46] Elevated levels indicate the presence of ongoing myocardial stress and potentially an underlying cardiac disorder.

Lp-PLA2: It is a marker for vascular-specific inflammation and also plays a causal role in the vascular inflammatory process, leading to the formation of vulnerable, rupture-prone plaque. Elevated levels have been shown to be powerful predictors of ischemic stroke and heart attack risk. [47] This marker is now becoming important in Alzheimer's evaluation. Researchers from the Netherlands make the following claim: "This is the first study to our knowledge that shows that Lp-PLA2 is associated with the risk of dementia independent of cardiovascular and inflammatory factors and provides evidence for a potential role of Lp-PLA2 in identifying subjects at risk for dementia." [48]

Lp(a): It is an inherited abnormal protein attached to LDL. Lp(a) increases coagulation and triples cardiovascular disease risk. Medical research shows the connection between AD and CVD through the following statement: "It is suggested that increased Lp(a) serum concentrations, by increasing the risk for cerebrovascular disease, may have a role in determining clinical AD. [49]

ESR or SED rate: This is a nonspecific test used to detect chronic inflammation associated with infections, autoimmune disorders, and cancer. This test has been used in trials that evaluated differential parameters for evaluation of dementia. [50]

F2-IsoPs: These are the "gold-standard" for quantifying oxidative stress. Increased free radical-mediated injury to the brain is proposed to be an integral component of several neurodegenerative diseases, including AD. Lipid peroxidation is a major outcome of free radicals' mediated injury to brain, where it directly damages membranes and generates a number of oxidized products. F2-Isoprostanes (F2-IsoPs), one group of lipid peroxidation products derived from arachidonic acid (omega-6 fatty acid), are especially useful as in vivo biomarkers of lipid peroxidation. F2-IsoP concentration is selectively increased in diseased regions of the brain from patients who died from advanced AD, where pathologic changes include beta-amyloid, neurofibrillary tangle formation, and extensive neuron death. [51]

Ferritin: Checking your iron levels is done through a simple blood test called a serum ferritin test. The study of iron in the human brain is particularly important in the context of Alzheimer's disease. Iron is both essential for healthy brain function and is implicated as a factor in neurodegeneration. The chemical form of the iron is particularly critical, as this affects its toxicity, and disrupted iron metabolism is linked to regional iron accumulation and pathological hallmarks, such as senile plaques and neurofibrillary tangles. [52]

Haptoglobin: Plasma haptoglobin is oxidized in mild cognitive impairment and Alzheimer's disease. Oxidation of haptoglobin contributes to amyloid fibril formation. Extracellular chaperones are impaired in Alzheimer's disease of which haptoglobin is one. Haptoglobin may be considered a putative marker of Alzheimer's disease progression. [53]

Uric Acid: Uric acid is a risk factor of cardiovascular disease, as well as a major natural antioxidant, prohibiting the occurrence of cellular damage. According to some research, "Notwithstanding the associated increased risk of cardiovascular disease, higher levels of uric acid are associated with a decreased risk of dementia and better cognitive function later in life." [54] However, other research suggests that the correlation does not exist. [55] Uric acid remains an important test that should be performed routinely to measure health and health trends.

Vitamin B6: Low circulating vitamin B6 is highly correlated to markers of inflammation that contribute to Alzheimer's disease. [56] This marker, taken together with other inflammation markers, helps strengthen the case for inflammation, when all are pointing at an increase in inflammatory body burden.

We have just listed over two-dozen tests, most of which involve drawing blood. Indeed, having these tests done raises the usual issues of insurance reimbursement, doctors catching up with emerging data, interpretations, and interventions based on the results. The biggest hurdle you face is that the best use of these tests is on the apparently "well person," as most of these tests should be used in a prevention/early detection mode.

We have not listed these tests in any particular order because every test provides useful information. The more tests you can obtain, the better. However, the order of listing of these tests is not completely coincidental, at least for the first half dozen tests.

Diseases Co-morbid with Alzheimer's Disease

The diagnosis of any of the following diseases is thus a likely diagnostic for Alzheimer's disease potential. Several of these were already explained above in the section titled, "Alzheimer's Risks That You Can Determine."

Mild cognitive impairment
Dementia
Glaucoma
Macular degeneration
Lyme Disease
Infectious disease(s) (chronic)
Diabetes Type II
Cardiovascular disease(s)

Amyloid-based diseases
Autoimmune diseases
Rheumatoid arthritis
Other inflammatory diseases

Neurological and Psychological Tests

First, being honest, no one enjoys undergoing the "challenge" or tests that measure your cognitive function. They are humiliating. However, the standard-of-care uses these tests and they provide a benchmark common to the neurological profession. The Mini Mental State Exam is the most commonly prescribed test to characterize the state of cognitive function. Other tests have emerged that claim to provide better performance in terms of accuracy and reproducibility. The best solution is to obtain measurements from more than one of these tests. This will give a broader assessment of cognitive function and also likely allow repeat testing to be less corrupted by memorization by the person taking the tests. The list below includes the more commonly administered tests:

Wisconsin Card Sorting Test
The Rey-Osterrieth Test
ADAS-Cog (Alzheimer's Disease Assessment Scale-Cognitive)
Wechsler Test of Adult Reading™ (WTAR)
Dementia Rating Scale-Second Edition (DRS-2)

Yet another cognitive test for "early" detection is in development. This is smartly named the AQ or "Alzheimer's Questionnaire." This quiz is reported to be 90% accurate in detecting signs of memory loss. The AQ should not be used as a definitive guide to diagnosing Alzheimer's disease (AD) or mild cognitive impairment (MCI). However, it is a quick and simple-to-use indicator that may help physicians determine which individuals should be referred for more extensive memory testing. In the scheme of early diagnosis, people who "fail" the AQ are late in the disease process compared to diagnoses associated with peripheral blood and eye tests.

3. Comprehensive Assessment

The comprehensive assessment is carried out by your doctor and includes all the elements of a detailed health assessment but must go well beyond the standard-of-care physical. It starts with a review and evaluation of all the testing and evaluation from the routine screening and baseline determination steps. These tests should be current, within one year of the comprehensive assessment. This assessment should include, at a minimum, the following elements besides those already stated here:

History review

Family history

Personal history

Travel history

Work history

Nutritional history and current nutritional habits

Concussions or other previous trauma

History of previous infections or viruses

Surgeries and any anesthesia

Current and previous medications

Current health profile with an emphasis on blood pressure, diabetes, cardiovascular disease, neuropathy, sudden weight changes, ocular conditions, and any inflammatory conditions including asthma, arthritis, and other joint pain

Current medications, especially those that impact blood pressure or have any known side effects that impact brain health

Oral health currently and historically including any periodontal disease and surgeries. If your current doctor does not ask you about your oral health and hygiene, find another doctor because he or she will not have the overall understanding of disease etiology (causes) and pathology to help you with AD.

General review of immune system function and health

4. In-Depth Root Cause(s) Analysis

Alzheimer's disease is substantially preventable. How do we know that? It is really a modern disease. The case presented by Dr. Alzheimer in 1907 was relatively rare a scant 100+ years ago. Indeed we are long lived but, to a large degree, we are living less healthy lives later in life due to chronic diseases. The May 2013 issue of *National Geographic Magazine* indicates that today, those with a life expectancy of 80 suffer 19 years of degrading health. Why are those of us who are relatively long-lived so unhealthy? Diet is a big part of the puzzle according to Paul Clayton, who studied the mid-Victorian and post mid-Victorian diet of England in the 1870s and later. The post mid-Victorian workers did not change what they ate by all that much. At that time, food processing and mass production of food was emerging. Clayton determined that the processing of food led to more empty calories and less general nutritional value, especially in the lower cost foods that poorer workers could afford.

Does nutritional consideration impact us as much today? Yes. Even more than in the past, we are all continually exposed to processed foods, a plethora of artificial additives, and other ingredients to win our buying patterns by creating desirable taste. The measurement of PUFA (polyunsaturated fatty acid also known as omegas) ratios is a good indicator of just how far out of balance our diets have become. From an evolutionary perspective, the PUFA 6 to PUFA 3 ratio is best at about 3 to 1. The American diet is 15 to 1 or more.

Plenty of people live long healthy lives and don't come down with chronic disease like Alzheimer's. You know some of them, and you also know how they have comported themselves over the years. You can do it as well, but it requires more commitment and vigilance than ever, because we are long lived, and there are much more unhealthy "temptations" available to all of us. Not to mention we are subjected to a barrage of media touting the latest fad, miracle prevention, or diet.

The good news is that chronic diseases like Alzheimer's are very preventable. Question everything. Seek multiple sources of corroborating evidence. Get your ideas from the most credible sources. Consider reading the *Zone* books by Dr. Barry Sears for good ideas on nutrition. Dr. Liponis from Canyon Ranch has published some very useful books including *Ultraprevention*. [57] This book gives some very good suggestions on how to maintain your health throughout your life.

Inflammation is the Diagnostic Clue

The decades of blaming cholesterol for chronic disease is rapidly coming to an end. Yes, there are 21,000,000 Americans on statin therapy, and these numbers will not drop precipitously. How can they? You cannot expect your doctor to just say, "Um, Mr. or Mrs. Patient, we were wrong about cholesterol, and I'm concerned about statin side effects, so I'm going to remove you from this drug immediately." A colleague was just prescribed Lipitor by Mass General Hospital! Mass General has raised the white flag when it comes to treating causes of cardiovascular disease.

The new "next big thing" appears to be a combination of inflammation and homocysteine. It looks like medicine has it right this time. However, the major emphasis has been on inflammation controlling or homocysteine controlling therapies. Again, the true root cause(s) of elevated levels of homocysteine and inflammation are taking a back burner. The standard-of-care has a model, like a romance novel writer, for diagnosing and treating disease. For example, cholesterol is high, and the patient is sick, therefore lower cholesterol. The next big thing looks something like this: inflammation is high, and the patient is sick, therefore lower the inflammation. Substitute the word "inflammation" with any other marker and that is what you can expect out of clinical medicine in the future.

Inflammation is a treasure, and it is our body's response to some type of imbalance. It is our immune system response. To keep it simple, let's consider (again) what has been known for centuries about the activity of our immune system. The following information is an excerpt from the www.pfizerpro.com website. There is a certain irony to this source because Pfizer markets Lipitor, the best-selling drug of all time, which just happens to be a statin.

Immunology Refresher

Immune System: A coordinated system of cells, tissues, and soluble molecules that constitute the body's defense against invasion by nonself entities, including infectious and inert agents and tumor cells.

The immune system has four key tasks:

1. Recognition: Detect infection or harm
2. Effector function: Contain and eliminate infection
3. Regulation: Control activity to avoid damage to the body
4. Memory: Remember exposure; react immediately and strongly upon re-exposure

The Pfizer site shows how the two aspects of the immune system, innate and adaptive, are different:

Innate Immunity

- Nonspecific
- Present at all times
- Immediate but general protection
- Activates adaptive immune response
- Does not improve with repeated exposure to a pathogen.

Adaptive Immunity

- Develops in response to infection
- Protective against specific pathogens
- Leverages components of the innate response
- Develops memory, which may provide lifelong immunity to reinfection with the same pathogen.

The recurring theme is that pathogens or infectious species trigger an immune response, thus inflammation.

Diagnose for Causes of Inflammation: Pathogens

Antibody Titers: Bacteria are not measured directly, but rather are determined by measuring "antibodies" that are targeted to a specific "antigen."

Definition of antigen: An antigen is any substance that causes the immune system to produce antibodies against it. The substance may be from the environment or formed within the body. The immune system will kill or neutralize any antigen that is recognized as a foreign and potentially harmful invader.

A sample is taken from the patient blood and is then challenged with known antigens to detect the presence of antibodies to these antigens. A titer is a measure of how much a sample can be diluted before antibodies can no longer be detected. Titers are usually expressed as ratios such as 1:256, meaning that one part serum to 256 parts saline solution (dilutant) results in no antibodies remaining detectable in the sample. A titer of 1:8 is, therefore, an indication of lower numbers of bacteria antibodies than a 1:256 titer.

There are concerns over the interpretation of such tests, however, as a high titer does not necessarily mean that a person is infected, nor does a low titer necessarily mean that they have either a low-grade infection or none at all. Antibody tests such as these detect only free antibodies in the sample, and those already bonded together with an antigen are not detected. As such, patients with a high number of antigen-antibody complexes may have a significant infection but this will not be borne out by testing if there are few free antibodies in their serum sample. A low titer may in fact demonstrate significant success on the part of the immune system in fighting off an infection with bacteria, whereas a high titer could show residual antibodies to a previous infection, or unsuccessful attempts to bond to the antigens in the bloodstream by the antibodies.

Measuring for the infectious species implicated at the root of Alzheimer's is tricky business.

Antibodies may take up to two months to reach peak levels, with immunoglobulin M (IgM) appearing between two and four weeks after infection, and immunoglobulin G (IgG) taking between four and six weeks to reach detectable levels in most cases. Ensuring that the correct testing, either for IgM, IgG, or both, is carried out at the appropriate time is also important so as not to invalidate the purpose of the test.

Most of the infection related chronic inflammatory diseases are cause by intracellular (inside the cells) infections. Antibodies that are formed and circulate are able to control but not irradicate these infections because the antibodies are not able to enter the cells. From time to time these microorganism escape the cells and there is reactivation of the immune reaction and elevation of the antibody titer. For example about 15% of the US general population is infected and seropositive for toxoplasmosis. [58] Those infected individual are usually asymptomatic but the the immune surveillance can fail and the infection can reactivate and result in loss of vision and neurologic illness. This chronic infection can be treated but not cured with antibiotics. When the infection reactivates the antibody titer increases and the spread of the infection halts.

In some cases a positive result on an antibody test may be false due to potential crossover reactions for antibodies to other bacteria, such as syphilis, or viruses, such as Epstein-Barr or human immunodeficiency virus (HIV). An autoimmune response in the body may also confound the results, as antibodies to the patient's own tissues may be detected in conditions such as Lupus or Rheumatoid Arthritis. However, in some cases, active bacteria are at the root of autoimmune diseases, a fact that is not well appreciated in medicine.

Polymerase Chain Reaction, PCR: Another method for detecting and measuring bacteria, especially those implicated in Alzheimer's disease, is polymerase chain reaction (PCR) testing. This test is used to detect the bacterial genese in a blood or tissue sample.

The traditional basis for the identification of living organisms usually requires their isolation and growth in the laboratory. Reliance on these parameters have limited our awareness of the role of bacteria in the pathophysiology of diseases. PCR tests are used to detect the genetic signature of bacteria in a blood or tissue sample. This method of bacterial detection of infectious agents is particularly useful in culture-negative samples (those that do not lead to growth by traditional methods) which is usually the case for atherosclerotic or brain tissue samples obtain at autopsy.

Broad-range PCR primers are first used to detect the evidence of all known bacteria, including the eubacteria (cells without nucleus) in tissue sample. Alternatively, PCR is also be used to detect the highly specific portions of the genetic signatures that is unique for each bacterium. The same type of genetic analysis is used in forensic medicine to determine if a tissue sample belongs to a human and to which specific individual human the sample belongs.

The presence of genetic information in a tissue sample does not mean that the detected specific information belongs to a living organism because the genetic evidence can remain in tissue for prolong periods of time after the death of the organism. A full horse genome was recently extracted from the bone of a horse that lived 735,000 years ago. In that same sample more than 12 billion additional DNA molecules were detected that belong to various bacteria that kill or contaminated the sample over that time period. The horse and the bacteria are long dead but the full genetic information of the horse and of the bacteria are still preserved.

This forensic type of bacterial information done at autopsy on the brain of AD patients has revealed a significant number of genetic bacterial markers. This does not necessarily indicate an active infection at the time of death but rather indicate that those identified bacteria could have played a role at some point in the disease process and that we should test for those bacteria in patients with early signs of AD. If a patients has a high CRP, a high homocysteine, and a high antibody titer to a disease causing bacteria it is better to treat those patients because, in our experience, it is the best and only way to decrease both the CRP and homocysteine and notice a beneficial effect in our patients.

Dr. Kilmer McCully, in his review paper, reported on the work of Ott and Stephan et al. who identified over 50 unique bacteria genetic markers in varous atheromatous plaques. [59] After studying a vast number of cardiovascular disease sufferers, affected individuals were found to have between 8 and 12 distinct species in their plaques. With regard to Alzheimer's disease, and to limit the amount of blood drawn, the "usual suspects" (those noted most in the literature) are those that should be tested for first. The following is a list of bacteria worth searching for in anyone with elevated inflammatory markers and any signs of cognitive impairment. This testing should also be considered for anyone with signs of cardiovascular diseases and the other "co-morbid" diseases presented in this and other chapters.

Chlamydia Pneumoniae
Mycoplasma Pneumoniae
Toxoplasmosis
Rickettsia diseases (the three most common)
Lyme disease (there are many and the standard Lyme test is for just one)
Tuberculosis (we see many patients with untreated TB, and it can impact the brain)
H-Pylori (there is a simple breath test)
Q-Fever
Periodontal bacteria

Recall that most with infections that appear to predispose people to Alzheimer's have a good immune system and are completely asymptomatic when infected. The best example is tuberculosis: Over 95% of the healthy infected people with tuberculosis are not aware that they are infected. This is the reason why all medical personnel in every hospital in the USA is tested for tuberculosis every year in order to detect those asymptomatic yet infected.

In the experience of Dr. Trempe it is not rare for patients with early neurodegenerative diseases to have highly positive antibody titers against rickettsial diseases. Those infections can be controlled but not completely "cured" with treatmen. These patients reuqire repeated treatments over the course of years. The problem is that rickettsial organisms are very small obligate (depend on the host for fuel) intracellular infection that have a close evolutionary relationship and share many common genetic materials with our own mitochondria. [60]

Remember the definition for Typhus:

"Typhus is any of several similar diseases caused by Rickettsiae. The name comes from the Greek word 'typhos (τῦφος)' meaning smoky or hazy, describing the state of mind of those affected with typhus."

Treatable bacteria cause this smoky or hazy brain.

5. Disease Management Program

It is very important to realize that many patients that have cognitive impairment and are diagnosed as having AD do not have the disease (Chapter 1). In a paper titled, "*Much of late life cognitive decline is not due to common neurodegenerative pathologies*," the authors performed analysis on 856 deceased participants from two studies of aging and dementia. [61] Their study provides information on the causes of cognitive decline. The participants had been evaluated regularly since 1994 or 1997 and had a mean age at death of 88. The authors examined the rate and timing of cognitive decline and linked these to the three age-related pathologies. Alzheimer pathology explained 22% of the decline, gross infarcts (strokes) 2%, and Lewy bodies 8%. When considered together, these were associated with a faster rate of cognitive decline, but accounted for only 41% of the variation in decline.

The Disease Management Program is all about making you well if you have true Alzheimer's or other causes of accelerated cognitive decline. Here your doctor takes into consideration the results from the screening, baseline measurements, comprehensive assessment, and in-depth root cause(s) analysis. This program is all about treatments, measuring how you respond to treatment, and then making treatment adjustments. What are the treatments? The answer to that depends upon the diagnosis. The next section provides proof that the right diagnosis and the right treatments will work. There is hope for the afflicted and even more hope for those in the earliest and asymptomatic stages of Alzheimer's. Please do get diagnosed (a differential diagnosis, that is). A proper diagnosis will ensure you the best chance to beat the processes leading to your cognitive decline, including Alzheimer's.

Hope for the Afflicted

We have discussed prevention and diagnosis at length but we want more; we want that treatment. We are programmed to ask, "What is the treatment?" It is a natural question because a diagnosis does not make us well, but the treatment might. It is not possible to suggest a treatment without a complete differential diagnosis. Hopefully you do not feel that this response avoids the tough issues about Alzheimer's.

Another way to address treatment is to address **"treatability"** instead. How sick, or how far progressed into the Alzheimer's disease process is too far for a person (patient) to expect either stabilization or improvement? Within the Amyloid Cascade Hypothesis, the assumption is that anyone with the slightest clinical sign of cognitive deficiency is too far gone for the therapy to work (Chapter 2). Fortunately this is the wrong therapeutic approach. We have many patients that have remained stable for years after a diagnosis of Alzheimer's disease was made. Some patients show clear improvement. There is hope for those clinically afflicted with early AD.

As usual, shall we consult with some researchers to get an answer to this profound question, "Who is too far gone to treat?" It turns out that hope for the sufferers of Alzheimer's has a strange "bedfellow," a study on cranial irradiation. Why? Researchers at Stanford University studied models for the inflammation created by radiation of the brain using dead bacteria (referred to as LPS). The researchers had the savvy to appreciate that their work extended beyond inflammation created by radiation because they, and many others, show that the same inflammatory process occurs in the brain whether it is stimulated by irradiation, concussion, or chronically by inflammation and infection.

Stanford University Study Provides Hope

The work of this Stanford group over a decade ago is extremely important in Alzheimer's disease. It essentially says that even those severely afflicted with Alzheimer's have some level of hope for recovery. This is tremendous news. Now let's get it into clinics!

What follows are excerpts from, and a blow-by-blow explanation of, the Stanford paper titled, "*Inflammatory blockade restores adult hippocampal neurogenesis*." [62] This article is cited over 1,000 times, thus there is a tremendous body of literature related to this topic since its publication.

First, here is an interpretation of the title:

- Inflammatory blockade = Stopping inflammation
- Hippocampal = Part of the brain, in particular, the gray matter that has a central role in memory processes.
- Neurogenesis = Birth of neurons

The title, in laypersons terms is thus:

Stopping (the cause of) inflammation leads to the birth of new neurons and the restoration of brain function and memory.

This is so exciting that the conclusion, as it relates to Alzheimer's, is provided here, first. Then this brilliant paper is reviewed in detail.

- Alzheimer's is recognized to be an inflammatory disease.
- A clear cause of the inflammation and neuroinflammation is a variety of infectious species including spirochetes, other bacteria, and viruses.

- Since the infection produces inflammation, and stopping the inflammation renews the growth of neurons, then treating the infection provides a solution (cure—read Appendix 3 for a definition of medical cure) for Alzheimer's disease.
- Treatment is not simply dosing with antibiotics. There are many stages to creating a host (you, the patient) that is highly receptive to controlling or eradicating the infectious species implicated in AD. The degree of difficulty is related to age, the burden and type of pathogen, and other aspects of your personal phenotype.
- Prevention is the best approach.
- For those who are afflicted with AD, review the recommendations of Dr. David Wheldon that are designed for MS but target Chlamydia Pneumonia, which is one of the pathogens that can contribute to the neuroinflammation associated with both Alzheimer's and MS.

From the Stanford paper (1):

> "**The birth of new neurons within the hippocampal region of the central nervous system continues throughout life**, and the amount of neurogenesis correlates closely with the hippocampal functions of learning and memory. [63,64] The generation of new neurons within the hippocampus is mediated by proliferating neural stem or progenitor cells (NPC) [65,66,67] that are widespread within the adult brain but instructed by local signaling to produce neurons only in discrete areas. [68,69] Alterations in the microenvironment of the stem cell may allow ectopic neurogenesis to occur [70,71] or even block essential neurogenesis, leading to deficits in learning and memory [72,73,74] such as that observed in patients who receive therapeutic cranial radiation therapy." [75]

Interpretation: The belief that we are born with a fixed number of brain cells and that the number of brain cells diminishes with age is a misplaced belief. Paul Allen, a Microsoft cofounder, funded research at Stanford to map brain stem cells. It turns out that the brain is full of stem cells, and processes that occur in cells in the rest of the body also occur in brain cells. For example, all cells have a relatively short life, referred to as senescence. When cells die, they are replaced through the action of stem cells, and the brain is no exception. The good news is that the birth of new neurons continues throughout life.

Changes to the brain, or local areas within the brain (the so-called microenvironment) may alter the behavior of brain stem cells. New neuron growth may occur in unexpected areas (ectopic) or be halted. If senescent (dying) neurons are no longer replaced, then brain atrophy will occur, leading to loss of brain function and disease labels like Alzheimer's.

From the Stanford paper (2):

> "In animal models, cranial irradiation ablates hippocampal neurogenesis, in part by damaging the neurogenic microenvironment, leading to a blockade of endogenous neurogenesis. [74,75] Injury induces pro-inflammatory cytokine expression both peripherally and within the central nervous system and induces stress hormones, such as glucocorticoids, that inhibit hippocampal neurogenesis.

> [72] The extensive microglial inflammation and release of pro-inflammatory cytokines that accompanies this irradiation-induced failure suggests that inflammatory processes may influence neural progenitor cell activity." [74,76,77]

Interpretation: Radiation therapy stops the birth of neurons. The radiation produces inflammation both locally and systemically, thus it can be detected in blood. The **inflammation produced by the radiation, and not the radiation itself, is suggested to halt the growth of new neurons**.

From the Stanford paper (3):

> "To determine the effects of inflammation on adult hippocampal neurogenesis, we injected bacterial lipopolysaccharide (LPS) into adult female rats to induce systemic inflammation. [78,79,80,81] The intraperitoneal (i.p.) administration of LPS causes a peripheral inflammatory cascade that is transduced to the brain via interleukin 1β from the cerebral vasculature [78] and causes a strong up-regulation of central pro-inflammatory cytokine production." [78,81]

Interpretation: What luck! They introduced bacteria (dead bacteria, also known as LPS) to simulate the inflammation created by radiation. Moreover, they introduced the bacteria into the body cavity, and the inflammation created there quickly migrated to the brain where more inflammation was created.

From the Stanford paper (4):

> "The neuroinflammation achieved in the LPS paradigm was accompanied by … a 35% decrease in hippocampal neurogenesis."

Interpretation: The mechanism for producing new neurons to replace those that die off was reduced by 35%.

From the Stanford paper (5):

> "To determine whether inflammatory effects could be countered pharmacologically, animals were treated concurrently with a single dose of intraperitoneal LPS and daily doses of the nonsteroidal anti-inflammatory drug (NSAID) indomethacin [2.5 mg/kg, i.p., twice each day]. The effect of peripheral LPS exposure on neurogenesis was completely blocked by systemic treatment with indomethacin, whereas indomethacin alone had no effect on neurogenesis in control animals."

Interpretation: Administering an anti-inflammatory allowed the production of new neurons to commence again and achieve levels of production that were present before the inflammation.

From the Stanford paper (6):

> "To determine the extent to which microglial activation might directly affect neural stem or progenitor cells, microglia were stimulated in vitro with LPS. LPS is a potent activator of microglia and up-regulates the elaboration of pro-inflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor–α (TNF-α). LPS-stimulated or resting microglia were then co-cultured with normal neural stem cells from the hippocampus under conditions that

> typically stimulate the differentiation of 30 to 40% of the progenitor cells into immature Dcx-expressing neurons. Neurogenesis in the presence of microglia was assessed as the increase or decrease in Dcx-expressing cells relative to control. Co-culture with activated but not resting microglia decreased in vitro neurogenesis to approximately half of control levels. LPS added directly to precursor cells had no effect on neurogenesis." [82]

Interpretation: The activated brain immune system cells, caused by the inflammation (microglia cells) decreased the creation of new neurons by about one-half compared to controls.

From the Stanford paper (7):

> "Activated microglia produce the potent pro-inflammatory cytokines IL-1β, TNF-α, interferon-γ (INF-γ), and IL-6. Progenitor cells were allowed to differentiate in the presence of each cytokine, and the relative expression of Dcx was scored after 60 hours. Exposure to recombinant IL-6 (50 ng/ml) or to TNF-α (20 ng/ml) decreased in vitro neurogenesis by approximately 50%, whereas the effects of IL-1 or INF-γ were not significant. [82] **Addition of neutralizing anti–IL-6 antibody to CM from activated microglia was able to fully restore in vitro neurogenesis. This implicated IL-6 as a key inhibitor of neurogenesis in microglial CM. Although recombinant TNF-α also suppressed neurogenesis, IL-6 blockade alone appeared sufficient to restore neurogenesis in the presence of microglial CM."**

Interpretation: They determined what inflammatory molecules appear to be responsible for the stoppage of neuron stem cells and the birth of new neurons. Specifically, controlling or removing IL-6 adequately restores production of new neurons. Note that IL-6 tracks with C-reactive protein. Both of these molecules were discussed in Chapter 7. We call C-reactive protein levels a measure of your chronic disease temperature. Clearly, putting out the fire (that is, reducing inflammation) helps the body and the brain recover and improve.

From the Stanford paper (8):

> "Chronic microglial activation and peripheral monocyte recruitment with the accompanying increase in local pro-inflammatory cytokine production, including IL-6, emerge as potent antineurogenic components of brain injury."

Interpretation: Inflammation injures your brain.

From the Stanford paper (9):

> "The in vitro data suggests that IL-6 inhibition of neurogenesis is primarily due to a blockade in neuronal differentiation rather than selective influences on cell death or proliferative activity."

Interpretation: Inflammation stops stem cell activity rather than killing existing cells. They die on their own in a programmed way.

From the Stanford paper (10):

> "Inflammatory blockade with indomethacin decreased microglial activation,

> accounting for part of the restorative effect of this treatment on neurogenesis after irradiation."

Interpretation: This study was performed on mice, not on Alzheimer's patients. The mice do not actually have Alzheimer's; however, they do have inflammation that blocks neuron stem cell activity. Do not interpret that indomethacin is an appropriate drug for Alzheimer's. Subsequent studies proved that patients treated with that substance did not improve or got worse. The mice do not have the disease. Inflammation was induced. People with AD have an underlying disease that causes the inflammation. That underlying cause must be treated. Remember, inflammation is actually a treasure of nature and is fighting that underlying cause of disease. If you inappropriately remove the inflammation, the disease will proliferate and ultimately create more inflammation and more disease.

From the Stanford paper (11):

> "In addition, the microvasculature of the hippocampus is a critical element of the neurogenic microenvironment [83,84,85] and both endotoxin and irradiation-induced inflammation disrupts the association of proliferating progenitor cells with microvessels. [74] The recruitment of circulating inflammatory cells is highly dependent on the endothelial status and elaboration of chemokines. One of the most robust effects of indomethacin in the present paradigm is the reduction in peripheral monocyte recruitment, suggesting that the inflammatory status of endothelial cells [e.g., expression of chemokines and/or ICAM (intercellular adhesion molecule)] may be normalized by indomethacin. Indeed, one known attribute of indomethacin treatment is the normalization of vascular permeability, which likely affects the neurogenic vascular microenvironment." [86]

Interpretation: The inflammation is in the blood, where the problem starts. Thus we can detect Alzheimer's-type inflammation through a blood test.

From the Stanford paper (12):

> "Neuroinflammation and microglial pathology are associated with many diseases of cognition in which memory loss features prominently, such as Alzheimer's disease, Lewy Body Dementia, and AIDS Dementia Complex. [87,88,89] Further, serum IL-6 levels in humans correlate with poor cognitive performance and predict risk of dementia." [90]

Interpretation: Many diseases of the brain and the body start with inflammation (and its causes). Regardless of the disease, the processes of inflammation are the same.

Hope Through Stopping Inflammation?

The Stanford team teaches us that, when inflammation is removed, regrowth of neurons commences. A team down the coast, at UCLA, showed a similar effect in a small but real group of patients with Alzheimer's. [91] They conclude:

> "An increasing amount of basic science and clinical evidence implicates inflammatory processes and resulting glial activation in the pathogenesis of AD. This small, open-label pilot study suggests that inhibition of the inflammatory cytokine TNF-alpha may hold promise as a potential approach to AD treatment."

Here is an inside look into this encouraging research.

UCLA (1):

Tumor necrosis factor (TNF)-alpha, a proinflammatory cytokine, has been implicated in the pathogenesis of AD.

Interpretation:

(TNF)-alpha is elevated in most (maybe all) Alzheimer's patients. It is one of several well-known markers of inflammation. The UCLA team implies that this inflammatory marker is part of the cause of AD.

UCLA (2):

To investigate the use of a biologic TNF-alpha inhibitor, etanercept was given by perispinal extrathecal administration for the treatment of AD.

Interpretation:

Etanercept binds specifically to TNF and blocks its interaction with cell-surface TNF receptors. By avidly binding excess TNF, etanercept functions as an extraordinarily potent TNF antagonist. Because of the known role of inflammation in AD pathogenesis, etanercept has been suggested as a possible therapeutic agent for AD.

UCLA (3):

We administered etanercept, 25-50 mg, once weekly by perispinal administration to 15 patients of average age 76.7. Main outcome measures included the Mini-Mental State Examination (MMSE), the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog), and the Severe Impairment Battery (SIB). There was significant improvement with treatment, as measured by all of the primary efficacy variables, through 6 months: MMSE increased by 2.13 ± 2.23, ADAS-Cog improved (decreased) by 5.48 ± 5.08, and SIB increased by 16.6 ± 14.52.

Interpretation:

These AD patients improved! This is not seen with standard-of-care medicine available today. Blocking (TNF)-alpha, thus stopping inflammation, leads to improved cognition in AD patients.

Why is this not treatment in the clinic today? Etanercept is a patented and approved drug that could be prescribed "off label" for the treatment of Alzheimer's disease. But somehow this approach has not caught on. Eight years after the UCLA research (published in 2006) a review article on this general topic appeared titled, "*Tumor Necrosis Factor Alpha: A Link between Neuroinflammation and Excitotoxicty.*" [92] Not much progress has been made on therapies to stop (TNF)-alpha and help AD patients. These scientists draw the same conclusion as from the past, "modulating TNF-alpha signaling may represent a valuable target for intervention.

We hesistate to use the term "all," but all studies using anti-inflammatory treatments do not improve patients with chronic inflammatory diseases. Sure, they can provide temporary relief and comfort and the etanercept example in AD is a classic example. However, if/when these studies are extended to 5 or 10 years, our guess is the patient

will have deteriorated more rapidly compared to placebo. Inflammation is a treasure of our health. We need to work with, not against, inflammation. It is your immune system at work for you.

What is your hope if it is not stopping IL-6 and TNF-alpha? Find the root causes of this elevation in inflammatory cytokines and treat those causes. When the levels of these substances go back to normal naturally you, as a patient, will experience the health benefits described in this research.

Hope Conclusion

Your body's immune system is there to help, and we know it is working when inflammation is detected. You can diagnose and treat Alzheimer's effectively if you are able to find the often treatable cause(s) of inflammation. It is the cause(s) of inflammation that, when treated, will truly help Alzheimer's sufferers.

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12
Personal Stories

My father (tjl) (Papa) was a tinkerer. He enjoyed solving problems around the house, especially his children's houses. He was a navy man and engineering officer on several destroyers during the Pacific conflict of World War II. Before the navy he had joined the merchant marines, and after the war, he went to both Northeastern University and Wentworth Institute to get his engineering degree. Upon returning to civilian life he worked at a high-rise in Boston as the head of maintenance and eventually became the superintendent in charge of all aspects of maintaining a building, including the renting of space, renovations, demolition, heating, and air conditioning. All of his children, my older brother, older sister, and I enjoyed an opportunity to work at "the building." The boys got to apprentice with carpenters, plumbers, roofers, and a variety of other skilled tradesmen. Thus the Lewis boys became handy and crafty, more like the jack-of-all-trades but really the master of none.

Papa often came to my aging, four-chimney farmhouse in southwestern New Hampshire. Where does his repair effort begin? I feared going to work because who knew what alteration he would make. The issue was that he didn't appreciate a "punch list," so he just did what he saw fit. And often his efforts and my desires didn't align. However, he ultimately always did something useful and clever, and I (hopefully) always showed appreciation.

In the fall of 1993, Papa, along with my mother "Neema" arrived and were accompanied by heavy rain and winds. Sadly the foliage took a hit and so too did the house. The house, being very old, had leaks and other problems exposed by the rain that Papa resolved to address. The issue of the day was the leaking roof over the porch. The porch didn't receive use except in the summer so there was no urgent need for repair. But this storm exposed the vulnerability of the roof and there was water on the porch floor.

Papa expressed dismay over the roof and the problem of the water on the floor. I dismissed the problem as something that required budget planning and that I would have it professionally repaired next year. Another day of work passed, and I came home to a chagrined household. "Go and check out the porch," said my daughter. I knew Papa had been up to his tricks. He would often fashion a Rube Goldberg solution when he wasn't inclined to travel to the hardware store, so I was prepared for an interesting solution to the leak. I inspected the porch roof from the outside and then the inside and saw nothing. Then I was instructed to look down. There they were—several **holes were drilled through the floor**. My father pronounced that the holes would let the water out and prevent the wood from rotting. This was a barely plausible explanation, but the solution was really very out of character for him.

Years later, when my dad began the outward signs of suffering with clinical dementia and/or Alzheimer's disease, I reflected back on this porch roof incident and now realize that the irrational behavior was the sign of a brain that was becoming diseased. However, in the early stages of disease, it appears that these departures are few and far between, so it is difficult to correlate one or two aberrant acts to disease as opposed to just a momentary lapse of judgment due to boredom or some other reason such as a senior moment. As time passed, however, these types of behaviors started happening more frequently, from occurring every few months to more weekly occurrences. That is when we knew that Papa must be sick.

Alzheimer's is clearly a very complex disease. We don't have to look far for proof either. Here we are in the 21st century; we have sent humans to the moon and unraveled the mystery of the human genome, yet all pundits and thought leaders, from the Alzheimer's Association to the National Institutes for Health, continue to assert that there is no cure or even a way to slow the progress of the disease. Treatments are simply palliative, easing some signs of cognitive impairment temporarily. Even more confounding is that there isn't a consistent equivocal diagnosis, let alone an unequivocal one for the disease. Most medical professionals in neurology quietly agree that Alzheimer's can only be definitively diagnosed upon death.

Here we have the most dreaded and costly disease ever to face humankind from the standpoint of human dignity, emotional and financial costs to loved ones, and overall cost to society, and we are essentially defenseless to even understand the disease at its most basic level, at least "officially," despite billions of dollars in research spending. Medicine has raised the white flag.

Papa's Steady Decline

With time Papa's memory lapsed more frequently as did his unusual actions. He was 80 years old when a specialist who took him through a further series of cognitive tests including the Mini Mental State Exam saw him. He did not score a normal "30" that even

a child of ten could pass with a perfect score. At that time he was diagnosed definitively with advancing cognitive impairment/dementia/Alzheimer's. The advantage of an actual dementia or Alzheimer's diagnosis meant that he would be prescribed pharmaceuticals, including Aricept by Pfizer or other so-called acetyl cholinesterase inhibitors. We were told that these drugs do not change the course of his disease but might make him more functional on a daily basis. These drugs are known to stimulate healthy brain neurons and thus provide more function to those not yet impacted by the disease. These drugs, we now know, stimulate the brain similarly to nicotine. However, the effect of these drugs diminishes with time because there are fewer and fewer healthy neurons to stimulate.

The prognosis given back in 2000, seven years after the roof incident, was that there was nothing that could be done to curb the course of the disease. That is still the mantra of standard medicine today. We were told to make appropriate plans for his care that included making sure that he had a stable, consistent, and familiar routine. This would allow him to use his longer-term memory and thus enable him to be more functional. We also received strong recommendations to quickly move him into assisted living, starting with part-time "day care" in facilities experienced with dementia patients. We were told that he would need full-time nursing home care in short order.

The slow transition from part-time dementia to full-time dementia is particularly difficult, especially in families of the 1940s and 1950s where the husband ruled supreme. My father always drove, managed the finances, and generally ruled the roost. He was not (I believe) aware of his periods of cognitive lapses, thus he was beyond reluctant to give up any of his command. One of the biggest challenges the family faced was his driving. Even as he became severely demented, it was very difficult to get him to cede to my mother when it came to driving. We all knew this created a danger to himself, my mother, and anyone unfortunate enough to be on the road when he was driving. That meant that either great risk was taken, or my mother and father stayed home, even when my mother was more than capable to drive, for example, the two hours to visit grandchildren. Needless to say, she could not leave him home alone, so confronting the driving issue was almost a daily struggle as life goes on and there are errands to run. Thank God we were eventually able to wrest the driving from him, and my mother could still venture out to take care of necessities and enjoy her family and her life.

My mother is very much "old school," having lived through the depression and "the war." She married my father at the age of 24 and was completely committed to family. She taught school briefly but then devoted herself to raising three children over the next 20 years. She went back to teaching, only to help the family financially in preparation to send us kids to college, and only after I reached grade school. She never could envision abandoning him to someone else but did concede to having him go to a nearby day care type facility a couple days each week. This allowed her to catch up with chores and daily household maintenance that she had now assumed completely at the age of 77.

My mother so completely and selflessly managed my father and the home that my siblings and I were somewhat insulated from his true condition. We did learn later that he was somewhat typical in that during his severe episodes, he would lash out and

become violent. She often explained bruises as being caused by her clumsiness. We later smartened up as we each educated ourselves and realized that Papa could get violent. This would happen during the height of care when she was doing simple things like dressing him or getting him to use the bathroom. We now understand that dementia sufferers have some level of awareness of what they want or should do, but cannot either do it or communicate their needs, like a very young child. Thus they apparently develop a great deal of frustration that is expressed as anger. This makes complete sense for a man like my father who was a leader of many, always in control of the helm, and fiercely independent.

Regardless of my father's behavior and the prompting of his doctors, my mother disregarded any suggestions to place him in full-time care. She had vowed, at the time of their wedding, to be there for him for better and for worse and in sickness and in health. She was not one to compromise on her promise.

Amidst tragedy, light moments can be found. Some of the things Papa would say were so off-the-wall that they were almost funny, especially to the innocent grandchildren. Here are some examples recorded in my daughter's journal:

Papa: "Where did you get your hat?"
Anya: "I don't have a hat on."
Papa: "You don't?"
Anya: "No."
Papa: "Somebody must be crazy."
Anya: "Are you going to bed soon Papa?"
Papa: (walks toward the window) "I'm going to go see what this one's name is."
Anya: "What?"
Papa: (lifts up curtain) "Yup, looks like this one is all the way."
Anya: "All the way what?"
"After hours of trying to get papa's attention by calling him, I realized that he didn't realize that he was Papa, the name I have been calling him for the past 17 years."

– Anya Lewis

My mother continued to be his caregiver with the exception of visits to the day care center. They eventually refused him because he became too difficult to manage. At that time, we explored full-time facilities that could take him. Being a veteran, a VA facility was available to care for him, but they did not have any immediate availability. My mother used that as an excuse to manage his care herself until a bed opened up. By now he was almost impossible to care for, incontinent, and frequently violent. All the doctors told my mother that she was going to kill herself by caring for him. She said she would submit when the VA facility opened. A bed finally opened in September of 2004, and he went there. She, of course, visited him daily. I don't believe any other family members had the courage to go visit him at that facility.

On October 8th, 2004, just one month after going to the VA facility, we received a call from a doctor with a deep and somber voice informing us that Daniel Lewis had passed. I took the call and my mother quickly joined. She managed the conversation. She didn't cry and just accepted the news. She had done all she could humanly do for him, and

now her job was completed. We buried him in a plot in Peabody, MA that they had reserved 40 years before.

We donated his brain to research. The family was pleased we made this contribution; however, we had no way to obtain feedback as to how his brain was used and how, if in any way, that donation contributed to finding either a cause or a cure.

Search for Answers

Charles Colton, British churchman and writer (1780-1832) wrote: "Body and mind, like man and wife, do not always agree to die together." We need to find out why the brain dies before the body, leading to the devastating disease now called Alzheimer's disease.

Throughout the decade of my father's Alzheimer's disease, my family was in relative denial. What could we do anyway; we were told there was nothing that could be done except to be supportive. With my mother being both stoic and capable, I contributed little and frankly gave little consideration to my father's conditions. Several things that make this disease so insidious exacerbated this.

First, the disease comes on gradually and often just in quiet waves. Thus, my two siblings and I did not frequently witness any big issue early on. Also, my sister, the classical caregiver of a family besides the wife, lived 5,000 miles away in Hawaii. My brother lived 1,200 miles away in Indiana and had a large tract of land, a farm, and many animals for which he provided care. This then left me to helping mom on a regular basis. During the period of my father's decline, I was involved in raising three children and all the trappings of family life.

I also yearned for a career beyond what I was doing, which at the time, was working for a mid-sized corporation. Nights and weekends were consumed with developing new opportunities. I also moonlighted consulting for a company in Pennsylvania. I eventually joined that company and wound up having a brutal travel schedule for the next few years. That company soon imploded, and I maintained a rigorous consulting schedule for the next couple of years that also involved substantial travel. While this was ongoing, I started a company from scratch with a local businessman. Because of financial issues, I continued the consulting work while working on this start-up.

All these family circumstances substantially left my mother to fend for herself. Life gets busy, and life goes on. Besides, we were told there was nothing we could do. And we children didn't have the same resolve to keep Dad out of a professional care facility. What I neglected to consider was that, since his fate was sealed, my efforts were not for my father but rather to help my mother. She was always so strong and capable, so I assumed that she could and would handle anything.

10 years after the passing of my dad, my mom, at the age of 91, is doing heroically well. And, dedicated to my father's memory, I am on a crusade to change the course of Alzheimer's disease with a little help from $1,000,000,000,000 of annual medical and related research.

Why did Papa become afflicted with Alzheimer's? That is a perplexing question because he had a large garden that fed the family fresh fruits and vegetables. Papa was very active but not an athlete. That means he obtained sensible exercise that is tied to better

brain health. His job was not particularly stressful, and he enjoyed it immensely. His home life was also free from stress. He didn't smoke, and he drank in moderation. He developed glaucoma about 10 years prior to being diagnosed with Alzheimer's. Had we known then what we know now, we would have done an exhaustive differential diagnosis to try to find root causes of the glaucoma. Proper management of glaucoma probably would have staved off his Alzheimer's.

Papa exposed himself to one major risk factor that, taken by itself, should probably not have caused him to have his disease. He almost never ate fish.

The Story of Dr. Lee

Did you just read, *Hope for the Afflicted* in the last chapter? The story of Dr. Lee is a real-life story of someone diagnosed with presumed Alzheimer's who was treated to remove the "inflammatory blockade." Dr. Lee improved.

I met Dr. Lee at a conference of concierge doctors in Scottsdale, AZ in 2011. He was the first concierge doctor in "the valley" of the Scottsdale area. Before he started that practice, he was one of the first doctors at the Mayo facility in Arizona and was a highly trained Mayo clinician. He is a robust man of about 6'2" who was a star at basketball during his college years. Three years prior, Dr. Lee had relinquished his medical practice because he was having severe memory problems. In a single patient visit, it was becoming an all too common event for Dr. Lee to ask a patient the same question three or more times.

When I met Dr. Lee in Scottsdale he appeared quite functional, but that was just on the surface at first glance. I asked him for his cell phone number and the stammering began. He could not come up with the number. Dr. Doug was well aware of his dementia problem and was, of course, very frightened by his prognosis. His former colleagues at Mayo diagnosed him as having Alzheimer's disease.

Shortly after our meeting, Dr. Lee flew to Boston to be evaluated. We cannot say he doesn't have Alzheimer's or another form of dementia. However, based on the experience of a doctor colleague, what we can say is that there were clear indications of what was causing his disease with very high certainty. He had elevated markers of inflammation in his blood and multiple infectious species. He has undergone one year of treatment under close supervision by Dr. Bryan, who took over Dr. Lee's medical practice. Dr. Lee's mini mental score has increased by approximately seven points, and he is clearly much more functional by all measures and according to everyone in his inner circle who interacts with him regularly. Dr. Lee would like to think he could return to medical practice. What is more important is that the MMSE score didn't decline over the year of therapy. At this stage in the disease, Dr. Lee could have experienced a 1-5 point decline in the MMSE. Thus a 7-point increase is really an 8-12 point turnaround!

The story of Dr. Lee is not a single, isolated, or coincidental event. His improvement is a direct consequence of the billions of dollars of research presented in this book. More importantly, it is the efforts of a courageous doctor willing to step beyond the standard-of-care, read the latest research, and translate that information for the benefit of his patients. This doctor is single-handedly circumventing the Trillion Dollar Conundrum.

You or your loved one could experience the same positive results if you are able to obtain a true differential diagnosis that guides your doctors to a path of curative therapy.

Mr. LP Holding Alzheimer's at Bay

I (tjl) met Mr. LP about 20 years ago. At that time he had sold his successful business and was interested in investing in new technology. We spent some time together evaluating some offerings by interesting entrepreneurs. Mr. LP eventually invested in one of those early-stage companies, and I didn't see much of him for quite some time.

A good friend of mine, Tom, moved next door to LP. He told me that he and his wife often went to dinner with Mr. LP and his wife. About eight years ago, Tom told me that they stopped going to dinner because Mr. LP was developing Alzheimer's (diagnosed at a local major hospital), as he was unable to participate in normal conversation and would get very antsy before dinner was finished.

I stopped by Mr. LP's home after hearing the news about his disease. His was an elegant old New England home. He was on the back porch attended by a visiting nurse. Mr. LP did not recognize me and, after some leading questions, barely remembered the small company in which he had invested a scant eight years before. He went to see my coauthor after long discussion with Tom, his wife, and the wife of Mr. LP.

Six years after his first clinical appointment and subsequent treatment, Mr. LP still lives at his magnificent home and dines out with his dedicated wife. Is Mr. LP cured of Alzheimer's Most would argue that he is not technically cured; however, his disease progression has halted by all measures, and in some areas he has actually improved. He still suffers from restlessness, but his memory is clearly improved compared to when he had his first clinical visit. Mrs. LP decided that the approach a local major hospital was using (that is, measuring Mr. LP's decay and using tired, old treatment) was not working, and she stopped those visits.

Objectively, it appears that Mr. LP's memory and overall functioning improved slightly within the first three to six months of treatment and has subsequently not deteriorated. The key to his treatment was a revealing differential diagnosis that directed a treatment regiment and a dedicated wife who kept him compliant with the program.

SF's Disease Reverses

According to this 75-year-old male and his wife and caregiver, he improved in many ways that impacted his ability to take on the basic activities of daily living and then some. He stated, "Dr. Trempe's unique way on treating healed my eye. Even more importantly his treatments led to my health improving on several fronts including improved muscle strength, the ability to walk without a cane, better memory, ability to do basic math, the ability to take a phone call, and vast improvement in the way my hands would shake and tremble."

Mr. 84 Improves Dramatically

Mr. 84 is an 84-year-old gentleman who came to my coauthor because of macular degeneration. From the very first visit, a loving daughter who oversaw his care

accompanied him. He had a myriad of diseases when Dr. Trempe first saw him, including macular degeneration, dementia (Alzheimer's?), and severe muscle atrophy.

During his first clinic visit he was asked a series of simple questions, akin to those on the Mini Mental State Exam, and he could seldom find words to articulate an answer. His daughter explained that he could often describe things, like an orange, but often could not come up with the actual word "orange." Here are some of the key differences before and after a comprehensive differential diagnosis and treatment.

Before: Walked with a cane and held on to a shopping cart for stability (poor balance), struggled to reach a standing position from a sitting position (muscle strength), tremor (so bad he required a straw to drink coffee), antisocial behavior (unable to engage with people around him), poor cognitive functioning (unable to find the right words to describe objects and things), and poor central vision.

After: He shed his cane and walks independently, stands up with authority, his tremor is completely gone, he is engaging (okay, a bit of a crotchety old-time New Englander), he can identify an orange without hesitation, and his vision improved using all optometric measure.

Mr. 84, when listening to his doctors and daughter talking about his memory seven months after initial treatment chimed in, "There is nothing wrong with my memory." No one had cause to disagree.

Some famous people who had Alzheimer's disease

Adcock, Joe	baseball player
Albertson, Mabel	actress
Andrews, Dana	actor
Balanchine, George	dancer, choreographer
Bing, Rudolph	opera impresario
Brooks, James	artist
Burrows, Abe	author
Campbell, Glenn	actor
Chen, Joyce	chef
Copeland, Aaron	composer
DeKooning, Willem	artist
Dorsey, Thomas,	father of gospel music
Fears, Tom	hall of fame professional football player and coach
Feraud, Louis	prominent fashion designer
Francis, Arlene	actress
Frankovich, Mike	movie producer
French, John Douglas	physician
Goldwater, Barry	Arizona Senator
Hayworth, Rita	actress
Henriquez, Raul Silva	Roman Catholic cardinal, human rights advocate
Klutznick, Philip	real estate developer, adviser to five U.S. Presidents
Leroy, Mervyn	director
Lewis, Daniel	my father
Lord, Jack	actor
MacDonald, Ross	author
Meredith, Burgess	actor

Murdoch, Iris	author
O'Brien, Edmond	actor
O'Connell, Arthur	actor
Owen, Marv	baseball player
Picon, Molly	actress
Preminger, Otto	director
Quackenbush, Bill	hall of fame professional hockey player
Reagan, Ronald	former President of the U.S.
Ritz, Harry	performer
Robinson, Sugar Ray	boxer
Rockwell, Norman	artist
Scott, Simon	actor
Shulman, Irving	screenwriter
Schwartz, Betty	first woman to win an Olympic gold medal in track
Swift, Kay	composer
Van Vogt, Alfred	science fiction writer
White, E.B.	author
Wilson, Harold	British Prime Minister

Letter from President Ronald Reagan to the American people: Nov. 5, 1994. [1]

"My Fellow Americans, I have recently been told that I am one of the millions of Americans who will be afflicted with Alzheimer's disease. Upon learning this news, Nancy and I had to decide whether as private citizens we would keep this a private matter or whether we would make this news known in a public way. In the past, Nancy suffered from breast cancer, and I had my cancer surgeries. We found through our open disclosures we were able to raise public awareness. We were happy that as a result, many more people underwent testing. They were treated in early stages and able to return to normal, healthy lives. So, now we feel it is important to share it with you. In opening our hearts, we hope this might promote greater awareness of this condition. Perhaps it will encourage a clearer understanding of the individuals and families who are affected by it. At the moment I feel just fine. I intend to live the remainder of the years God gives me on this earth doing the things I have always done. I will continue to share life's journey with my beloved Nancy and my family. I plan to enjoy the great outdoors and stay in touch with my friends and supporters. Unfortunately, as Alzheimer's disease progresses, the family often bears a heavy burden. I only wish there was some way I could spare Nancy from this painful experience. When the time comes I am confident that with your help she will face it with faith and courage. In closing, let me thank you, the American people, for giving me the great honor of allowing me to serve as your president. When the Lord calls me home, whenever that may be, I will leave with the greatest love for this country of ours and eternal optimism for its future. I now begin the journey that will lead me into the sunset of my life. I know that for America there will always be a bright dawn ahead. Thank you, my friends. May God always bless you. Sincerely, Ronald Reagan."

Final Thought from a Chemist

Did you take chemistry in high school? How about basic chemistry in college or the dreaded "P" chem.? Physical chemistry in particular provides us with many useful ways

to describe and understand the world around us. Medicine and human physiology is very much part of that world. Real-world concepts that chemistry teaches us are thermodynamics and kinetics.

Thermodynamics is a measure of the energy required for something to happen, while kinetics is a measure of the rate at which something does happen. Take the burning of gasoline for example. When it burns, it does so violently, releasing plenty of energy in the form of heat and light. This reaction is always ready to go because the products (water and carbon dioxide) are more stable compared to the reactants (gasoline and oxygen). However, the gasoline and oxygen could stay combined indefinitely without reacting. Why? There is an "activation barrier" to overcome.

The overarching measure that determines if a reaction is even possible is the Gibbs Free Energy (ΔG). If ΔG is negative, the reaction has enough energy to go; if the kinetics is right, the activation energy can be overcome.

Aging tells us that the ΔG of the human body is negative. We are more stable by returning to our base elements compared to the marvelous and intricate structures God created that allows us to be alive. Our goal to maintain our health is a simple one, to raise the activation barrier bar as high as possible to slow the reactions to our more stable state, then return to Earth as ashes and dust. All aspects of bodily homeostasis, immune health, and emotional well-being contribute to raising the bar.

Stay Well.

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About the Authors

Dr. Lewis holds a Ph.D. in Chemistry from MIT. He served in various research capacities prior to starting a scientific consulting business in 1997. In 2005, after the passing of his father from Alzheimer's disease, he has dedicated his time and career to finding a solution to this disease. After finding a clinician, Dr. Trempe, with a profound understanding of Alzheimer's diagnosis and treatment, Dr. Lewis spent the past several years verifying the findings of Dr. Trempe using the vast medical and scientific literature available. His research over the past several years culminates in this book.

Dr. Trempe received his MD degree from Ottawa Medical School, Canada. He furthered his studies at Harvard's Schepens Eye Research Institute (SERI) and Massachusetts Eye and Ear Infirmary, Boston. He has been on staff at Harvard Medical School teaching hospitals since the 1970s. He is the author of hundreds of medical scientific papers and two pending patents.

Dr. Trempe didn't set out to solve the Alzheimer's conundrum; he did set out to treat eye diseases in a different way, however. He, and many others recognize that a sick eye does not reside in a healthy body. A sick eye is, for the most part, in a sick body. Treat the causes of the sick body and the health of the eye will also improve. Dr. Trempe is one of very few Ophthalmologists who take this approach. Why? Because eye doctors treat eye diseases, cardiologists treat heart diseases, neurologist treat brain diseases, and so on. These specialties seldom collaborate. Each medical discipline has its own set of diagnostics and drugs for their special ailments.

When Dr. Trempe started diagnosing and treating his "eye" patients for systemic (whole body wide) diseases, back in the 1980s, their eyes did indeed get better. In fact they got much better and stayed much better compared to people who were treated as if their eyes existed in isolation from the rest of the body.

Most importantly, many patients with serious disease beyond the eye reported back to Dr. Trempe that these other conditions improved upon his "eye" (whole body) treatments. One of those conditions that improved was Alzheimer's disease.

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