Brain Matters

The Prevention of Aging, Alzheimer's and Stroke

Mark Brody, M.D. and Joseph Mauceri, M.D.

About the Cover

One is only micrometers wide. The other is billions of light years across. One shows neurons in a mouse brain. The other is a simulated image of the universe. Together they suggest the surprisingly similar patterns found in vastly different natural phenomena.

BRAIN CELL
Mark Miller, a doctoral student at Brandeis University, is researching how particular types of neurons in the brain are connected to one another. By staining thin slices of a mouse's brain, he can identify the connections visually. The image shows three neuron cells on the left (two red and one yellow) and their connections.

THE UNIVERSE
An international group of astrophysicists used a computer simulation last year to recreate how the universe grew and evolved. The simulation image is a snapshot of the present universe that features a large cluster of galaxies (bright yellow) surrounded by thousands of stars, galaxies and dark matter (web).

Source: Mark Miller, Brandeis University;
Virgo Consortium for Cosmological Supercomputer Simulations.

"Your brain **is** your universe."

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For Lynn

For Ellery

For all those who come in Hope

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INTRODUCTION

Another self-help book, you say? Yes, another book – but hardly the same kind of book as the others. This is a scientific book, a challenging book, challenging you to study it and respond to the challenge of a total strategy for brain health.

We decided to begin the book with a brief description of some of the clinical faces of Alzheimer's disease for two reasons: one is to alert readers and their families to the insidious and dramatic changes that can occur early even before diagnosis, and the second reason is to use patient stories as the introduction to the molecular biology, systems and structural links among three diseases, Alzheimer's, stroke and cardiovascular disease.

The scientific material is essential for grasping the causes of these diseases, the rationale for all preventive strategies, and the unity of the goal… "you." This is all the more urgent given the increasing number of early middle aged subjects presenting with Alzheimer's disease and stroke as the effect of the obesity epidemic "matures," linked to the cumulative effects of hundreds of man-made toxic molecules being dumped on us and in us to the great destruction of brain cells and all somatic cells. When these events play out in the background of increasing social and economic stress, hence, personal stress, the mix becomes a medical "H" bomb. But since we can't take cover, we must mount a defense, even first strike interventions. That is the business of this book, that's our business in the clinical and research world of Alzheimer's disease and stroke. Serious readers will follow closely and begin the work of building an integrated, science-based strategy for brain health.

The book is in three sections. Section I is the science, Section II is the management strategy with particular emphasis on the "big three," – exercise, diet and stress. The book also provides the single most detailed and comprehensive plan for laboratory assessment as an essential part of your personal strategy, with particular emphasis on lipids, clotting risk, inflammatory molecules, brain toxic chemicals, genetics and proteomics. Section III is a brief discussion of research with emphasis on what we do at *Brain Matters Research*.

Mark Brody, M.D. is a clinical and research neurologist in stroke management and Alzheimer's disease. He is founder and president of *Brain Matters Research* (www.brainmattersresearch.com), one of the leading Alzheimer's clinical research centers in the United States. He is one of a small group of neurologists whose careers spans academic and clinical practice as well as extensive clinical research.

Joseph Mauceri, M.D. is an Internist recognized by the American Board for Advanced Achievement in Internal Medicine. Dr. Mauceri is a fellow of the Catholic Academy of Sciences for Medicine and Bioethics, including the ethics of Clinical Research. He was an Advisor to the Holy See (Catholic Church) at the U.N. and a member of the working group on the international treaty banning human cloning.

Alzheimer's – One Disease, Many Stories

You are about to enter the world of the human brain, the most sophisticated and powerful "machine" in the universe. The brain is the most powerful machine because it builds all the others, great and small. It can probe the invisible atomic world or probe the galaxies; it can go inside the universe of microbes, or the universe. But more than all of this, these brains of ours are the wonder of us. They are us! Einstein said that we are the wonders of the universe because of our brains. What a tragedy it is, then, to lose them.

More precisely, our "universe" is brain and mind together. Indeed it is mind which configures all things. It may be grounded in matter but the material brain has no power to contemplate the transcendent of itself. A single thought, after all, is beyond weight and measure yet our concern in this book is the brain and those pathologies which destroy it and all of those non-material powers which are uniquely ours, and uniquely human. The term "dementia" is a general term which simply implies a loss or significant decline in higher brain functions. These might include learning and memory, computation and calculation, conversation and context, concentration and connection, word finding and naming, and insight and judgment as well as intellect and executive function.

We briefly outline how neurons talk to each other (billions in an instant) but do not confuse this molecular signaling with human speech. Brain talk is as remote from the gift of speech as a great art work is from the primary colors. While it is the brain we are treating, it is the mind we are defending!

When we say dementia describes impaired brain function, we mean impaired mental function and all of the mysterious powers of the mind. In dementia billions of brain cells, neurons, are lost with a parallel decline of higher functions, "mind power" measured as progressive dementia. We can never say in an individual case how quickly this progression will occur, and we can never know the precise sequence of the decline in higher function domains.

The evidence available tells us that by mid-life we are normally losing brain cells at a rate of 5-7% per decade with a parallel decline in vital neurotransmitters such as acetylcholine in the hippocampus and dopamine in the nigrostriatal tract. If the loss of either is more rapid and severe, either Alzheimer's Disease (AD) or Parkinson's Disease (PD) will follow.

In pathologic neuron loss, death comes when 80% of our neurons are gone. No one knows how many neurons we begin with, an accepted estimate is 100 billion, hence the minimum compatible with life is 20 billion cells. Irrespective of the numbers, the ongoing loss of function is devastating to all who love and care for these patients.

The Alzheimer's brain is losing billions of neurons and thousands of miles of wiring – all the material which cooperates with the magnificent power of the mind to give us all those things that mark us as persons and personalities.

So, we invite you to follow along to learn more about your brain and some of the numberless connections among proteins and molecules to disease and dementia. We will "talk science" because we have to give you some of the basics about the chemistry of the brain, the remarkable neuron, and all the things that do harm, including psychological stress factors, which can run away with our brains and bodies. You need at least a minimum of science to understand the brain and the disease.

Our work in research at *Brain Matters Research™*, and in the treatment and prevention of Alzheimer's disease at *The Brain Health Institute™*, is a journey of discovery. We have learned that the most distressing part of discovery is to see the myriad ways this great destroyer of brains shows itself in its victims. But we also see the courage of the victims, the heroic care of the loved ones, and the incredible ability of the brain to fight back, to try to reclaim itself with our help, at least for a time.

Alzheimer's disease destroys the brain by wrapping its deadly proteins around and inside our brain cells, the neurons and all of the connections to each other, billions of cells, thousands of miles of wiring. The brain is suffocated and loses reality in a way that parallels the deconstruction of the mind that comes with mental illness and psychoses. There are diseases of the mind and diseases of the brain. The tragedy of Alzheimer's is that it is both. The victims lose their minds and can be extremely delusional, as we shall see, but rarely do they become psychotic in the classic psychiatric sense of the term.

The disease begins by slowly stealing away the brain's power to organize our lives, make the countless judgments and decisions we make each day, simply continuing to be the persons we are. "You know he (she) is not quite the same, something is different." Friends or family can't put a finger on the specifics, but something is not right. Perhaps it is a matter of forgetting objects, appointments, destinations, deadlines. We may miss a word or thought in conversation or have to think a second or two to get the right name of a person or an object. Each of

these, even all together, may not mean disease is coming but might only be signs of normal aging, although more recent evidence, and our own wide experience, suggests that even early, subtle signs may portend something more. These events may have no connection to each other at first, so we get a little more forgetful, but if we then begin to forget that we forgot, even when reminded, or mistakes or forgotten tasks add up, there is little doubt that it is Alzheimer's disease.

We might point out here that early changes are difficult to call, that is, age appropriate or early disease, because the disease has no specific baselines from an ordinary observer's point of view. Early and correct diagnosis is the most important step, but the disease is woefully undiagnosed in its early stages. On the other hand, we are concerned that in a rush to correct this Alzheimer's disease may be diagnosed prematurely or inappropriately with aggressive over-testing and over-interpretation of results in an attempt to hunt down the disease. Over-testing certainly has not resolved the question of the benefit of early diagnosis (or "pre" diagnosis) of prostate cancer, as a diagnostic example, or coronary artery stents, as a therapeutic example, of hunt and kill interventions that may be mortality neutral but morbidity positive (presenting more risk than conservative management). We are extremely careful about this in research so that subjects have either prodromal biomarkers or solid historical evidence for active Alzheimer's Disease before enrollment in a trial.

An incorrect diagnosis can do as much harm as a missed diagnosis, both for the patient and the family. We must keep in mind that memory and cognitive decline are part of normal aging with rare exceptions. The goal is always, either in normal aging or in early Alzheimer's disease, to guard the person. After all, in the larger scheme of things we can all get by with forgetfulness and declining cognitive and intellectual capacities but none of us want to lose our personality, our ability to recognize and respond to our loved ones and their needs. Remember always, there is a person to help as much as a disease to be treated.

There are some reliable biomarkers to help us make the correct call objectively, thereby removing observer bias or error. Two of the most important of these are the level of various proteins in the spinal fluid and changes on more sophisticated neuro-imaging studies. These markers are objective indicators whereas patterns of memory and cognitive decline never come in the same way or in the same chronology in any two patients. After all, each one of us has our own library of memories, knowledge base, intellectual interests, emotional history, our life story. On the other hand, the obvious decline and deficits we mentioned are common features of the disease at some point in each patient.

There are several changes which do have a very unique pattern to them, first among these being changes in mood or affect. You may notice a loved one or friend is more agitated at times, or more impatient or contentious; perhaps less sociable or conversational. Others may become more garrulous, more social but also more socially inappropriate, repeating stories from the past or telling the same jokes over and over. They may be less retrained, and sometimes actually more pleasant than before, at least for a while. In any case, these changes in mood and affect, and their resistance and anger when you try to get your loved one to change this behavior, will be early warning signs of a coming storm.

Early disease, on the other hand, is no guarantee that there is plenty of time before trouble comes. A wonderful man with only early disease, and only occasionally lost when driving, was on vacation with his children. Each morning he walked around the block of an unfamiliar neighborhood. One morning, he went an extra block and into a major thoroughfare. He was killed instantly. The danger, you see, is that for a period there is no danger, no big mistakes, then the first big mistake comes, a momentary lapse or mental block that can be costly or fatal. Early disease is a disease, and, as such, is unpredictable. <u>There is always a first event</u>.

There are subtle signs early in memory and cognition and it takes skilled professional evaluation to help define whether or not there is normal decline or early disease. This is essential to begin to guide caregivers in how to "accept and manage" changes that will inevitably come. If you know your loved one is facing a downward course from a disease where behavior appears to be willful but is not, you will deal with it more appropriately. Most spouses or loved ones have a very difficult time "rewiring" their own thinking about what they are seeing or hearing. For these reasons early diagnosis is essential to guide treatment or to guide your loved one into research and the hope of more definitive treatments which might slow the progression of the disease, even for years. (We address the topic of research in the last section of the book.)

Many family members are often as afraid of the word "Alzheimer's" as they are the disease, be it for social reasons, or fear that friends or family members will pull away. Sometimes family members or spouses want to hold the patient responsible in some way for what has happened, irrational as that is. We find that sentiment reveals the deeper need to believe that if you try to train it away or talk it away, it will go away.

Early diagnosis allows patients and families to take the necessary steps regarding safety issues, driving, home and money security, power

of attorney, home care assistance, outreach and community services. All of these may prevent a disaster, while early diagnosis and understanding of what this disease can do may prevent harm to a marriage or family by removing all doubt about the causes for the changes in behavior.

There are several very disturbing issues that can present in early or moderate disease. The first of these is money. Many patients lose interest in money, finances, and their own economic security. A number of these patients fall prey to scam artists and professional cons who have stripped them of bank accounts, bled down their credit cards, or worse, cleaned out all of their assets. The tragedy here is that these events go unreported until a family member or friend discovers the problem. We know of one case of "patient extraction" that took place monthly for four years, the crook withdrawing a little each month after the patient's social security check came in so that withdrawals appeared a part of normal banking activity.

We recently had an unfortunate victim of an international fraud ring. The thief convinced her to begin wiring money for a huge investment return. They took everything and only when the electricity was turned off did a son learn of the magnitude of the theft and the parent's disease. The unfortunate patient had accessed this inadvertently online and from that point on everything came under the control of the criminals. The patient was simply too impaired to protect her assets or herself.

A third victim met a "wonderful gentleman," as she later related to her family, at a senior's dance. Unfortunately, the wonderful gentleman was a career rogue, expert at getting money from lonely and vulnerable Alzheimer's patients. Before the crime was discovered, over $100,000 was transferred. The crook disappeared but the victim either did not know or did not care what happened to the money but was very distressed to learn he was not coming back. A tragic disease ignored can bring tragic consequences.

Equally curious, and perhaps more painful, are the large number of patients who become incredibly suspicious of anyone who they believe could get their money. They become secretive and hostile, often hurling terrible accusations against spouse or anyone who steps in to reassure them that it is not about their money. For these patients it is only about money and no one, absolutely no one, will change their minds. At other times these patients will harass banks, financial advisors, extended family, including grandchildren, about their greed and the patient's justified attitude. One patient even called the IRS several times to let them know what evil crooks they were, demanding all the stolen (tax) money be returned (we were not unsympathetic!)

Sex is the second issue that can bring out the same disordered thinking and shock to spouses, friends or family. Once again, we see a range, from sexual inappropriateness to sexual aggression, even sexual assault. The first rule is to remember that you are living with a demented patient with a dying brain. You need to know that and continually remind yourself so that you will not lose heart.

Patients with magnified sexual delusions can move in either direction, as with patients fixated on money. The sexually inappropriate will repeatedly tell sexual jokes, make lewd or suggestive comments, or gestures. Another group of patients will become completely indifferent to anything sexual, including personal modesty, dress, etc. There is yet a third group who become highly sexualized, demanding sexual acts. They will have explicit sexual obsessions or fantasies, and will sometimes try to act on them with the spouse, friends, or a stranger. We have had families call asking for help because a loved one was reported for public lewdness. A wife was overcome with distress when her husband inappropriately touched another woman, a stranger, in a theater.

We know of a sad case, an elderly woman, who believed various men were trying to have intercourse with her. She would insert papers or towels or other objects to protect herself, which finally caused physical harm to her. Another woman, always reticent and shy, purchased a sexual object and carried it out into the street exhibiting it. A kind police officer contacted the family who promptly provided around-the-clock care for their mother. What was most baffling was that their mother knew about the object and where to find it, although she claimed she had no idea what it was, which was most likely true.

Finally, we see patients with delusional sexual paranoia. They accuse spouses of infidelity, especially with relatives or close friends. Sometimes the accuser will also try to strike out physically against the unfaithful spouse or demand the spouse leave. These delusions are perhaps the most painful that a spouse might endure, and they have been the occasion for separation, or divorce, or more often, and appropriately, placement of the demented spouse in a long-term care facility.

Medications can help in the these delusions, be they about money, sex, or other issues, often requiring dosing that is more sedating. That tradeoff may be absolutely necessary for the spouse or caregiver to go on. Memory drugs do not specifically treat behavior and do not actually intercept the disease process, so it becomes a matter of using potent and potentially dangerous anti-psychotic drugs to control behavior even though the delusions are the result of damaged brains and not damaged psyches, per se.

These stories are a tragic reminder that unexpected extreme changes in behavior may come. What is so striking is behavior which is manifestly out of character for your loved one; aggression in an otherwise docile person, or docility and silence in a once commanding and controlling personality. These behaviors are aspects of the paradoxical brain in a disease with a wide spectrum of behaviors, sometimes in the same person. On the other hand no one can deny the inscrutable contradictions that are part of each one of our lives and the mysterious powers of the brain behind them. In normal patients extremes of behavior are considered "willful" and neither pathological nor paradoxical, but this is simply not so in Alzheimer's disease.

These are extreme situations, but you need to know about them to better judge your loved one's situation. Many patients remain quite at peace, pleasant and eager to please as best they can. This is no more a matter of willed behavior than is other behavior, it is a matter of the individual patterns of disease, although a happy and pleasant patient generally remains so. Perhaps the words of one patient best capture all of our hopes for this, "I am a happy person, and I thank all of you, especially my husband, when I can remember." Many patients arrive at a point where happy indifference replaces agitation, anxiety and behavioral issues. Interestingly, a good number of patients become surprisingly engaged with their past and in quite surprising ways, even as the disease advances.

Some patients become very reconnected to people and events from the remote past. We recall a retired physician who would awaken and tell his wife about his schedule and patients for that day. His wife recognized the names as she had been his nurse, but the remarkable thing was that the doctor's "schedule" for the day was really about a day forty years earlier.

A wonderful patient with advanced disease was in our office when he heard a song in the background. He immediately, and we believe for the first time in many years, began to sing through his Frank Sinatra repertoire, perfectly. It was a dramatic, powerful and inexplicable moment from a man who had not sung professionally for twenty-five years.

The family of another patient reported that they were losing communication with their mother; she had reverted to speaking Yiddish, the language of her childhood in Eastern Europe. We recommended a facility in New York with Yiddish speakers on staff, and the family reported that for many months after their mother thrived until the disease finally robbed her of the "Joy of Yiddish."

There are many other stories of a recaptured past, glimpses back to a time when the patient's life was full and meaningful within the growing silence of disease. We always encourage family and friends to "go with it." Let these glimpses of their past be part of your present for them. The fact that they have no connection to today for us is not the question. These recaptured stories may be the last substantial conscious inks to the validity of their lives and in a mysterious way console them, but not always. Sometimes traumatic or sad events from the past spill over, especially those involving loss or psychic pain. These, too, have great meaning, although the meaning is hidden from us and perhaps from them. Nonetheless even with traumatic memory perhaps it is equally necessary to go with it while at the same time doing everything you can to minimize the trauma of the memory. In all cases assist your loved one with "the purification of memory."

As the disease advances to a severe state of dementia, docility, quiet and peace usually preside in the patients during their waking hours, which are usually no more than six to eight hours. The excessive sleeping marks severe pathology, but it is in another sense, also protective. The patient no longer knows, only you know, but at least you know there is no emotional suffering in your loved one, and, surprisingly, much less physical pain if other diseases or disabilities come.

One other point: Alzheimer's disease is utterly democratic and neither high station nor high I.Q. is protective. Although education level and high intelligence can mask early disease, more properly, these set the diagnostic bar at a higher level, likely due to one's ability to "cover" symptoms and compensate better for early declines. Beyond that, there is no advantage and neither education nor I.Q. has predictive value insofar as rapidity of decline once the disease is "active," including possible behavioral changes, and may, in fact, be a disadvantage. This capacity seems more "developed" among math, science, music and computer people but this compensating ability may have the downside of delaying diagnosis and, hence, opportunities for research and disease-modifying drugs.

We mention behavior again because even with good memory compensation patients simply cannot mask or cover the behavioral changes that can come with disease, even early disease. Intensified negative behaviors (e.g., short temper, impatience, criticism, resistance to advice, even verbal hostility) or apathetic behavior (e.g., declining interest in people or activities or more indifference to family or social demand) may be early warning signs even in the absence of obvious memory or cognitive issues. It requires great skill by professionals, to separate depression from early disease, as they can occur together.

There are other behavioral and memory disorders which may be easily confused with Alzheimer's disease, such as Frontotemporal Demention (FTD). FTD is more likely with changes in "executive" function, higher decision and discipline functions, and decline in social censors. Inappropriate responses to situations, lack of control and common sense restraint are early signs that FTD may be the cause. Other patients may have only minimal behavioral changes at first but impressive symptoms of deteriorating language function, word forming and word making, sentence structure and content, hallmarks of Primary Progressive Aphasia. Both of these diseases may have amyloid and Tau protein, as in Alzheimer's disease, and higher incidence of Apoprotein E4 heterotypes, which until very recently were thought to be specific for Alzheimer's disease.

Lewy Body Dementia (LBD) is a more aggressive dementia characterized by visual hallucinations, delusions and behavioral issues including REM sleep disorders. Parkinson Disease (PD) findings can appear, not surprisingly, as the abnormal protein synuclein is found in lewy bodies and in PD. We also mention Pick's Disease among the dementias with early behavioral changes, emotional liability, including overeating and, in some patients, repetitive word making, "echoalia,"and aimless motor activity or wandering. Pick's Disease may be a cousin to FTD because of the overlap in symptoms and abnormal proteins including amyloid, tau and TDP-43 protein, and ubiquitin inclusions, which can be found in an autopsy in a small number of cases. These findings demonstrate the importance of abnormal proteins and protein configurations in all of the neurodegenerative diseases, and their relation to the molecular substrates we discuss in Section I which follows.

In summary, the symptoms of memory change, behavorial change, or language fluency may be the early warning signs of disease. Here it is a matter of judicious intervention, finding a way to have your loved one agree to see a professional. Our own experience instructs us that patients with behavior and personality changes are more resistant to this than are patients with memory or speech changes. So, while it might appear that these behavioral changes are age related or "depression," or simply represent change without a cause, the likelihood is that there is a cause. The hope is that your loved one will acknowledge this possibility and willingly seek the necessary help.

QUESTIONS:

1. Alzheimer's disease usually begins with short-term memory loss.
   ❑ True ❑ False
2. The frequency of Alzheimer's disease increases with age.
   ❑ True ❑ False
3. Alzheimer's disease is a disease of aging.
   ❑ True ❑ False
4. Behavior changes are common.
   ❑ True ❑ False
5. "Use it or lose it" brain work may slow memory decline.
   ❑ True ❑ False
6. Some cases of Alzheimer's disease are genetic.
   ❑ True ❑ False
7. Everyone's memory declines at the same rate with aging.
   ❑ True ❑ False
8. High education and high IQ can prevent Alzheimer's disease.
   ❑ True ❑ False
9. Everybody gets dementia if they live long enough.
   ❑ True ❑ False
10. Alzheimer's disease is the most common cause of dementia.
    ❑ True ❑ False

NOTE: Answers to all question pages on page 131.

A Note from the Authors

We prepared this with a careful emphasis on the science, the correct terms and definitions with a brief discussion of all risk factors for aging, disease and dementia. We have kept opinions and speculation to a minimum so that you can weigh the evidence objectively and discuss it with professionals comfortably. Let the facts speak to you so that you can speak for your own interest, what the facts mean for you !

The concept is simple enough. We line up the most basic molecules which are conspiring silently against you, building to a critical mass, to molecular fusion, which is the real cause of the two most dangerous vascular killers, heart attack and stroke, and the most feared brain cell killer, Alzheimer's disease.

Figure I

When your doctor sends you for a plaque heart test on your coronary arteries or carotid arteries, he is looking for result, not the cause. The same goes for brain scans to look (indirectly) at the effects of brain plaque, a result, not the cause. The first plaque type is the product of inflammatory lipids; the second type is made up of inflammatory proteins. They have a common source in epigenetic dysregulation, inflammatory fats and their traveling companions such as lipases and isoprostanes, and proteins like Homocysteine and friends, to name a few of the many hundreds of molecular events. When these are joined to abnormal insulin-glucose regulation, toxic molecular and vascular effect of psychophysical stress, and the metabolic syndrome with its deadly centripetal (visceral) fat, defective cell aerobics, excessive blood viscosity, blood pressure and sticky platelets, you have the perfect biological storm releasing toxic molecules throughout the body.

Figure II

A partial lineup of toxic proteins and molecules.

Figure III

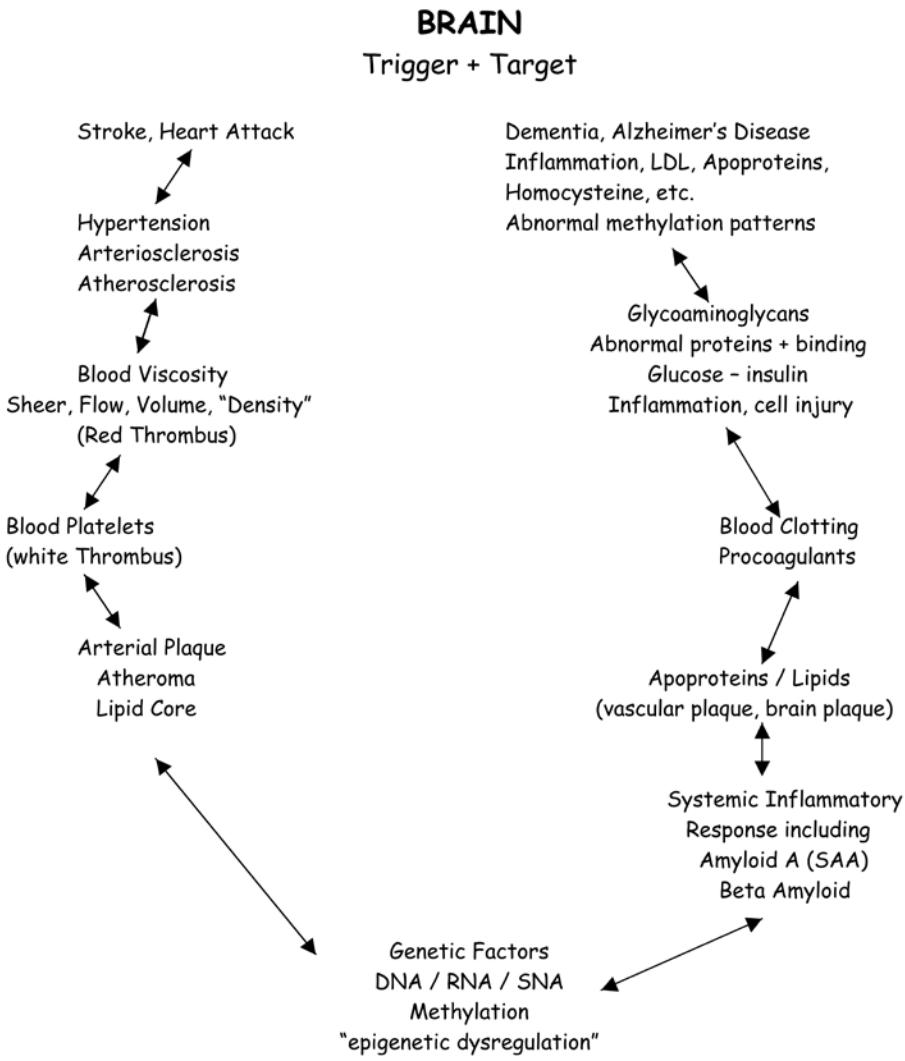
A simplified schema of the effects of the stress response.

Figures IV and V

Sympathetic N.S. "Neural Trigger"

Figures VI and VII

Neurons "talking".

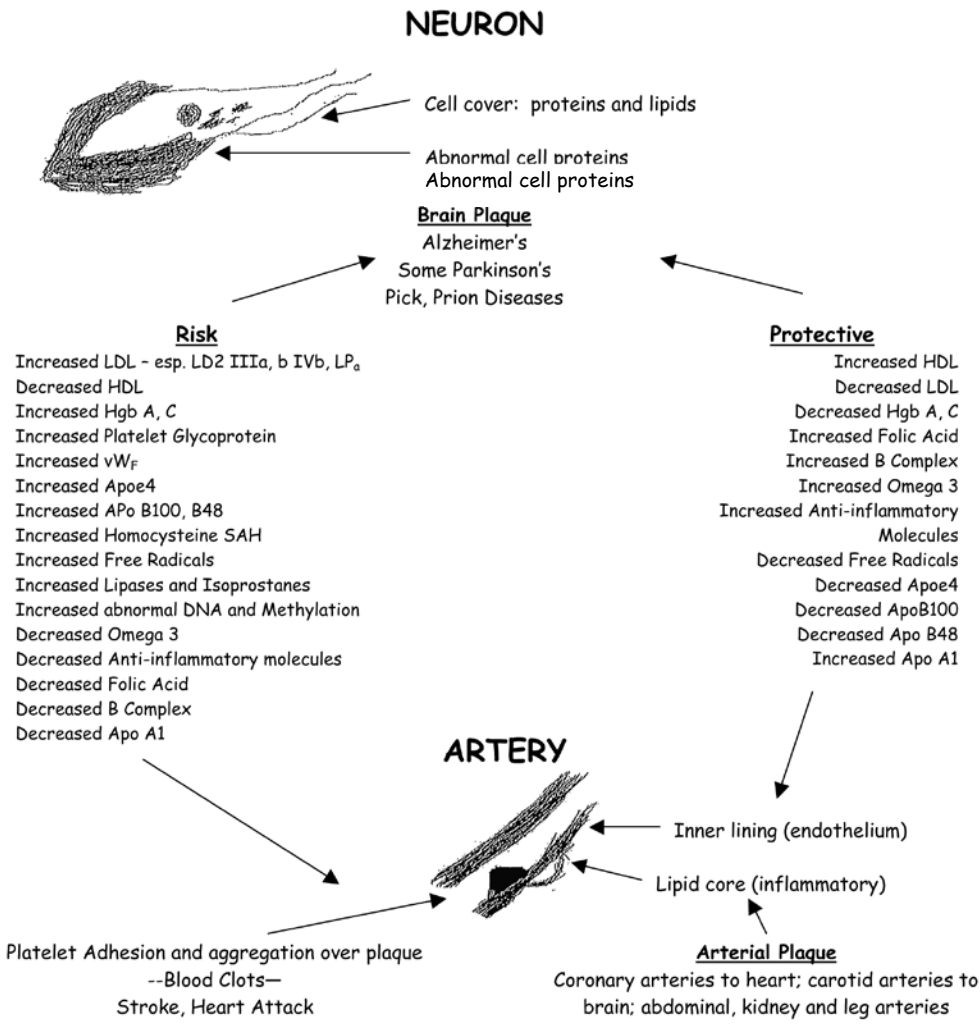


Common Pathway for:

Cardiovascular Disease / Stroke / Premature Aging / Alzheimer's Disease

All factors converge and act together, effects are both immediate and remote (Years to Decades)

Figure I



The same molecules (Protective or Risk) in Brain Plaque and neuron damage in vascular plaque and strokes, heart attacks, vascular clots

Each neuron is in intimate contact with its microscopic size nutrient blood vessel. The perfect interface for movement of inflammatory and clotting cells and molecules between the two.

Figure II

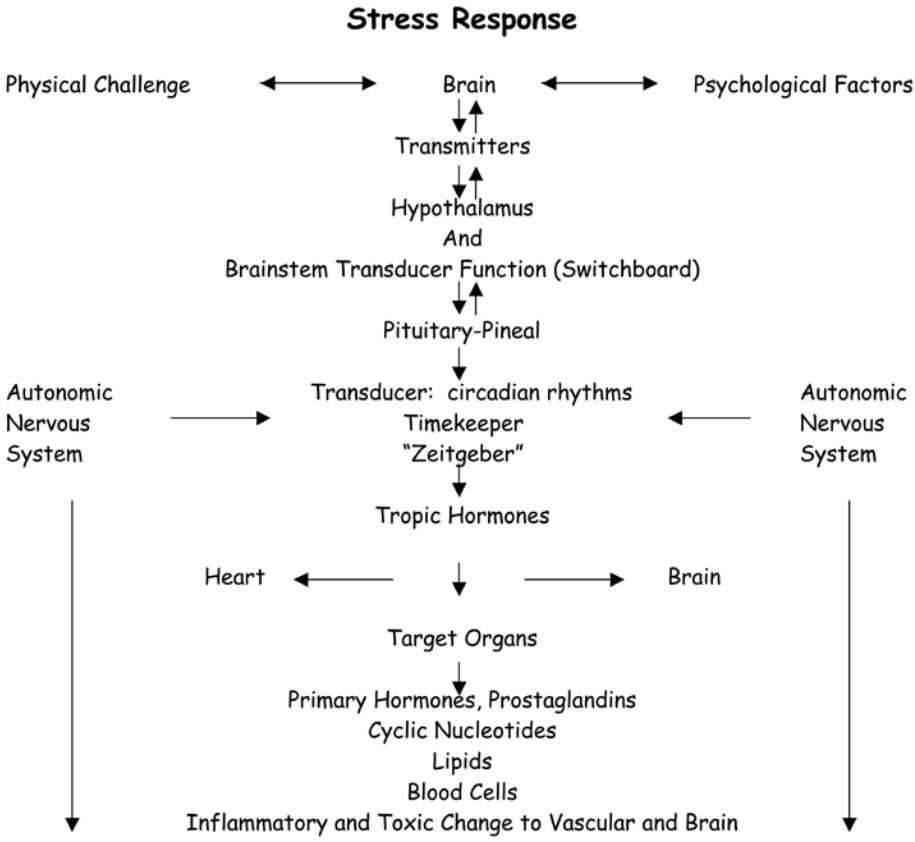

Stress Response
Physical Challenge
Brain
Psychological Factors
Transmitters
Hypothalamus
And
Brainstem Transducer Function (Switchboard)
Pituitary-Pineal
Autonomic
Nervous
System
Transducer: circadian rhythms
Timekeeper
"Zeitgeber"
Autonomic
Nervous
System
Tropic Hormones
Heart
Brain
Target Organs
Primary Hormones, Prostaglandins
Cyclic Nucleotides
Lipids
Blood Cells
Inflammatory and Toxic Change to Vascular and Brain
Acute Effects:
Sympathetic and
Parasympathetic Balance
Blood Pressure, Pulse, Breathing,
Blood Flow, Energy Rate, Strength
Sudden Death
Related, in part, to reciprocal
activity of sympathetic and
parasympathetic limbs of A.N.S.
Coronary Spasm
Ventricular fibrillation
Cardiac Arrest
Chronic Effects – Immunity, Circadian Rhythms, Sleep Dysfunction, General Adaptation,
Chronic Diseases, Cancer, Brain Degeneration, Premature Aging

Figure III

INFLAMMATION (See diagrams)

Molecules called cytokines travel among cells and signal them to release yet other cell messengers. Most of these molecules have receptors on cells and are especially active in special cells dedicated to fighting bacterial and viral infections (e.g., mast cells, macrophages as well as target cells in the vascular system, endothelial cells, and macroglial cells, astrocytes and neurons in the brain).

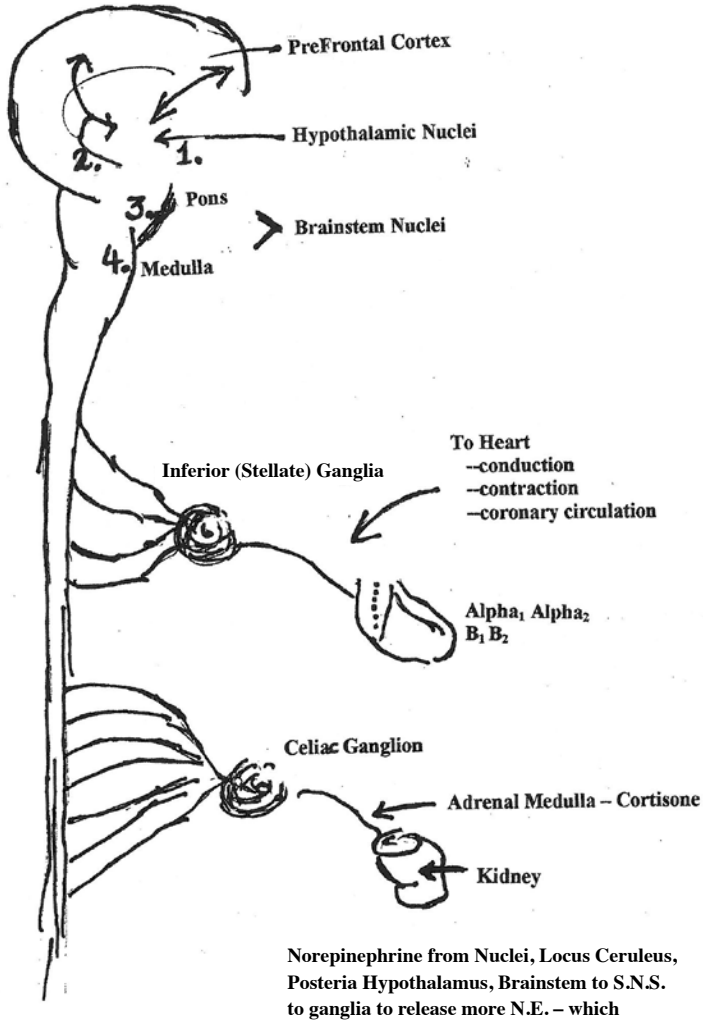
All of these cytokines are essential to our resistance to infection but at the same time can be agents of inflammation, cell death, and the formation of deadly plaque in the arteries of the heart, neck and brain. Accordingly, as they are part of the complex matrix of vascular plaque and chronic inflammation in the brain, there is great research interest in developing antibodies, genetic or epigenetic modifiers, to their action or expression.

The major cytokines are Tumor Necrosis Factor, a pivotal molecule in inflammation and cell death, good if it helps kill cancer cells but deleterious if it helps kill brain cells. Following Tumor Necrosis Factor are interleukins IL-1_a and IL-1_b which are primary actors in coronary artery plaque and brain astrocytes and neuron inflammation. IL_6 is another major pro-inflammatory interleukin whereas IL_4 and IL_{10} offer some protection against inflammation. IL-1_a, IL-1_b and IL_6 initiate the release of other actors and a progressive cascade of cellular and molecular recruitment that pulls together blood clotting factors especially VonWillibrands factor and platelets. Fibrinogen and blood factor VII and X, as well as changes in plasminogen activator, a natural clot buster but in inflammation changes in plasminogen acting as a pro-inflammatory, pro-clot protein.

All cells in the body have phospholipids and glycated lipids, lipid polysaccharides. These lipid matrices are a rich source of and target for inflammatory cytokines. Leptin in macropages and fat cells can be pro-inflammatory especially in visceral fat, signaling Tumor Necrosis Factor, IL_1, IL_6 and targeting vascular endothelial and brain response. Homocysteine and its family members are part of the mix, to name a few players in inflammation vascular disease, neuron injury, and abnormal thrombosis (clotting).

We must include other non-inflammatory pathways from mast cells that generate prostaglandins and leukotrienes through metabolism of arachadonic acid, which play a huge role in allergic reaction, and vascular collapse in shock or sepsis. In the latter case they are linked to the pro-inflammatory Tumor Necrosis Factor and ILs as well as the clotting factors in an extreme and often deadly molecular shock to the vital organs of the body.

SYMPATHETIC N.S. "NEURAL TRIGGER"



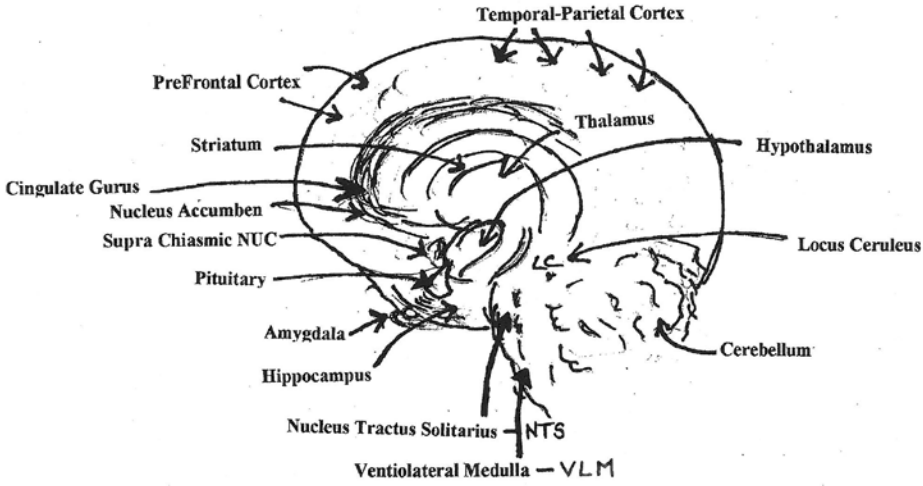
Norepinephrine from Nuclei, Locus Ceruleus, Posteria Hypothalamus, Brainstem to S.N.S. to ganglia to release more N.E. – which

- **↑ Blood Pressure**
- **↑ Heart Rate**
- **↑ Cortisone**
- **↑ "Flight or Fight" Response**

Main Nuclei for Norepinephrines

1. Hypothalamus
2. Nucleus Accumbens
3. Locus Ceruleus
4. Ventrolateral Medulla

Figure IV



Main Neurotransmitter Centers

Dopamine – Striatum, Nucleus Ceruleus, Amygdala, Hypothalamus

Norepinephrine (NE) – Locus Ceruleus in rostral pons, VLM, Hippocampus, Hypothalamus

Histamine – Tuberomamillary Nucleus, Hypothalamus

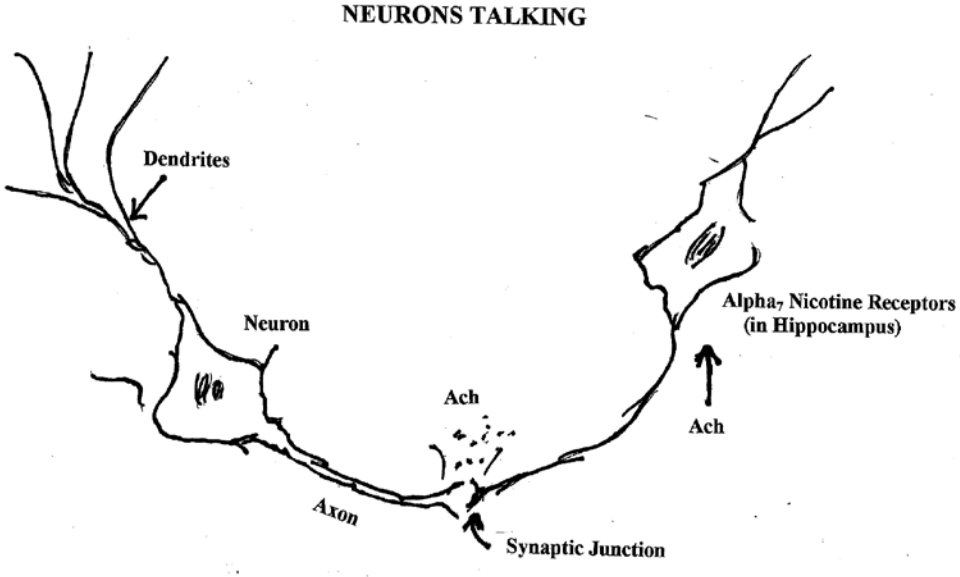
Serotonin – Pons, rostral/raphe, caudol

Orexins – Lateral hypothalamus, Locus Ceruleus

Limbic System

Long projections from various nuclei in hypothalamus and brainstem to cerebral cortex and back. Cybernetic inhibitor system is the so-called "limbic", or visceral, brain. It is a system more than a site, and within this arousal, action feeding, fear, sleep and rest are modulated, in conjunction with higher cortical inputs and collateral pathways. It is a key system/locus for mediation of stress and regulation or dysregulation of the individual's response to stress.

Figure V



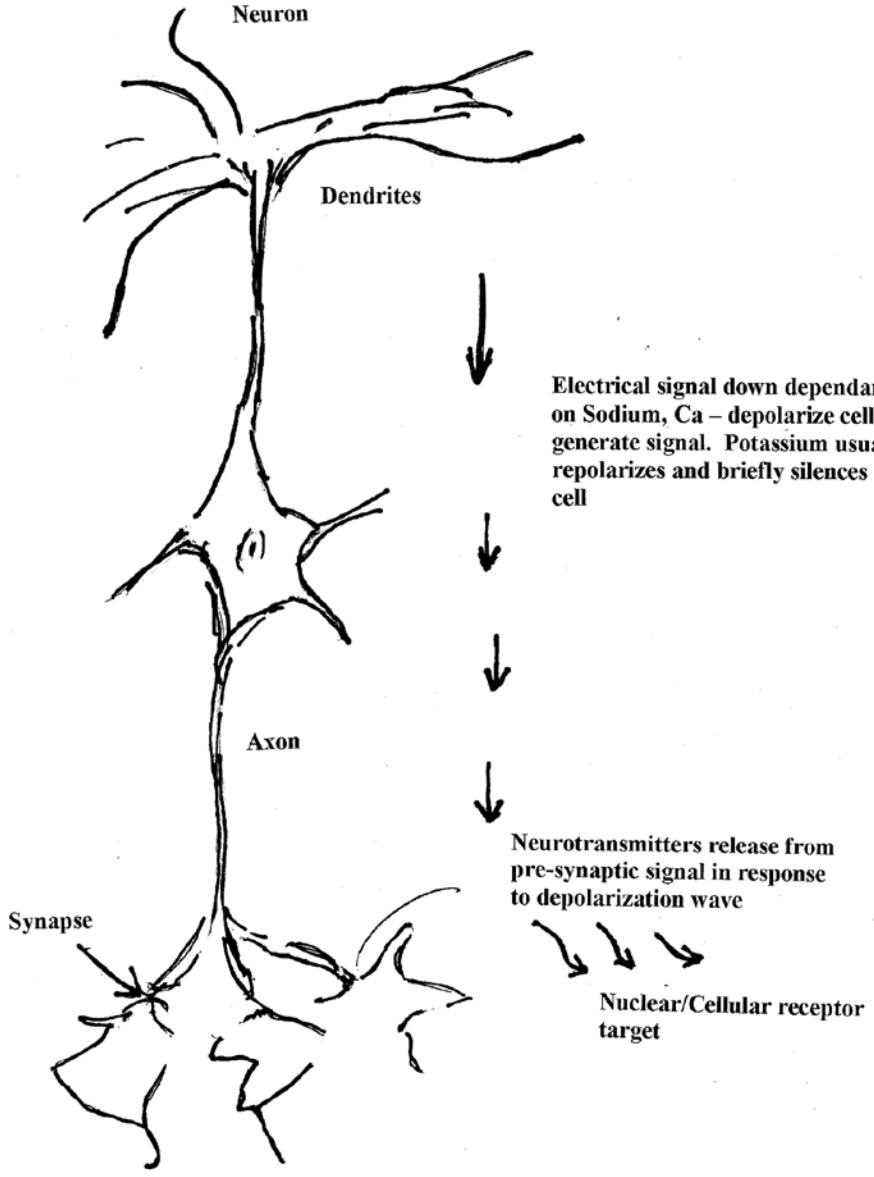
Memory "Talk"

In the hippocampus, e.g., depolarized cells, and then axons, send electrical signals to the synaptic junction to release the memory chemical Ach. In a nanosecond thousands of hippocampus neurons fire and release Ach which is the substrate for memory, especially immediate or short-term encoding of memory in the neurons.

The main damage to neurons in Alzheimer's disease is related to amyloid plaque suffocating the neurons and Tau fibrils destroying neurons from the inside and wrapping around the axonal connections, shutting them off from communication.

Figures VI and VII

Neurons Talking



100 Billion Cells

100 Trillion Synapses – Nestler et al.

Neurons – main functioning cell for cellular communication

Astrocytes – "starlike" – lock in blood brain barrier, metabolize neurotransmitters

Glia cells – brain immune system, may also produce growth factor and cytokines

NT - Neurotransmitters

Figure VII

SECTION I

BRAIN HEALTH, BRAIN DISEASE – THE SCIENCE

We invite you to read this section carefully without being too concerned about unfamiliar terms. It is the overall "picture" that we are trying to give you, and we have tried to simplify the science and present clear explanations of the way all of the complex pathways, molecules and proteins are involved in brain health and the way they can turn into brain damaging molecules and proteins. This is very important for you to know so that you will make better preventive and interventional decisions. In that sense the book is a handbook, but it is also a workbook for those of you who visit us on the web or come to us for comprehensive brain health management at *The Brain Health Institute of the Palm Beaches*.

The Science

When you took your supplement and your 2-mile run and prepared your power breakfast this morning, did you stop to calculate the real gain from all of this preventive diligence? Did the hour you invested give you an hour's return in slowing aging and heading off a disease event? Is the gain 1:1 or some multiple, or small enough that over all those years you may only get 1 or 2 more, in which case it just may not be worth all the sweat and supplements after all?

During the hour you spent on prevention this morning you aged an hour. The question is did your biological clock tick off the same hour or did you actually slow it down, and how much? Did you head off a stroke or heart attack because of your diligence? Did you flush some brain toxins that might otherwise have started you down the road to Alzheimer's? It's even more basic, did the rigorous exercise loosen or stiffen you, did the knees hurt more or less, did your spine flex a bit better or did you simply strain it again. Did you feel better all around, mind and body, after your supplements and your routine?

Do all of these interventions make more than a small change in our prospects if we are "factory set" genetically at the moment of conception? Actually, it is not a moment but an 18-hour process, called "syngamy," which pairs the paternal and maternal DNA in the new single cell,

the zygote, and then reprograms the DNA for expression and imprinting via epigenetic events. This process gives us new human beings who are for that "moment," at 18 hours, single cells with their own genomes and their own materials to begin to grow and develop. The epigenetic phase of syngamy is a huge key to the factory set business as the methylation groups run up and down the genome like a "zipper effect" to activate or silence various genes. This epigenetic reprogramming occurs in every single cell that will form in our bodies until the last cells. So we ask again, if the future is written in the first 18 hours, does epigenetics offer hope of change or modification? The answer is "yes," but what change is another matter, and that is where all of our efforts in prevention and disease modification come in.

We have learned that epigenetic reprogramming is highly responsive to countless environmental, dietary, molecular, toxic and stress factors, including our own mood, mental health and attitude. Yes, our genetic setting may form a lot of these aspects in us, but, in turn, our own efforts, both preventive, psychological, emotional, and moral (believe it or not, very important) play a role in resetting things to the positive side. We simply have no idea how much we can change and how early we should begin. For one thing, we simply do not know at what time a bad gene begins to send out its disease proteins and molecules like tiny boats that are going to crash on the shores of our arteries (heart disease), organs (cancer) or our brain cells (Alzheimer's).

Take the example of the Alzheimer's proteins, the Beta Amyloids and the Amyloid precursor proteins which are much of the subject of this book. It is fascinating to realize that for all the harm and hurt those proteins can do as we age, or become Alzheimer's victims, they are, in more benign configurations, essential to the development of our brains from the beginning of the primitive neuraxis at three weeks (an embryo) all the way forward.

So when do these essential amyloids begin to turn on us, when we are fifty or sixty or do the first subtle and imperceptible changes begin at fifteen or sixteen? It is the same question for all the genes, save for those with high penetration and almost immediate onset of disease activity at birth (or before!), a few of which we will mention briefly. So much of gene expression depends on mutation rates and the activity of epigenetic changes over time in trillions of cell replications. It is possible to thwart some diseases, or slow their progress or lower their intensity by epigenetic modification while at the same time possibly lengthening our biological clocks, cooling down whatever is heating up the aging process.

There is one more question, how early do we begin? Do we, for instance, want to take the information on the human genome, your own personal genome, and commercially sequence it for perhaps only $1,000, and modify everything that looks bad? Do we want to sequence our children's genomes and jump in with pharmacy level supplements, drugs or other molecules for their lifetime? On the other hand, if bad genes can be identified and epigenetic modifiers are available in a generic rather than gene-specific sense, should we start as soon as we can?

We can tell this much, all the information we will give you in relation to this discussion will help you get the jump on the enemy years earlier. If the biological lead time for Alzheimer's disease is measured in decades before the first symptoms appear, then early intervention is key and what you do today matters!

Alzheimer's Disease and a President

Few of us think of aging, disease and brain fitness when we are young. We simply don't feel vulnerable, even if family history or lifestyle tells us that we're already at risk. But time moves along, the clock on the wall does its twenty-four hour cycle, and so does your own biological clock, your 24-hour cycled "circadian" rhythm, which, by the way, is not identical in any two of us, similar, but not identical. So the clocks move and then one day something does happen, you have a clinical event, or your wife or your husband or a friend tells you that you are becoming forgetful. They notice early but clear signs that you're not "connecting" like you did.

A few years after the end of his presidency Ronald Reagan shared a dramatic moment with us when he appeared for a final goodbye. He knew that he was about to descend into the shadows of mental life to become a person without a personality, alive but increasingly separated from reality, literally losing his mind and his "self" in the mysterious darkness that is Alzheimer's disease (AD).

Unlike the psychotic who loses his mind but is often still able to construct an elaborate mythology or delusional system, the peculiar "logic" of the insane, the Alzheimer's demented lose even that, he loses everything that belongs to the mind, to the person. Reagan had the good fortune of a devoted wife and caregiver and while Nancy Reagan no doubt knew the prognosis, she could hardly have known how long or how deep a person could go to be demented, but that, of course, is Alzheimer's.

The President, physically well his entire life, lived beyond the expected 74 years for a male of his generation. Such longevity itself has been

called a risk factor for AD but two other presidents tell us otherwise. John Adams and Thomas Jefferson made it into their eighties without dementia and with the luck, if you will, of a once in history anniversary death. Adams died on the evening of July 4, 1826, exclaiming "Jefferson lives" not knowing that Jefferson had died earlier that morning, fifty years to the day that they had signed the Declaration of Independence. I suppose this is as much a mystery as Reagan's dementia, three famous men growing very old, only one of them didn't know it!

Youth in Old Age. Old age need not bring a calamity of diseases with it. Many patients live remarkably vigorous lives into their eighth or ninth decade, an octogenarian who would swim across the Hudson River and back (a mile each way), an ex-World War II paratrooper who made an annual jump until age 83, the daughter of southern slaves who dies in her bedroom rocking chair at 102, a Catholic priest who almost died of Tuberculosis in a Brazilian rainforest and lived to nearly 100. We know about people who age better and longer than the rest of us, and those exceptional few who seem to be a living refutation of all things biological. One 97 year old, petite to almost tiny, can still do all of her lawn maintenance, and house painting, and read three newspapers a day. There is no obvious evidence she is brain aging (she has seemed to overrule nature in her case). All of these people we have mentioned die, of course, but it's always a matter of being suddenly interrupted. We call it natural causes, but it seems that they are just called.

Sadly, there are other stories and a much different reality. There was a friend, a coach and fitness director, who died suddenly at age 43, the autopsy revealing that all of his major coronary arteries were filled with cement. He looked older than his age, and only a week earlier we had seen him at an event and very briefly thought that he didn't look quite right, but who would have guessed? Another friend, lean and kinetic, who smoked heavily, developed diffuse vascular disease in his early fifties. He was gone by sixty. Another friend smoked as much, and drank more, and made it to eighty. We know of a 600-pound person who made it to his early sixties without a single abnormal heartbeat or trace of diabetes, and a young fit runner with "juvenile" diabetes, well controlled, who barely made forty. Then there was a man who experienced a personal tragedy and aged overnight. His hair whitened, his face became lined and joyless overnight, not over a few days or weeks. One night he became an old man, and apparently a sick one. He fell over dead at an ATM machine three months later. So, while there are statistics and predictors of risk, there are no rules, no two patients are the same.

There are many epidemiologic studies of populations living past the statistical life span for the larger regional or national population. Com-

mon to these smaller groups, farm villagers in China, fishing villagers in Norway, mountain dwellers in the Caucasus, Sicily or Peru, is a "simple life" but one physically challenging and emotionally satisfying. These people live in harmony with the rhythm and pulse of nature, they enjoy simple and spontaneous diets, they have high regard for the family and faith, and they have a deep respect for the ancestors, a poetic memory of the forefathers, their villages, and the other families. They do not live by the motto "it is not enough that I succeed, others should fail." That is the tombstone for a huge number aging far too quickly, or dropping dead suddenly, or collapsing into depression, or exhaustion from the pressure to "get it now." Paradoxically, equal numbers are getting sick because the opportunities to "get it" are disappearing.

These studies are of great epidemiologic interest but some claim that data from a simpler time and place have no applicability to our situation. It is true that the metrics were very subjective, what the people themselves reported as their keys to youth in old age, but do you think that lifestyle, contentment, mental and physical activity, a belief system and community are not as important today as they were then? Since there is so much less of these today, their absence might seem irrelevant until we look more deeply at the physical, social and mental cost of their loss. All of these remain powerful modifiers of risk and their impact on our lives and longevity in completely unquantifiable ways. We have learned this much about lifestyle and attitude, for many millions of us, we are our greatest risk. There are few genetic markers for personality traits but all of these, personality, attitude, and lifestyle, which is really life interests, are relevant to aging and disease, bad hearts and demented brains. They are all linked in mind, brain and spirit. Our job, your job, is to secure the good links and break the bad ones.

Let's begin, then, by looking briefly at aging and disease, our first stop on the way to the self-help and prevention programs which conclude the book. Biological aging, the rate of aging indexed to your "clock" age isn't necessarily the absence of disease or disability, but neither of these need shorten life expectancy, the "actuarial" end point. Aging well is marked most of all by "durability", and yet it is not physical strength, better mental powers, or specific intellectual or personality traits which specifically confer longevity. No doubt each of these help, but they do not give a lifetime warranty. They are traits and while the good ones might point toward a long life when the right mix is there, does the mix make the molecules or is it the other way around? What biomarkers actually specify longevity? What molecules, genes, or proteins actually confer the benefit of slowed biological aging, and age-related disease risk reduction? The answer is we simply do not know, even

with our growing knowledge of cell senescence, telomeres, and tumor suppressor genes.

If your heart begins to fail, or your kidneys, the effects are easily measured and have prognostic value. We call these diseases and we usually make a distinction between an aging organ and a sick one. With the brain things are different, as soon as we become forgetful, repetitive, garrulous, or quiet, we are getting old.

This is very subjective and it depends on how we appear to others physically and mentally, however, with all of the cultural and personal prejudices. None of this is any more than crude empiricism which forms our idea of Chronological Aging, our clock age, how we look and function referenced to our age. Even physicians' notes might record "patient appears older than stated age" or "patient has aged well" suggesting that such observations imply medical status, health risk, or prognosis, when they may mean nothing at all.

Aging is also judged in relation to the presence of disease or disability. This is especially true for vascular disease in the heart, brain, kidney or peripheral vessels which thicken and clot earlier than expected, leading to organ damage which can bring "the look" of premature aging. Some will take this as evidence for premature aging but ask yourself this question, "If I have a heart attack at age forty, am I biologically older than forty, are my arteries fifty or sixty?" The answer may be "yes" or "no." If you find out you had an isolated lesion, the answer might be "no." If you have diffuse coronary disease, it might be "yes." Insofar as the arteries you may be sixty, but are you a biological sixty, the whole of you? It is impossible to say, but the process is less important than the remedy. If we can correct the problem and put you back on your chronologic track, you may conclude that it is not aging you show, but a disease you overcame. This leaves us with the unsettling prospect that for the near future we will not be able to separate biomarkers for disease protection from biomarkers for the aging process, since we have no idea what the aging "process" itself is specifically. Hence the distinction between chronological aging from biological aging, and either of those from the effects of medical events is unclear. Are we slowing down or retarding some of the molecular events related to bio-logical aging with treatment or prevention of medical events. It seems intuitively that the answer would be "yes" since multiple events, especially vascular events anywhere in the body, manifestly age us.

We simply cannot unwind these to the degree of certainty that we can tell our forty-year-old patient that he is aging more quickly than a sixty-year-old without any coronary artery disease, that whatever the

biological movers of bio-aging, the forty-year-old with heart disease is moving faster. If that turns out to be the case, it is still possible that another forty-year-old without any medical history could still die before his counterpart with coronary artery disease, all along appearing to be aging well.

The message today and for the near term is that disease and infirmity are independent of biological aging or markers for various diseases in an absolute sense. The reason is that since we do not know what the life principle is (i.e., the essential or effective "cause" of life and what the life sustaining forces are), we cannot say what aging is, since they are ultimately inseparable. This sounds like we are turning this into a philosophical question rather than a biological one; we are not.

We cannot "examine" philosophical "data," there isn't any. Philosophy is contemplation, a very interesting distraction for those of you who are following along with us in other sections of this book and the relations between mind, brain and psyche; and the differences. In the meantime as science is measurement, we must measure; so we mention several new attempts to further define the biology of aging and methods to intercept it.

The Metabolic Syndrome is the target of multiple measure and assessments for aging, as well as disease risk since its effects are systemic. The inflammatory, vascular and cellular damage presumably related to the metabolic syndrome can be tracked, especially if the syndrome is in its full blown state with obesity, elevated blood sugar or glucose intolerance, elevated triglycerides, low HDL (high HDL is a putative marker for longevity) and an elevated C-reactive problem (CRP), a measure of inflammation and specifically cardiovascular risk.

The most important component of the syndrome is obesity, especially (exclusively?) centripetal obesity (i.e., large fat accumulations in the abdomen, especially in the lining (the omentum), a curious word as it may indeed be an omen, and in the liver. This visceral fat produces a number of highly toxic antioxidant and pro-inflammatory molecules, speeding rapidly throughout the body. The fat in the liver is actually a syndrome within the metabolic syndrome called "hepatic steatosis. When the metabolic syndrome presents with elevated liver enzymes and fatty liver changes on abdominal imaging or biopsy, the "omen" is much worse, not only for heart disease but for cirrhosis of the liver and liver failure after several decades.

While the metabolic syndrome has impressive credentials for vascular disease, heart attack and stroke, its links to accelerated bio-aging

are inferential. Clearly, widespread vascular disease and the steady pounding of cells everywhere, especially the brain, by the metabolic toxins are ominous, but the syndrome is both reversible or to some extent controllable. Does that translate into a slow down in bio-aging or does the cellular change triggered in the syndrome take on a life of its own? What actually happens to cells (e.g., heart and brain) since these organs do not develop full infiltration the way the liver does? No, they don't, but both the coronary arteries and brain neurons can become "inflamed" by the circulatory fats and toxic products, showing us a very dramatic link, once again, between the molecular change of plaque in the coronary arteries and protein plaque on the neurons. In fact, the links are becoming increasingly defined by recent observational biomarker research suggesting fat markers (actually, phospholipids in blood or spinal fluid) may have predictive value for Alzheimer's disease years before memory changes (see the section on "Lipids"). It will be interesting to see if this preliminary data holds up and if it has predictive value for brain aging, even systemic aging, as well as Alzheimer's disease.

Another approach attempts to slow aging by the use of stem cell therapies. The idea is simple enough, get enough young cells into vital organs and manipulate the respective native cells to generate new, fresh cells whose lineages will age more slowly than the native cell lines in the various organs (e.g., brain, heart). (See page 104)

Recent murine (mouse) experiments involving a technology called parabiosis is claimed to slow aging. Parabiosis simply means "living together," the procedural variant of this is to join the circulation of two test animals, one younger, and note a change in cell populations in specific organs, and corresponding repair or rejuvenation of organs. Several experiments have suggested that in these parabiosis models the younger animals do transfer progenitor (very young) cells into the circulation of older mates. When the organs are examined the older animals show younger heart muscle (e.g., than expected for their age), while the corresponding younger animal, the donor, actually shows changes of premature "aging" (older cells).

One can hardly interpret these findings as evidence of anything regarding the slowing of aging in the animal. The results are what they say, younger cells in some organs, presumably via stem cells from the younger animal of the pair. Likewise, it must also mean that cells from the older animal entered the organ of the younger animal. Nothing, by the way, demonstrated that the older animal is actually living longer.

These experiments and potentially exciting rejuvenation therapies remind us of the first transfusion experiments in animals (and humans)

over two hundred and fifty years ago. Dr. Richard Lower of London was one of the first to do these, along with the famous architect Christopher Wren, and the chemist Robert Boyle. In some of these classics "many dogs looked younger and barked and jumped more." Even the ancient Romans tried blood therapy, taking blood from gladiators and putting it into the veins of wealthy Romans for strength and vigor. They all died.

Aging is something beyond the sum of the changes in organs, or disease events, just as youth cannot be restored or the clock slowed by attacking various metabolic syndromes, genetic markers or youth to age cell therapies. When we know what life is, the first principle of life, then we can find the keys to aging, and its reversal. Today nobody knows what the life "force" is, we are only describing its effects.

The task of retarding aging faces another difficulty. Somatic cells from different tissues in the body neither multiply nor die at the same rates. Perhaps this is a function of differential rates for shortening of telomeres, an observation common to humans and research animals. Telomeres are endstops of DNA in replicating cells, including germ cells. As the number of cell divisions move further out from the original progenitor cells, telomere shortening is observed. Once again, while cell aging occurs in relation to telomere shortening, older cells having shorter telomeres and less telomerase, this may simply be associational rather than causal. This is all the more puzzling as the evidence indicates that after a specific number of cell divisions and telomere shortening, telomere breaks occur and the DNA structure of the telomere is degraded. Both of these changes are hallmarks of programmed cell death (apoptosis). We concede the point that cell death may be the result of other factors, as well, and that such programmed cell death may not be the final endpoint of cell aging. For now, all we can say is that the cause of aging eludes us, and the relation between all of our positive interventions and the slowing of biological aging is unknown. (See page 29)

There is, however, recent preliminary data showing the relation between infant (less than 2 years old) stress and telomere shortening as predictors of more disease burden as an adult, and a shorter life span. One particularly damaging stressor is the emotional detachment of the parents, especially the mother. Other stressors include infant exposure to violent language or events, or psychic stress and emotional liability in the mother, which the infant "cues" on. The effect at the cellular level includes measurable telomere shortening, which may reset the aging "program" negatively from then on.

Altered cortisol patterns are also detected in these infants and seem to parallel changes in telomere length. This data is new regarding telo-

mere length and more research is needed which may prove that the powerful link between stress and aging can begin very early, and telomere lengths may be a significant predictor of a decreased life span. What the research does not examine, yet, is the possibility that the infant or young child may be able to recover psychically and, therefore, at the cellular level telomere length reset more favorably.

Diseases with Premature Aging Without Dementia. There are several exceedingly rare disorders with specific genetic profiles in which the hallmark of the disease is premature aging. Both Progeria and Primary Dwarfism leave their tiny victims at risk for cardiovascular disease and stroke within the first decade of life. Osteoporosis and bone fracture, cataracts and neurosensory hearing loss follow along with all the obvious signs of aging. The "children" are usually dead by twenty. Werner's Syndrome is highlighted by premature atherosclerosis, cataract, and skin aging, with death usually by age 25-30. Alzheimer's disease does not occur.

There is little doubt among the experts that these diseases are manifestly the most extreme forms of accelerated biological aging, at least in the visceral organs and circulation, but curiously the patients do not develop Alzheimer's disease or dementia. Is this so because these patients die too early to have Alzheimer's disease, or does this suggest that Alzheimer's disease is not related to accelerated aging? Another possibility is that while somatic aging and brain aging have the same substrates, they may have different timetables. If that is true, perhaps these patients are not true experiments of nature in accelerated aging but an unfortunate combination of genetics and disease that kill them prematurely. In progeria (the Hutchinson-Guilford Syndrome) scientists have found measurable premature cell death in cell cultures. Skin fibroblasts taken from Progeria victims die after 2-14 cell cycles (cell division) instead of the 40-50 cell cycles in normal subjects. The nuclear material in Progeria cells show chromosome breaks and copying errors and other aberrations as well. Interestingly, the Fibroblasts do not exhibit abnormal telomere shortening or decreased telomerase and are similar to skin fibroblasts in Werner's Syndrome, which also have reduced multiplications.

With Dementia – but not Alzheimer's. There are other diseases which are noteworthy for early and frequent strokes and widespread, but not uniform, vascular changes. Non-Alzheimer's dementia is typical and early death as well. One of these syndromes, Binswanger's Disease, includes hypertension as part of the clinical profile whereas the so-called CADASIL syndrome has a genetic marker on chromosome 19 and a history of migraine headache in a third of patients. The relation of these vascular syndromes to premature or accelerated biological aging

is not definable. Certainly, the crippling effects of multiple strokes and dementia take a heavy toll on the body. Likewise, stroke and destroyed blood supply to the brain may initiate a cascade effect of brain cell damage leading to dementia. It should be noted that the proteins and plaque changes seen in Alzheimer's disease are not a feature of either of these vascular dementias.

Several extremely rare diseases with accompanying dementia are considered mitochondrial DNA muscle disorders, and interestingly, the gene defects are also carried on chromosome 19. The Kearns-Sayre Syndrome causes eye muscle paralysis, heart block, diabetes, dementia, deafness and early death. The MELAS complex presents with childhood strokes, encephalopathy, seizures, and dementia and death. Once again the dementia is not of the Alzheimer's type. So we have two more syndromes with complications of and dementia and early death yet without any way of defining these diseases as models of accelerated biological aging.

A Prodigious Memory Syndrome. In contrast to these early dementia, early death syndromes, we know of the exceedingly rare and poorly understood phenomenon called Hyperthymestic Syndrome which describes individuals with exceedingly precocious memory and recall abilities, people able to store, catalogue and retrieve huge amounts of data and facts. A few of these individuals show overdeveloped or hyperfunctioning cortical, hippocampal and caudate loci, precisely those areas which are shrunken and hypofunctional in Alzheimer's disease. It will be fascinating to find out what happens to these patients as they age, what special molecules or proteins confer this, and the implications for possible diagnosis and treatment of dementia syndromes.

Diabetes is one of the few systemic diseases with the potential for widespread premature organ aging and dementia. The vascular disease that is associated with diabetes can lead to early stroke and vascular dementia, as well as widespread vascular damage and the heart, kidneys, and the blood vessels of the eyes. Diabetes seems to be the one metabolic disease that leads to multi-organ disease and failure with many of the signs of aging. Diabetic patients are also at higher risk for Alzheimer's dementia because of the intracellular (neuronal) fate of glucose, itself potentially toxic to neurons. Thus, the potential for diabetic patients to exhibit mixed forms of dementia, vascular dementia and Alzheimer's disease, marks these unfortunate patients for accelerated aging from systemic organ damage. This frames the question of aging in another way, in regard to its most important end point, premature death. Diabe-

tes, while not a specific biomodel of accelerated aging, certainly presents more risk factors for early death.

Is early death in diabetes from early aging? The answer is no, the prevention of diabetic complications does not mean that we are slowing aging, but that we are simply postponing potentially fatal events. We can prevent premature death which is not the same as slowing biological aging. We treat diseases, some of which accelerate some of the biological signs of aging, some of which would otherwise be fatal and lead to premature death. We cannot emphasize the importance of the distinction and the implication for a huge industry in alternative medicine, and to a lesser extent homeopathic medicine, which purport to "treat aging".

We are not saying that you should empty your bottles of vitamins and "alternatives", or stop exercising, or drop your Mediterranean diet and go for the Buffalo wings or Big Mac and fries, not at all. We can tell you that whatever you do as part of your anti-aging and brain disease prevention program today will confer a real dividend in the future. You simply cannot compute it until you have lived long enough and well enough. Since your aging curve is utterly unique, no one else will have the same chronology, diseases or risk factors in precisely the same order or number. But we are living in exciting times when advances in molecular biology and the sharply rising incidence of Alzheimer's disease, the most recognized and feared disease of aging, are converging. The "science" of aging is meeting aging's most distinguished disease, and we are beginning to connect the dots between disease and dementia, and dementia and aging.

Alzheimer's Disease –The Common Cause of Dementia – The New National Health Crisis

Alzheimer's disease has exploded in the last two decades, and will be epidemic in the next, paralleling the explosion in diabetes during the last half century. Some say that Alzheimer's disease is predictable following the increased life expectancy we have enjoyed but that is only partly true. Something else is happening. We are speaking of three things: The first is psychological stress; the second is the damage to our DNA, from pollutants to plastics, polymers, prefab home items to pesticides, and paints, electromagnetic waves (e.g., cell phones, computer screens), with their special effects on brain cell transmission, cables and wires, water, air and soil contamination and toxic waste processing centers in high density urban centers. The third factor is the multiplier effects of the "industrial diet" on cellular metabolism, gene expression and molecular toxins hitting brain and body.

Interestingly, there are no animal models for Alzheimer's disease although veterinarians have observed cognitive declines in dogs that parallel some of those in humans, namely, confusion, spatial and location disorientation, behavioral changes and disordered sleep. On autopsy these dogs have substantial deposits of Beta Amyloid and extensive neuronal death. There is a laboratory model for Alzheimer's disease, transgenic mice with an extra chromosome 21, hence high levels of Alzheimer's precursor protein (APP), as is seen in Down's Syndrome. The problem with the transgenic model is that it is a leap over decades of molecular and pathologic change in real patients. The mice have a "factory set" gene with high penetrance for amyloid protein but it does not replicate all the steps to get there. If it turns out that the amyloid plaques are the last phase of the pathologic processes, the mouse model is even less applicable.

Sadly, we do have an accelerated disease process in humans – former boxers and football players with multiple concussions and early onset severe dementia. Some of the victims' brains were examined post mortem to reveal extensive (80% – 90%) destruction of neurons and axonal elements by Tau proteins.

All of this presents an opportunity to correctly apply our research knowledge. If we can reduce risk factors and intercept pathways earlier, we can alter biological destiny insofar as we advance our technological successes relating to aging, disease and dementia. So we begin with some causes and links to the most common disease of aging and aging itself.

The first thing to consider is that the abnormal brain proteins seen in Alzheimer's disease may only be the end of the story. For a long time many scientists thought the Alzheimer's disease was simply a severe form of brain aging, the bad luck of aging poorly. It turns out that if we live long enough, each one of us will have some level of abnormal protein including Beta Amyloid and Tau, two of the "diagnostic" proteins for Alzheimer's disease. The problem is that these proteins are hanging around the brain cells of almost everyone over 60 years of age and showing up in other diseases such as Parkinson's disease and Prion disease. On the other hand, even with abnormal brain Amyloid, Tau and other proteins in low volumes, most of us will age normally with only minimal or mild memory loss or cognitive impairment. We also have the interesting fact that Tau, Beta Amyloid and its precursor protein, APP, are essential proteins in the development of fetal neurons. These proteins nourish neurites, brain cells with their long tentacle-like axons and dendrites, with their synaptic clefts that put billions of brain cells in contact

with each other to give us our brainpower. In one form of configuration or stacking, the Amyloids and Tau are essential brain growers. In another form or configuration, they are brain killers. We will look at some of the molecular culprits that "flip" these proteins, and in the other sections how we might "nip the flip."

We remind you again that Amyloid and Tau are the last stop on a long molecular train.

There are many precursor culprits already identified but many, for sure, as yet unknown, without which neither Amyloid or Tau would have turned.

Obviously, then Amyloid and Tau are not the cause of Alzheimer's in the formal sense but only as the efficient (proximate) cause. In this regard it is also wise to keep in mind that molecular targets for them, e.g. antibody protein busters, are akin at the micro level to clot busters in coronary arteries at the macro level — the proof of failure to identify and control the molecular precursors in either case, despite the advances in our knowledge of coronary plaque that has accumulated over the last fifty years.

Another troubling aspect of these proteins is their overlap in various neural diseases. For instance, Parkinson's disease and Prion (of which Mad Cow is a species) have Amyloid and Tau, and 15% of Parkinson's disease patients have Amyloid-induced dementia. Other Parkinson's disease patients have Amyloid-like Lewy Bodies which are also brain toxic. Prion victims also exhibit Amyloid protein but Prions themselves are unique in that they are infectious "bodies" without DNA or RNA. Viruses, the smallest previously known infectious agents, have DNA or RNA packed inside a protein cover. When viruses invade cells they trigger an immune response, something which does not happen when Prions invade. Nonetheless, Prions are normally present at low levels in neurons and become cell killers when they change their shape in a fashion similar to the changes which make Amyloid and Tau neurotoxic. Tau is an essential protein normally forming microtubules which are part of the infrastructure of neurons. When Tau changes shape to form paired protein filaments, called neurofibrillary tangles, it damages neurons. In Alzheimer's disease it appears that Beta Amyloid and Tau work together, while it is the Beta Amyloid which is thought to come first. Recent research suggests a much closer connection between amyloid and Tau pathology, both in the onset of Alzheimer's disease and in its progression. Indeed, Tau damage may flood axons and disturb or destroy axonal function well beyond any amyloid plaque damage to the neuron itself might initiate.

Previously, the thinking was that amyloid was the big daddy protein, while Tau trailed along as a secondary player. The new view is more "collaborative". Neither goes very far without the other and both are needed for all the clinico-pathologic changes of Alzheimer's disease. The other change in thinking, as we indicated, is the prion like behavior of these proteins.

Viruses, at least, were respectable invaders; they had DNA and could replicate within host cells. The behavior of prions is more uncertain, adding to the mystery of the progression of Alzheimer's disease if the spread of the disease is via prion like activity.

Tau is also being recognized as playing a much wider role in other neurodegenerative diseases, especially in the front-temporal dementias (FTD), and more recently being identified in Amyotrophic Lateral Sclerosis (ALS) where the ratios of tau in the spinal fluid may be a marker for the disease. Accordingly, some researchers are placing ALS in the family of "tauopathies". Tau is also making news because of its presence (cause) in traumatic brain injury (TBI) and chronic traumatic encephalopathy (CTE), increasingly identified in former athletes with severe dementia and extreme loss of impulse control, and violent acts, even suicide. In these unfortunate victims post mortem examinations of the brains demonstrated massive tangle formation and loss of neuron and glial cells.

We mention for completeness sake two members of the FTD family with conspicuous tau deposition but with only late dementia, the first being Progressive Supranuclear Palsy with tau destroying neurons and astrocytes in the basal ganglia, with speech loss, nystagmus and gaze loss (upward) along with signs of Parkinson's disease. Corticobasal Degeneration is closely related with gait and movement disorders, loss of muscular coordination, and late dementia.

The main evidence that tau is a primary actor in all of these diseases is, first of all, the obvious low level of amyloid plaques in these disorders, and experiments with mice genetically bred for Alzheimer's disease but without tau genes, so called "knockout" mice, in which the genes that form tau are taken out of the animal's genome. In the latter experiments tau knockout seemed to provide protection against both amyloid plaque formation and memory loss. Much more research is necessary, especially in clinical trials which target pTau and tau, comparing anti-tau strategies with anti-amyloid strategies. There is a curious thing we note as researchers: why the close and necessary collaboration between amyloid and tau in one disease (i.e., Alzheimer's disease) and their dis-association in the tauopathies, why no amyloid? The answer is different

diseases, but that is no answer at the molecular level unless ultimately they are not different diseases but one dementia template molecularly, with greater or lesser amounts of tau or amyloid the only difference.

So we have three ultimately fatal brain diseases with a background of normal proteins being reshaped and contoured into toxic neuronal proteins. One patient has some Amyloid, even substantial amounts, without real damage while another progresses to be severely impaired, ultimately succumbing to his disease. Where, then, is the line between natural aging and pathological aging? The answer is that we cannot definitively draw such a line. The best we can do is to look at the "usual suspects," molecules and proteins that seem to always be in the background of aging, vascular disease and neurodegenerative disease. What are the various connections among them? Do they get together via inflammation, genetic pressure, epigenetic changes, abnormal glycation or oxidation, or oxygen deprivation (hypoxemia)? Is there a failure of cellular housekeeping to clean away abnormal proteins and cell products, failure of lyzosymes, and capases, to carry off these collections of cellular debris or otherwise reprocess them to be nontoxic?

The Amyloids – Alzheimer's; An Amyloid Disease? Amyloid in Classical Greek means starch. It is a hybrid compound of starches and proteins, complexed as glycosaminoglycans (see GAGS). There are a number of amyloid disorders, some related to blood diseases such as myeloma, some related to chronic infections, and a third group called primary amyloidoses, which behave similar to cancer but are not cancers in the technical sense.

Amyloid also appears in the brain and is the hallmark of the most common cause of dementia, Alzheimer's disease. There the amyloid of interest is Beta Amyloid. It is a species of Amyloid with subunits identified by their amino acid length, one of which is AB_{1-42} a major "cause" of neuronal death in Alzheimer's disease. AB_{1-42} is derived from Amyloid precursor protein (APP), a normally occurring brain cell protein which regulates cell and synaptic functions. Beta Amyloid (AB) is a major cleavage product while APP is present in fetal brains and orients neuronal alignment and synaptic formation. Beta Amyloid (AB) is present in all age groups, and circulates at low levels throughout the blood and all body fluids, as does inflammatory Amyloid (SAA). Neither the physiologic role for circulating AB is established, nor its links to other circulating or tissue Amyloid species.

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Multiple triggers can reset the cleavage of APP yielding more of AB_{1-42}. Some of the triggers are genetic, some are epigenetic (post DNA replication), some are inflammatory or toxic. These can alter the activity of secretases which are normally present. If alpha secretases act preferentially, Amyloid AB_{1-40} is produced. If, on the other hand, Beta and Gamma secretases act in concert then toxic Amyloid, AB_{1-42}, and other Amyloid subspecies are produced. The secretases are critical as they determine the amino acid splits from APP. Gamma secretase is under the genetic control of presenilin 1 gene (PS1) on chromosome 14, which marks for familial early onset Alzheimer's disease, and presenilin 2 (PS2) on chromosome 1 which codes for early, severe Alzheimer's disease. Chromosome 21, which codes for Amyloid precursor protein (APP), has no secretase gene but with trisomy 21, Down's syndrome, is associated with early Alzheimer's disease independent of the presenilins but dependent on an extra copy of APP. There are also missense mutations on APP, such as valine for isoleucine on position 717, and perhaps two dozen other point mutations which increase the risk for Alzheimer's disease, all unrelated to extra copy APP.

Mutations in the presenilin genes increase Beta and Gamma secretases to build AB on the neuronal membrane and inside the cell. Presenilin mutations can also cause cuts in Beta Amyloid at 21, 22, and 23 positions leading to Cerebral Amyloid Angiopathy (CAA), a Beta Amyloid degenerative disease of cerebral vessels causing about 15% of hemorrhagic strokes in the elderly. Additionally, inhibitor RNA, which generates non-coding sequences, increases Beta secretases, especially in the background of stress factors such as elevated glucose, heat, and AB_{1-42} itself. In this way RNAi increases Amyloid plaque via beta secretase which otherwise remains at physiological levels.

The proportion of Amyloid of various amino acid units is critical, whereas AB_{1-38} and AB_{1-40} are neuronal protective, AB_{1-42} is neurotoxic. It is the insoluble proteins which are reshaped and then held together by

protein binding glycans which act as sealants. Thus a low ratio of AB_{1-40} to AB_{1-42} increases the risk for dementia, while intracellular AB_{1-42} is now believed to be at least as important as extracellular AB_{1-42} plaque. On the other hand insoluble AB_{1-40} may be a marker for cerebral Amyloid Angiopathy (CAA), responsible for a significant number of lobar strokes. So the number of amino acids is important but the pathology is highly dependent on protein folding and glycan binding. This is true for all of the neurodegenerative diseases; it is their conformational changes which are key. The question for us is what drives these conformational changes? We have to look at some of the key elements, molecules, and diseases which are major players in aging and the age-related disease burden, linked as they are at the basic molecular level via inflammatory pathways, epigenetic changes, methylation, glycation, oxidation, and cell hygiene.

Epigenetic Regulation. Epigenetics, "second DNA," resets genome and determines expression or silencing after the genome has been sequenced. The key phase in epigenetics is methylation, the donation of methyl groups to DNA. The "universal donor" of these methyl groups is S-Adenosylmethionine, SAM, a major transition molecule on the way to homocysteine (Hcy) and a highly active molecule on its own. Epigenetic events occur in every cell throughout the body, 220 different cell types. Methylation patterns play a role over many years in aging, vascular disease and Alzheimer's disease. Keep in mind that each and every time a cell divides anywhere in the body, its genome is reproduced in the daughter cells. Then the genome has to be reset, if you will, through the demethylation and remethylation process as part of its epigenetic ("after the gene") reprogramming millions of times every minute of our lives. It is remarkable how stable the system is in terms of chances for error and disease relative to total epigenetic activity. On the other hand, in absolute terms, the chances for "error" are quite real simply by the number of events, errors determined by other molecules and factors effecting methylation patterns.

We are now learning that there is a high rate of epigenetic dysregulation induced by a host of environmental, atmospheric, and dietary toxins. The addition of food stabilizers, coloring and taste molecules, dyes, sulfites, nitrates, and hydrogenated fats present toxic and oxidative stress to molecular DNA and are serious modulators of the methylation-hypomethylation process. These occur at a very high level in the gametogenesis (spermatocytes and oocytes), the silencing of the second X chromosome, at fertilization, and DNA replication in somatic cells. Hypomethylated islands which would ordinarily have been properly methylated and silenced might involve small but critical DNA sequenc-

es that have been previously quiet. These could then transcribe for toxic proteins to produce pathological degradation of brain cells.

DNA changes, especially single nucleotide polymorphisms, SNPs, and epigenetic events are even more frequent in mitochondrial DNA (mtDNA). The mitochondria are the energy pumping stations of the cell, producing 13 protein bases and the requisite RNA and molecules to do this, and mtDNA is much more susceptible to oxidative stress and inflammatory-toxic molecules than nuclear DNA. Any discussion of aging and disease and mtDNA may have special implications in neurons and dementia, and somatic cells, in relation to mitochondrial burn out and toxic waste accumulation. This may bring accelerated aging and cell death.

Homocysteine and Inflammation. SAM is a key molecule in epigenetics, but SAM also generates S-adenosylhomocysteine, SAH, a highly toxic molecule that can lead to vascular disease and dementia. SAH is an intermediate step back to Homocysteine, now identified as a major toxic molecule at higher levels, destabilizing both collagen, the glue of bones and joints, and ground substance, the glue of blood vessel walls. Elevated homocysteine disrupts vascular integrity and increases platelet stickiness, thereby working as a dual action molecule promoting inflammation and clotting. It is a direct neuronal toxin as well via inflammatory pathways and microvascular injury, along with SAH and SAM. (See page 47)

Homocysteine metabolizes to and from methionine, reactions promoted by L-Methylfolate and Methylcobalamin, relatives of folic acid and B_{12} respectively, both of which are needed to block the deleterious effects of high levels of homocysteine, SAM and Homocysteic Acid. All of those molecules can promote cell toxicity, inflammation and oxidation. These toxic effects are worsened by defective methylenetetrahydrofolate reductase (MTHFR), the enzyme which generates L-Methylfolate.

There is another pathway for homocysteine through cystathione to cysteine which yields glutathione, an important brain antioxidant and cell cleaner. Glutathione is essential for clearing heavy metals from cells (e.g., mercury, aluminum and lead). Glutathione also helps stabilize the cell's energy pumps, the mitochondria, the failure of which is one theory for the aging of the cell.

Obviously, the observations on homocysteine metabolism, just one molecule with its pathways, tells us how sensitive each cell is to homeostasis, the balance of the beneficial or toxic pathways of the molecules and proteins in the cell. This incredibly delicate balance is maintained

or breached second by second, minute by minute, throughout the life of the organism. The wonder, then, is not the profusion of diseases and the irreversible march to old age, but the time it takes to get there, and how many of us do!

Other Common Risk Factors. Hypertension is, no doubt, both a silent killer and disease risk for heart, brain, and kidney, especially in relation to psychological stress and lifestyle pressures in modern technical society, a disease and risk simply not present in agrarian and less developed societies. Hypertension, in turn, places tremendous "mechanical" stress on the vascular system and the "target" organs, especially the brain and heart, both for sudden cardiac death or massive stroke, and more sustained damage to the heart muscle (cardiomyopathy) or the brain cells (dementia). Even though hypertension appears not to be a direct risk factor for Alzheimer's disease, it does promote microclots, microhemorrhages as well as larger strokes, and ischemia (decreased blood flow to the brain) which trigger many cellular and chemical reactions which end up being brain cell toxic. If hypertension is joined with diabetes, the effect on brain cells can be devastating.

Diabetes promotes vascular disease and can lead to premature brain cell death. Diabetes is a supply side (not enough insulin) and a demand side (receptor sites) disease but it is also a microvascular (small artery) disease. It is a major risk factor for accelerated arteriosclerosis and atherosclerosis. Likewise, unstable blood sugar control, including low blood sugar events, does great harm to brain cells. We must note that the risk of diabetes from dietary sugars is not confined to glucose, high fructose corn syrup, and corn starch; common additives in "diabetic safe" labeled foods, are as dangerous as glucose.

Recent animal studies have shown that elevated glucose has a promoter effect on free radicals which directly damage the lining of smaller brain arteries. When diabetic mice with increasing levels of blood sugar are tested, higher levels of Beta Amyloid are found in the small blood vessels in their brains. The increase in free radicals ("superoxygen") that follows then promotes the destruction of the lining of vessels, with more Amyloid deposition. This effect is magnified by increasing levels of blood glucose and both are worsened by the pressure of the Alzheimer protein, Beta-Amyloid, itself an inflammatory protein and cell toxin.

Paradoxically, adjusting for the ambient blood sugar levels in diabetes, there is growing evidence that both impaired glucose metabolism and decreased glucose at the neuronal level increase inflammation and the production of Beta Amyloid and Tau protein. The diminished energy

metabolism is controlled by decreased expression of regulator genes and oxidation products of LDL bound radicals rather than any primary defect in the neuron.

Inflammation. Inflammation in biological systems is triggered both by changes in atomic structure in cells, especially via the net loss of electrons, a process called oxidation, or by mobilization of cells and molecules which are part of the defense system against invading bacteria, virals, or protozoans. This system sends white cells and big cells macrophages or unleashes antibodies. There are times when these systems "misread" and actually turn on other molecules and proteins in the body producing autoimmune diseases. The abnormal proteins in Alzheimer's disease are promoted by all of these mechanisms, perhaps even the autoimmune responses although we do not yet have a way to measure that at the low levels this might be in play. (See page xxv)

All of these inflammatory events and protein building leave the brain cells with another problem, waste management. Where do the dead proteins go if they are not swept out or reprocessed? The answer is they will overwhelm the cell and kill it. In fact, one of the theories regarding Alzheimer's Disease is that it is a waste management problem. Cell clean-up units, called lysosomes, send out enzymes that break down proteins. Usually this waste management operates in balance with protein and inflammatory cell production. If the lysosomes fail or are overwhelmed then toxic levels of proteins, Tau and Amyloid, can build up and attack the inside and cover of the brain cell and the long axons that conduct cell signals among billions of brain cells.

In any case the changes in cells, oxidation, and inflammatory cell signals (cytokines) are major movers along the molecular pathway to the development of amyloid proteins in the brain. The net loss of electrons in molecules makes them highly reactive "free radicals." Such a molecule is free to steal electrons from neighboring molecules. This sets off a chain reaction of oxidation, and reduction. Some cells gain, some lose, but all of them that are oxidized (net electron loss) initiate epigenetic changes, inflammatory cascades and numerous other biological events that can lead to cell death or abnormal cell expression, cancer and degenerative brain diseases. All of this, by the way, is very likely a major factor in brain cell injury and the proliferation of abnormal proteins.

For one thing the brain is rich in fat; phospholipids, lipoproteins and cholesterol, and these are easy targets for inflammation as lipid peroxidation is an ongoing risk and the brain is the most lipid filled organ in the body. Inflammatory molecules, acting both locally and remotely,

play a major role in Alzheimer's disease, neural disease, CAD and aging. We have already looked briefly at homocysteine but there are hundreds of other molecules as well. Beta Amyloid may also be related in some way to other inflammatory proteins such as Amyloid A which is an acute phase reactant. When there is long-term inflammatory reaction anywhere in the body, the systemic Amyloid may promote Amyloid deposition in tissues. Amyloid A (SAA) levels rise in the blood and tissues when there is active inflammation and SAA, in turn, stokes the coals of inflammation to increase the cellular damage. We do know that the ratio of SAA to LDL cholesterol is a risk factor for coronary artery plaque while the specific connections between SAA and Beta Amyloid in the brain are not yet defined. Our own view is that the systemic Amyloids, inflammation, and altered regulator genes and the toxic (Beta)Amyloid in the brain are deeply connected at a "primitive" molecular level.

The relations between neuronal Amyloid and vascular Amyloid (congophilic Amyloid Angiopathy) must be significant considering that the vascular changes of smooth muscle degeneration in brain vessels occur in most Alzheimer's disease patients as well. On the other hand, we cannot make any direct connections with Beta Amyloid to the other amyloids. Some amyloid diseases are genetic, such as amyloid heart disease, some are inflammatory, as may be the case in diabetes where amyloid deposits can be seen in the liver, kidneys, and areas of the pancreas where the insulin-making cells have burned out. Perhaps inflammatory amyloid helps destroy the cells, or perhaps the amyloid moves in after. We simply do not know the answer, just as we do not know if SAA, the acute inflammatory amyloid in blood, spinal fluid, and tissue fluids is the link among all of these, especially in the brain.

The Systemic Inflammatory response is a complex of proteins which modulate the response to injury, infection, or insult (toxic, anoxic, or stress induced). These inflammatory cytokines, "cell movers", trigger the breakdown of cells and can bring cell death. Amyloid inflammatory protein, SAA, releases these molecules systemically and the body, in turn, sends its systemic fighter cells and molecules to the site of inflammation in response to these cell signals, be they cells, hormones, cell enzymes or antibodies. It is a vast organizational effort for defense and yet it can easily trigger disaster. (See Inflammation, page xxv.)

One local inflammatory condition which has drawn attention is periodontitis, the chronic inflammation of the soft tissues surrounding our teeth. Periodontitis is a powerful initiator of remote inflammation with a predilection for the coronary arteries, including bacterial cell products invading the coronary arteries. Amyloid A may be one of the substances caught up in the mix of molecules raising the question of its connections

to Beta-Amyloid in the brain, as well as the relation between inflammation in the body and brain, and vascular plaque, lipid cores (LDL) and elevated homocysteine and SAH. The inflammatory molecules also affect the fats in the blood and fat build up in arteries (plaque), plaque inflammation, and Beta-Amyloid and Alzheimer's disease.

Another very important link to inflammatory changes in the brain and vascular system is through various glycoproteins that promote clotting and stimulation of leucocyte (inflammatory cells). Remember that the hundreds of billions of brain cells (neurons, glial cells) are in intimate contact with thousands of miles of tiny blood vessels, smaller even than capillaries. This huge network of microscopic-sized blood vessels has to nourish every single brain cell, deliver oxygen and nutrients to it and take away toxins from it. On the other hand, the ceaseless bio-exchanges between neurons and the microscopic blood vessels in the brain deliver toxic, oxidized pro-inflammatory molecules and blood factors, including platelet factors and pro-coagulant glycoproteins, such as ultra large Von Willebrand's antigen, into the outer cover of the neurons. Here, in the complex phospholipids cover, all of the molecules and glycoproteins begin the steady destruction of brain cells and the formation of Alzheimer's proteins. Likewise, the same elements in the blood vessels can trigger microclots and microhemorrhage which also destroy brain cells and increase the abnormal protein burden.

"Fat", the Necessary Enemy. The Lipoproteins (LP) are essential components of all cells, delivering lipids, cholesterol and triglycerides. Lipoproteins vary from very low density molecules, VLDL, to high-density HDL. In addition to their essential physiological role they can be markers (causes?) for vascular diseases and stroke, heart attack, and Alzheimer's disease. One class of lipoprotein, however, is protective of these events. This is the HDL molecule and at levels above 60 the incidence of arterial plaque and heart attacks drops (50% for heart attacks and 20% for strokes), plus reductions in sudden cardiac death and peripheral vascular disease.

Independent of its protection against atheromas HDL is a remarkably good marker for longevity. HDL levels of 60 or more correlate very well with life expectancy into the 80s. HDL levels of 60-70 likewise are protective against brain degeneration and Alzheimer's disease. This is not to say that HDL is the definitive "fountain of youth" molecule, but it does say that HDL marks for numerous positive factors which confer the benefit, be they anti-inflammatory, vascular stabilizers, or modifiers of immunologic triggers. The reduction in the number of patients with memory deficit at age 60-65 with HDL levels >70 might approach 50%, irrespective of LDL, triglyceride or cholesterol levels. A recent study

showed that the protective effect of high HDL is good enough to offset the effects of the Apoe4 Allele which is a marker for early Alzheimer's disease.

Cholesterol is the most essential "fat" as it makes up half of the brain and all of the wiring in the nervous system. Cholesterol also serves as the precursor for various steroids produced in the adrenal glands, including cortisol, the major stress hormone in the body, and progesterone, a major sex steroid. Early in the cortisol path pregnenolone is produced, itself a precursor to the other steroids. Just as importantly, pregnenolone is a parent molecule to a number of other related steroids produced in the brain, neurosteroids.

The neurosteroids are essential regulators of the major inhibitory neurotransmitter in the brain, gamma-aminobutyric acid (GABA). GABA receptors key the neuronal synapses to slow down the pace of neurotransmitter release and uptake, so in one sense GABA calms the brain, as is well demonstrated by the effectiveness of $GABA_A$ receptors in keying various benzodiazepines such as Ativan, Valium, Xanax and Clonazepam, all of which soften anxiety ($GABA_{A2}$ receptors) and induce sleep ($GABA_{A1}$ receptors).

$GABA_{A2}$ is the major GABA receptor among hippocampal neurons, the site where immediate encoding of new memory first takes place. The role of N-methyl diethyl aspartase, or NMDA, which yields glutamate, the most active excitatory neurotransmitter in the brain, is also needed for long term potentiation or more sustained depolarization and synaptic release to "hold" memories. In any case, both GABA and NMDA glutamate are affected early in Alzheimer's disease, especially in the hippocampus, and the drug Memantine (Namenda) is used to increase local glutamate to offset memory loss and, paradoxically, agitation.

Neurosteroids can act as anxidytics (control anxiety) and as sedatives, even as antiseizure drugs, in relation to GABA effects, so that disruption of normal neurosteroid function, as in inflammatory and oxidatie stress, can be significant factors in the "collateral damage" from amyloid plaque and tau tangles in Alzheimer's disease.

The interplay of neurosteroids, neurotransmitters and neurons and glial cells in relation to inflammation and lipid peroxidation lead us back to a very important message regarding aggressive lowering cholesterol to prevent heart disease. First of all, it doesn't; secondly, over the long term the brain may pay an unknown price in defense of the heart. This is why our discussion of lipoprotein classification is so important, because LDL cholesterol lowering has to be more target specific, not every elevated LDL presents the same risk, or any risk.

Remember, when we move one piece on the biological chessboard, the whole board moves. Nothing is treated in isolation of any other parts, and adverse effects of treatment may be discovered long after treatment had taken place.

Arachidonic Acid is another fat related molecule, a product of the action of phospholipase A_2 ($PPLA_2$) on precursor lipids. Arachidonic acid then moves through two pathways, one via cyclooxygenase (COX_1, COX_2) to produce various prostaglandins, including prostacyclin, a vasodilator and platelet inhibitor. An alternate cox pathway yields thromboxane, a vasoconstrictor and platelet aggregator. At low doses aspirin promotes prostacyclin, at higher doses thromboxane.

Arachidonic Acid (AA) can also move through the lipo-oxygenase pathway to yield leukotrienes, which are pro-inflammatory and mediate allergic reactions, including bronchial (airway) swelling and edema.

Likewise, AA can yield various prostaglandins which have diverse actions in the body, some protective and some proinflammatory. A subset, named isoprostanes, are markers for inflammation and cell damage. Isoprostrine F4 interacts with DHA, a neuroprotective omega 3 fatty acid. F4 can oxidize DHA just as lipoprotein LDL can be oxidized/peroxidized to cause major damage to neurons and glial cells, a pathway to Alzheimer's disease, along with many other inflammatory and oxidative reactions. F4 is identified as a neuroprostane to distinguish it from F2 isoprostanes, which are linked to coronary artery plaque, again, along with oxidized LDL, and homocysteine derivatives, to name a few of the major culprits, all of which are factors in the aging process as well, via actions both related to specific vascular and neuronal damage as well as stealth activities on cells that drive aging independent of disease connections.

LDL is a major lipoprotein in atherosclerosis, heart attack and stroke, injury to neurons and dementia – Alzheimer's disease. LDL is bound to virtually every cell in the body at the LDL receptor sites. LDL is particularly sensitive to abnormal glycation or oxidation, especially in the setting of elevated glucose. The LDL membrane itself is rich in phophotidylcholine, an essential molecule for health which can be oxidized to lysophosphotidylcholine, an extremely pro-inflammatory agent and cell toxin. This is especially dangerous with LDL in relation to the vascular endothelial cell and the initiation of inflammatory arterial plaque leading to heart attack or stroke, and perhaps inflammatory changes in neurons as part of the events that lead to Beta Amyloid production. It appears that LDL small particle size and increased LDL numbers facilitate this.

We know that LDL isoforms have a number of complex reactions which are pro-inflammatory and cell toxic. At the neuronal LDL receptor site Apoe4, which is secreted by glial cells, will attach and can initiate abnormal protein formation which is cell toxic. Lipoprotein "little a" (LP_a) can complex with LDL promoting peroxidation, oxidized LDL then toxifying the neuronal phospholipids cover. Likewise, LDL interaction with lipoprotein lipases ($LpPLA_2$) yields lysophosphotidylcholine (LP_c) and nonesterified fatty acids; both are cell toxic and pro-inflammatory. Literally hundreds of other glycoproteins and lipid metabolic products are at play, driving both inflammation and epigenetic changes which will promote the deposition of amyloid, including AB_{1-42}. (See page 40-44)

Homocysteine and its metabolites and Apo and Lipoproteins contribute as well, and these and the other molecules we mentioned seem to work in the same deleterious fashion in the coronary artery plaque and the neuron-glial cell axis. This is why LDL is a critical molecule and LDL "management," including reduction of LDL species and down-regulation of inflammatory LDL itself, is so essential, especially LDL III_a, III_b and IV_a.

As it is likely that our baseline (childhood) LDL levels are somewhere in the 30-40 range and that environmental, dietary, lifestyle and epigenetic modifiers help push the levels increasingly higher, lowering bad LDL's appropriate, with the understanding that we have no way of modifying the genetics of LDL and HDL, likewise no way to directly modify corresponding Apoproteins.

The Apoproteins (AP) are protein covers around the Lipoproteins which promote cellular adhesion and penetration. The APs, like their companion LPs, are essential physiologic molecules, either protective (e.g., ApoA1) or aversive (e.g., ApoB100) in concert with their paired lipids; ApoB100 and LDL or ApoA1 and HDL. ApoA1 comprises about 70% of HDL and the higher the levels of ApoA1, the higher the HDL level with the corresponding protection against vascular events. In fact, mice bioengineered to make ApoA1 are resistant to atherosclerosis.

Elevated ApoB100 and Apoe 4 promote premature vascular disease. The ApoB100 effects involve multiple pathways but one of the most important for vascular disease, strokes, and heart attacks is its promoter effect on LDL. ApoB100 binds to aggressive inflammatory cells, loading them with lipid to make foam cells, a major part of the lipid core of vascular plaque and an initiator of inflammatory plaque. The breakdown of the plaque cover and release of the lipid core then causes local and remote clotting leading to heart attacks and sudden death, strokes, microemboli and microhemorrhages in the brain and

other insults to smaller brain blood vessels – all of which are factors in Alzheimer's disease.

The role of ApoE isoforms in glial cell damage in the Alzheimer's diseased brain is of interest as glial cells have major functions as support (astrocytes), lining (ependymal cells), so called scavenger cells (microglial cells) and oligodendrocyes which form the myelin sheath that covers nerve cells. Recent research has indicated that glial cells have some role in memory signaling as well. The deposition of Beta Amyloid affects all of these cells as well as the neurons.

Blood, Clotting and Inflammation. The molecules and inflammatory proteins we have just looked at are all circulating factors which then either target inflammatory sites or move into them to push the toxic cascade further. But what about blood itself, does blood present its own risks? The answer is yes. Blood elements play a role in at least three ways; abnormal blood clotting, increased sticky platelets, or increased blood viscosity (shearing force, turbulence, flow rate, and the lumping and layering of the red cells). Thick blood threatens every organ and promotes the formation of toxic proteins in the brain.

Abnormal clotting is determined either by mutations in normal factors or the introduction of abnormal procoagulants. Aside from these is the naturally occurring homocysteine which, when elevated, is a major risk factor for arterial clots anywhere in the body, and possibly premature aging and dementia (Alzheimer's disease).

The most common pro-coagulants are the antiphospholipid antibodies and the lupus anticoagulant. These present a real risk for arterial thrombosis and they also have the paradoxical property of prolonging the laboratory measures for clotting (P.T., P.T.T.) suggesting that the risk is for increased bleeding when, in fact, it is for increased clotting. The case for the various genetic mutations is clear for clotting in the venous system but less so for the arterial side, although Factor V and P20210A variants may present arterial risk along with decreased Protein C or Protein S. Elevated Factor VII is likewise a stroke risk, as is an increased level of plasminogen activator Inhibitor (PAI) and increased levels of Von Willebrand's antigen and its interaction with platelets. The platelet effect is well known, as millions of patients use antiplatelet drugs, especially aspirin, every day to prevent platelets from sticking together and initiating a "white thrombus".

Blood Viscosity is the third element, causing perturbations in flow and slowing the movement of the blood making it more like sludge. Abnormally heavy proteins in the blood can also slow the blood but

this is much less common than the elevated hematocrit (measure of the thickness of the blood, of its red cell mass). We know that the higher the hematocrit the greater the viscosity. This not only slows the flow of the blood but actually deforms the shape of the red cells which become more flattened. These altered cells are particularly susceptible to turbulence and clot initiation in the brain and coronary arteries at sites of vascular narrowing or branching. Increased viscosity and the morphologic changes in the red cells have the net effect of decreasing oxygen delivery to vital organs, which adds to the risk for heart attack, stroke, and neuronal damage.

In the 1950s and 1960s epidemiologists studying heart disease risk, especially cholesterol, found incidentally that elevated hematocrit (over 45) was an independent risk for heart attack. Doctors were familiar with the risk of very high hematocrits (54-55 or higher) but few of them even today know that normally accepted hematocrits (45-50) also present a risk for heart attack and stroke, brain microhemorrhage, and hypoxic neuronal damage which can promote dementia. Interestingly, we have learned that patients whose hematocrits have fallen even as low as the low- to mid-20s can tolerate this dilution of their blood but are then put at risk for increased clotting when their hematocrits are raised above 31-33 (lower levels than we normally have by 25%). Even so, these lower HCT levels represent values closer to what some researchers would consider a "settled optimum" of 35-37 in terms of best viscosity.

The significance of all these, procoagulants, genetic variations and viscosity, for stroke, heart attacks and multiple smaller micro-vascular insults to the brain and dementia and Alzheimer's disease is very real and must be incorporated into a holistic prevention program.

Starch and Protein – Substrates of All Cells. The glycosaminoglycans (GAGS) cover LPs and virtually all other cell membranes. GAGS are chains of carbohydrates of varying lengths which are integral to cellular function, cell wall integrity and extra cellular matrix, and to proteins where they attach as polysaccharide multiples to give structure and function as well as substrates for breakdown or degradation by enzymes.

GAGS are very important in inflammation, cell death, and abnormal protein production, all of which contribute to Alzheimer's disease. Glycoprotein interactions can generate inflammatory cytokines which then recruit cellular and humoral immune responses. There is a great deal of interest in supplemental intake of GAGS to offset the effect of highly refined, poor quality carbohydrates diets for ongoing maintenance of these integrated immune functions. Likewise, proper GAG function and

stabilization may be directly related to metabolic degradation of glucose and overall cell metabolism, whereas, the adverse impact of "industrial strength" processed foods can be offset by adequate GAG function-supplement to modify glycation (glucose-protein binding).

GAGS have a large role in the biology of degenerative brain disease and Alzheimer's disease, and prion formation. Prions are degenerated glycoproteins which invade and kill brain cells in like manner as the effects of Amyloid and Tau protein in Alzheimer's disease. Indeed, prion proteins are directly amyloidogenic! One approach to Alzheimer's disease might be the use of molecules which mimic GAG function and then bind them to antibodies to inhibit NF tangle formation in Alzheimer's disease. In fact, sulfated GAGS drive the formation of Tau to helicial filament forms, promoted by RNA proteins and Arachidonic acid (a suspect molecule in ND disease). In addition to abnormal glycation, Tau becomes hyperphosphorylated (and insoluble) and highly neurotoxic, not only in Alzheimer's disease but in most of the ND diseases which are protein configuration diseases.

The Aging Cell – What Happens? It is necessary to look at Alzheimer's disease in relation to cell senescence and biological aging even though the physiology of aging and the extreme variations in aging rates are poorly understood. We know that cellular aging has a strong genetic base, but is also driven or modified by stem cell-progenitor cell kinetics, tumor markers such as BCL-2 (B cell lymphoma) which inhibits apoptosis, cell death, and tumor suppressor genes, of which p53 and INK4 are noteworthy. Telomere length, the stop code ends of DNA pieces, as well as the telomerase enzyme which can lengthen the telomeres or bridge DNA stops, are likewise of great importance.

Telomere Units are amino acid sequences, TTAGGG repeats, attached to DNA as integral multiples. The shorter the telomere length, or the greater the structural alterations, the shorter the life of the cell (measured by number of replications). Telomere length is set very early in embryogenesis and shortens infinitesimally over the decades of cellular multiplications until the shortened telomeres in a cell signal its approaching death. This does not mean that telomere length over time determines longevity, but it does mean that telomere length is a critical measure and the factors that lengthen them or shorten them will mark out our years.

The tumor suppressor gene, p53, is an important vector here as it drives stem cell kinetics in favor of progenitor cells and cellular maturation to the specific mature cells for the specific tissues. p53 is also a built-in system for senescence as cell death (measured from the original stem cell – Progenitor cell) occurs after 40-50 replications. Increased p53 activity in

favor of this pattern of differention – maturation – terminal division can be signaled by telomere shortening as well as by DNA Oxidative damage. On the other hand, tissue injury slows down p53 which favors stem cell replications without further differentiation. This forms a larger pool of cells which will then assist tissue repair.

Telomere shortening switches on p53 which is cancer protective but cell aging. Likewise, upregulation of INK4 – retinoblastoma protein, and bcL-2 and other protein modifiers connect back to gene imprinting, epigenetic reprogramming, DNA breaks and repair failure. All of these are susceptible to toxic, environmental, atmospheric and nutritional-oxidative inputs which can cause epigenetic dysregulation, and disruption of DNA repair and other cellular protections against the countless mutational threats which occur daily. These are estimated to occur at reprogramming (methylation) frequencies at least 100 to 1000x greater than single nucleotide (gene) polymorphisms (SNPs), the most common DNA replication errors.

Somatic cell lineages typically burn out after 40-50 replication events by simple cell senescence. The cells get older and less vital. Keep in mind that through the preceding cell divisions, the mother cells actually do not die, rather they decompose vitally, meaning that their "cell stuff" is transmitted live to the daughter cells.

In programmed cell death, apoptosis, the cell shrivels and its nuclear material fragments and is swept away by lysosomes. In cell necrosis, the cell is killed directly by biological virulence, viruses being the most common agents. Inflammatory cells can gobble up cells as well. In any case, the drop off in stem cell renewal and terminal differentiation after 40-50 cell replications connect cell aging to degenerative diseases, especially in the brain where aging neurons are much more at risk for pathologic protein. Curiously, Tau protein, and possibly Beta Amyloid, are neuroprotective at low levels and low levels of Tau and reversible Tau phosphorylation stop apoptosis in vitro. We also know that Alzheimer Precursor Protein is active in early embryogenesis to assist neuroplasticity when primitive neuronal cells are formed. This plasticity is much more active in the aging brain than previously thought and is maintained by neuronal differentiation, which allows the aging neurons to renew cell division cycles. It is also possible that mensenchymal cells migrate from bone marrow to brain and morph into neuronal cells, suggesting stem cell therapies might be useful.

There is the same evidence for more active neuroplasticity after brain injury, stroke and with NDs such as Parkinson's and Alzheimer's. In regard to the NDs, however, the enhanced activity of neuronal stem-pro-

genitor cells still presents its challenges for scientists to find key genes and proteins that will augment this. The other challenge will be identifying and interrupting pathways which promote abnormal protein accumulation. At least now there is hope that such a two-pronged attack will be effective clinically quite soon.

Stress – Everybody's Risk

The Stress Response is the sum of the physiologic and psychologic changes that occur in response to a physical threat or emotional "crisis." It is, in its totality, the most important global regulator of all physiological systems, including oxidation, inflammation and epigenetic dysregulation, the immune system and the cortisone and adrenalin systems, and the sympathetic nervous system, accelerating heart and respiratory rates and blood pressure. Unfortunately, along with mounting this primitive defense the stress response floods the heart and the brain with hormones and cytokines that do acute damage to these target organs. With chronic stress there is system-wide damage which can kill suddenly or wear us down over time, accelerating our biological aging and weakening our resistance to infection, disease (including cancer) and our psychic coping mechanisms. The sustained activation of molecules, hormones and proteins that attack the vascular system, heart, and brain also promote perineuronal changes (vascular, immune, epigenetic, inflammatory, etc.) which predispose us to dementia and Alzheimer's disease.

We know that major life stressors such as the loss of a loved one, financial losses, and especially long-term anger or unhappiness, can aggravate memory and cognitive functions in patients who have early signs of Alzheimer's disease. In fact, recent studies demonstrate that sustained elevations of cortisone, even levels only slightly above normal, can cause shrinkage in the hippocampus, an important memory center characteristically damaged in Alzheimer's disease. The sustained elevations of cortisone also increase resistance to insulin. Brain sugar rises and this presents its own Alzheimer's disease risk over time.

Stress and Your Bioclock. One of the main systemic effects of stress is its effect on our biological clock, factory set for release of multiple hormones and bioactive molecules related to an ultra-sensitive light-dark sensor-transducer system in the brain auto-regulating multiple neurotransmitters, brain and gut secretagogues, and hormone release. This 24 hour, circadian, rhythm regulates development, fertility and reproduction, resistance and immunity, cognition and memory, and internal regulation of the organ systems. The incredibly complex transducer function is the Zeitgeber, the timekeeper of the human machine, a uni-

versal pattern of synchronized signaling which is essential to life. This system is extremely sensitive to diseases and to disorders of the clock itself, especially in the sleep-wake cycle and those critical eight hours lived in a non-conscious state which determines the functionality of all of our conscious life. Disturbed sleep disrupts the clock, the dysregulated clock harms brain and body.

Our knowledge of the Zeitgeber has increased considerably with the understanding of hormone release and the "hardwire" electrical connection between the brain trigger and the heart target and gut function. We know that clock-time stress, including shift worker stress, especially when day-night shifts are regularly shifted, and the stress of sudden sleep interruption as part of the job description for cops, doctors, firemen, EMTs, military personnel, are particularly dangerous. Likewise, many systemic diseases affect the internal clock, especially heart and lung disease, chronic pain and dementia. Sleep disorders, likewise, disrupt the signaling our circadian (24-hour) cycled rhythms.

The medical implications of disrupted sleep-circadian cycle capture every disease, as well as responses to treatment. Perhaps this is most dramatically demonstrated in sudden cardiac death, especially with the combination of intense psychological stress, sleep dysrhythmia and circadian dysregulation (see Figure III). Sudden cardiac death risk is magnified by sleep deprivation or REM sleep disorders, or sleep apnea perhaps the single most damaging sleep disorder. The combination of daytime stress and nighttime bioclock disturbance may be the most important cause of sudden cardiac death in otherwise healthy patients, far outweighing the usual list of risk factors. We will review this in our section on Stress Management.

Stress strikes brain cells with severity. We know that sustained psychological stress and circadian rhythm dysregulation can turn on the brain itself, so that the trigger organ becomes its own target, both brain and psyche. Mood disorders are extremely common early on, and in time they can become much more severe and difficult to treat, sometimes to a paralyzing degree. Victims can snap and act out extremely violent impulses. There are, likewise, long-term effects on memory and cognition. We are not saying this is directly causal of dementia or Alzheimer's disease, but we know from our research in the dementias that stressors and circadian dysregulation are part of the background substrates for toxic and inflammatory damage to brain cells. This, of course, is separate from the short-term effect of stress and sleep disturbances on memory and cognition which is much more likely due to altered neurotransmitter function and hormonal release than to inflammatory-toxic

effects on neurons and deeper brain centers. It is both the sustained effects of inflammatory molecules and cortisol, glucose, and lipid oxidation that begin to damage neurons, as well as the "secondary effects" of hypertension, diabetes and changes in the smaller brain blood vessel and clotting elements. All of these bring a spectrum of neuronal death from "normal" aging to accelerated aging and cognitive and memory deficits to full dementia.

Sleep Deprivation is often unrecognized by its victims. Obstructive sleep apnea, once thought to be uncommon, is very common and often overlooked because the frequent long pauses in breathing, 30-60 seconds, occur while the subject is sleeping. Sometimes the pauses awaken them with vivid dreams, choking sensation or rapid heartbeats, but the real danger is when the subjects are not awakened and continue to live with daytime fatigue, hypertension, cardiac arrhythmia and long-term effects on work performance, memory and cognition. Sleep apnea is sleep deprivation independent of the stress sleep disorder, but it can still effect circadian function significantly and impact basic neuro-circulatory functions, and accelerate biological aging as well as multiple disease risk, including cognitive decline and stroke.

There are, as well, a small number of tragic cases of Fatal Familial Insomnia, a genetic disorder which leaves its victims with gradual to complete extinction of normal sleep. With onset of symptoms, physical and psychological declines accelerate and death occurs within 6-12 months. There is progressive dysautonomia affecting heart rhythms and blood pressure and central nervous system functions to such an extent that it might well be called fatal familial dysautonomia as well.

Hypersomnia is excessive sleep, the exception to decreasing sleep requirements, as hypersomnia most often suggests an underlying metabolic (e.g., thyroid) or functional (e.g., heart failure) disorder. It is also a hallmark of advancing dementia and progressive neuronal death. Typically Alzheimer's patients will sleep quite well at night and then begin requiring one or two naps a day, morning and afternoon. By the time the disease is in an advanced state, patients can be sleeping a total of 14-16 hours a day. Obviously we distinguish them from another group of patients who shift their sleep cycle dramatically over time, staying awake (and often busy) most of the night, then falling asleep around dawn or an hour or so earlier. Our own experience suggests that many of them fell into that pattern because of a combination of factors, including alcohol and depression, not realizing that alcohol is a major disrupter of the normal sleep cycle. Often this is aggravated by the addition of sleepers and sedatives which further disorganize sleep and circadian cycle.

One patient, a psychoanalyst of great talent, found herself in her sixties living and working a complete light-dark shift, seeing patients in her home from 6pm to 2am, then reading, dining, and finishing her notes until 7am or 8am, then sleeping 4-5 hours. She is a recovered alcoholic, a chain smoker and a manifestly obsessive individual who either reset her biorhythms to meet deeper needs or completely lost control of them. Interestingly, the last three days of her life she almost never slept, only occasionally closing her eyes for 5-10 minutes – simply as the maximum expression of her completely pathological sleep habits.

Summary

Earlier we cited studies of longevity, lifestyle and prevention but now an ongoing study of several hundred descendants of eastern European Jews suggests something else. Many of their descendants made it to their 10th or 11th decade despite high fat diets, smoking, stress and little exercise. The one thing that was common to them was the longevity of their ancestors who passed on good genes and biomarkers for "Super Aging" getting their children and grandchildren to 100 or greater relatively disease free. Scientists want to know how the rest of us can get there! Any positive change in lifestyle is good, but maybe just not good enough. As the lead investigator noted "healthy living can get you past 80, but not to 100." In the meantime, let's see how we can at least make 80.

QUESTIONS *(circle one or more where appropriate):*

1. Alzheimer's disease relates to:
   a. Protein plaque
   b. Inflammation
   c. Oxidation
2. Alzheimer's disease is more common if you have:
   a. Diabetes
   b. Hypertension
   c. Anemia
3. Suspect proteins include:
   a. Tau
   b. Myosin
   c. Beta amyloid
4. Epigenetics resets:
   a. Genes
   b. Blood pressure
   c. Protein formation
5. Patients with premature aging diseases always have Alzheimer's disease:
   ❑ True ❑ False
6. Biological aging:
   a. is individual
   b. can be slowed down
   c. is genetic
7. Homocysteines cause:
   a. Inflammation
   b. Blood clots
   c. B_{12} deficiency

8. The brain is _____ fat.
    a. 10%
    b. 30%
    c. 50%
9. Thick blood can lead to:
    a. Stroke
    b. Heart Attack
    c. Dementia
10. Normal aging has:
    a. Increased arthritis
    b. Hardening of the arteries
    c. Changes in memory
11. The Circadian Rhythms are:
    a. Day/Night
    b. Light/Dark
    c. High/Low
12. Circadian Rhythms control:
    a. Hormones
    b. Immunity
    c. Blood Pressure
13. Body cells normally divide:
    a. 10xs
    b. 30xs
    c. 50xs
14. Telomeres may control aging:
    ❑ True ❑ False
15. Aging brain cells are different from Alzheimer's brain cells:
    ❑ True ❑ False

16. Fat oxidation can cause:
    a. Heart Disease
    b. Stroke
    c. Neuron Damage
17. Normal fat and cholesterol levels mean no Alzheimer's disease:
    ❑ True ❑ False
18. Brain cells cannot multiply (reproduce themselves):
    ❑ True ❑ False

SECTION 2

The second part of this book breaks down the various interventions that you can perform to lower your risk for stroke, dementia and cardiovascular disease. All of these elements of preventive intervention play very important roles in preserving and improving brain health and extending the functional life of the cognitive brain – the brain functions that structure your personality and interpersonal relations. Brain health, in a word, is personal health. All other diseases or organ damage compromise specific physiological functions. Brain damage from stroke, and especially from dementia, take away you. Defend you and follow our program, the most detailed and science-based methods available to you.

PART I - COMPREHENSIVE LABORATORY EVALUATION

HCT Hematocrit – for blood viscosity

HGB Hemoglobin – for blood viscosity

Serum Iron, Ferritin – measures of inflammation

Platelet Count – platelets stick to arterial wall inner lining – the endothelium. This is promoted by Thromboxane A_2 and Von Willebrand Factor (Aspirin blocks platelet adhesion)

Aggregation – platelets clump together, promoted by Phospholipid llb/llla, ADP, and Fibrinogen (Plavix blocks platelet aggregation)

$LpPLA_2$ – Lipoprotein phospholipaseA_2—metabolizes phosphotidylcholine (PC) to highly inflammatory molecules, phosphotidylinositol (P.I.) and free fatty acids

Elevated $LpPLA_2$ is a bio-marker and is bioactive for increased vascular plaque instability. (Serum $LpPLA_2$ is an effective blood test for vascular plaque risk.) $LpPLA_2$ is also a major player in neuronal inflammation.

Lab Screen for Memory and Vascular Risk

Serum Iron, total Iron binding, Ferritin, Homocysteine, B3, B6, B12, (methylmalonic Acid), Apoe 2, 3, 4, ApoB100, TSH, DHEA, Testosterone, Zinc, Magnesium, VitD3, Folic Acid or Tetrahydrofolate, HDL, LDL isoforms, size and particle number.

*Iron is an essential element for neuron DNA synthesis and myelin formation but high levels of oxidized Iron increases Amyloid and oxidative stress to neurons

Legend: ↑ = increase/more
↓ = decrease/less

Apoproteins / Lipoproteins

Apo "little a"	
LP_a	–travels with ApoB100 on LDL, along with certain isoprostanes, with increased vascular risk. High level of Apo "little a", LP_a, is a major risk factor for cardiovascular and stroke events
Apo AI "Milano"	
"Apo AI M"	–highly protective subset of ApoAI. Gene therapy with ApoAI Milano cleans coronary plaque. *There is a study underway to see results of Infused Apo AI "M" to protect against CV event.
Apo AI, Apo AII	–cardiac, stroke, and memory protective. Travels with HDL (gene altered mice with high Apo AI have no atherosclerotic risk)
ApoB100	–increased vascular risk, travels with LDL, may be a better predictor of risk than LDL
ApoB48	–increased vascular risk
Apo CIII	–increased vascular risk
ApoE 2,3,4	–ApoE2 and ApoE3 may be brain protective. ApoE4 increases Frontotemporal Dementia, Primary Progressive Aphasia, Cerebral Amyloid Angiopathy and cardiovascular risk.
HDL	–↑; increased longevity, cardiac, stroke and dementia protection; HDLb2 most protective of 5 HDL species
LDL	↑ =increased risk for all of above, especially with Lipid peroxidation converting LDL into an inflammatory molecule (see LpPLA & Isoprostanes) – LDL IIIa, IIIb, IVb highest risk of 7 LDL species. Small LDL and ↑ LDL numbers is ↑ risk for cardiovascular disease
VLDL	↑ =increase risk for cardiovascular disease
Total Cholesterol (TC)	
T.C. ↑ ↓	–increased risk – normal levels of TC are essential for brain and nervous tissue and all somatic cell

	structure and function. Relation to HDL and to LDL number and size important.
Triglycerides (TRI)	–increased risk – vascular, proinflammatory. High TRI associated with ↑ LDL particules, and small LDLs – both linked to ↑ cardiovascular disease risk.
Isoprostanes ISOPs	–markers (mediators?) for oxidative stress – Lipid peroxidation, inflammation, ISOPs increase as free radical formation increases. F2 ISOPs – good predictors of vascular plaque and neuron damage – increased ISOPA2 anal ISOPJ2 cause Apoptosis and cellular degeneration (in somatic tissues they may be anti-inflammatory). ISOPs may be measured in urine, plasma or CSF
*Omega 3 Eicosapentaenoic Acid (EPA)	–reduces inflammatory effect of F2ISOPs on neurons. In the brain ISOPs are neuroprostanes, a subset of which also are potent anti-inflammatory agents. Can be measured in blood, CSF
Docosapentaenoic Acid (DHA)	–may be more neuro-protective whereas EPA may have the edge in coronary artery protection. Can be measured in blood, CSF
Blood glucose levels	(especially to check extreme hypoglycemia) Hgb A,C = 3 months "memory" for blood glucose average. Urine – prealbumin and albumin.
Serum creatinine	–assessment of kidney function, along with the creatinine clearance and urinary albumin and microalbumins.
Clotting Risk	Thrombophilia panel – especially if family or personal history of clots anywhere, artery or vein Factor Assays (may generate arterial clots as well) 1. Factor V Leiden variant; Protein C, S deficiency (usually venous clots) 2. prothrombin 20210 A variant and MTHFR (methyltetrahydrofolate reductase) mutations, MTHFRC677T and A1298C

3. Antithrombin III deficiency
4. Homocysteine
5. Anticardiolipin Antibodies (measure both IGG and IGM, may be transient)
6. Antiphospholipid Antibodies (measure both IGG and IGM: may be transient elevations with infection or stress)
7. ↑ Plasminogen Activator Inhibitor
8. ↑ Factor VII
9. ↑ Von Willebrand Factor ($_{V}WF_{ag}$)
10. ↑ Fibrinogen
11. HR2 Haplotype
12. D dimer: (venous) thrombosis marker and acute phase inflammatory marker
13. Beta 2 GPIAb: $I_{G}G$, $I_{G}M$

The VonWillebrand Factor, vWFg; and glycoproteins GP1a, b, IIa, III, and GPVI are linked to initial adhesion (attachment) of platelet to endothelial cells in arteries (heart and brain especially). This adhesion is also promoted by thrombin and fibrinogen and other cofactors. These also drive the second phase, platelet aggregation, where the platelets clump together and release their own factors as well to initiate the third phase. The third phase clots the blood by two pathways which bring the various blood factors into the mix to form a thrombus, "the clot".

Likewise, many of the platelet factors, vWFg, and the glycoproteins initiate inflammatory changes in lipid rich areas, including the neuron. This is only one way in which clotting and inflammatory pathways are linked, a link well serviced by homocysteine and its relatives, which may turn out to be as an important step in neuronal damage as it is in stroke and heart attack.

Hormones

DHEA	–low, decreased memory and possible relation to heart disease
Testosterone	–low, decreased memory, cognitive impairment
Growth Hormone	–low, decreased memory, cognitive impairment
T4	–low or TSH – high – dementia, heart disease *New guidelines set TSH range at .3-3.00
↓Vit D3	↓cognitive function

Inflammatory Battery

- Measures acute phase reactants to injury or inflammation anywhere in the body: Several new assays; hs CRP, $LpPLA_2$, SAA/ HDL_2 for cardiovascular or stroke risk.
- Increased Lipoprotein phospholipase A2 Assay ($LpPLA_2$) – For vascular plaque risk and neuron damage
- Increased High Sens CRP – Vascular Plaque risk, coronary artery lipid core
- Increased D – dimer for CV and stroke risk
- Increased Fibrinogen – aggregates platelets, promotes clotting, elevates SED rate
- Increased Systemic Amyloid – (acute inflammatory Amyloid) a measure of acute or chronic inflammation)
- Increased F2 Isoprostanes – marker for vascular plaque inflammation and neuron damage

Optional: –costly testing (usually in research setting)

–CD 40 Ligand

–Homocysteic Acid

–S-Adenosylmethionine (SAM) – promote clotting and Inflammation

–S-Adensodylhomocysteine (SAH) – Inflammatory plaque in arteries, Amyloid plaque in brain

–Inflammatory Cytokines IL_1, IL_6 Leptin

–Metalloproteinases MMP 2, 3, 9

–Vascular endothelial growth factor (VEGF)

–Platelet derived growth factor (PDGF)

–ILA – Insulin Like Activity

–TNFα–Tumor Necrosis Factor

*Virtually all the biomarkers are bioactive. Studies suggest that inflammation, lipid peroxidation and oxidative stress work as a unit as a major final pathway for coronary and carotid artery lesions and brain cell (neuron glial cell) damage.

AMYLOID, INFLAMMATION AND COGNITIVE DECLINE

Amyloid species, including AB_{1-42} and other oligomers, are pro-inflammatory and attack glial cells, synapses and monocytes as well as the neuron. AB species ↑ IL_{1a} IL_{b} IL_{6}, TNF as well as reactive oxygen species (free radicals). ↑ glucose (diabetes and derangement of intracellular neuronal metabolism) also react with amyloid and make it more inflammatory. The defects in glucose metabolism in neurons also down regulate genes that control the various metabolic cycles for cell energy aggravating (causing?) Alzheimer's disease.

Gene defects for Presenilin family and Secretase family of genes, as well as multiple genes for metabolic pathways in the neuron, are abnormal in many patients with Alzheimer's disease and some other dementias. We do not yet know if the genetic changes reset the brain proteins negatively and cause the declines or if inflammation/oxidation and free radicals reset genomic expression by effects on DNA methylation and histone acetylation.* Either way, gene therapies are not an option (yet) but aggressive management of inflammation, including more precise identification of "critical levels" of multiple inflammatory biomarkers and bioactive molecule is possible. This is a primary thrust of the work in the *Brain Health Institute*, both as "ahead of the curve" clinical management, and the clinical application of molecular databases identified in clinical research. (See Figure I, II and page xxv)

*Recent identification of genetic marker for Homocysteine (Hcy), e.g., and a study of over 50 genes coding for Krebs cycle, oxidative phosphorylation, etc. in mitochondria. No gene therapies available but treatment of inflammatory pathways can be effective.

ANTI-INFLAMMATORY THERAPIES

Statins	Lower AB_{1-42}, expression of $IL_{1}B$ and IL_{6}, N.O. Synthetase and reduces isoprenyl intermediates of cholesterol synthesis, all of this lowers inflammation at neurons.
Olive Oil Extra Virgin Cold Press	Oleocanthal reduces the reaction of AD species especially at synaptic clefts. This effect on amyloid oligomers including AB_{1-42} can intercept a crucial step in early AD progression.

OM3FAs (Omega 3 Fatty Acids)	Product of α–Linolenic (N-3) Acid metabolism, EPA and DHA lower inflammatory cell adhesion, platelet adhesion, Thromboxane A_2 ($TBXa_{2)}$ and Von Willebrand Factor, and reduces Insulin resistance via multiple peroxisomal proliferation receptors (PPARs). (This is considered to be the main action of the sirtuin resveratrol (Longevinex™)) as well. DHA and EPA are endothelial relaxers (DHA more so) whereas DHA may be more neuroprotective. Both lower F2 – Isoprostanes which are excellent biomarkers of systemic oxidative stress. OM3FA also increases BDNF (Brain derived neutropic factor, a cell "grower"). DHA protection of neurons may work decreasing neuronal zinc, hence inhibiting cell death. Recent research on telomere length and telomere indicate that the addition of OM3FA increases telomere length in leucocytes (↑ longevity) but shortens telomere length in tumor cells (↓ longevity).

The main sources of OM3FA are cold water fish especially wild salmon, herring, anchovies and sardines; also sheep and goat cheese, eggs from chickens fed plant sources high in OM3FA and supplements. Our experience with OM3FA supplements suggests that underdosing is significant. Most patients take 2 fish oil capsules a day. If these are 1200 mg capsules, then one is only getting 720 mg of DHA-EPA. We believe that optimum antiflammatory and antioxidant effects to be 2,000mg to 3,000mg of OM3FAs per day, requiring 6 to 8 1200mg capsules of fish oil in divided doses. Subjects allergic to fish can obtain their sources from nuts, cheeses, eggs (Eggland™) or Lovasa™ RX.

Bioflavonoids and Plant Cytosterols	The natural combinations of antioxidant molecules in berries, colored vegetables, some herbs (such as rosemary, curry, basil, etc.)

Various Vitamin And Mineral Supplements	Great variety of opinions on the best combinations and specific benefits. Few studies of appropriate size and duration are available. On the other hand, these should leave little doubt that dietary and nutritional prevention and supplementation over years and decades will be beneficial if taken in prudent dosages with medical supervision (see Section II, Paragraph E – More Supplements).

B6, B12 and Folate for Homocysteine

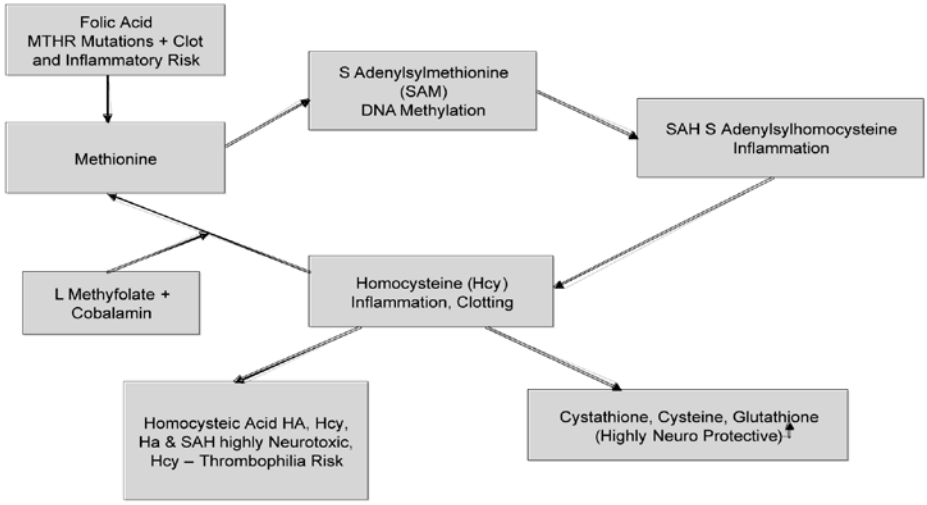
Homocysteine and its derivatives, including circulating SAH and Homocysteic Acid, are potent pro-inflammatory molecules. Folic Acid and B12 combinations are often used but may be ineffective in the presence of high oxidative stress, which blocks the conversion of folic acid to L-methylfolate (LMF) the active agent. Cyanocobalamin (B12) serves as cofactor for the action of "LMF" to generate methionine from homcysteine. If Homocysteine (Hcy) is not metabolized and levels increase, it is very pro-inflammatory, toxic to neurons and the endothelial lining of arteries. It also promotes accelerated clotting in the arterial system. In the neuron, Hcy raises oxidative stress, raises glutamate and promotes cell death, apoptosis. Hcy can directly induce increased levels of $AB_{1\text{-}42}$, as can homocysteic acid. Both molecules increase DNA breakage in the neuron and glial cells and promote increased neuro-fibrillary tangle formation. N-Acetylcysteine lowers the oxidative stress reaction between Hcy and $AB_{1\text{-}42}$ and is thus included in some formulations along with tetrahydrofolate and cobalamin.

Glutathione is noteworthy as the main cellular cleanser in the brain. Accordingly, some neutraceuticals include glutathione but adequate levels can be achieved with Alpha-Lipoic acid and N-acetylcysteine as well as milk thistle, broccoli sprouts, arugala, watercress, collards and red cabbage. Glutathione is the brain's most powerful antioxidant.

Other Nutrients and Dietary Elements for Brain Health

Resveratrol	– In the Sirtuin family, which stabilizes mitochondria, found in grapes, red wine, dark cherries: – Lowers glucose, increases Insulin receptor activity via peroximate proliferator protein

HOMOCYSTEINE FAMILY



Niacin (Vit B3) – precursor for major mitochondria energy via Nicotinamide Adenosine Dinucleotide NAD+ →NADH

N-Acetylcysteine – precursor to glutothione neuronal stabilizers, clears heavy metal

Mitochondrial Stabilizers

L. Carnitine, COQIO (ubiguinone family) for mitochondria energy production.

All B complex family: B_6, B_{12} and folate for homocysteine reduction

Curcumin – in curry and yellow mustards, green tea (plant phenols)

Inositol & Choline (B complex) – (choline precursor for all memory molecules)

–Eggs high in OM3FA – VITE Family

–Peanuts carotene, lycopene, etc.

–Lentils

–Flaxseed – VITA Family tocopherols

Citrulline Malate – removes ammonia radical

Glutothione and any "promoters" of same

Leucine, Isoleucine, Tyrosine, Valine and COQ10 stabilize mitochondria—recent study shows combinations of L-carnitine and αLipoic acid did the same, acting as mitochondrial antioxidants

Lemon extract or fresh lemon – extremely effective antioxidant and anti-inflammatory in brain health. Liminoids appear to be the active molecules, a family of natural antioxidants.

Vegetable and fruits – special mention of eggplant as a vegetable with very high levels of antioxidant activity

Omega Fatty Acids – effective anti-inflammatory agents at high doses (e.g., 3000mg EPA for neuronal protection, especially DHA

Vitamin E – in addition to alphatocopherol the other species of Vitamin E must be included for benefit. Rx with Vitamin E alphatocopherol only is inadequate

Aspirin and Nonsteroidal Anti-inflammatory (NSAID) – not proven for prevention of early Alzheimer's disease; however, aspirin is an essential part of any program for vascular protection and antiplatelet effect – both for stroke and "indirect" neuronal protection. Minimum of two 81mg tablets twice a day.

A Note on B_{12}:

As we age, or use certain medications, B_{12} absorption decreases. Likewise, some patients with B_{12} levels at the lower side of normal may actually be deficient, and have early Alzheimer's disease symptoms. We recommend that all patients with "low normal" B_{12} be treated. Low normal deficiency can be verified by high methylmalonic acid levels in blood, a precursor of B_{12}.

A Note on Folic Acid:

For patients with low folate levels and dementia, use L methyltetrahydrofolate as it crosses the blood brain barrier better than folic acid.

Always include pyridoxine (B_6) in treatment with B_{12} and folate.

QUESTIONS:

1. Platelets cause clots by:
    a. Sticking to arteries
    b. Sticking to each other
    c. Sticking to fat
2. High HDL cholesterol:
    a. Lowers heart attack risk
    b. Increases dementia risk
3. $ApoE_4$:
    a. Prevents Alzheimer's disease
    b. Increases the risk of Alzheimer's disease
    c. No effect
4. Arterial clotting can be caused by:
    a. Homocysteine
    b. Omega 3
    c. Fibrinogen
5. Memory problems can be due to:
    a. Low thyroid
    b. Low Vitamin D
    c. Low cholesterol
6. Omega 3 EPA:
    a. Protects the brain
    b. Lowers Inflammation
    c. is present in chicken fat
7. High blood counts can cause:
    a. Stroke
    b. Heart attack
    c. Alzheimer's disease

8. High homocysteine is corrected by:
   a. Folic acid
   b. B_{12}
   c. B_6
9. We can measure your Omega 3 in blood:
   ❑ True ❑ False
10. Isoprostanes are markers for:
    a. Oxidation
    b. Cell damage
    c. High protein

Self Assessments

We place great emphasis on your continuing self-assessment in coordination with programs at *Brain Health Institute*. Nothing is as reliable in terms of data-based medical evidence than your personal risk assessment, along with self-directed and physician-directed interventions (diet, exercise, antioxidant therapies, stress reduction and periodic check on risk factors) of most concern to you. In fact, periodic entries into your physician's medical records regarding your own comments, insights and life events are an essential part of your medical record. The controlling principle at our Center and the various programs we have designed is that "there are no diseases, only patients." Your medical story is part of your life story and is inseparable from it. We never divide the story; we are not reductionists, we are integrationists.

Blood Pressure (Hypertension) – perhaps the single most important self-monitoring anyone at any age should do is meticulous and faithful monitoring of blood pressure. If your blood pressures over a 24-hour cycle, the circadian cycle rhythm, are all normal, then periodic checks (every 3 months) are sufficient. We emphasize, you must first exclude circadian fluctuations in your blood pressure. For example, blood pressure and pulse can surge higher from 3-4am to 9-10am. This so called "dawn surge" is intensified by sleep disorders, obesity, intense dreams and wear off effect of antihypertensive medicines, mood stabilizers and pain medicines. The dream-related surges can be very intense especially with vivid or frightening dreams which occur in stage IV – V sleep cycling every 90-120 minutes, sometimes with marked blood pressure increases and very rapid pulse rates. This is complicated by irregular heart rate patterns in patients with sleep disorders, especially sleep apnea. Hypotensive (low blood pressure) events can also occur in patients with hypertension, those can be induced by the medications or be secondary to autonomic dysfunction or dehydration, which are extremely common in older patients. Hypotensive events, also called orthostatic when they occur upon sitting or standing, can lead to syncope (loss of consciousness) with severe head injuries or fractures, especially hip fractures. Therefore, you must check your own blood pressure sitting and standing, especially if you are on medications. The readings in the doctor's office are simply not accurate. Digital units are easy to use, accurate and cheap. We recommend at least 4 to 6 readings a day, lying and sitting and standing until you find your circadian trend. Plot these on a graph on your computer to keep a record of your trends, and the times in the day you may be too high or low. (See page 139)

1. Baseline – in bed or sitting upon first awakening

2. Mid-morning to mid-afternoon
3. Noon to mid-afternoon
4. Early evening
5. Bedtime

Blood Pressure Medications – There are a great number of blood pressure drugs available, many of them advertised as one a day drugs. Our experience does not confirm the claims for most of these. Patients metabolize drugs at different rates and the drugs themselves begin to decline in efficacy within 2-4 hours of dosing and may be only 40-60% effective at 12 hours and much lower at 24 hours. You must insist that your doctor monitor this with you and adjust the dose and dosing schedule according to your own blood pressure trends, the most important reason for you to monitor your blood pressure especially with the addition or withdrawal of a drug.

In any case, Hypertension remains an under-diagnosed risk for all of the medical problems we are discussing. If you refer to the section of "Stress and Cardiac Events" you will note the various pathways in and out of the brain that have blood pressure effects, signals from Hypothalamic centers and the brain stem to the blood vessels and heart relay raised blood pressure and increase heart rate, signaling which can be blocked by alpha blockers (particularly Prazosin which is highly lipophilic and thus penetrates the brain to reach alpha one ($\alpha 1$) centers in the brain centers and in the medulla to decrease outflow of alpha one ($\alpha 1$) signals, as well as inhibiting alpha one vasoconstriction on the arteries. Beta blockers in use for decades, block the other active receptor, the beta one receptor, to slow the heart and decrease blood pressure. Clonidine works by amplifying alpha two ($\alpha 2$) receptors in the solitary tract (NTS) in the brain stem which, via alpha two stimulation, feeds back signals from the heart and blood vessels to the brain center to "back off". The net effect is lowering of blood pressure. (See figure IV, V)

We mention these centers and drugs and emphasize again the importance of regular monitoring of your blood pressure, especially during the night, and in the early morning, especially 4:00a.m. to 6:00a.m. There are times when significant increases in blood pressure can occur, especially during REM sleep dreaming, which also raises the heart rate. Many patients with good daytime control of blood pressure have dangerously high early morning readings that need to be treated with the alpha one (block) and alpha two (promote) strategy as well as beta block to reduce the risk of stroke or heart attack.

You have to monitor this to find your particular pattern and then present the numbers to your doctor. Interestingly, for some patients dream anxiety and blood pressure changes can be related to daytime stress, in which case the addition of an anxiolytic (Ativan or Xanax) can effect a significant drop in blood pressure, as they promote the release of GABA, the major inhibitory neurotransmitter that calms us down. One caution here, this class of anxiolytics, the benzodiazepines, can cause significant chemical dependence (the brain needs more drug) which is different from addiction (you need more). In either case, this requires monitoring and if properly managed these drugs can be significant adjunct treatment in hypertensive care.

Global Rx for Blood Pressure Control

- Adjustment of single-does drugs to twice a day where appropriate
- Avoid generics or combinations when careful titration of drug doses is necessary, especially where there are wide daily swings in your blood pressure

Drug Classes

Diuretics	Very important initial management and as addition to other classes. Begin with HCTZ (Hydrochlorothiazide) 12.5 – 25mg a day, or Aldosterone antagonist – spironolactone. Very important to help reduce salt burden which is very heavy in processed foods, canned foods, most restaurant foods. Many of the other blood pressure classes of drugs increase salt retention as well, hence, the need for a diuretic with these.
Brain Blockers	Alpha2 Agonist (booster) cuts the output of brain signals that raise blood pressure (e.g., clonidine)
Arterial Blocker	Alpha1 blocker (e.g., prazosin)
ACE +ARB	Block angiotension or its receptor (e.g., ACE-Enalapril / ARB-Irbesartan)
Calcium Blocker	Increased calcium influx into blood vessel walls raises blood pressure
Beta Blockers	Reduce work of heart and abnormal heart beats, also work as chemical sympathetic block of neural triggers to heart (e.g. Metoprolol. propanolol)

Alpha and Beta Blocker Combination	Labetalol, Coreg
Direct Vasodilators	Very powerful for refractory cases to control blood pressure, high risk of orthostatic (e.g., Minoxidil)

*Renin levels (serum), NA, K, Mg levels baseline will help determine Rx.

Blood Sugar / Diabetic Care

Diabetic Management is similar to blood pressure management by measuring your finger stick blood sugars (FSBS) on a circadian cycle because a number of hormones and chemicals which affect your sugar have different peak set points (and lows) in the 24-hour cycle. Paired FSBS should be done fasting and somewhere between 60-90 minutes after a meal, 3-6 times a day initially to establish your trend, or whenever there is a change in your medication. The usual fasting blood profile ordered by your doctor is simply inadequate, paired fasting and post-meal readings are essential!

You must keep a chart, or plot curves on your computer for blood sugars and blood pressures. It is very important to identify low blood sugar readings (below 50-60). A severe hypoglycemic event to the brain is very damaging to neurons, and multiple events over time can be a greater risk for dementia than long standing elevations.

We are learning a great deal about glucose metabolism in the brain cell and the implications of early onset Alzheimer's disease or worsening of a mild cognitive defect. Obviously, the implications of untreated or poorly controlled hyperglycemia for the heart, brain and kidney is established. What is not yet settled is the magnitude of effect in prevention between good control and meticulous control. If meticulous control brings attendant increase in hypoglycemic events, one has to pull back on the levels of control to avoid dangerous drops in blood sugar which are extremely harmful to brain cells. Such damage might outweigh the otherwise clear benefit of good to very good (tight) control, even if it means allowing peak glucose levels of 180-220 more often to avoid drops to 40-50-60.

Interestingly, a recent research protocol has been designed to better stabilize neuronal glucose levels with the use of nasal inhalation Insulin. As Insulin does not easily cross the blood-brain barrier, brain

and spinal fluid glucose levels are dependent on peripheral Insulin dosing. We believe that glucose metabolism at the cellular level (neurons and glia) has major implications for dementia prevention and on the vascular side of the brain for micro-hemorrhages and small strokes. Likewise, neuronal insulin resistance has adverse effects on brain function and imposes statistically significant Alzheimer's Disease risk over time.

Sleep Assessment

We sleep one third of our life. We need to monitor that if there is any suspicion of a sleep disorder, especially often missed obtrusive sleep apnea. If there is a history of daytime fatigue, snoring, vivid dreaming especially with increased weight, history of HTN, diabetes, or abnormal heart rhythms, especially atrial fibrillation (AF), a sleep study is essential and may be life saving:

1. For Obstructive Sleep Apnea (OBS) - OBS increases risk for stroke, heart attack, AF, and cognitive declines. The cognitive decline can be substantial over time and lead to a diagnosis of early Alzheimer's disease.
2. For Rapid Eye Movement (REM) disorders — especially extreme dreaming, morning surges in blood pressure or heart irregularities.
3. For Parasomnias – Behavioral changes, either within sleep or upon awakening, usually related to non-REM sleep.

Note: Alcohol, caffeine and nicotine interfere with normal sleep, sometimes severely, as can some medications and medical disorders.

Patients with dementia can have interrupted night sleep with behavioral acting out and increased daytime sleep.

Dementia, Stroke and Cardiovascular Risk Assessment – include some or all of labs and screens mentioned. Individual risk assessment and testing assures you the most comprehensive evaluation available with individual risk management testing and preventive strategies. Special studies may be necessary including thorough evaluation of cardiovascular function and anatomy, carotid and intracranial blood flow, for more obscure causes of cardiovascular or metabolic disorder. Special neuro-imaging and spinal fluid studies may offer early and more accurate diagnosis of Alzheimer's disease. These studies must be individualized, appropriate to either risk level, symptoms, or "index of suspicion."

Stroke Risk Assessment

We emphasize again that all previous outlined risk factors and all preventive strategies (e.g., exercise, nutrition, stress management, etc.) have equal applicability to both Alzheimer's disease and stroke prevention, as well as cardiovascular protection and best-effort strategies for prolonging brain health and slowing aging to the extent that is possible.

Obviously, lipid disorders, hypertension, diabetes, and certain blood and clotting disorders are well identified risks. On the other hand there is considerable failure in ongoing measurement and early intervention. This is why we continually emphasize home monitoring of those variables that are easy to monitor and manage yourself.

Stroke prevention, likewise, demands the same diligence with the addition of several technical measurements that are very important in first event profiles. Carotid ultrasound is well known; however, specific measurements and interpretation are highly variable. Carotid artery assessment should include measurements of the thickness of the lining of the artery, internal thickness, and careful assessment of plaque burden in relation to certain ratios between areas of concern and carotid bulb measurements in relation to acceptable normal ratios.

Cardiac Ultrasound (see specific comments):

1. For increased left ventricle size
2. For evidence of long-term hypertension with increased wall thickness
3. For ejection fraction and assessment of decreased cardiac efficiency
4. For evaluation for dilated cardiomyopathy where weak heart muscle generate clots in the ventricle that can enter the general circulation, including the brain
5. Estimate of valve size and pressure gradient, especially mitral-valve for Atrial Fibrilation-related stroke and aortic valve for syncope (loss of consciousness) and coronary event

MRI: Useful for detecting clinically silent brain vascular event; thus leading to more aggressive prevention/intervention.

CT/MR"A": with contrast agent to assess carotid artery status more definitively. Also allows for visualization of entire anterior and posterior brain circulation although such studies are not usually necessary in routine clinical practice, they are essential for hemorrhage stroke risk from

aneurysms, malformed vessels or suspicion of blockage in vessels acceptable to stenting.

Atrial Fibrillation (AFib): The most common arrhythmia (AFib) can occur at any age and either in short bursts (paroxysmal AFib) or sustained over decades. It is a high risk arrhythmia for embolic stroke, small clots that form in the paralyzed left atrium in the heart to enter the general circulation, especially the arteries to the brain.

AFib should always be treated with anticoagulation, either the old standby Coumadin™ (no generics) or the newer direct thrombin inhibitor or activated factor X (Xa) inhibitor. The later two are much more convenient as they do not require periodic blood thinning measurement.

We are particularly concerned about stroke risk and consider several measurements and tests to be very important warning signs for AFib.

Cardiac Ultrasound: to measure the size of the left atrium and the dimensions of the mitral valve. The larger the left atrium, the greater the risk for AFib. Likewise, the wider the opening in the mitral valve (mitral regurgitation), the greater the risk. Extreme narrowing of the mitral valve also presents a risk. Both cause enlargement of the left atrium.

Thrombophilia Risk: As mentioned in relation to clotting risk and stroke without AFib, the same genetic abnormalities increase the risk of clot formation in AFib. (See page 20, 33-34)

Thyroid and Thyroid Stimulation Hormone (TSH): High thyroid and very low TSH levels present an increased risk. Patients with low thyroid disease (hypothyroidism) who are being treated with thyroid should be aware that a TSH level below 2.5 may represent that increased risk. Unfortunately, new guidelines for normal TSH levels have changed the level to a range of .5 to 5 uu/ml. It is our judgment that older patients should settle for a slightly higher thyroid than a low level of 2 to 4 as that will have no appreciable effect on your metabolic status but will increase AFib risk.

Hypertension (HTN): All levels of blood pressure over the ideal baseline increase the risk of hemorrhage. Guidelines regarding ideal blood pressure are being readjusted lower, both systolic and diastolic readings, for all age groups. It is essential to monitor your blood pressure regularly even if your levels are normal at present as levels can rise briefly and return to normal each day or gradually increase to dangerous levels without any warning. Here measurement is prevention.

"Thick Blood": High red cell count with high hemoglobin and hematocrit (Hct). As discussed, the risk for thrombotic stroke (clots) increases

steadily above 46 to 48 Hct (red cell) count. Likewise, elevated platelet count (over 500,000) presents its own risk and while experts differ on what levels are critical (some even say 10^6), we recommend anti-platelet therapies at much lower levels, especially if there are multiple risk factors for stroke.

Inflammatory and Lipid Markers: Especially helpful in risk assessment are Hs CRP, $LpPLA_2$, small particle LDL number, low HDL, and high fibrinogen and vWF Ag (blood and platelet elements that contribute to inflammation. All of the tests reviewed in our section on Laboratory Assessments play a role in heart, stroke and Alzheimer's disease risk.

Genetic Abnormalities in Clotting: Thrombophilia risk. We cite again certain genetic abnormalities that are still small considering stroke risk but must be measured:

Protein C, Protein S deficiency

Factor V Leiden variant

Prothrombin 20210A variant

Homocysteine and metabolism disorders reflected in defects for methyl hydrofolate reduction enzyme

Lupus Anticoagulant

Anticardiolipin Antibodies

Antithrombin III deficiency

Factor VII increased

Plasminogen Activator Inhibitor increase

These abnormalities, especially Factor V Leiden variant, Prothrombin 20210A, and Lupus/Anticardiolipin, pose significant risk to women on long-term estrogen, progesterone, or combination hormone management, whatever the clinical indication. The stroke risk is then further increased by smoking. The clotting and stroke risk may remain at risk over time, for several years, although no definitive studies are available. We emphasize both the underreporting of risk and professional inattention to this.

Obstructive Sleep Apnea: "Arrested breathing." Sleep apnea may be due to brain disease or metabolic disorders such as severe hypothyroidism or sever congestive heart failure. Obstructive Sleep Apnea (OSA), on the other hand, is a mechanical problem—collapse of the muscles in the back of the throat obstruct the airway during sleep, depriving the brain of oxygen. OSA is one of the main causes of Atrial Fibrillation, thereby

linking it to embolic stroke risk. OSA also presents a direct stroke risk (hemorrhagic stroke) by markedly elevating blood pressure in surges during the apneic (oxygen-deprived) cycles during sleep, which could number many hundreds of apneic cycles lasting as long as 40 to 60 seconds.

A careful and detailed sleep history is essential to stroke and Alzheimer's disease prevention. OSA has significant impact on cognitive and intellectual function and may, over time, lead to dementia by the death of or damage to oxygen deprived cells). The absence of obvious or observable apneic events does not exclude the disorder, so that any symptoms such as daytime fatigue, increasing forgetfulness, difficulty with complex intellectual tasks, or personality changes require a sleep study, especially if the subject is overweight and has indices for neck size greater than 17 inches or waste size greater than 38 inches, with or without snoring. It is also possible that thin people with good indices can have severe disease. Any new diagnosis of Alzheimer's disease, Af, or hypertension might be reason enough to refer for a sleep study, especially if there is difficulty controlling heart rate or blood pressure.

Finally, if the diagnosis of OSA is made, it is absolutely essential for the patient to use the positive pressure machine (CPAP) with a comfortable mask or nasal pillar with a chin support to prevent deep sleep jawdrop with loss of pressure effect in the hypopharynx. Remember, CPAP is not a cure, it is sleep event management and every event must be managed.

Cerebral Amyloid Angiopathy: While it is not possible to assess risk for CAA by laboratory screens, we know that CAA is almost always present where Alzheimer's disease is present. CAA hits small- and medium-sized cerebral vessels, flooding them with amyloids with some evidence that Amyloid $Beta_{1\text{-}40}$ is a significant oligomer. CAA risk is increased with Apoe4 genotype, as for Alzheimer's disease, FTD and PPA. CAA is the major cause of lobar strokes and microhemorrhages. We list CAA here because of the obvious connection between stroke and amyloid diseases. Keep in mind CAA stroke is not due to thrombosis but to amyloid and whatever generates it.

QUESTIONS:

1. Blood pressure can fluctuate:
   - ❑ True ❑ False
2. Low blood sugar is not dangerous as long as you do not faint.
   - ❑ True ❑ False
3. Blood pressure is controlled by:
   a. Frequent monitoring
   b. Drugs
   c. Low salt intake
4. Diabetic control includes checking:
   a. Fasting blood sugar
   b. After meals
   c. At different times of the day
5. Sleep apnea can cause:
   a. Abnormal heart rhythms
   b. Daytime sleep
   c. Stroke
6. High blood pressure is a risk for:
   a. Stroke
   b. Heart attack
   c. Alzheimer's disease
7. Low blood pressure is never a risk:
   - ❑ True ❑ False
8. "Dawn surge" brings:
   a. Increased heart rate
   b. Increased blood pressure
   c. Increased clotting risk

SECTION 2

PART II – DIET AND NUTRITION OR "MANURE," MACHINES AND MOLECULES

Diet and Nutrition

An appropriate prescription for diet and nutritional improvement must be individualized. There are, however, some points on which there is agreement as to their general applicability. We will present you with these points and help you understand their importance to your health program. These are easy, physiologically sound, and certain to be beneficial within a short period of time.

The diet guidelines we use are not ours, we didn't develop them, we didn't test market them. They are commended simply by generations of use. This diet regimen fits just about everyone, and can substantially reduce the incidence of the common killer diseases. One other point, it is never too late to change, and it is never too soon. In either case the benefits begin the first day, even if we can't measure this immediately. The benefits are both preventive and reparative, in other words, if you already had an event, these interventions can reverse, at least in part, some of the preliminary damage that brought the event. We emphasize again the benefit begins when you begin, there is immediate reduction in inflammatory reactants, with slower alterations and diminution in vascular plaque, brain plaque, blood pressure, blood sugar, nasty fats and lipids, uncomfortable and disease producing bowel habits and overall pick up in your sense of well being, energy, mood, affect, alertness and efficiency. All of this will follow if you follow the plan!

1. A change in habits and in the types of food eaten does not have to be punishment. Healthful eating habits are so much more compatible with good health than starvation diets or fad or esoteric diets or medications, many of which are dangerous.
2. Recognize the economy of nature. It provides all of our basic requisites in forms that are safe and easily obtainable. Nature has

constituted foods so that in proper combinations and amounts everyone can be nutritionally fit. This economy also provides the terms of habit; how to eat, when to eat, and how much to eat. We must relearn the rules.

3. The balance of nature has been disturbed and the stability of the ecosystem has been upset. Because of this, selective additions of supplements, vitamins and minerals may be appropriate for a great many of you.
4. The shift from processed to natural foods is essential. Synthetic processing presents significant disease and dementia risk. The risk of GMOs (genetically modified) is not yet identified, there may be none.
5. Proper dieting and attention to nutrition are to be *life long* activities, not engaged in merely to affect a reduction in weight over a specified time.
6. Diet habits and nutritional status are directly related to disease and infirmity. Their modification will lessen certain diseases already operating and reduce considerably the risks for acquiring other diseases and disability.
7. Ethnic diets, what your grandparents ate, have the imprimatur of time. The proof of the dictum is what happens when ethnic diets are replaced by the industrial diet, people get sick, and sooner.
8. The final rule: Food kills and fine foods kill more. If only "back to nature" were possible, just as the benefit of the Mediterranean diet is living there!
9. Beware diets du jour, the most recent species of which is the gluten-free diet. A history of food facts for you: about 6,000-7,000 years ago we went from hunter-gatherers to planter-harvesters. Whole grains and rice fed mankind with vegetables and fruits also cultivated. Incidentally, the most common colon ailments in the Western world are irritable bowel syndrome and diverticular disease, which do not occur with lifetime high-fiber whole grain and vegetable-fruit diets. Indeed introduction of unprocessed whole grains is the treatment!
10. By and large, if your body says you need it, then eat it, assuming a normal body with normal needs.

The "Economy" of Nature

Nature provides man with countless varieties of food items and in every part of the world vegetable and animal life supports the human organism. The domestication of animals, improved agricultural methods, and methods for preparing food allowed man to eat nutritionally and without risk throughout much of history. Regrettably, in advanced societies food technology has superseded the production of basic food in their unaltered states, and large amounts of capital are committed to feeding people in a fashion that is detrimental to health and longevity. In the affluent West poor nutrition and nutritionally related diseases are having as great an impact as classical malnutrition is having in underdeveloped and third-world nations. We have forgotten nature's economy and its bias to health and recovery.

Foods widely distributed in nature or readily available with simple domestication and agricultural techniques, particularly those foods which have been part of cultural history, are meant to be eaten. Thus, many foods which are removed from current "therapeutic" diets should be restored, and many foods which have been maligned as contributing to cancer, heart disease and other diseases, should be eaten as they are excellent sources of essential elements. Nature doesn't deceive us by presenting us with common foods that are factors in disease. Widely available foods, vegetable and animal alike, must be good for us. We cite the egg as one example.

The egg has a built-in manager of its own cholesterol, its yolk contains large amounts of lecithin which acts to keep cholesterol particles from coalescing. Likewise, cream or natural butter are better than processed, artificial dairy aids or polyunsaturated margarines. Eggs and natural dairy products have been so widely used for so long that it would be unreasonable to suspect that their moderate use could be detrimental. It is clear now that what has replaced fresh dairy products and eggs is deleterious. The processed non-dairy creamers, the polyunsaturated oils, the margarines and the synthetic egg all have adverse effects on the mineral content of bone and on tissue structure, thus accelerating the aging process. Finally, plant fed poultry yield eggs high in "omega 3s" in their yolk.

"Industrial" foods. The meat and poultry our grandparents enjoyed is hardly the same as our meat and poultry today, treated with hormones, antibiotics, and fattened on huge amounts of "industrial" grain. Industry has rendered all of these potentially dangerous agents of arteriosclerosis, cancer and degenerative brain disease. Our meat and poultry is processed before the kill and is processed again for shelf life and

esthetic appeal. We are done in twice, by two levels of processing that were never intended by nature.

Beef, poultry, etc. are pumped with sex steroids and growth hormone additives, chemicals, and antibiotics for maximal food efficiency (translation: "profit"). You get what's grinded out of a machine. The problem is the food machine is grinding up your cells and DNA with toxins, your brain cells as well. Their grain sources are full of pesticides. When these are fed to animals, their residues are retained by the animals. When we consume their meat, we ingest those residues. The fish also accumulate pesticide residues from feeding on smaller fish which retain residues from industrial sources. Such contaminated supplies of meat and fish make it imperative that we look at the impact of this on cancer, immunity, and dementia. Of equal concern is the evidence that pesticides remain in the soil and environment for years after they are sprayed so that effects are not merely related to single exposures in specific time periods but are "time release." Pesticides are a continuous threat once they are applied.

The same concerns apply to farm-raised fish, a huge commercially profitable "fish bastards." Farm-raised fish have higher levels of exogenous toxins, from food sources, from metals such as mercury, as well as their own internal toxins. Farm-raised fish is also much lower in beneficial fish oils, while their own fats and oils contain high levels of fat soluble chemicals. Farm-raised fish is no friend. The people we know who were in the fish business won't touch farm-raised fish. "Meat is safer," one said, "even bad meat!"

Food packaging, especially plastics stabilized with phthalates and related compounds, and countless other additives to packaging. Phthalates are especially harmful and leech into food and fluids. Their biological effects are both direct cell toxicity, especially brain cells, and epigenetic dysregulation with great implications for cancer and brain diseases, including Alzheimer's. So, don't forget the packaging because it won't forget you.

Industrial diets, originally developed as a war time need, provided cheap, safe food free of food pests, deadly bacteria and toxins. Nutrition improved and caloric needs were well met, but the rapid commercialization of these and franchising of processed fatty foods have overwhelmed us with a flood of high caloric industrial-composite foods. Our disease burden simply follows that food chain. This is not to mention the chemical tidal waves loosened in your body by food additives. Consider that an average 70-year-old American might be taking 7-10 prescription drugs each day and ingesting, inhaling or applying hundreds of man-

made molecules each day that did not exist 50 years ago, each one having multiple effects on inflammation and epigenetics and disease gene expression or silencing.

The Physiology of Digestion

Man has a digestive system suited for meat and vegetable foods. Within the animal kingdom the classic meat eater has a short digestive tract, and the small intestine and colon are designed to allow for quick passage of digested meats through the organism, reducing the potential for absorption of toxic waste materials. Vegetable eaters have longer small intestines and colons, allowing for the processing of the fiber elements. Man has an intestinal tract somewhere between these two, but more like that of the vegetable eaters. In addition, the folds and convolutions of the human intestine increase the surface area for absorption and facilitate vegetable and plant digestion. Thus, in terms of digestion and elimination, man is well equipped for meat or vegetable intake although the evidence argues that he is primarily vegetarian. Dental evidence also lends weight to this. While man is equipped with teeth that will permit both a vegetable and animal diet, he clearly does not have the dental apparatus of animal meat eaters. The distribution of man's digestive glands also supports this. Our protein enzymes are elaborated by the pancreas, and the salivary glands produce enzymes that break down carbohydrates. Among classic meat eaters the salivary glands elaborate protein digesting enzymes, however, and not enzymes that work on carbohydrates.

Hunger and Appetite

The balance of nature regulates our diet (if we let it), our patterns of eating, and the amounts to be digested. In man and higher animal forms there are hypothalamic centers which control appetite. Manipulation of these centers can result in extremes of feeing behavior. In laboratory animals it is possible to control food intake very closely. If a nutritious food is presented in a diluted form (increased volume but the same caloric content), an experimental animal will eat more to attain its required calories. If calories are then presented in a concentrated form, the animal will eat less volume but continue to take in his usual caloric requirement. In either direction of the volume, the animals usually maintain an isocaloric diet. If animals are force-fed and gain weight, they voluntarily reduce their food intake to bring their weights back to normal when allowed to do so. On the other hand, if the hypothalamic control centers for appetite are destroyed, the ani-

mal's instinctive behavior to closely control weight and caloric intake is upset. One area of the hypothalamus can be manipulated and the animal will eat uncontrollably and voraciously. A manipulation in another area very close to the first will cause the animal to reject food and starve to death. In man, similar controls are built in but higher sensory and psychological factors can modify more basic levels of function and override the instinctual responses that tend to conserve the organism.

Hypothalamic areas in man function as they do in animals. These hypothalamic centers will respond to increases in heat, both ambient and internal, by affecting a reduction in food intake. In a hot climate with ingestion of food, or by exercise, both of which increase core heat, appetite is decreased. In cold weather or after periods of fasting when the body temperature drops, appetite is stimulated.

Animals in the wild state regulate food intake to maintain optimum weights and function, and swings in weight are not seen unless these factors are altered. If you have ever observed animals and infants during a heat spell, you will notice a reduction in solid food intake and increased fluid consumption. Infants will automatically reject meats, hot meals, etc., in favor of liquids. This is also observable when infants or animals are ill, especially with fever. In addition, animals eat when hungry and then reject food for varying periods depending on the species, until such a time that hunger is present. In domestic pets that are chronically fed table food, progressive obesity and metabolic changes foil the homeostatic mechanisms, as they do in us. Extreme pet obesity is now as epidemic as human obesity.

No clearer evidence for the economy of nature can be presented to demonstrate that physiological mechanisms will signal the appropriate time and amount to be taken. It is true for animal and man alike. In nature's bias to conserve and to compensate, but not overcompensate, we have a guide with which to make judgment about our diet habits and food selection. This is physiologically "set" but we can upset it dramatically, and very early in life!

When to Eat

BELIEVE IT, when you eat may be as important as what you eat. Do you remember circadian rhythms. Well, some of us are morning persons; some night owls, some are both, some are neither. The point is your energy requirements are individually set by your circadian cycle, levels of physical or mental activity, sleep cycles, mood and stress.

Food is simply energy, nothing more, in a strict physiological sense, but your energy quotients are a balance of all of the above plus the presence of any metabolic disorders or stress disorders. Likewise, what, when and why you eat can be part of the therapy (primary therapy) of the metabolic syndrome and many stress disorders. The metabolic syndrome is a combination of visceral (tummy) fat, insulin resistance, even low levels, early hypertension and elevated blood lipids. The metabolic syndrome is the number one metabolic disorder in the United States by a factor of 10x at least.

Only you can establish your best food-energy cycle in relation to your circadian cycle – your light-dark, day and night cycle of work-rest efficiency quotient. Morning persons can have their high carb meals in the morning (pasta, potatoes, rice, cereal, etc.) and burn the calories off by evening, whereas evening carbs in these people "stick." On the other hand, many of us have early morning hypoglycemia or medication (diabetic medication or Insulin) induced hypoglycemia and evening or late-night, high density, low glycemic carbs (e.g., lentil, beans or nuts) may stabilize the morning drops. That is just one example of timing. Another example is the high-fat meal at night. Research indicates that a high-fat meal in the evening can risk nighttime heart rhythm problems or stroke. The same fats spread out during the day and properly metabolized are much less likely to be an acute risk, but they may still be a long-term risk.

Why We Eat What We Eat

BELIEVE IT, the most important factor in choosing your next meal is your last meal! The most common reason for overeating high-calorie, low-nutrition value foods is the previous meal of the same processed carbs (sugars) and poorly enriched and prepared complex carbs (starches), washed down with "chemical fluid" high sugar or diet drinks. That is the reason why you are eating the way you do. You have reset the brain and gut sensors to print out "hungry" when in fact you are "starving" from high count empty calories, or highly toxic, low calorie fluids and food substitutes which neither your brain nor gut sensors can read because they are completely foreign chemicals. We take in hundreds of these molecules every day resetting our epigenetics and confusing our metabolism.

Stress also disturbs eating, digestion and nutrition. Sadness, depression and anxiety can make us eat less or much more, and it is equally true that if we are happy, joyful, and if we receive great news, we may eat as much or more than we overeat because of stress. Ethnic, cultural,

economic and social factors also play a role in how we eat, usually for the good. Ethnic foods prepared the way grandma did are safe and appropriate calorically. But who does that any more? Grandma has been replaced by the vending machine, and the old kitchen stove has been replaced by high-speed radiation. So we can rewrite the old maxim – it's not "you are what you eat," but, "you eat as you are," and you are caught in the cycle we just described!

There is widespread nutritional deprivation in the face of voluminous caloric intake. The most obvious consequences of this is obesity and fatigue and lethargy that follow the average American meal. There are also the considerations linking diet and diseases, and brain health, and over the long term, Alzheimer's disease, diverticulitis, colon cancer, and appendicitis, among the most common afflictions of the middle-aged and elderly on a Western diet. These are rare among those people who eat generous amounts of grains, fibers, and nuts, as is Alzheimer's disease.

Hypoglycemia – a Common Symptom. The high content of refined sugar leads to hypoglycemia. This is not strictly a disease but an exaggeration of normal responses to sugar intake, the brisk and exaggerated release of insulin after a high carbohydrate meal. This insulin release causes a prompt reduction in blood sugar level. With this precipitous drop, patients can feel fatigue, hunger, sweating, nervousness, irritability, and light-headedness. Perhaps the hunger sensation is the most dangerous of all since it prompts the patient to eat again. A situation develops in which the appetite is turned off and on in successive periods that are shorter than normal feeding periods. Consequently, two of the hallmarks of hypoglycemia are appetite and weight gain.

The treatment, very simply, is a reduction in food intake and a modification of diet. It is important that the "junk" content of the diet be reduced or eliminated since this is the main agent in the cause of the swings in blood sugar and the production of hunger. The long-term effect of junk foods is that the body resets to a higher caloric and sugar intake than would be normal. Patients feel chronically hungry and feel the continuing urge to eat. This is a false hunger, however, produced by over-eating the wrong foods.

Allergies and Food. Other consequences of eating processed foods include the wide-spread problems of allergy, headaches, and hyperactivity. Many people with one or more of those complaints are experiencing their symptoms solely on the basis of their diet. The additives, preservatives, coloring agents and refined sugar can produce all of those symptoms. There has been an impressive reduction in the numbers of

hyperkinetic children with simple diet modifications. Only a decade ago many of these children were placed on medications and their families were led to believe that they had basic behavioral problems. Just as with the hypoglycemia diagnosis, in our haste to make a diagnosis for these children, we mistakenly labeled them with a disease. The emotional consequences for many could only have been negative. In actuality, the problems were purely dietary and could be remedied.

Numerous asthma, allergy, and headache patients are likewise being inappropriately managed with drugs. A reduction in additives, coloring agents, preservatives, and other artificial components of food could relieve the problems. How many of us suffer fatigue, decreased work and exercise tolerance, and changes in mood because of our dietary habits? How many patients are folding into cognitive disorder and the beginning stages of Alzheimer's disease and declining brain health?

Agribusiness, Aging and Disease. Earlier we mentioned some of the consequences of modern agri-business and food processing methods, rendering our foods increasingly inadequate in terms of vitamins and minerals. The over-utilization of farm land and the damage to soil and water from pesticides and industrial waste can have cumulative effects on the soil, depleting it of vital vitamins and minerals. One of the effects of substituting mechanized plowing and harvesting for the farm horse has been the accelerated deterioration of the soil quality. The horse has been removed as the central recycling element and we have lost his valuable contribution to the quality of our food, manure. The loss of manure in its natural state has had dramatic effect on the continued depletion of essential minerals, vitamins, and trace elements which had been previously replaced by the manure.

The marked decrease in soil quality is playing a significant role in numerous diseases including altered behavior states. There is evidence that these deficiencies may also be related to the aging process. Certain changes in the body which parallel the aging process are accelerated by processed foods deficient in basic elements. Conversely, people who shift to fresh and less processed foods, a reduction in calories and vitamin and mineral supplementation, can ameliorate some of the symptoms of aging including memory and intellectual function, bone structure, strength and endurance, skin texture, and blood pressure, lipids and glucose. More dramatic, perhaps, is the laboratory evidence related to this. In a number of animal experiments, slowing of the aging process was noted with reduction in caloric intake. In controlled situations calorie-restricted rats lived almost twice as long as their well-fed brethren. In other experiments, rats subjected to repeated fasts of one to three

days tended to live considerably longer than those on regular feedings. Needless to say, the strict applicability of this to human medicine is unclear, but considering the risks of inadequate amounts of vitamins and minerals, and useless calories, we can link these to human aging and degenerative diseases, including the dementias.

Fasting

The enthusiasm for fasting comes from the belief, and animal research, that fasting prolongs life and dramatically limits the infirmities of aging. Recent studies of deliberately overfed, obese macaque monkeys prove the same. The obese macaques die earlier and exhibit accelerated atherosclerosis, insulin dependent diabetes, dementia, altered lipid metabolism and elevated levels of pro-inflammatory molecules and proteins. Fasting dramatically extends life and reduces age-related diseases in test animals. The knowledge that fasting and long-term calorie reduction is beneficial for physical and psychic health should stimulate you to begin your own program of intermittent fasting tailored to your health, age, level of physical activity, and your determination to lose weight or to adhere to the program. There are also some prerequisites for fasting, some basic rules, which are applicable in every case.

How to do it! Fasts should be modest initially. Perhaps it will be convenient to begin by skipping one meal a day. If these initial brief fasts are handled well, the fasting periods can then be increased to twenty-four to thirty-six hours. During these periods of fasting, adequate fluids, especially water, fresh fruit juices, and soup broths are necessary.

There are several points regarding this. You may initially notice some weakness, fatigue, headaches, and other non-specific changes as you first shift from the highly refined diet to the more natural diet. Certainly you will notice these with your initial fasts because the body is adjusting to a different caloric intake and qualitatively different diet. These also reflect the elimination of toxins, or a reduction in their production with the shifts in diet. These irritating but minor symptoms will disappear over a period of days and the positive mood changes of fasting will appear. You will notice a totally different change in the way you feel psychically and physically.

The dramatic improvement in your sense of well-being and your endurance will be sufficient to motivate you to continue these fasts. During these periods vigorous exercise such as competitive sports, hard jogging, or heavy physical activity must be limited. The risks of bodily harm from strenuous physical activity while fasting for more than sev-

eral days has been pointed out. Light exercise such as casual swimming, walking, garden work, or light housework are certainly appropriate, and if performed with reasonable regard to their intensity and duration, there should be no problem.

The benefits of fasting include a reduction in the level of toxins built up by the metabolism of refined and meat diets. This will assist in the return of normal hunger signals so that even if you find that fasts of more than twenty-four to thirty-six hours are not for you, you will at least be able to distinguish legitimate hunger from the false signals constantly being flashed when you were on your old diet, eating many times during a twenty-four hour period. Many find that trials of fasting have allowed them to establish an eating pattern of one meal in twenty-four hours or two smaller meals during the same period. If these people no longer desire to fast, at least they will have trained themselves to eat in response to genuine hunger. Many never return to the traditional, but arbitrary, three "squares" a day but have optimized their own cycle of meals, snacks, exercise and rest. If you make diet and nutrition a part of a comprehensive circadian rhythm-based plan, huge changes will follow.

We duly note that some of you may not be able to fast. You may be among the frequent snackers who need a small amount of quality protein or carb every 3-4 hours, and fewer meals, to keep your metabolic engine purring. This may also be a more effective pattern of eating for weight reduction or control than intermittent fasts. It is very invidualized and dependent on what you eat and when in relation to circadian and metabolic rhythms, which you will identify both by measurement and controlled "studies," you being the control and subject. In any case, in every case, all of this will be in concert with the world's best diet, which is…

The Mediterranean-Middle Eastern Diet

"The World's Best Diet". The diet we generally recommend is not the American Heart or Diabetic Association diets. The clinical nutritionists have pretty much been behind the curve here. In fact, recent pooled data from a number of cardiovascular prevention studies following thousands of patients over decades indicate that the traditional Mediterranean diet (e.g., southern Italian) was at least twice as effective (50% fewer cardiovascular events) than the repeatedly revised American Heart Association diets. We actually expand this to include traditional Middle Eastern foods joined with the Mediterranean diet "MED-MED", the "Mediterranean-Middle Eastern Diet". In fairness, maybe the best benefit of the Mediterranean diet is just living there! Mediterranean and other ethnic or regional diets of long tradition and custom are less atherogenic, carcinogenic and brain toxic. In fact, when nationals from other cultures abandon their traditional diets for our "industrial composite" diet, they have more disease and earlier deaths. The industrial composite diet is high fat, high sugar or fructose, refined flour, additive and filler rich, heavily salted, partially hydrogenated, and transfatted. When you couple that with industrial sized portions, you get the disease and obesity epidemic we have now.

The Mediterranean-Middle Eastern Diet is completely balanced, high in antioxidants, low in sodium, low to modest in carbohydrates, and virtually without saturated fats. It is not only the best diet in the world, it provides all of the known, and all of the unknown, molecules, trace metals, and microelements in ratios and combinations that no amount of supplements in any combination can provide. This diet, linked to some caloric restriction, is the most important consideration you can make regarding future risk reduction for aging, disease and dementia.

A. List of Food Items *(Alphabetically, not in order of importance)*:

Beans and Legumes–e.g., chic peas, black beans, red beans, lentils, are especially beneficial

Beverages—included as "protective" are vegetable juices and red wine, pink grapefruit juice, pomegranate juice, grape and berry juices, all with less glycemic impact than orange juice. All sodas are toxic! Alcohol-red wine is best / 1 glass per day

Breads—whole grain, multigrain, dark (e.g., rye, wheat, oatmeal breads – the darker and seedier the better)

Cereals—unprocessed miller's bran / whole oat cereals, are especially beneficial. Commercial breakfast cereals including the "organics" are used only sparingly; they are all high in carbohydrates and calories.

Cheese & Dairy—essential part of diet—sheep and goat cheese, especially sheep/feta cheese, locatelli Romano (sheep), both of which are very high in Omega 3. In general, hard cheeses are better than soft ones. Read labels for salt and additive content.

Yogurt—excellent probiotics help reduce gastrointestinal distress while being heart healthy, especially live culture Greek yogurt.

Fage™ , Chobani™ and **Oikos™** are high protein, low carbohydrate yogurts

Eggs—Lecithin, essential constituent, high levels of phosphotydylcholoine. Eggland™ eggs are plant fed, high in Omega 3s.

Fish—for protein, Omega 3s especially sardines, anchovies and fresh non-farm raised salmon, and mackerel, all high in Omega 3.

Fruits—All "black and blue", e.g., blueberry, blackberry, raspberry, tart cherries, dark grapes, pink grapefruit, pomegranate, figs, dates, prunes, raisins, apricots, apples, and melons (watermelon is an extremely efficient antioxidant). Special mention of lemon being an extremely efficient antioxidant as well.

Honey—raw unprocessed—propolis in honey is antibacterial, anti-inflammatory; www.weebeehoney.net ™

Meats & Poultry—lean cuts of lamb, veal, pork, beef, chicken (roasted or grilled); avoid cold cuts and fatty meats. Limit meat to twice a week.

Nuts—excellent source of protein, and Omega 3, e.g., almonds, walnuts, pecans, peanuts, and pistachio (raw, non-roasted and unsalted). Add them to yogurt with honey (same for natural crunchy peanut butter).

Oils & Olives—Olive oil (extra virgin cold pressed), all olives, green and black (especially Greek, Sicilian and Spanish). Natural antioxidant-oleocanthols.

Onions & Garlic – antioxidant, especially red onion and garlic which has alium potent vasodilator, antiplatelet and antioxidant, as well as carnasol and carnosil acid.

Soups & Water—Essential to your diet, homemade with bones, for marrow contents. Marrow soups are an extremely important source of trace metals, microelements and other unidentified essential elements. Generous water intake with fresh lemon and lime is both antioxidant and will enable you to cut off carb and sugar "addiction" quickly.

Veggies—You must eat your veggies, or your other foods will start eating you! Veggies give roughage, water, heart-healthy pigments, and antioxidant molecules. Grilled or lightly braised, their important elements are preserved; dark green leafy to brightly colored peppers, tomatoes, carrots, pumpkin and sweet potatoes, spinach, kale, broccoli, collards, escarole, dark colored leaf lettuce, arugala, asparagus, red cabbage, brussel sprouts, eggplant and zucchini, all pasta and rice dishes with generous veggies.

Specific Diet Points and Supplements – High fiber, low fat, low sugar diet covers all major disease categories.

High Fiber / Low fat "BESTS":

Unprocessed Miller's Bran, Oatmeal

Oatmeal – best is McCann's Irish™ – stone cut, long cook—20 minutes.

Whole grain-dark breads, multigrain oat, rye, barley, nuts

Nuts—raw, unsalted, not roasted

Lentils, beans, legumes—all slightly undercooked

Toubouli, humus, chick pea, lentil salads

Raw or braised grilled vegetables

Whole grain brown rice, sweet potato

Dates, figs, raisins, prunes, berries

B. Dietary Interventions

High fiber food—removes toxins, free radicals

Vegetable products:

Flavonoids—in colored fruit/vegetables, dark chocolate antioxidant, lipid lowering

Carotenoids—Lycopene—Cardio protective
Tomato, pink grapefruit
Lutein—eye protection/dark green vegetables
Zeaxanthin—eye protection
Also vascular protective

Tocopherols—peanuts, almonds, legumes, Vit E (10 different tocoretinoids [including alpha tocopherol] in "total" Vit E)

Tocotrienols—rice (whole grain dark), barley, rye, wheat

Alpha Lipoic Acid—Anti-inflammatory

Oleocanthols—olive oil, flaxseed

C. Omega Fatty Acids OM-3-FA

The primary source of these are two Microalgae species: Schizochytrium Species / Crypthelodinium Cohnis

Secondary sources include: eggs from poultry with omega acids supplement, have 2x-4x EPA + DHA levels—very beneficial

Fish—Salmon, anchovies, sardines, tuna (must be wild, not farmed!)

Sheep Cheese – e.g., feta cheeses, pecorino romano, etc

Raw Nuts—walnuts, almonds, and pecans

Need to supplement 2-3 grams/day of DHA and EPA (total), equivalent to 8-10 grams (10,000mg) of fish oil

Omega 3 (see Section II, Part I - "Anti-Inflammatory Therapies")

DHA—Docosahexanoic Acid; Anti-inflammatory, ↓arachidonic acid, ↓TNFa

EPA—Eicosapentaenoic Acid; stabilizes vascular plaque and aids memory; strong anti-inflammatory; DHA neuro-protective; Phospholipid DHA and EPA levels may be measured in blood

"Memory Cocktail" must include B_3, B_6, B_{12} and folic acid to reduce homocysteine, include Omega 3, choline, L-carnatine and Alpha Lipoic Acid for better neuronal protection

D. Essential Elements, Supplements

Magnesium—chelates Ca++ - neuro-protective

Copper, Boron – mitochondrial function

Selenium—Cell stabilizers, especially neurons

Zinc—Chelate iron – Iron can be neurotoxic

Chromium—Stabilizes, "facilitates", Insulin receptor site activity

Omega "3" Fats	Omega "6" Fats
ALA—Alpha Linolenic Acid	in 1 to 3 ratio to Omega 3
DHA—Docosahexaenoic Acid	Linoleic Acid
EPA—Eicosapentaenoic Acid	Gamma Linoleic Acid

Sources—microalgae, schizochytrum species, crypthelodinium chonis

E. More Supplements

The "B" Complex — Essential cell Mitochondrial functions

B1—Thiamine-Anti-inflammatory and Antioxidant (some)

B2—Riboflavin- Anti-cell aging

B3—Niacin- Essential to energy production – Mitochondrial (NAD-NADH)

B5—Pantothenic Acid

B6—Pyridoxine, +Neuronal, also lowers Homocysteine

B12—Cobalamin, +Neuron, blood cells, increased methylmalonic acid more reliable if low normal B12

Inositol — Boosts brain GABA which lowers stress levels and stabilizes mood

Choline — Precursor for neurons and nervous system

Phosphotidyl Choline Antioxidant, cell integrity

Folic Acid — As tetrahyfrofolate; neuronal, blood cell health. Always give with B_{12} and B_6 if neuro or cognitive Rx.

L-Carnitine — Increases synthesis of Acetylcholine, memory and cognitive neurotransmitters, mitochondrial antioxidant

Alphalipoic Acid — Cell stabilizer, mitochondrial antioxidant

Coenzyme Q10 — Antioxidant, cell stabilizer, mitochondrial stabilizer

Replacement Therapy *significant side effects with long-term normal interventions

Vitamin D_3

Testosterone

Thyroid (T_4, T_3)

Growth Hormone

DHEA

*Obviously, any essential hormones, vitamins, minerals or amino acids must be replaced to physiologic levels. The benefit of supraphysiologic doses for some of these is unclear, whereas for others listed above the evidence is either neutral or positive. Excessive doses of Vitamin C and perhaps Vitamin E may be counterproductive, actually increasing

oxidation burden in cells. This is why we recommend dietary changes first and foremost, to assure physiologic doses and combinations that cannot be replicated in a pill. On the other hand, there may be soil depletion and insufficient levels even in organic produce and fruits. Hence, the role of prudent supplementation.

Special mention items:

Soup broths, with or without veggies, we stress once again, as a primary modality for "full spectrum" intake of fiber, fluid and all nutrients.

Generous, as much as two quarts per day, or more, of water with liberal amounts of fresh lemon and fresh lime (L&L) juice. Our experience with this has been dramatic in helping patients break away from sugar as well as begin to mobilize fat and toxins.

Avoid absolutely all colas or sodas, diet or regular. They are as toxic to you as water and soup are nourishing.

Alcohol is a cell killer and diet inhibitor. Stop all alcohol if you are trying to lose weight and replace with soup broth and water with L&L.

QUESTIONS:

1. Low carb foods:
   a. Decrease blood sugar
   b. Reduce weight
   c. Have more calories
2. Eggs can lower cholesterol:
   ❑ True ❑ False
3. A balanced diet is:
   a. The same for everyone
   b. Equal parts of starch and protein
   c. Anti-aging
4. High sugar diets cause:
   a. Hypoglycemia
   b. Increased neuron damage
   c. Fatigue
5. The "Med-Med" diet is:
   a. High fiber
   b. Low sugar
   c. Antioxidant
6. All calories are nutritionally the same:
   ❑ True ❑ False
7. Everyone must eat three meals a day:
   ❑ True ❑ False
8. Eating must be tailored to your:
   a. Circadian rhythms
   b. Energy needs
   c. Medical risks

9. Processed meats are high in:
    a. Antibiotics
    b. Salt
    c. Hormones
10. Dark and colored fruits and vegetables are:
    a. Heart healthy
    b. Antioxidant
    c. Empty calories
11. Food additives can cause:
    a. Epigenetic changes
    b. Cancer
    c. Neuron damage
12. The easiest way to lose weight is to:
    a. Eat less
    b. Exercise more
    c. Use diet medications

SECTION 2

PART III - EXERCISE

Since early recorded history, the long distance runner has been a legendary character. *Hermogenes* of Xanthos was one of the great runners of antiquity. Nicknamed "The Horse," he reputedly won eight wreaths in twelve years of competitive running. A distance runner named *Lasthenes* is said to have beat a horse across the main river at Thebes. *Polymnestor*, the Milesian, won acclaim by catching a rabbit on foot. *Coroebus*, the Spartan, is recorded as the first winner of an Olympic race, and *Pheidippedes* is remembered as the runner who made the two hundred kilometer distance from Athens to Sparta in less than two days to secure Spartan aid against the Persians, thus gaining his immortality.

Running contests were common throughout the Greek and Roman world. Often the runners were naked and described as possessing long limbs and perfect, but modest, physiques. Some matches included runs with various amounts of armor, shields, helmets, and weapons. Running claimed its first recorded victim when the Spartan, *Ladas*, collapsed at the finish of a foot race in the games of the fifteenth Olympiad. Every history book tells of the young runner who ran from the plains of Marathon to Athens shouting the news of the Persians, collapsing at the gates of the city as he finished. Other reports through the ages recognize great running feats, and episodes of sudden collapse after them.

Here's the good news, you don't have to run, but you do have to walk. We don't suggest that everyone who runs should stop (some should). We simply point out that virtually the same benefits can be gained from walking with none of the long term wear on joints, your back, and other parts for the ladies. Walking can be undertaken by anyone who is contemplating an exercise program as part of his or her total health and it is the safest of all the exercises.

What happens in the muscles. With the initiation of exercise a complex interaction of functions is brought into play, and a host of changes occur regularly in the body. The first, and most basic change which subserves all of the others, is the activation of energy source mechanisms. These supply the energy units for cardiovascular and muscular work. The energy supply for exercise is provided through two systems, the aerobic or oxygen dependent system, and the anaerobic, or non-oxygen system. The balance of these two systems and their contributions

to the energy supply for a given exercise is dependent on diet, state of health, prior level of conditioning, and many other factors. Conversely, the amount of each used determines fatigue and oxygen debt, two measures of the efficiency of the systems and their relative contributions in a specific exercise. With progressive intensity and duration of exercise, the metabolic requirements are net by an increasing reliance on the non-oxygen system, as this system supplements the energy needs supplied by the aerobic system. The exercises which are described as aerobic are those which improve the efficiency of the cardiovascular system and the oxygen use in tissues. The anaerobic reserve is incorporated more efficiently when it becomes the major supplier of energy later in the exercises. Walking, jogging, running, swimming, rowing, cross-country skiing, and cycling are the classic conditioning aerobic exercises employed to develop cardiovascular fitness and endurance. At the onset of any of these a number of events occur in the body which can be easily measured and monitored throughout the duration of the exercise.

The Physiology of Exercise. The first change is an increase in the heart rate, which accelerates due to neural factors (remember the "flight or fight" stress response?) as the exercise progresses and a rhythm is established. The neural factors that modulate this may act by releasing the heart from its usual state of controlled rate (an average of sixty to eighty beats per minute). This release is accomplished by a prompt reduction in the activity of the parasympathetic portion of the autonomic nervous system, a primary control circuit regulating normal heart rate in the non-active state and during sleep. With the cessation of exercise the pulse rate falls off rapidly with neural release of the sympathetic branch of the system. This system had been activated at the onset of exercise when the parasympathetic system inputs were being reduced. The sympathetic system, and the stress hormones, are responsible for the high pulse rates and changes in blood pressure which we observe in exercise. In young adults the maximum heart rate achievable with exercise is about 200 beats per minutes. As one ages this drops off to a maximum of 140 to 160 beats per minute. In the highly trained subject, however, the increases in heart rate needed to accomplish the same level of exercise are not as great as in the untrained because the conditioned heart empties more effectively and is able to deliver more blood per minute than the non-conditioned heart. The change in heart rate is perhaps the most dramatic manifestation of the stress response as it relates to exercise and is one of the main determinants of exercise tolerance, that is, the body's ability to withstand intensive, on-going exercise stress.

A second change that develops is the change in blood pressure. As the heart rate increases the systolic pressure rises and the diastolic

pressure drops significantly. The result is that the mean arterial pressure drops. This is due to a relaxation of the arteries in the muscles, and with progressive exercise and heat production, relaxation of the arteries in the skin. The arteries in muscles can relax to their maximum so that more blood flows through, delivering more oxygen for aerobic energy. The arterial relaxation in the skin provides for increased sweating, thus cooling the body. At the same time arteries in the digestive organs tend to constrict to enhance the above effects. The arteries of the heart dilate maximally so that heart muscle continues to receive as much oxygen as possible. With the increase in heart rate and the increased efficiency of each heartbeat, especially in the conditioned person, the amount of blood pumped per minute can increase many fold, fifteen to thirty times more than in the resting state. This increased output is aided by an increase in the return of blood from the muscles. With exercise, the veins in the muscles of the legs dilate to their fullest, and with each muscular contraction these veins are squeezed of their extra blood, which is pumped to the heart to augment its output. Obviously, with all these changes the heart is working harder during exercise to meet the requirements of muscles and vital organs. The heart's ability to respond may be limited by hardening of the coronary arteries or weakness of the heart muscles, as I will discuss later.

Aerobic – Anaerobic. Increasing intensity and duration of the exercise pushes the aerobic system to its maximum. The anaerobic system then kicks in a larger share of the energy supply, but this cannot be sustained indefinitely. Several events follow upon progression of the exercises as the anaerobic system becomes the main energy source. The increased anaerobic metabolism produces lactic acid which is a factor in the development of muscle and body fatigue, and the muscle pain seen with exercise. Lactic acid also stimulates vital brain centers which control breathing, partially explaining the increase in breathing rate with exercise. (The production of heat and the increase in body temperature are the other stimuli to rapid breathing.) The breathing rate, like the heart rate, can increase rather quickly and rhythmically for the duration of the exercise, then fall off gradually with its cessation. The falling off of the breathing rate is variable, because the lungs must repay the oxygen debt and restore the oxygen dependent energy system to normal. The debt is repaid by the continued oxygen consumption noted after the exercise. Oxygen consumption is a good index of efficiency and a measure of the debt incurred during any exercise. In sub-maximal exercise (exercise in which the subject does not push himself to the limit), the oxygen intake, and oxygen consumption, and the debt, are much less. With an increase of exercise towards the individual's maximum, the energy expended will outpace the oxygen supply. The oxygen debt and the lactic acid

production increase, contributing to fatigue and the limits of tolerance. With training, the subject increases the efficiency of the use of energy sources so that elevations of lactic acid will be less pronounced. The rapidity with which breathing and heart rates return to the resting level for that individual is a good index of the conditioning that individual has attained. This is so because training diminishes the oxygen debt and allows it to be repaid more quickly.

Another consequence of exercise is the accumulation of body heat. With sustained moderate to intense physical activity body temperature can rise several degrees. This heat is dissipated by the cooling and sweat mechanisms of the skin, as well as by removal of heat by rapid breathing. Recall that the calorie is a measure of energy, including heat energy. With any exercise calories are expended and heat is produced in the process. This heat must be discharged, as it were, from the body or else serious damage can occur to vital brain centers. The body mechanisms for removal of heat include radiation of heat from the skin, convection of heat, conduction of heat from core to the skin, and sweating. In situations where these cooling mechanisms are impaired, or in extremes of climate and ambient temperature, the strains on these mechanisms can be perilous as the core temperature reaches 105 to 106. At these extremes of internal body temperature (core temperature) fatal arrhythmia, ventricular fibrillation, can issue. The increased core temperature can also cause irreversible damage to higher brain centers involved in cognitive functions, as well as to more primitive centers controlling life functions. Recently, there have been demonstrations of the effects of lactic acid and increased core temperature controlling appetite. Both an increase in lactate and in body temperature effect a reduction in appetite and thresholds for satiety, lending support to the common observation that exercise assists in limiting appetite rather than increasing it.

Exercise and Stress. Research has demonstrated that events in the brain and the autonomic nervous system that serve the exercise response are the same as those in the stress response, including the release of naturally occurring pain killers within the brain, endorphins and enkephalins. These neurohumors seem to have the same effects on the body as morphine; relief of pain, permissive effect on sleep, and euphoria. When these compounds are injected into the hypothalamus of test animals they stimulate release of many of the stress hormones, including growth hormone and cortisone stimulating hormone. During exercise, the endorphin and enkephalin levels can increase markedly. This may well explain the reports of beneficial effects of exercise on pain, and its contribution to the sense of well-being and euphoria described with exercise. These are especially commented on by long distance runners

and other high performance athletes. The brain morphines are very powerful and there is evidence that their potency might promote an addiction-like phenomenon in long-distance runners. Certainly a psychological dependence on exercise and "withdrawal" symptoms have been observed. The brain morphines promise to be an exciting area for investigation for pain control, modification of depression and anxiety, and the treatment of drug addiction.

Another hormone involved in the stress response which is increased during exercise is prolactin. It may be of interest to note that levels of prolactin are also raised during sexual intercourse in women. Curiously, some aerobics participants report an increase in sexual performance that parallels their physical conditioning. There may be some correlation between these observations and changes in prolactin levels and other stress hormones during exercise.

Perhaps the most significant changes of all induced by exercise are those affecting the levels of neurotransmitters. Transmitter substances such as serotonin, norepinephrine and choline derivatives play pivotal roles in the maintenance of "normal" emotional balance. They are operational in all life processes by their role in triggering other events in the autonomic nervous system, higher brain centers, and glands and organs throughout the body. Changes in levels of transmitters have been implicated in depression, sleep dysfunction, altered behavior states, and mental illnesses. Exercise appears to have a salutary effect in these conditions by raising the levels of transmitters. The present management of many of these disorders involves pharmacologic interventions which may do the same thing, but at some risk.

Exercise and Sleep Patterns. It is noteworthy that sleep dysfunction may be intimately related to the levels of transmitters. There has been a long-standing association between depression, anxiety and altered sleep. Sleep dysfunction is also a common event in the aging process. We now know that sleep is not a steady state phenomenon but a dynamic process involving various stages appearing cyclically throughout the night. These stages involve changes in transmitter levels as well as varying intensities of sympathetic and parasympathetic nervous system activity. The importance of normal sleep with its appropriate "doses" of the different sleep phases cannot be stressed too much. The release of various hormones and active neurohumors is dependent upon this sleep-wake cycle (the circadian cycle) and on the amount of time the brain manifests the different sleep stages. This normal sleep is an essential part of good health and yet it is often not considered part of good health in the overall health status and medical evaluation. Exercise promotes positive

"resetting" of neurotransmitters and the normal sequencing of the sleep cycles. (See page 55)

Altered sleep patterns bring altered behavior. Changes in transmitter levels that result in particular types of sleep patterns tend to parallel those in various behavior or mood states such as depression or anxiety. Drug treatments for one tend to ameliorate the other by effects on transmitter levels. Likewise, drugs which tend to deplete transmitter levels cause both sleep dysfunction and depression, as well as other problems related to autonomic nervous system and hormonal function.

The changes induced by exercise "turn on" a great number of body systems and profoundly affect basic life sustaining functions such as breathing rate, heart rate, blood pressure, and thermal regulation. With the new information regarding the effects of exercise on endorphins, brain morphine-like substances and other transmitters, we have a biochemical and physiological rationale for encouraging regular exercise. The evidence is very strong that regular exercise also plays dramatically on what and how much we eat, our mood and feeling state. Exercise promotes that most essential experience, our sleep, and thereby plays an important role in slowing the aging process by its diverse effects on transmitters, hormones and biological events. It is no longer arguable that exercise is necessary; exercise *must* be a major part of the total program for stress control, fitness, brain health, and longevity.

The benefits of long-term exercise for reducing Alzheimer's disease are now better established as well. Recent studies of subjects exercising regularly at levels of at least moderate intensity for more than 30 minutes four or more times a week were compared to a sedentary group. MRI studies confirmed that the exercise group had a 1-2% increase in the size of the anterior hippocampus, a critical area for damage in Alzheimer's disease. The sedentary group over the same time interval had approximately 1–1.5% reduction in the size of the anterior hippocampus.

Now, that information does not state or imply that exercise will prevent Alzheimer's disease, but it does show that a critical memory center responds to long-term exercises like a muscle, it gets bigger and we believe that in the strategy to prevent Alzheimer's disease bigger is better! With that brief comment, let's return to our discussion.

Isometric Exercise. The second "type" of exercise that is essential to optimum fitness is isometric exercise, such as weight lifting or the use of resistance equipment (a set weight or force). These isometric exercises are very efficient fat burners and effect metabolic benefits for many

hours after completion (the same is true after brisk walking, cycling, or rowing).

Strength and muscle size are not the goal. The goal is repetitive exercise – sets of "reps" – over 10-30 minutes to burn calories, improve blood pressure, reduce stress and increase overall fitness including brain fitness. The exercise sets should be targeted to your level of conditioning, overall health, including blood pressure or heart concerns, and a plan for graded increase of number or duration of sets of the specific weight or resistance, best defined by an exercise specialist, at least at the beginning and until you are moving in a positive direction and can proceed on your own.

We recommend an exercise instructor initially so that you maximize the efficiency of your workout while protecting your back and joints. The "reps" (repetitions) or sets we recommend involve hand weights or free weights. We do not recommend barbell presses, squats or arm curls; they are simply too dangerous for the novice weight trainer.

There is another way to do this, however, and score your isometric points without ever lifting an ounce. In any position you are comfortable, or while walking, contract your muscles – any group of muscles or as many as you can recruit. Hold these muscles in tonic contraction or a time and release for a brief period, repeating this as often as you like with proper breathing technique. It can even become your isometric program of choice (see Fulmetrics). We recommend that you check pulse rate and blood pressure before, during and immediately after (as we do for weight or resistance training) both as a precaution and as a barometer over time of increasing muscle and circulatory fitness.

Establish your rhythm. If you increase your aerobic stress you will find that the second-wind phenomenon becomes established. This second wind is really the result of oxygen consumption being in equilibrium with oxygen utilization. This usually indicates that any lactic acid produced is removed at a sufficient rate so that a large excess is not built up at the time of completion of exercise. Your body will sense this as breathing and muscle activities synchronize, allowing you to feel the rhythm established. You will find this pace can be maintained considerably longer with progressive conditioning. The oxygen debt is much less and is replenished in considerably less time, reflected in a more rapid return of pulse and respiratory rates to their resting levels.

Learn to monitor your pulse. One of the best indicators of the effectiveness of your program will be the reduction in resting pulse rate, and the rapidity with which your pulse returns to normal after exercise. A

successful conditioning program will affect a 10 to 20 beat per minute pulse reduction and will bring the pulse close to normal within two to three minutes after completion of exercise. Of course, many other factors contribute to the pulse rate, including infection, drugs, foods, and beverages, sleep and ambient temperature. When you monitor your pulse changes on a regular basis these must be considered.

Ful-Metrics

As part of an isometric exercise program, or in place of one, we recommend a very basic and highly effective program of exercise called "Ful-Metrics" from "Fulcrum Isometrics". The fulcrum is your own body and the body axis, no machines or external resistances are employed. The isometrics "same length" indicates that these exercises are dynamic increases in muscle tension without full muscle contraction.

The beauty of this program is that you provide the levers, the resistance and the muscle tension of single, paired or universal muscle groups. The other great part of this exercise is that it can accomplish all of the goals of kinetic (motion or strength) exercises while you are at rest, sitting, lying down, relaxing, or in motion, walking, or while you are involved in mental work. Once the simple breathing pattern and the muscle tension work become habit you can simply plug in anywhere, anytime without any thought to technique.

You must begin with controlled breathing so that the slow air movement in and slow release of air from your lungs begins to feel as if you have completely filled and then emptied the airways. The key is slow, deep rhythmic breathing. This enhances the muscle work while defending the blood pressure and strain on the heart. You must avoid straining especially Valsalva-like breath where you inadvertently close your airway and strain down – a common mistake with weight lifting or resistance exercises. The Valsalva maneuver first drops your blood pressure (less blood is returned to the heart) while breathing out against closed airways followed by a rebound higher blood pressure after expiration. Slow, rhythmic breathing prevents this !

After a brief period of controlled rhythmic breathing, you can begin to recruit any or all muscle groups by simply increasing the tension in the muscles. This is a matter of tightening the muscle groups which is in effect short contractions without muscle group shortening, e.g., tightening biceps/triceps without flexing or extension against resistance. The same applies to any muscle groups you recruit; but remember that the slow in and out rhythmic breathing is the key to the muscle work in any

combination and sequence you wish, all the while continuing your controlled breathing. The breathing is key because either with hyperventilation or strained breathing (Valsalva maneuver) there is strain on heart and blood pressure.

You will immediately see that even with 15-30 seconds of Ful-metrics, the dynamic muscle tension you generate can be a huge calorie burner with more repetitions and more muscle groups recruited. But the caloric burn is only one benefit. You also tone up quickly at increasing fitness and strength levels and lower weight. It is our belief that this Ful-metrics approach is the best exercise prescription for anyone unable to do significant aerobic or ordinary isometric exercises, especially those with disabilities. But make no mistake, Ful-metrics is also as good as any, or better than, regular exercise programs when done consistently over time. And remember this, Ful-metrics can be done at any time, for as much time as you like, in any place you like, in any position you choose. Only two things are required: proper breathing and dedication to this incredibly simple program.

Target Groups

Breathing rhythm first; abdominal (Abs) crunches without crunching:

A.

1) Draw in and tighten Abs and hold
2) Press hands against Abs with heavy pressure
3) Continue to hold Abs while pressing Abs against hand pressure
4) Continue rhythmic breathing throughout 15-30 second "crunch"; Repeat as often as you like

   Above is the single best Abs toning available, and this best captures lumbar spine groups as well. Cost $0.00

B. For better burns keep Abs tight, rotate torso 60-90^{o} to pelvis and hold them alternately, etc. This recruits lateral abdominal groups ("love handles").

C. While sitting, lift one thigh against hand pressing against it while Abs are tight; rhythmic breathing; alternate thigh resistance.

Upper Body; Arms:

A. Hands in prayer position in front of chest, increase tension in hands and recruit arms, upper back muscle groups. (Lower back is recruited in the Abs crunches).

B. As above, recruit buttocks and thighs. Combining A and B intensifies caloric burn several hundred calories every 10-15 minutes.

Neck; Upper body:

A. Tension to neck-strap muscles and posterior neck muscle. Move head/neck any direction holding muscles tight. Great way to build protection to cervical spine.

All Groups:

A. While lying on back and supporting neck and back of knees, tense all muscle groups, legs first to neck muscles, all extremities, Abs and spine groups. Proper breathing is essential. Increase muscle tension for burn or lessen muscle tension to relax. Maximum burn with maximum tension to greatest number of muscle groups.

Enjoy your day while everyone else is knocking themselves out at the gym or lifting weights, etc.

Some Points About Exercise

1. Do medications interfere with the program?
   Yes. Heart, blood pressure, and circulation medications affect the heart's response to exercise but do *not* prevent you from walking. Check with your doctor about the specifics of this.
2. Can I go too fast?
   Yes. Initially, the pace should be gradual and both pace and distance increased gradually. The point is that this assures proper conditioning rather than cardiac "stress."
3. Should I skip the program at all?
   Yes. Every 4 to 7 days take a day off. This reduces boredom and fatigue.
4. Should I have a stress test (EKG test) before initiating the program?
   Most of you will not require it but if there is a family history or you have significant risk factors, it would be prudent to do so.
5. Why not run or exercise to maximum heart rate?
   You can if you are able to, adjusted for age, if you are heart healthy and in peak fitness.
6. Which is better, speed or distance?
   A moderate pace over a longer distance conditions better.

7. Should I walk if I feel under great emotional stress?
   Absolutely. Fifteen to twenty minutes of brisk walking can reduce your anxiety level dramatically.
   1. Learn to "stretch" walk with your upper torso held back and the pelvis and hips held more forward so that you are walking off your heels fast. This allows you to stretch your walk and tighten your abdominal and back muscles. By pushing off of your heels fast you also increase the metabolic work of your walk.
   2. Increase both pace and distance in the best timeframes for you. Both are important for your conditioning.
   3. You should try to include light weight training 2.5 to 10 pound hand weights, with various sets of repetitions 10-20 reps at a time. At all times support your back by lying on a bed with your neck supported, or in a chair with your back supported. Both flexor and extensor reps should be done as part of your total program to give you both isotonic (walking) and isometric (weight) conditioning. Low impact weight reps, incidentally, are very protective against osteoporosis.

QUESTIONS:

1. All exercise is the same.
   ❑ True ❑ False

2. With Isometric exercise the calories you burn equal the number you eat.
   ❑ True ❑ False

3. Regular, moderate exercise decreases:
   a. Blood pressure
   b. Weight
   c. Dementia risk

4. You should push your heart to the max for your age.
   ❑ True ❑ False

5. Exercise will help you sleep.
   ❑ True ❑ False

6. Exercise is an antidepressant.
   ❑ True ❑ False

7. Rapid decline in pulse after exercise is:
   a. Cardio protective
   b. Slows hardening of the arteries
   c. Not a factor in health

8. Exercise can "burn down" stress hormones.
   ❑ True ❑ False

9. Exercise in old age:
   a. Slows aging
   b. Improves your balance
   c. Make no difference

10. "Fulmetrics" exercises:
    a. Are very efficient
    b. Tone muscles
    c. Not as good as running

SECTION 2

PART IV – STRESS AND ITS MANAGEMENT

Stress is the term we give to the psychological and emotional "hits," brief or over-extended periods of time, which set in motion the complex physical and chemical changes which we identify as the "stress response" (see the section titled "Stress Response and the Brain" which begins on the next page; also see Figure III). But stress can also be "positive," and essential insofar as the individual adapts to stress and uses it for positive outcomes, so called "Mu stress" since one of the chief effects of positive stress is to increase brain morphines, endorphins, in the brain's Mu receptors (see "Meditation"). It is precisely that tension between good stress, harmful stress and its dangers, and our ways of adapting to that stress which we emphasize in this section. After all, stress can kill but it is also true that without stress there would be no achievement. Stress exists and it is a major driver of our health as the "first responder" reactive system in the body against harm, danger or emotional distress. The stress response is not set in motion by us, it is a "reflex" but with discipline and practice we can begin to tame it and reduce its negative effects on brain and body.

So much has been written about stress and stress management that it is stressful just to go through it. Thinking too much about your stress is a stress disorder. On the other hand, stress response modification is essential for disease prevention and life extension. Your response to stress, which can drive the neurochemical and autonomic nervous system in the stress response, is a major determinant of life expectancy, the biology of aging and brain health and function.

What is the stress response? It is a primitive survival mechanism which prepares the organism for physical threat. In human beings, the stress response is much more complex because of conscious awareness and the capacity for self-reflection. Here stress can turn on the subject and become harmful, even deadly.

Neurohumors (brain hormones) and neurotransmitters (chemical packets which transmit signals in the brain) are released in an immediate reaction to a stress stimulus as the body prepares to protect and resist. The harmony of the response is exquisite: muscle tense, pulse accel-

erates, blood pressure elevates, breathing quickens and blood surges to vital centers. The person who moments before may have been resting is now at peak awareness, maximally prepared for physical resistance and exertion. With physical execution the biochemical and neurohumeral inputs to the response are dissipated.

Contrast this to a situation in which an emotional threat is received over a longer period. The mediators of the stress response don't "pulse" abruptly, rather there are more subtle and sustained changes involving the very same mediators. As the stress is both different and unrelieved, the rapid diffusion of the mediators does not occur because the stress response is not focused. Since there is no physical execution, and therefore no release, the mechanism of survival then becomes the agent of illness and even death.

The Stress Response and the Brain

The brain acts as both trigger and target, the neurophysiologic trigger wired to its target organs, especially heart, gut, vascular, immune and hormonal systems. But this neural trigger can also turn on itself; the brain trigger becomes the target brain. When all of these pathways are activated the brain is working as a cybernetic system at the crossroads of psyche and soma, brain and body. Virtually any disease can be connected to this, including the neurodegenerative diseases and Alzheimer's disease. Likewise, the stress response and the reciprocal firing of the trigger and target may be the most important driver of accelerated biological aging, after the genetic factors. Virtually all of the proteins, pathways and molecules discussed previously are part of this, and all of them are modulated by the stress response, acutely and over time.

Mediators of the stress response incorporate diverse brain systems which affect the entire organism, but the primary roles are played by the autonomic nervous system and the hormonal systems of the body which are under the control of vital brain centers. One is in the brain stem, phylogenetically more primitive, containing centers that control breathing, blood pressure, and heart rate. The other is the hypothalamus, a brain center that integrates signals from various organs and glands. We could call it a brain switchboard. Through this function the hypothalamus modulates hormonal release by its control of the master gland, the pituitary. The pituitary gland, responding to signals from body organs through one limb of the autonomic nervous system, from the pineal gland and from the hypothalamus itself, then sends out hormones which stimulate the adrenal gland, the thyroid gland, the pineal gland, and the release of growth hormone. These release a second wave of hormones,

such as body cortisone, which is a major stress hormone. In addition, the autonomic nervous system stimulates another part of the adrenal gland to release another important stress hormone called adrenalin. Growth hormone and thyroid hormone may also function as stress hormones, as can hormones which control salt and water balance and circadian (twenty-four hour) rhythms. There are many other hormones which interact in countless ways, depending on the nature and the duration of the stress applied. The net result of all of these interactions is the stress response with its changes in blood pressure, pulse, breathing, endurance, and muscle strength. (See Figure III, IV)

Acute stress, which elicits the immediate "flight or fight" response, releases hormones and mediators abruptly, and in huge amounts. In ongoing stress, hormonal release may be less intense but more prolonged. These sustained releases of hormones take on an added significance because of their effects on body rhythms and basic body functions. In the normal relatively unstressed state, the hormones which we have mentioned follow a circadian rhythm, fluctuating or oscillating release over a twenty-four hour period, all mediated by brain centers. Growth hormone levels, for instance, tend to peak about one hour after sleep begins. Body cortisone tends to peak early in the morning and fall off late in the afternoon. Severe stress can alter these oscillations, and the impact on sleep can be significant and might partially explain the sleep disturbances we see in stressed individuals. The pineal gland may also play a role in stress-related sleep disturbances as its hormone, melatonin, peaks at night and may regulate the biological clock of other organs and glands. The effect of body hormones on organs may persist for extended periods following the drop off in their release, a phenomenon known as hysteresis. Also, long-term exposure to the stress mediators, especially adrenalin, and cortisol may reset target organs so that lower amounts of mediators produce the same effects.

Long term release of stress hormones and transmitters impairs body function. Sustained elevation of blood pressure and sleep disturbances are obvious results of this. Continuing elevations of cortisone can impair the body's immunity and thereby reduce its resistance to infection, perhaps even to cancer. Cortisone can also break down body proteins and elevate the blood sugar, as can the growth hormone. Changes in the levels of these hormones and in thyroid, salt, water, and sex hormones can alter behavior and mood. The metabolism of fats and cholesterol as well as sugar can also be affected. Adrenalin has even been shown to damage heart muscle directly. Another family of compounds, not strictly hormones, altered in stress is the prostaglandins. These can produce changes which can contribute to ulcers, asthma, and blood clotting.

Stress and Sudden Death, the Brain as Trigger

Sudden death is the ultimate expression of the stress response, and it occupies a special place in the mythology of death. In the literature on sudden death the elements of witchcraft and voodoo mix with science and psychology. Most of us know someone who dies suddenly, or at least can relate an incident told to us about such a death. Very often the stress factor is emphasized, but there are many incidents of sudden cardiac death in which a stress factor was not identified. Even in these patients, however, stress may well have been operational. In fact, there is a growing suspicion among doctors that very few sudden deaths occur without some warning to the victims, a warning somehow linked with the stress element. There are situations which are commonly associated with sudden death in the popular consciousness; anniversary reactions, grief reactions, and events evocative of great feeling come to mind. Death often comes to spouses of decedents around the anniversary of their passing. The death of a relative or a close friend can quickly follow the death of a loved one. Death can follow soon after a major life crisis or a personal triumph or a reunion, and after events with great mystical impact, as with priests involved in exorcism. All of these indicate the tremendous power the psyche holds over soma – mind over body.

We recall a "dehexing" in a large New Orleans hospital some years ago. A woman was brought to the ward in an uncontrollable panic, fearful for her life. A voodoo priest had cast a hex on this poor woman which in her culture meant death. Her blood pressure was dangerously high, her pulse extremely rapid, and she was sweating profusely. We were concerned about a cardiac catastrophe. Very soon after her arrival her family gathered quickly, accompanied by a "priest," but it was apparent that an elaborate ritual was accomplished with chanting, gibberish and screaming. The woman became calm and secure, saying that spirits had been driven from her and that her life was saved. We believe that if it were not for the "dehexing," she would have quickly died of overwhelming fear resulting in fatal cardiac arrhythmia.

Some classic experiments with rats demonstrated that loss of control or a sense of futility experienced by animals in stressful confrontations caused their sudden death. For example, if rats are placed in containers of water after their whiskers are removed they die within minutes, presumably because they feel helpless without a primary mode of contact with the sensible world, the whiskers. Other rats shorn of whiskers but trained to adjust to increasingly prolonged immersions could remain in the water several hours; their training had reduced the stress factor. In crowding stress, when animal populations exceed normal density,

sudden death is often seen among the inferior animals. Autopsy studies show that many of these had adrenal gland swelling or hemorrhage and evidence of severe blood stream or parasite infections. Zoo captivity stress also causes sudden death, unusual behavior, or aggressiveness. Animal psychologists suggest that in these stress states adaptation is lost and "emotions" turn on the stress response, leading to bizarre behavior or sudden death.

The changes in the adrenal glands in these aversive stress experiments mimic the finding of adrenal hemorrhage in humans with overwhelming physical stress, usually related to infection and shock. The adrenal hemorrhage is the result of multiple factors, perhaps even the wipeout of the production of cortisol in the adrenal cortex, cortisol being the first and most important hormone to respond in defense of physiological stability in biological stress, e.g., infections, trauma, surgery, blood loss or tissue injury.

Cortisol has a different role in psychological stress, where it turns on the body and wears down the immune system, disturbs circadian rhythm and damages brain cells, as well as "resetting" many of the cell signals and molecules designed for defense but now damaging organs and disrupting metabolic systems.

The pituitary (brain) adrenal gland/axis is the key feedback circuit in maintaining cortisol levels which normally peak at 8a.m. at levels twice as high as they are at 8p.m. This is one reason why we feel worse at night if we have a cold, sore throat, arthritis, and many other symptoms, the symptoms of which daytime cortisol can cover.

The main switchboard for managing cortisol is located in the hypothalamus, which we describe in stress and sudden cardiac death. In regards to cortisol, however, and other key hormones especially thyroid and growth hormone, the hypothalamus releases or holds back respective stimulators (e.g., cortisol release hormone (CRH) or thyroid stimulating hormone (TSH) which sends messages to the anterior pituitary to signal release of the target hormone to engage its target organ. Likewise, neuropeptides released from other hypothalamic centers control the release of antidiuretic hormone (ADH), also known as vasopressin, an essential hormone for water balance and fluid and vascular defense in shock or hemorrhage. The hypothalamic centers also signal for prolactin release factor to stimulate breast feeding, and in stress as a putative defender of homeostatis.

This is precisely the point. The psychological backdrop and the subjective elements in stress can place people at risk for sudden death. This

woman was manifesting a response not unlike those described in voodoo. It is safe to assume she has been raised in a cultural milieu which reinforced the validity of voodoo curses, black magic, and other rites. Accordingly, she was prepared for the inevitability of the pronouncements made earlier, in her case perhaps related even to her death. We must suppose that as the time approached for the unwelcome event, whatever it might be, she became increasingly anxious and stressed. Her psychological set was one of anticipation of some calamity, and so she worked herself to a point at which the earlier pronouncement would be self-fulfilling. This reveals the power of the psyche and the potential of the stress response. If all of the elements of the response were activated at the "appointed hour," this woman would have died.

We recall two patients with severe financial and personal (marital) stress. One was hospitalized in a CCU on a cardiac monitor. When his wife tried to enter his room, his EKG tapes immediately registered changes of acute injury to the heart muscle. He was sedated, she was removed, and his EKG returned to normal! This occurred a second time when she tried to see him again, with all of the changes on his EKG of diffuse coronary artery vasospasm, non-fatal because it was very brief (10-15 seconds). This case captured the intensity and danger of salvos of nerve impulses traveling from cardiac centers in the brain down both sides of the neck (sympathetic tracts) to heart rhythm centers and the coronary blood vessels. The patient could have died immediately from either sustained arterial spasm or from a fatal cardiac arrhythmia, ventricular fibrillation.

The second patient entered the hospital for control of severe hypertension. Curiously, he described large bumps on his arms and legs when his wife confronted him. They were in an extremely tense and volatile relationship, and it was taking a great physical toll on the husband with severe sleep deprivation and very accelerated and refractory elevations in his blood pressure. In the hospital, his wife suddenly entered his room and raised some personal issues, almost immediately giant urticaria (hives) formed on his forearms. When his wife was asked to leave the urticaria began to clear. A neural trigger targeted his skin and blood vessels, the hives resulting from a volley of nerve discharges releasing chemicals into the mast cells of the body, releasing histamine and other chemicals causing urticaria (and potentially many other events). The sustained blood pressure elevations were likewise "sympathetically" mediated but we do not know about the role of other bioactive molecules and neurotransmitters on this, or other physical-chemical connections, between psyche and brain, and the non-physical triggers as well.

These two patients sound "exotic" when in fact, millions are at risk because of stress, sleep loss and circadian dysregulation, especially harmful when there is ongoing unresolved conflict, anger, guilt, and perhaps worst of all hopelessness. "My situation will never end," "I'm in an impossible position," "I'm trapped." No matter the cause, these are alarm signals for sudden death, and psychological "autopsies" of sudden death victims revealed severe acute or ongoing stress in most of them.

Brain Trigger, Heart Target
Aversive Stress and Cardiac Arrhythmias

Animal research has provided us with a great deal of knowledge about sudden cardiac death and stress. In now classic experiments with dogs forty years ago, it was shown that repeated low dose electrical shocks lowered the dogs' susceptibility to ventricular fibrillation, a fatal arrhythmia. With multiple repetitions the electrical dose could be progressively lowered or even eliminated and the dogs would fibrillate just on seeing the electrical wire. When the dogs were sedated and shocked, nothing happened proving that it was the mechanism in conscious aversive stress that killed them, not the electric shock.

These experiments helped define the critical role of the Autonomic Nervous System (ANS), particularly the sympathetic arm of the ANS, the arm that prepared for flight or fight to defend. The problem comes when a system factory set for defense goes on offense against its owner. [See Figure IV, V]

First of all, the term "autonomic" suggests automatic, that is, a system not directly under conscious control, operating rather as a complex reflex, and that is true. On the other hand, the cortical brain, especially the frontal cortex, immediately responds to stress as a matter of consciousness, and it is at this intersection between the autonomic reflex response and the conscious response where we meet the brain-mind problem. Which, in fact, is the first trigger in so many physiologic responses, brain (cells, chemicals and molecules) or mind, a power beyond cells and chemicals?

The frontal cortex is the conscious loop of the feedback between the emotional and stress response; limbic/hypothalamic centers, limbic meaning the borders between higher cortex and the mid-brain where the hypothalamus, hippocampus and amygdala and other centers are located. It is more a functional distinction than an anatomical one insofar as it is automatic as well as under cortical signaling. The hypothalamic

centers are the main relay system for flight or fight states, signaling back to the frontal cortex and downstream through the brain stem to the spinal cord. (See Figure IV)

The first responders at the reflex level of the sympathetic system are nuclei in the posterior hypothalamus, in close proximity to nuclei that send the release factors to the pituitary, as described. These sympathetic nuclei lie astride the floor of the third ventricle in the hypothalamus, and from there signals are sent to major noradrenergic nuclei in the brain stem, especially the locus ceruleus (LC) in the pons and nuclei on the ventral lateral medulla, the lowest part of the brain stem, which connects to the spinal cord and is protected by the cervical spine.

The electrical system of the heart is extremely sensitive to input from the sympathetic system. Both physical and emotional stress can accelerate the heart, but, importantly, usually only the inputs related to emotional stress induce abnormal heart rhythm in a structurally normal heart (normal muscle, normal size). The various arrhythmias can include fatal ventricular fibrillation, as in the dog experiments. As a result of salvos of norepinephrine, and adrenalin from the adrenal medulla, there is a lower threshold for heart muscle irritability and sudden death.

Norepinephrine is delivered via nerve roots that exit the spinal cord and join together to form ganglia, bundles of NE nuclei in the neck, the inferior (stellate) ganglia being the most important for the heart. Another ganglia along the spinal cord at the abdominal level, the celiac ganglia, stimulates the adrenal medulla to release adrenalin which also works on the heart, and the blood vessels throughout the body with norepinephrine. Adrenalin adds a huge power boost to muscles and acutely increases strength, speed and resistance to muscle fatigue in the acute stress flight or fight event.

Norepinephrine can also bombard the heart muscle directly without effecting heart muscle depolarization and fatal arrhythmias. Catecholamines (the family name for NE, Dopamine (DA) and Epinephrine) damage the heart muscle and can dilate the heart and weaken it. Takosubo cardiomyopathy is one such syndrome, in which the apex of the heart "balloons" out and weakens. The patient can experience all of the symptoms of a heart attack, but the coronary arteries are normal and free of clots indicating the damage is due directly to catechols.

These same catechols (NE and E) can cause coronary artery spasm and a classic heart attack as well as fatal arrhythmias secondary to the loss of oxygen to the heart muscle beyond the area of spasm, a variant of that spasm syndrome is known as Prinzmetal variant, often occurring

in the early morning, often during sleep, with either heart muscle damage or arrhythmia. Usually a narrower segment of the coronary artery lies just above the area of spasm. We do not know if this variant is due to the release of local metabolites unrelated to norepinephrine, or if local catechol activity is the main cause of the variant.

All of the events we have described thus far can occur in otherwise normal subjects with normal hearts and blood pressure, both of which destabilize from acute or chronic stress, especially the stress of a long standing unresolved conflict, which bears down on the heart, the immune system and the GI tract.

A brief comment, the other arm of the ANS, the parasympathetic or vagal system, is also primed in hypothalamic centers which signal the nuclei of the 12 named cranial nerves, the vagus nerve being the 10^{th} N. The chief functions of the vagal system include slowing heart rate and breathing, and promoting digestion and other gastrointestinal functions.

The vagal system is very sensitive to stress, considering that the presynaptic part of the system is under control of norepinephrine, as are all of the synapses of the sympathetic system. The difference lies in the post synaptic vagal system where acetylcholine is the neurotransmitter, the same neurotransmitter which functions as the memory neurotransmitter in the brain neurons. Keep in mind that there are more neurons in the gastrointestinal tract than in the spinal cord and you immediately understand how psychic stress hits the GI tract so hard, with the resulting gastric ulcers, colitis, Crohn's disease, irritable bowel and mobility syndromes, all of which have "connections" to chronic stress.

Animal subjects have fatal and non-fatal cardiac arrhythmia provoked by aversive stress, and similar experimental data confirms the clinical fact in humans. Even the ancient Hippocrates intuited the risk of emotions on the heart, "Anger doth contract the heart, and strong feelings fell the man." Therapeutic verification of this intense neural trigger-heart target axis-comes from fifty years of successful "blockage" of this with beta blocker drugs, and if they fail, removal of the left stellate ganglion along the sympathetic nerve tracts in the left side of the neck. In dogs subjected to adversive stress ventricular fibrillation, this stellate gangliectomy virtually abolished the risk. Other animal studies showed that electrical stimulation of brain centers that exert control over the heart through the autonomic nervous system reduced the threshold for heart fibrillation.

Heart fibrillation is the usual event associated with sudden death. In fibrillation the heart generates its own chaotic electrical signals which

cannot induce an appropriate contraction of the heart muscle. Blood is not pumped and death is rapid. Though these electrical signals are intrinsic to the heart, the heart also receives impulses from higher centers, particularly the brain stem, the hypothalamus and cortex, and the impulses travelling along the autonomic nervous system. Stress can increase the activity in all of these centers and cause salvoes of impulses to travel to the heart's own pace maker cells making them respond chaotically. Loss of oxygen to the heart muscle can also generate these chaotic signals and the fibrillation of the heart muscle. This, incidentally, is what often happens in heart attacks when a coronary artery that supplies blood to the heart muscle is blocked by a clot or goes into spasm. Even the clot formation, however, and certainly the spasm of coronary arteries can be related to stress factors with inputs from higher centers. The stresses can set off an imbalance in the autonomic system and cause the spasm of the arteries. Very recent studies demonstrate that this spasm is a common cause of heart attacks and gives further weight to our concept of stress in sudden death. (See Figure IV, V)

We hasten to point out that even though sudden death seems to be just that, it may not be. When someone collapses and dies quickly, we assume that all the events involved with this were immediate. It may be, however, that ongoing psychological stresses of weeks, months, and even years altered basic cardio-vascular and other body functions in such a way that the final "sudden" episode might have been predictable. There is no question that everyone involved in health care, especially in its preventative aspects, should be looking closely at the predictors of sudden death, and use these to fashion interventions which might prevent their unhappy conclusion. The point is this, sudden death may not be so sudden, and sudden cardiac death may be primarily psychological sudden death, and not cardiac death. But the long-term effects differ from the short-term risk. Over time repeated brain trigger events will target the brain as well. Brain cells will be damaged and the long-term risks for cognitive decline and Alzheimer's disease increased.

Stress and Brain Disease, the Brain as Target

The brain is the most unique organ in the body because it presents the physical and chemical backdrop for the rational (and irrational) mind. It is also unique in that the brain is both the trigger organ in the stress response and the target organ – it suffers the consequences of its own action – functioning both reflexively and consciously. We said in the beginning of this section that the stress response is automatic – we cannot modulate its neurohumoral cascade. Yes, that is true, but only up to a point, the point of our own consciousness. After all, lit is our

conscious awareness of a stressful event that "triggers" the automatic response. It is likewise with various modalities (biofeedback, hypnotherapy, cognitive therapy, prayer, meditation, exercise) we can bring the response under some control. We may become good enough at our own conscious override of these complex phenomena that we learn not to react to our stresses and thereby hold back the neural and chemical surge that would otherwise come.

There is another consideration, however, regarding stress and the brain. And this is the long-term biological effect of emotional stress on the brain cells, especially the neurons. You recall from our discussion that many inflammatory molecules and hormones (especially cortisol) are continuously pumped into our blood with ongoing stress. All of these chemicals pass through the blood/brain barrier to directly hit the neurons (our "thought" and "memory") as well as the immense microvascular reservoir that nourishes them. The neuron is exceedingly sensitive to this as it is a cell which has only a thin and highly porous outer lining or cover, comprised mainly of fats, phospholipids. These are easily oxidized to become toxic, a highly inflammatory species which are hitting the very cell, the neuron, they are supposed to shield. Now you have two phenomena linked together, the release and oxidation of fats and other molecules in the blood that washes over the neurons, and the neuron's own cover becoming toxic and reactive as well. (See Figure I).

This perfect storm of chemicals summoned by stress and the neural trigger then alters brain DNA by epigenetic-dysregulation, especially mitochondrial DNA, loading the brain with toxic forms of protein as a result of inflammation, abnormal glycation and failure of the waste removal system in the neurons. This can also occur with glial cells which were believed to have only structural support functions but are now identified as actively participating in memory-cognition. Both neurons and glial cells are damaged in the stress response with the resulting cognitive impairment and increased risk for dementia and Alzheimer's disease.

There are other pathways activated in this stress-induced brain "storm" as well, including blood platelets, the first responders to injury or inflammation in the tiny arteries in the brain reservoir, and the large arteries that feed that reservoir, such as the carotid arteries. In many cases, the platelets respond to inflammation by moving in and then releasing their own aggregating and pro-inflammatory molecules. This sets off a second wave of clotting which can then initiate a major stroke or flood the reservoir system with tiny clots which plug the terminals of these vessels and damage the neurons by depriving them of oxygen and nutrients, while at the same time kicking up more inflammation.

The stress response sets up all of the conditions for long-term brain cell damage years after the stress has lessened. The neuron is the perfect target, as we have already outlined. For one thing, neurons are the only cells in the body that do not renew vigorously. In great measure, when they are gone, they are gone. The exception to this is the effect of adult stem cells (ACS) or progenitor cells from bone marrow, e.g., from the olfactory bulb in the tips of the nose which contains neuronal cells. Even progenitor cells from fat tissue, and a particularly good source of very undifferentiated cells, cord blood can serve as effective stem cell lineages. In the brain, for instance, olfactory bulb cells might quite easily morph into mature brain neurons, or precursor monocytes or macrophages in the bone marrow might morph into the microglial "immune" cells of the brain.

At the cellular level it might seem reasonable and predictable that this could be in principle, but scientists still cannot outline the specific protein and molecular triggers for this transformation. It is as if progenitor cells "read the field" and travel to injury or inflammatory sites in the body (e.g., brain with Alzheimer's disease or stroke, or heart after heart attack) to start repairing and forming new cells. This is certainly what happens as a "learned response" by stem cell progenitors to remote damage in other organs. Scientists have been able to de-differentiate or return to a more primitive state some cells by a technique called induced pluripotent stem cell (IPC) production by blocking protein or molecular triggers that cause the cells to differentiate or mature, but that still does not explain how the induced pluripotent cell knows where to go and what to become. The specific mechanisms have not yet been worked out but adult stem cells and IPC are already working in spinal cord repair, heart muscle repair and in some animal models of neurodegenerative disease. The implication for stem cell medicine, but only adult stem cells or IPC, not embryonic stem cells, are very exciting. The objection to embryonic stem cells (ECS) are biological; they overcommit, they are oncogenic, they don't work, and they violate an order of nature and life we simply should never trespass.

Something else about stem cells: they perform their progressive transformation just as any progenitor cell. They decompose vitally, which means that as they mature and differentiate to pass into new cells, they don't pass on! With embryonic stem cells, we face an entirely different reality. Those cells destined to become a human embryo are diverted to become tissue cells in another person. The embryo never gets the chance to become its own person.

We should mention glutamate and gamma amino butyric acid (GABA) here as they are the major excitatory and inhibitory neurotrans-

mitters in the brain, both of which are profoundly affected in stress, even though we do not measure these or follow the perturbation in these neurotransmitters by any specific clinical monitors. The effects are presumed (e.g., anxiety, agitation, other behavioral changes (increased glutamate and decreased GABA) or "penumbia" brain injury in stroke or trauma (increase glutamate)). By and large, then, in stress disorders glutamate is overactive and the synaptic inhibitor GABA is dampened.

Glutamate is an essential neurotransmitter for immediate memory encoding, particularly robust in the hippocampus, the area of the brain which is an early casualty in Alzheimer's disease. Glutamate promotes long-term potentiation (LTP) (i.e., synaptic "memory" by stimulating NMDA receptor sites amplified by increased calcium). LTP translates into the molecular event of synaptic or neuronal plasticity, the synapse hangs on to the memory chemical longer which means the memory sticks, all of which is completely ridiculous when you think about it. No multiple of synaptic memory is going to either produce or hold on to a memory, for memory too, is thought, and thought equals mind.

In any case, the message is that the brain is generously populated with NMDA glutamate receptors for memory and AMPA glutamate receptors for excitation (which could be injurious in the stroke-trauma setting). GABA, on the other hand, is anxiolytic, it cools down the emotional content, and GABA receptors are also generously sprinkled about, along with Benzodiazepine receptors which occupy a part of the $GABA_A$ receptor domains. Commonly used "benzos" such as Ativan, Xanax, Valium or Clonazepan tag to $GABA_{A1}$ receptor sites where they are more anxiolytic, or $GABA_{A2}$ where they are more sedative hypnotic. Obviously, the disturbances in acute and chronic stress require more GABA to offset the excitatory and toxic glutamate; the perfect short-term fit here is increased synaptic GABA via Benzodiazepines acting at the receptor sites at GABA sites.

This part of the dynamic of drug management in acute psychic stress, also in relation to management of depression (e.g., serotonin) and addiction and dopamine. In fact, all of these neurotransmitters are changed in stress, especially in effects on sleep, as all of the major neurotransmitters (norepinephrine, serotonin, acetylcholine, histamine and dopamine) are built into the "limbic" sleep-arousal-feeding system along with orexins. As sleep and feeding can be dramatically affected in stress, we note the complex interplay of all the major neurotransmitters and neuropeptides, both brain neuropeptides and gut neuropeptides, referenced within this book under the section on the autonomic nervous system, and the rich supply of neurons in the G.I. tract, especially the small bowel and the pancreas. (See figure V)

We have identified only a few of the players in the extraordinarily complex and as yet little understood or marked out pathways and how specific molecule actors engage each other but many of those actors, we have seen, damage the arteries of the heart and form highly inflammatory lipid plugs in the same way that we believe they can generate toxic neuron-killing proteins n the brain lending to progressive cognitive decline and Alzheimer's Disease.

In summary, then, the stress response is a lifetime risk, and the prevention of heart disease, stroke and dementia requires assiduous attention to risk management, both of the primary stressors (psychological) and the secondary neurochemical and hormonal pathways (physiological). This is absolutely essential to brain health. Putting this another way, brain health is essential to your overall "health" and both need your stress response to be under your control to the greatest extent possible.

QUESTIONS:

1. Stress is a primary risk factor for all diseases.
   - ❑ True ❑ False
2. Stress can:
   a. Increase blood pressure
   b. Increase stroke risk
   c. Lead to Alzheimer's disease
3. The stress response includes:
   a. Brain trigger
   b. Heart target
   c. "Flight or fight"
4. Primary stress hormones include:
   a. Cortisone
   b. Prolactin
   c. Estrogen
5. Primary stress mediators include:
   a. Adrenaline
   b. Prostaglandin
   c. Gastric acid
6. Long-term stress can:
   a. Cause immune disease
   b. Lower immunity
   c. Increase risk of infection
7. The heart and vascular system are the first targets of acute stress:
   - ❑ True ❑ False
8. The stomach is a target organ of stress:
   - ❑ True ❑ False

9. Stress on the heart can be lowered by:
    a. Drugs
    b. Cutting nerves to the heart
    c. Stents
10. Stress-related sleep disorders are the most common causes of insomnia:
    ❑ True ❑ False

SECTION 2

PART V - MAINTAINING BRAIN HEALTH

Everything we have reviewed thus far, from risk factors to laboratory assessments to self-assessment and preventive strategies, is essential to brain health. All of these must be part of your comprehensive plan for lowering disease and dementia risk. There are several other modalities we will briefly review now as they are equally important to you. The difference is they depend completely on you, you must have them in your "psychological tool box" and take them out on an ongoing basis for the rest of your life. None of these are mind altering techniques primarily, rather they are mind techniques which can alter your brain chemistry. Good brain chemistry then becomes the essential part of your work for stress control and dementia prevention. These techniques are for long-term optimization of your chances but the benefits begin immediately. These techniques are non-interventional, non-technical and risk free, and they are essential!

The successful management of stress symptoms include both the recognition of inducing factors and a holistic program to control them. The program will incorporate a reevaluation of proximal and long-term goals, consolidation of psychological responses, exercise, proper nutrition and conscious manipulation of some of the physical events of stress. This can be accomplished through hypnosis, biofeedback, meditation or prayer – all incorporating essentially the same psychological devices. Music therapy, humor therapy, group therapy, and other approaches have also been popular historically, and we now recognize them as valid therapy for stress control and good health. The "mind" exercise programs, such as meditation and hypnosis, can reduce the bodily changes in stress. The physical exercise programs dissipate the "chemicals" that control these bodily changes. Hence both types of exercise (mind and body), control the stress response and promote health. We begin, then, with some psychological work" for you:

1. Identify *three* areas of psychological pressure or emotional demand in your daily life. Try to select those which cause you the greatest anxiety or distress and which relate to work or home life or both. As helpful hints in recognizing these, consider which

ones occupy your thoughts frequently, cause sleep disturbances, or are a source of anger, resentment, or controversy with co-workers or family members.

2. Initiate an *active* program in those three areas to bring them under your control. The single best thing you can do for yourself, after identifying the problems, is to discuss the problems with those who are part of the problem or who may be helpful in their solution. Communication and dialogue are necessary and therapeutic. Any strong feelings (good or bad) which are disguised, held in or dwelled on can cause emotional and physical illness. Express your anger, frustration, guilt, desires, and needs appropriately. You must *verbalize*, not *internalize* !

3. List improvements in your own behavior or response which you can make to better the situations which are troubling you. Review these actions regularly and chart your progress.

    - Am I communicating better?
    - Do I make my feelings known?
    - Do I give the other person a hearing?
    - Are things as bad as I picture them or do I magnify and distort events?

    1. Ask others who are involved with you on a regular basis (spouse, children, co-workers, and friends) what you can do to improve relations.
    2. Select a hobby, exercise program, or a service project which you might enjoy that will bring positive elements into your life. Develop this regularly.
    3. Take active steps to help someone else who is hurting. Nothing makes you feel as good as your "therapy" for someone else.
    4. *Practice* relaxation. Enjoy some time alone each day to reflect on positive steps for your total sense of well-being. No matter how difficult your economic or personal situation is, you need time for *you !* Learn how to meditate, pray or use hypnosis for your relaxation and awareness.
    5. Reduce your material needs. It is amazing how many necessities are really costly luxuries which you can dispense with and lighten your burden.

6. Make a decision. If a difficult choice presents itself, we tend to work over the implications of different responses to the point of heightened anxiety and mental distress. There is incalculable benefit to taking a stand and moving ahead. If it is true that "most choices are between the disagreeable and intolerable," it is true until the decision is made. Then relief and fresh resolve can follow.

Medical Hypnosis

Let us quickly distinguish legitimate medical hypnosis from other brands. Medical hypnosis is conducted by a trained therapist skilled in directing the subject to focus and concentrate for a specific therapeutic endpoint (e.g., smoking cessation or phobia control). At the same time the subject may be asked to separate various cues or triggers mentally or "unfixate" attention or obsession, in relation to habits, phobias or such issues as insomnia, overeating, even anxiety disorders or substance dependence. Here it must be noted there is considerable overlap between the goals of hypnotherapy and biofeedback, especially EEG Biofeedback.

In this method of biofeedback the subject consciously by concentration, willing and thinking the result, alters EEG patterns, even functional MRI or PET scan imaging, as part of reaching the therapeutic goal. Hypnosis is an altered awareness, actually a change in direction of focus, whereas biofeedback is active, engaged "wide awake" focus to endpoint. In that sense, they are different modalities but in the sense that they represent mind over brain techniques they are therapeutic cousins.

Hypnosis represents a method of achieving an altered or heightened state of consciousness-awareness for stress control. Self-hypnosis is easily accomplished by repetition of induction exercises (as also applies to meditation). There are several key points.

Hypnosis is a conscious state, not a sleep state, and as such depends on many factors which can vary from day to day (diet, level of arousal, fatigue, stress level, receptivity and expectancy).

A necessary requisite for entering the hypnotic state is the exclusion of analysis of the induction exercise. The mind focus must be directed away from the hypnosis experience itself. In other words, just let it happen without scrutinizing the experience.

A simple induction exercise would follow these general lines:

1. Assume a relaxed position, preferably lying down.
2. Allow your jaw muscles to relax.

3. Visually focus on an object and fix your attention to it. A small object or logo on the ceiling will do nicely.
4. Allow the sensation of heaviness in the eyelids to ensue. You may open and close the eyes as you like "reflexively."
5. Relax the body muscles by beginning with the facial muscles.
6. Work through the large muscle groups down from the head, relaxing arms, abdomen, legs and feet. (The muscle relaxation may take some minutes, but with practice this will be facilitated.)
7. Allow breathing to be uninhibited throughout this process. Do not react to changes in breathing patterns or avert them.
8. You will experience many thoughts during this process. Let them drift in and out. Many subjects prefer to "focus" on a pleasant thought or experience as a thought touchstone. Either way, do not *analyze* your thought content or accompanying physical changes.
9. Allow sufficient time (20 to 30 minutes) to experience the psychic and muscular relaxation which follows the first steps.
10. If you are using the hypnotic experience for habit control, at this point you may introduce the object of your concern and focus on its removal from your consciousness. This is to be practiced and repeated during each session.
11. You can leave the trance by counting backwards 5,4,3,2,1, and resume the aroused state.

The first sessions are better if you are "conducted" through the hypnotic experience. Anyone experienced in the technique can introduce you, and you then can practice the method(s) on your own. Remember, practice facilitates the experience.

Meditation

The practical aspects of meditation are simple and can be engaged in at home or in the workplace, in a group or in solitude. The essentials are:

1. Quiet.
2. Assumption of and maintenance of correct posture.
3. Selection of a position which will allow you to maintain such a posture for 15- to 30-minute periods.

4. *Concentration* (Mind Focus). This can be achieved by softly repeating a single work or thought, by chanting, by repetition of an unspoken word or sound (mantra japa) or by prayer.

5. *Reflection* on a concept, belief or experience of personal significance can enhance healing and the relaxation benefit of meditation.

The last two points obviously fit the spiritual awareness religious groups strive for by prayer. There are great therapeutic implications to the "power" of prayer, aside from the theological one. Prayer conducted as a meditation experience should be regularly practiced by those of all faiths who seek to improve psychic health and well-being as well as experience mystical awareness.

With attention to correct posture and maintained body position, the following physiological changes occur:

1. Reduction in blood pressure.

2. Slowing of pulse.

3. Changes in breathing pattern. As you become aware of this, however, you may feel air hungry. This is because your consciousness is overriding autonomic control of breathing. A key part of the meditation experience is that you can regulate its depth and rate. Breathing control is a healing and soothing experience and figures importantly in stress control.

4. Relaxation or slowing of general metabolic activity. This is a conserving function in the body, as in sleep, and conscious manipulation of this is extremely health giving. This also results in changes in the electrical potential in the brain (as in biofeedback).

We must note another very important benefit of meditation, the sustained slight increase in brain endorphins. The endorphins, or enkephalins, are naturally occurring morphines in the brain. The endorphins are neurotransmitters with a special dedication to mind relaxation. Interestingly, both mind relaxation and physical exercise will increase them, although with exercise the uptake is more brisk and temporary. With regular meditation, quiet downtime, or prayer, there are sustained long-term beneficial effects on stress, anxiety and depression, partly, at least, by the increase in endorphin stores. The benefit on heart, blood pressure, stroke and dementia risk might be considerable.

The family of opoid receptors are located in various areas but especially the periaqueductal gray matter and the locus ceruleus (LC), the

main norepinephrine neurotransmitter center, as previously noted. The opoid-endorphin effects in the LC may help offset blood pressure, heart rate and rhythm problems by increased NE.

Dopamine "satisfaction" centers may also benefit by meditation, exercise, and other positive events. Dopamine is especially active in the nucleus accumbens, hippocampus and amygdala, all three parts of a "reward circuit", the nucleus accumbens being especially targeted in addition-reward cycles spawned by substance abuse.

We previously mentioned the brain cannabinoids (related to marijuana) as well amantamide, which has its own receptors in the brain stem. Serotonin receptors and serotonin play a significant role, as well, in relation to levels of anxiety, the target of serotonin uptake inhibitors such as Paxil and Zoloft and related drugs to increase the ambient serotonin. These are only a few of the neurotransmitters that play a role in helping smooth out our emotions and contribute to what is rightly, but incompletely, identified as "the endorphin effect."

The effect of endorphin release in exercise can also be sustained if the exercise is regular and of sufficient duration. Most of you are familiar with "exercise high," the sense of well being, calm and the reduction in anxiety after exercise. This effect tends to dissipate some hours after the exercise is finished and is gone by the next day. Obviously daily exercise gives a boost each day and exercise physiologists tell us that the workout need many have is a response to the decline of endorphins. We need our "boost."

Silent prayer or meditation works differently and it can be done throughout the day, even while working. First of all, the "stimulus" and the effect are controlled by you, and the effect is horizontal. With a steady low "dose" boost and very little high or low as with exercise. This is particularly true of those persons who have integrated this into their daily routine with the control of the background "noise" that hits us every day.

The state we have just described is obviously one of the goals of Yoga and the so called Buddist way, but it is also the state of many religious people in the West, and it is open to each one of us. Obviously, it begins as a practice long before it can be lived as a habit, but the beneficial effect mediated by the endorphins are very quickly being encoded. Over time, the endorphins become a primary modulator of the stress hormones and chemicals, resetting them at lower levels. This endorphin effect is perhaps the primary biochemical effect of hypnosis, meditation and prayer, and even biofeedback.

We include biofeedback since it does not require any tools to simply talk or think our heart rate or blood pressure down, or your breathing. This is easily verifiable by checking your pulse and blood pressure before you start and then recheck them every few minutes. Invariably, within 10 minutes, most of us will be able to measure the change.

"Spirituality" for Stress

Things spiritual reduce stress and emotional distress, and are numbered as positive aspects of a person's life experience. But "spiritual" is a relative term depending on the level of practice or belief the person has and the more precise meanings of the word "spiritual."

One definition claims that spiritual includes any ritual, practice or psychological disposition oriented toward the non-physical (not measurable or quantifiable) aspects of our life. Such a definition requires neither a belief in God nor membership in a religious congregation or movement. It simply states that spirituality is anything the individual wishes it to be in relation to psychic benefit received. There are no doctrinal norms or moral rules specific to any particular religious or ethical system. In that regard any practices or exercises, physical or mental, can plug into this spiritual "energy," to use a word frequently connected to spirituality.

The other spirituality is the antithesis of this. This is spirituality which is derivative, doctrinal and defined, in reference to a belief in a personal God, as in the three monotheistic religions: Judaism, Christianity and Islam.

We do not endorse a specific religion, denomination or affiliation. However, we do endorse the health benefit of serious engagement in things "spiritual." These may include areas of service or volunteer work and individual outreach to family, friends, or even strangers to assist them in any particular way which would conform to your spiritual needs and sense of social justice.

All of us, of course, recognize the spiritual (psychic) benefits of such efforts, but others limit their spiritual activities to practices which lower their stress level, and increase their personal sense of well-being, irrespective of any interpersonal relations. While the benefits, once again, are noted, we also believe that approach might risk cutting you off from the great benefits of person-to-person spiritual "work."

Objective research has confirmed that religious practices, worship as a community, regular prayer life and the reading of the respective spiritual texts (Torah, Bible, Koran) and the writings of the great teachers and

holy men and women of your tradition, give you more adaptability to stress events, a higher level of interaction with others, and less anxiety about the future. Obviously, those who believe in God and afterlife have a psychological advantage in times of loss or personal stress, they have an "invisible" means of support!

QUESTIONS:

1. Meditation or prayer can:
   a. Lower blood pressure
   b. Slow heart rate
   c. Lower blood sugar
2. Anger damages the brain by:
   a. Increasing blood pressure
   b. Inflammation on neurons
   c. Increasing risk of stroke
3. Stress managements that work include:
   a. Helping others
   b. Making decisions
   c. Not looking back
4. Talk is therapeutic.
   ❑ True ❑ False
5. Going it alone will reduce stress.
   ❑ True ❑ False
6. Brain endorphins can be increased by:
   a. Prayer
   b. Laughter
   c. Exercise
7. Brain health is independent of body health:
   ❑ True ❑ False
8. The brain is connected to the heart by:
   a. Nerves
   b. Hormones
   c. Other chemicals

SECTION 3

Research for Alzheimer's Disease

The *Brain Health Institute* is the prevention arm of *Brain Matters Research, Inc.*, the premier Alzheimer's clinical research center. Many of our brain health clients have family members or friends in research with us, and many of our research patients have been with us for more than one research trial. The goal in both the Institute and the research center is to attack all of the risk factors that we have reviewed with you in the book and guide you to proper research trials when the evidence suggests that the time has come for more than prevention – treatment is now necessary.

If you Google "Alzheimer's Research," you will immediately recognize the names of the usual suspects, all of the proteins and molecules we discussed in Section I of the book. All of these suspects are the target of our prevention intervention at The Brain Health Institute. They are the reason our programs are essential, especially if you or other family members carry a suspect gene, or if you have relatives with Alzheimer's Disease, all the more necessary in these cases is early and diligent prevention and intervention.

The research emphasis is on neutralizing or slowing the formation of Beta Amyloid and/or Tau. Those are the "big daddies" at the moment, although there is a great deal of discussion about their primary or secondary role, even their partial protective effect! These are matters we look at regularly and discuss with other scientists and pharmaceutical researchers on an ongoing basis.

There are many other trials directed towards inhibiting the formation of Beta Amyloids by blocking enzymes that split "Big Amyloid" into the smaller brain toxic amyloid proteins. Other studies will target inflammatory pathways, oxidation, insulin resistance, killer molecules such as Homocysteine tumor necrosis factor or interlukins as yet there are no clinical trials specifically targeting genes, or epigenetic modification, or the use of RNA inhibition. These will be areas of basic science investigation. In the meantime, when prevention interventions are no longer useful or the disease has announced itself even in very early, prodromal form, research is the hope. The hope is that something will "pop up" out of the research box as the first real Alzheimer's modifying drug, the Penicillin of the 21st century!

Keep in mind that once Alzheimer's Disease begins to advance, it is 100% fatal. If the patient does not die from other causes, he or she will ultimately succumb to Alzheimer's Disease in its very advanced stages. Keep in mind two other sad facts, Alzheimer's will visit more people over 75 than cancer will, and yet private and public funding for Alzheimer's research is no more than 10% - 15% of funding for cancer.

When we say that we are working to find treatment of significance, we mean the identification of drugs by research trials that will slow the progression of the disease and/or modify some of its worst effects. Our greatest hope is that one or more drugs will soon accomplish that, or more, perhaps leading to longer term stability such as we see with some cancer treatments.

WHY RESEARCH ?

The simplest answer is that it will be the only opportunity for you or a loved one to receive a medicine which might slow the progress of Alzheimer's in ways the available drugs today do not.

Drug research is long and costly. Sometimes a new drug takes 15 years and a billion dollars from the first chemical assembly through the conclusion of successful human trials in increasingly expanded study groups. There are rigid controls in all of this to protect subjects and assure absolute integrity of methods so that the outcomes are valid. This is one reason why Placebo Controls are so important. The placebo group is selected, evaluated and tested exactly as the subject group, but within the context of a specific study will vary in the percentage of subjects who will receive an inert molecule that looks exactly like the study drug. The assignment to the placebo group or study drug is double blinded, the doctors do not know whether you are receiving placebo or drug and neither do you. This is FDA mandated.

So, you ask, why take that chance and receive an inert (i.e., "useless") drug? Well, here are three reasons:

1) Yes, you are playing the odds hoping to get the real drug, but in every study the odds are at least 50/50, and usually better. Those odds are much better than the zero opportunity if you do not participate.

2) Entry into a study whether you receive the real drug or the placebo assures you thorough evaluations and testing your physicians cannot do on a regular basis, with attention to your overall medical status and specific data related to Al-

zheimer's Disease. You are regularly tested, checked and interviewed at no cost to you.

3) You may stabilize and have positive benefits as a placebo subject since up to 10-15% of placebo subjects in any research trial may report positive benefits or measure positive results.

Selection of subjects for research – This is a very complex process in which we and you must judge your overall medical status, the risks of a study drug to you, your overall emotional and psychological state insofar as neither research testing (blood tests, MRI test, etc.) nor the schedule and visit requirements would be difficult for you (objectively, none of this is difficult, but some patients have great anxiety about all things medical!). This is a very important part of ethical research, to always follow the number one principle "first, do no harm," so that any research is undertaken for the benefit of the sick or suffering.

INFORMED CONSENT

Informed consent is a very important ethical responsibility to assure you complete and honest information so that your consent is guided by the proper information. Informed consent includes discussion of risks, benefits, the nature and frequency of testing and procedures, enumeration of the various inclusion and exclusion criteria for a specific study, and the best assessment of the proper studies for you as an individual. All of these elements must be present to guard against unscrupulous research luring a subject into a study that would have no benefit, or may impose undue risk. The two rules then, for the good of the patient always, and with the patient's full knowledge or consent, or that of the legal representative, allow the patient to choose with proper and fully informed consent. We also consider it our ethical duty to advise a subject of the lack of efficacy (no benefit at all) when it is obvious that continued participation in a specific study will be of no avail, and therefore consideration of another study would be in the patient's best interest. In this regard, you or your caregiver, or surrogate, have complete freedom to withdraw from a study at any time. You enter (consent) freely and likewise you can end your participation at any time. Hopefully, the only reason for such a decision would be in anticipation of entering another study.

We look at informed consent very thoroughly at *Brain Matters Research*. It is never, for us, a matter of enrolling a patient in a study simply because the patient qualifies, that is, satisfies the criteria of a particular research protocol. We consider a strategy over some years, especially if

the disease is in its earlier stages, so that our patients will have the opportunity to perhaps benefit from research drugs in sequential trials. We have many patients who have gone through three or more trials with us, which has provided them the hope of therapeutic continuity at a time that no real disease-modifying drug is commercially available.

Informed consent also means something more to us, the ongoing discussion of a patient's changes and prognosis, the likely long-term pattern of illness. This is especially important to family members and caregivers, and since we have long familiarity with prognosis, we endeavor to give a long view that is both reassuring and realistic. Informed consent then, for you or your loved one, does not stop at the terms of the protocol but is a commitment to caregivers and the family over time so that we can care for you while you care for them.

Research Drugs and Your Drugs. Another aspect of our meticulous attention to informed consent weighs very carefully a subject's disease history and present medications beyond the requirements of a specific protocol. We have found that often the doses of medications or medication changes can be made that will benefit you irrespective of any specific study. We always work in consultation with your physicians on all specifics. On occasion, however, our own experience, both clinical and research, suggests a different approach and this we present to the patient and caregiver directly if it is in the best interest of the patient to seek a change.

This policy applies equally to our approach to study drug evaluations and possible side effects. We evaluate each and every laboratory value that is submitted to us, many hundreds to thousands of individual numbers or electrocardiograms each week. If abnormalities appear, we work assiduously to determine if these are 1) due to other medications; 2) due to new or chronic medical illness; or 3) due to study drugs, thereby determining if there are any safety issues warranting cessation of the study or a brief study drug holiday. Keep in mind that almost always lab or EKG changes are not due to study drugs.

This brings us to the term "side effect." In research trials a side effect is anything that happens, is reported by you, not restricted to the study drug, but anything. In that sense the term "side effect" is incorrect in that it suggests an unintended effect of the drug when most of the time symptoms which occur are usually due to common ailments or diseases. Nonetheless, part of due diligence is to record these so that any possibility that accumulating data may identify a side effect as a drug effect is not missed.

You are not an Experiment! Some patients or family members are initially concerned that an "experimental" drug is being given: "Doctor, are you experimenting on me?", or "Doctor, am I going to be like a laboratory animal being tested?", or "Doctor, since the drug is not approved, am I really doing this for someone else's benefit later?", or, as several heroic patients stated, "Doctor, even if it can't work for me, I want to help fight this!"

Let's answer that last sentiment first. We would never be involved in a study that offers no hope. Regarding the other questions about "experimenting" and "laboratory animals," the first thing every patient needs to know is that all study drugs have passed the animal phase and initial human phase of safety, and usually the initial phase of patient efficacy (some of the subjects in the early studies were helped).

Our research is categorically not "experimental" if by that you believe you are receiving something no one knows anything about, or does not know what will happen if the drug is given. The drugs we are studying have been developed over years, or decades, with real expectation of benefit. Research studies represent a huge financial and intellectual investment by the pharmaceutical companies, they want the drugs to succeed, they want you to succeed!

"How about the placebo, doctor, if I get a placebo I'm not getting anything!" True, you will not be getting a drug, but as part of the study and as part of the work we do for you, you will be often retested, and always carefully monitored and if ongoing decline suggests either that you are receiving placebo or drug without effect, it is our ethical duty, as we see it, to guide you to either another research trial or cessation of all trials. At the very least patients in placebo arms are much more carefully evaluated and advised than if they did not participate at all.

What happens if I am doing well and the study ends? This is a frequent question and the answer is that while a study drug may be working for you as an individual, it may not be showing the same positive effects in the full study population, hence either the FDA or the drug company makes the decision to stop a study. Likewise, a study drug may be showing positive effects throughout the study population but the protocol deadline is met (the specific duration of the study) which can be extended in some studies but not in other studies. In the latter case, subjects who completed the first part of a study may be invited into the open label phase of the study where all participants receive the real drug and no one is assigned to a placebo group. This is an important reason why you should try to finish the study you enter. Even if open label extension is not offered when you consent, the drug company may decide for open label as the data on the study accumulates.

The doctors and staff at *Brain Matters Research* will be your guide in these issues for your best possible outcome. Our team is continuously searching for new study protocols to offer options for those who wish to continue research after a trial has ended, or to close an option when your own situation is not met in the trial you are in. Dr. David Watson, our Director of Clinical Research, will turn down a drug trial that he judges has either methodology flaws or too low an expectation for success, and certainly if there are unusual safety issues. Because of these factors, many of the subjects who have come to us have participated in 3 or 4 studies in succession.

What is involved? – Essentially only your time. There are no financial costs to you, and many benefits. You will be getting an opportunity to receive a potential new medicine that the drug company has spent many millions of dollars to bring to research, and many thousands of dollars – perhaps $100,000 – on you in the duration of the study. You are a huge investment for them – they want you to succeed.

Each protocol (study directives, testing, procedures, visits, percentage of study drug, percentage of placebo, etc.) is different. The most important part of research is selecting the best study for you in the context of where you are in the disease process, your general medical condition, your availability for scheduled visits and lab tests, etc. all of which are essential to track your progress or decline, including any potential effect on your blood tests, for liver and kidney function especially.

Will there be a cure soon? By cure we mean complete reversal of the disease. This is not possible, but we are seeing some very positive results in different studies we are conducting in which the progression of the Alzheimer's symptoms is being slowed down with stabilization of mental/cognitive functions, but we remind you these successes are not guaranteed. We do have some subjects who have been stable (little disease progression for several years). They have not deteriorated!

Isn't this just a business? Yes, it most definitely is a business, the most important business there is, the business of relieving pain, suffering and disease, and it takes a lot of money to do it! The doctors at *Brain Matters Research* are very good at what they do as physicians in the best sense and traditions of ethical medicine. Both Dr. Brody and Dr. Mauceri had dedicated physician fathers whom they continue to emulate by providing the highest level of care and competence.

The *Brain Matters Research* team covers all of the medical specialties relevant to clinical research and patient care with special emphasis on Alzheimer's and its multi-factorial causes. Their mission is you and your

loved one; they bring you the most comprehensive, current and ethical research and medical direction when needed, to support you and your primary care and specialty doctors in the community. We do all of this as our business, "the business of hope."

QUESTIONS:

1. Informed consent includes:
   a. Known risks
   b. Possible unknown risks
   c. Probability of efficacy
2. Clinical research requires:
   a. Placebo groups
   b. "Double blind"
   c. Your completion of the study
3. The placebo effect is psychological:
   ❑ True ❑ False
4. The placebo effect is negligible.
   ❑ True ❑ False
5. Clinical efficacy indicates:
   a. Drug is more effective than placebo
   b. No side effect
   c. Everyone improves
6. Informed consent is always:
   a. Free consent
   b. Decision of the subject patient
   c. Decision of a legally authorized representative
7. A side effect in research is usually not due to the study drug:
   ❑ True ❑ False
8. If a side effect appears, the study must be stopped:
   ❑ True ❑ False
9. Clinical research is an experiment on you:
   ❑ True ❑ False

Placebos, Research and a New Paradigm

We have kept this discussion separate from our chapter on research for reasons that will become immediately obvious, as well as the fact that we are all still working and participating dutifully within the current research structure. We present our ideas as a way of opening up discussion on the best way to do this in the future, and perhaps the near future, perhaps a new paradigm for research that no longer requires slavish devotion to blinded, placebo-controlled trials. Keep in mind it is a discussion not a demand.

Research at Brain Matters Research is FDA approved, double blind, and placebo controlled, meaning we do not know up front who will receive study drug and who will receive placebo (inert compound), and neither will the subject know. In any specific case that is never a decision made by us, the pharmaceutical sponsor, the FDA or the IRB (review board). The entire process is randomized; it is neither a coin toss system nor every third or fourth subject to placebo. For instance, if a research study is to include 300 subjects and two-thirds of them are to receive study drug, it means that 200 will receive study drug and 100 the placebo by randomization without specific order or grouping.

By and large this system has worked fairly well, but both new information technologies and a rapidly expanding ability to more precisely gene target or epigenetically modify drug effects present a new reality about the best way of gathering safety and efficacy data in relation to the ethical duty to subjects in more advanced phase trials where efficacy is already suggested.

Current trials are set up so that patients are randomly assigned either to the study drug arm or the non-drug (placebo) arm to compare the two groups in terms of efficacy, putative outcome, and safety; the number and kinds of side effects that could be attributed to the study drug.

The first point to note is that it is impossible to match placebo and treatment arms in every way since it is impossible to match any two subjects in terms of their medical profiles. Let's say that a study excludes anemia, that doesn't mean all participants have the same blood counts. They may vary by 20%; the same for blood pressure, glucose levels and so on. In all normals there is a range and while all participants are within the range for a particular study they are not the same. This is not even

considering quality sleep time, in fact sleep is a huge unmeasured variable, as are stress levels, emotional quotients, personality traits and attitudes, and the placebo possibility itself is unquantifiable and unpredictable. Remember no two patients are the same, even more important remember that "there are no diseases, only patients."

The second and most important point is that in the non-drug (placebo) arm invariably some subjects will respond as if they were actually receiving the study drug. Many theories have been offered for this so-called "placebo effect" but perhaps the best explanation is the word itself, "to please." Patients want to be helped, cured if possible, and that very hope can powerfully amplify the desired outcome. You can call this wish fulfillment, mind-over-matter or any other term that would suggest this, including the desire to please doctors and researchers, to be a good and "successful" subject, even the noble desire to be part of a potential treatment or cure for others. Whatever the motives, it is clear that in the placebo world the psyche can move the brain in the direction of the outcome most desired or expected. Indeed, the expectation of a positive outcome is the most powerful placebo mover of all.

The real question then becomes one of judging the efficacy of the study drug measured by the number of positive responders over those in the placebo group. But there is always one imponderable, what percentage of study drug recipients also succeeded because of the placebo effect. Remember, the effect always operates in both arms of any study so in one sense it should be a matter of establishing that the study arm "under-performed" in regard to the placebo effect but that simply is not possible. In fact, it is possible that placebo effect actually amplified real drug effect, but to what extent that happens is unquantifiable. The best we can do is the statistical differences between the treatment arm and the placebo arm, which may significantly underestimate placebo effect in treatment arm. This may be driven by both expectation or by an early real drug effect that "convinces" the subject and that conviction is recorded as a drug response.

The possibility of placebo effect is always there, either as a positive determinant or as a negative one. For those who subconsciously or willfully sabotage their own treatment, "anti-placebo" effect can be very real, especially among patients who do not wish to be well for whatever perceived gain, including some patients with emotional disorders, those with "refractory" anger or malignant behaviors, and some patients with chronic pain, depression or anxiety. These patients cannot be treated because they will not be treated, their resistance voids both placebo effect and drug effect.

Some experts claim that there is little evidence that psychotropic drugs outperform placebos. These therapists believe that psychotherapy with effective identification with the therapist is the key. This is not strictly the placebo effect as we understand it in the context of controlled research, but it is a powerful argument that mental health drugs may be no better than other therapies, and research trials with anti-depression and anti-anxiety drugs show only marginal benefit of drug over placebo, and that is often measured in months and not years.

It is equally difficult to separate the placebo effect from efficacy in trials that are measuring drug effect in disease categories with high stress, emotional and psychic qualifiers; gastrointestinal diseases, such as ulcer anal colitis and "functional" bowel disorders, cardiovascular diseases, such as hypertension and cardiac arrhythmias, and metabolic disorder, such as diabetes and thyroid disease, not to mention fertility and psychosexual disorders.

"Null placebo" effect can follow when a subject or patient believes he or she is not receiving a study drug, or is not benefiting from a prescribed drug. Here the effect is the reverse of placebo, if one believes they are not benefiting, they are less likely to benefit. Null placebo is heavily front loaded insofar as the earlier in a research trial or clinical setting a subject believes the drug is ineffective, the more likely this will adversely affect the outcome. Obviously, then, in any research or treatment while placebo effects are not always controlling, they are always a possibility and no objective factual override will ever eliminate this.

Alzheimer's Disease research presents unique challenges in regards to placebo or null placebo insofar as the very endpoint of measured success, cognitive function, is itself the primary determinant of the operation of placebo effect. That is, as subjects begin to decline cognitively they are less able to set or reset the psychodynamics of complexities of the placebo effect. Here, it must also be said, the situation of placebo "mind over matter" loses its force in every subject as disease progression continues. The challenge in Alzheimer's Disease research and placebos is to more precisely mark out the stage in each subject's disease that placebo thinking could no longer be in place. The fact is that in early disease there simply is no way to make the call and thereafter no call is necessary.

The employment of placebo arms in the past was certainly consistent with the need for "objective" statistical evidence, by comparing treatment and placebo groups, but that has always left us with two ethical questions. Is it ethical to continue placebo controlled treatment once the evidence for efficacy and safety is available? The second question

is more vexing, should we urge the placebo effect in order to maximize outcomes in both arms, as the goal of the research is to help the patient just as the doctor does in practice? If the doctor presents his prescription with confidence in the outcome and resets patient expectation positively, the chances of successful treatment increase and that is certainly good for the patient. Is it "honest" to front load treatment with a sales pitch, however subtle or professionally it is done, or is it worse for the patient either in research or practice, for the doctor to maintain clinical detachment? At the same time, the physician has to list the possible side effects, which increases the likelihood that the subject will experience one or more of those. This part of informed consent is not in the "therapeutic" interest of the patient but is part of the ethical duty. Likewise, if the ethical duty is to help, should we not recruit the placebo whenever we can, even in research?

The ethical question is even broader, should the details of placebo effect, including psychic and molecular factors, such as brain endorphins, dopamine, serotonin and histamine, to name the biggest placebo players, be part of informed consent? If you answer "no," is it because you believe that by explaining the effect you might explain it away, destroying its anonymous power? If you answer "yes," did you so answer because the ethical obligation to truth in advertising and scientific rigor override this? Difficult questions, are they not? What do you say?

A New Paradigm

We have reached a time and capability where placebo arms in research are no longer necessary, at least for later stage trials, since we have such extensive medical data that we can use this to position the subject as his own baseline and comparator. We have immediate access to streams of data and disease incidence and side effect profiles drawn from very large populations. The thousands of pages of Medicare coding and huge databases of HMOs and insurance companies can provide diagnoses and their relative incidence and an anticipated percentage in any study. These huge databases arguably can change the rules and give subjects in most studies 100% chance of study drug. Everybody has data on incidence, treatment, even prognosis and certainly cost. Why can't we index the safety arm in a research trial to those databases rather than running placebo arms?

Take atrial fibrillation, e.g., the most common cardiac arrhythmia. The incidence for white and African American males over 50 is 6.7% and 3.9% per 1000 persons per year. So, if you wish to know the AF risk of your study drug, you have a much better predictor if the study drug is

indexed against those numbers from large populations rather than from screened, lower risk, placebo groups.

Some will argue that you can only know the raw risk of study drug by the incidence in two groups, study and control (placebo group) with relatively similar disease and medication profiles. We have already noted that the match ups are much more heterogeneous in any trial, but the other point is this will always give results that underestimate risk in the general population. The fact is the study drug aspires to make the general market and it is there we will finally judge safety and efficacy. This is established post-marketing with special warning or recalls. We are not saying the placebo controlled arm is artificial, it is no more artificial than the drug arm. It is simply a matter that neither arm is real world, real time. The studies are as advertised, "controlled," but our proposal to significantly cut back placebo arms and to peg safety to data for all of the most common diseases and symptoms is not the absence of controls but a much wider broadening of the category.

Further proof of the logic of our proposal is the fact that safety and efficacy become different matters in clinical practice, and the value of placebo control guidelines can quickly become irrelevant. An example of this is the rapidly expanding disease risk for tumor necrosis factor inhibitors (TNFI) employed in autoimmune disease treatment. The specific biological activity of TNFI brought them to market with guidelines about due caution in patients with a history of fungal diseases and tuberculosis, but there was much less consideration of wider scope of risk in the general population, so that the most recent warning for TNFI drugs includes increased incidence of Legionella disease (pneumonia) and listeriosis (fatal sepsis). It took wider application of TNFI use in a much larger population than a controlled study population to identify these new risks.

This story is becoming much more common as drugs are being developed with much more specific and intense modification of biological systems. The placebo controlled trials are simply inadequate, the answer only comes when side effect incidences of various diseases are noted to be higher than expected in the population of treatment interest. We have those numbers, we have huge stores of data with virtually immediate retrieval today. We also have virtual studies with no risk, and increasing numbers of genomic or biomarker targeted drugs where both efficacy and safety will be much more predictable.

Efficacy is a different matter ethically. After all, the proof of good therapy is that it works, and at the most fundamental level that is all that matters to the patient seeking relief. The patient neither knows nor cares

if it was the doctor's prescription or the doctor's pitch which did it. In a clinical trial the assessment of efficacy would no longer be measured against a placebo group but against the common sense "discipline" of a sound investment for the pharmaceutical company and effective and safe treatment for the FDA.

The pharmaceutical companies make every effort from the beginning of a drug's development through all phases of testing to monitor and identify risk and efficacy. After all, they are in an intensely competitive, highly regulated and litigation rich business, almost predatory product liability litigation risk follows every drug once it reaches market. Least of all concerns, then, would be that the pharmaceutical companies are going to risk it all with poor research and development or lack of diligence, the very few notable exceptions proving the point.

The concern with generics is much heightened perhaps not so much regarding safety although even here poor manufacturing standards and quality control are becoming an issue, but certainly regarding efficacy. The generics simply do not have to go through rigorous research and development. They buy the trade drug as soon as its patent expires and sell the generic within a much wider (looser) set of bio-availability parameters so that a given dose of the medication may be under or over trade standards by 20% and still be acceptable by the FDA. Here all "controls" are market ones and it becomes a matter of patients or doctors identifying dosing and efficacy issues. This is a huge market and getting bigger every year, and if the absence of any controlled studies in generics is the price for priced-right medication, why a different model for the original drug and market?

The placebo effect will be there in research just as it is in practice, and in most cases the carryover in percentage of responders from trial to practice should hold. Who, then, would quibble the placebo effect if the sick are helped. We ask you, when you present yourself for treatment expecting that it will work, and in fact it does work, will you really want to know why, or is the better part of getting well just keeping some of the mystery in it?

Notes for Caregivers

We will conclude with a few remarks for you, the caregivers, the spouses, loved ones, or professionals who are the light in the surrounding darkness of Alzheimer's disease. The first thing we would say is that there are no absolute rules for you. Some days will bring their own challenges, and sadness, but other days will bring strength and even a certain peace that you heard the call of your loved one, and you answered, "Yes." You must also answer "yes" to the difficult times when you are exhausted, burned out, angry, frustrated, certain that "I can't do this anymore." All of these feelings are right, reasonable and must be recognized. Reject any guilt and tell your family, your friends about these feelings; it will be therapeutic. Say "yes" to your frustrations and your fears because if you deny them and internalize them, you will get sick.

The first rule, then, is to know yourself and the situation so that you do not get lost in the disease. Do not let the room of your loved one become a room of gloom. Keep the "light" shining, and when you are sure you can't, ask others to shine it for you. You will need repeated "R & R" for your own light, your own sanity, but you can't leave unless you have help – family, friends, church or temple volunteers, support groups, agency help. All of these are there if you ask.

Millions of us pay billions to talk about our troubles, our feelings, our pain, more to relieve ourselves than to change our situations when most of the time we cannot. Talk therapy works so you must talk and let it all out, and <u>you</u> are entitled to do it for free! If family and friends are not ready to hear you, they are neither – they are simply part of your suffering.

If you get to the point that you really can't do it anymore, then stop. Either summon ongoing help or make the decision to place your loved one in a facility where they can do the work without dying from it. You, in turn, will extend your own capacity to visit and be with your spouse, and those hours and days will be less damaging to you, mentally and physically. Remember, loss of sleep, poor nutrition, depression, anxiety, physical strain or injury overtake the spouse or caregiver who is doing it alone for too long.

Depression and physical illness can sneak up on you, and the signs may not be read by you initially. All of a sudden, a crisis comes and the weight of it all might fall down on you. Do not let that happen, take the early signs to be that, signs of worse times to come if nothing is done!

The second most important rule to follow is to always keep in mind that this is a disease which cripples the brain the way heart disease weakens the patient. You would not tell your spouse with a heart ailment to be stronger, or breathe more easily because your spouse can't. The same is true with Alzheimer's disease; your spouse can no longer listen and respond appropriately. Alzheimer's patients are patients!

We began our book by noting some extreme cases of behavior. You read that patients can become impulsive, agitated, frustrated, and angry. Often there will be inappropriate sexual talk, or behavior, or foul language, even to strangers. Your loved one may accuse you or others of stealing or hoarding money when, in fact, your loved one is doing so. Your loved one cannot help it; these behaviors are involuntary. Remember that if the situation were reversed and you were the one with dementia, you might do the same. Do not take these things as personal attacks or signs of a "bad" person; understand that they come from a disease of the brain.

You will have your own anger and frustration, sometimes wishing it will all end soon. You are allowed to have these feelings – they are normal, even "healthy," if you know how to manage them. Talking about these feelings to friends, family, clergy or counselors is both essential and freeing. You learn you are not "bad" and that you are not alone with these feelings. Talk helps you to continue to do the great work of mercy you are doing.

No one can do 24/7 duty in anything, including LOVE! Everyone needs a break, especially a caregiver. Keep up with friends, hobbies, and take sufficient "downtime." Remember, each one of us has a different capacity as a caregiver. What is important is not the most time logged in, but your best effort in the time you do it.

Remember the past with your spouse. Go through albums, letters, travel experiences, work history, and family memorabilia and talk to your spouse about these memories, and let your spouse talk about them to the extent possible. It is amazing what will come out from deep in our past that is good and "therapeutic," however brief the memory.

"Be a coach, not a cop." Encourage mental, physical, and social activities to the extent possible within the limits of your spouse's capacity. Always use positive reinforcement rather than negative statements, criticisms, threats, etc. Again, you are contending with a disease more than a person – work against the disease but for the person. After all, the goal is to keep the "person" as long as possible. If your spouse resists, pull back and keep the peace. Don't over-manage, just care for your loved one! This is particularly important when the patient forgets a conversation a

few minutes later, or a scheduled event or appointment, or any number of details in a given day. Remember, it's the memory and it is much wiser for you to let go of what your loved one lost rather than trying to force the correct answer from them, invariable that strategy will lead to agitation and frustration for both of you, or further silence and shut down in your loved one. Balance your pressing desire to stimulate or "shake out" their memory against the cost in stress, especially for you!

In that regard you will have to prudently judge your loved one's further capacity for activity and social engagement? This requires a real understanding that your loved one is less able to do these things. His or her increase in sleeping, or passive sitting (so many caregivers say my loved one just sits) is due to the advancing level of disease. Remember that the sleeping is a sign of increasing neuronal loss. We always remind caregivers that your loved one's need to rest is also your chance to rest … take it!

Symptoms such as lessening activity and interest, especially when accompanied by expressions like, "I don't want to stay alive like this" or "I wish it were over" are expressions of the impact of the disease and do not usually represent depression or a risk of suicide. In fact, classic clinical depression is not a hallmark of Alzheimer's disease although so many are treated for it. In fact, antidepressants have little effect at all on the symptoms we have described but may have more benefit in behavioral issues such as acting out rages, agitation or repetitive behaviors.

You may notice other repetitive behaviors in your loved one, especially picking or touching the skin, or repetitive actions with no obvious purpose. The answer is there is no obvious purpose and these seemingly compulsive motor activities most likely represent an imbalance among various neurotransmitters, especially dopamine and serotonin. Antidepressants or anti-anxiety medications such as Ativan or Xanax may be helpful.

Be diligent, and firm, about medication safety. Your loved one will start missing doses, or repeating doses, long before you suspect it, so move in to supervise medications as early as you can.

As the disease advances, your loved one will eat considerably less and lose considerable weight. Remember the active normal brain burns 20% of all daily caloric intake. Your loved one is doing less and less brainwork as well as less physical activity so the caloric needs may drop to half of the requirement five to ten years earlier.

Keep close friends involved. Let them visit even if there is little expectation of either positive feedback or dialogue with the patient. The

duty of friends is to still be there when there is nothing in it for them except mitzvot, blessings. If you are a member of a church or synagogue, incorporate that into your "treatment plan" for your spouse and yourself. We know of couples who pray together and say that has been of great help.

Stick to simple, repetitive routines, words, phrases and familiar "routes" in the house. It is useful to use "we" whenever you need to direct your loved one. "We need to …" or "We are going to …" emphasizes that you are right there.

Learn to "read" the eyes and body language (gestures, facial expressions, etc.) In advanced stages when there are few words, these are ways your loved one communicates. Likewise, inappropriate and uncharacteristic words, deeds, accusations and delusions may occur. Let none of these harm you since they are not under your loved one's control.

Music therapy, especially soft or classical, is very comforting. Likewise, good soft lighting, comfortable furniture with back and neck supports, and a comfortable, safe sleep environment are very helpful.

Each one of us has unpaid "psychological" debts. If the one you love and care for has any unpaid psychological bills, help him or her to pay them off – estranged family members, old emotional injuries or painful experiences. Teach and preach forgiveness and repair. You will be surprised how often painful memories are present, and how often drawing them out will reduce anger, frustration, etc.

Practice attention to accident prevention and safety (stairs, baths, doors, etc.) Make your home as safe as possible; anticipate the risk of falls and home accidents, especially during the night. A thorough inventory of accident risk is essential.

Work closely with your doctors and other caregivers so that other health concerns are neither overlooked nor neglected because your loved one has dementia and "there is nothing else we can do." That is false – "There is always something we can do!" This is especially important when behavioral issues arise, and proper selection of medicines can help a great deal, and help you.

Make plans for future care. In consultation with doctors, family, clergy, etc., develop a long-range plan to meet medical contingencies, especially those that would require life-sustaining technologies that might prolong suffering instead of treating an illness.

At the same time you will need to pay particular attention to these special concerns:

- Alcohol. Alcohol will accelerate dementia of any cause, increase bleeding and stroke risk as well as fall and fracture risk. It is essential that you try to minimize or eliminate alcohol at the first signs of Alzheimer's disease, even if it is not yet diagnosed in your loved one. It is medical malpractice for the doctors to ignore the risk or avoid the discussion your doctors must have with your loved one, especially in early disease when every single drink adds to the "cell count." Alcohol is the most brain deadly drug available to us. It destroys brain cells each time it is ingested and over a prolonged period of time even so called harmless social drinking will have destroyed millions of brain cells. While alcohol is not a direct cause of Alzheimer's Disease, its devastating effects long term will both shorten the time of onset of Alzheimer's Disease and amplify the dementia because of the added cell death and damage to brain cells not yet destroyed by the disease or the alcohol. Alcohol is also deadly to heart and muscle cells, liver cells, and all nerve cells throughout the body. Because of its toxic effects on liver cells, alcohol can be the direct cause of hemorrhagic stroke by impairing the liver's ability to produce clotting factors. Likewise, alcohol can be pro-inflammatory in brain cells and surrounding vascular support, especially in the presence of diabetes and hypertension. In this setting alcohol becomes a major stroke risk and promoter of more rapidly progressive dementia, either on a vascular basis or in promoting effects on amyloid protein production or damage to cells that clear out toxic proteins from the brain.
- Hearing. A significant number of patients who come to us are hearing impaired, some quite severely. Decline in hearing from whatever cause both increases dementia risk and progression of disease by the obvious loss of the most important sensory impact to language. We require every patient we see to have a thorough evaluation if there is any history to suggest hearing loss.
- Concurrent medications can have an impact on cognitive performance and will add to the burden of memory and intellectual decline in patients with Alzheimer's disease, even in its earliest stages. Particularly noteworthy are the benzodiazepines (Ativan, Xanax, etc.) and codeine-morphine pain medications. Other classes of medications can have similar impact by virtue of their anticholinergic properties. Keep in mind that none of these drugs are toxic to neurons, their effects are on various neurotransmitters whereas alcohol is a direct neuronal poison.

- Balance and Gait. Patients with dementia invariably have difficulties both with visual spatial orientation and gait imbalance. As dementia progresses there is a parallel increase in fall risk, not only in high hazard environs as the bathroom or stairs but in open spaces as the combination of declining spatial vision and increasing inability to evaluate safely, even in a once familiar safe environ. Remember the key word here is a once familiar environ or route, etc…now no longer so. At some point, often quite early in disease, it is prudent to accompany your loved one on walks, etc. both for safety and to prevent wandering, which, once again, can happen with surprising suddenness.
- Driving, bicycling, etc., including golf carts in resort or golf areas. First event driving accidents can come with no apparent warning that your loved one is a compromised driver (e.g., contact accidents in parking lots, running over curbs, sideswiping other cars or objects). These are the usual events premonitory to a significant accident, but not always. We ask you to consider driving risk with the same diligence you should for alcohol and medications, once again bringing these to the responsible doctors as they can and should tell your loved one that it is time to stop driving, adding that they will notify the proper authorities (motor vehicle department, local police, etc.) if your loved one refuses this. As difficult as it is emotionally as well as logistically to take him or her off the road, it may well be a matter of lives in the future, theirs or others. We know this is a particularly difficult issue for older couples without family or other support if you, the caregiver, are already off the road, but the reality is that every time your medically impaired loved one is driving, you are the passenger at greatest risk.
- Protect assets Place yourselves safely with people you know and trust to guard your assets, your home, and your peace of mind. This also means removing any control of assets from the patient to avoid calamitous financial or legal mistakes on their part.

Common Medical Issues

Dehydration and Fluid Imbalance

Dehydration is the most common problem elderly patients face along with changes in sodium (Na), potassium (K), magnesium (Mg), and calcium (Ca), all essential to cardiac and brain function. By far, however, the most frequent and dangerous problem is dehydration, due either to

poor fluid intake or diuretic therapy, poor fluid intake being much more likely.

The symptoms of dehydration, especially chronic dehydration, are often subtle. It may be a matter of simply having less energy and not feeling quite right. Mild nausea, non-specific headaches and weakness may be clues, but more serious changes in brain function, including cognitive change and regulation of temperature, pulse and blood pressure can occur because of chronic water deprivation to critical brain centers. Keep in mind this problem occurs in normal aging as well as in any medical or neurological conditions. Older patients simply begin to take less fluid over time, and those who care for them must make fluid intake a daily priority! One of the most potentially serious consequences of dehydration is a significant drop in blood pressure upon standing. In fact, this finding is so important that it is mandatory that you always measure your blood pressure sitting and standing. A 20 point drop in your systolic or 10 point drop in your diastolic (bottom reading) pressure standing may be a warning that it will get worse over time and you will pass out or fall, or both, at some point.

The second serious complication of dehydration is kidney failure. This may not be suspected if urine flow remains normal, in which case the rise in Bun and creatinine are the measure of risk. Dehydration and water pills are a high risk combination here, along with certain blood pressure drugs, so called "ACE" inhibitors. When all three are present, kidney function can deteriorate rapidly. You must have your kidney function and sodium (NA), potassium (K) and magnesium (Mg) checked immediately if you suspect a change, feel weaker, feet swell, or urine output drops. In any case, however, these should be measured several times a year, at minimum.

Inadequate fluid intake with dehydration is the number one problem. On the other hand there can be adequate water intake and a deficiency of Na, K, Mg or Ca because of failure of proper regulation of these as we age. Likewise, all four of these are also dependent on normal renal (kidney) function which also declines steadily with age, or more rapidly with dehydration, even within several days. The combination of these factors can make fluid and "electrolyte" balance and kidney function dangerously impaired. Therefore, a minimum of two quarts of water over 24 hours is necessary to keep all the cells in your body "watered." A convenient way to be sure that you are adequately hydrated is to note the color of your urine. The darker the urine the dryer you are! The urine you void should be almost as clear as the water you drink.

One way you will know how much hydration is enough, and not too much, is to be familiar with the exact reading of your baseline numbers for Na, K, Mg, Ca and Bun and creatinine (kidney tests). All of these numbers are more important to you in the short term than your cholesterol. Your cholesterol is not going to change much over weeks but electrolytes and kidney function can change very quickly with infection, surgery, chemotherapy, heart medications, heat stress or hormonal abnormalities.

Perturbations in electrolytes, Na, K, Mg and Ca, can profoundly affect mental function leading to confusion, stupor and coma if sodium is very low, or brain hemorrhage and seizure if it is too high. Low K, Mg, and Ca, separately or together, can lead to irregular heart beats and if very low levels are present, fatal arrhythmias. It is simple enough to measure these vital elements through your blood tests every three months, at least if you are on multiple blood pressure medications, if you are diabetic, and if your kidney function is declining.

A quick way of judging salt in your body is to gently press with your thumb on the inside of your leg one hand width above the ankle. If you make an indentation the size of a thumb print and as deep it usually means there is too much salt, which is holding water in the tissues. The two most common exceptions to this occur when your body is not carrying enough protein (especially albumin) or when the leg veins or lymph channels are blocked. Nonetheless, the majority of you with this so-called "pitting edema" are taking in too much salt, and a visit with your doctor is indicated.

There is one other simple measurement you should be able to do in an instant; that is to take your pulse. If you are right handed, simply place your index, third and fourth fingers over the inner aspect of your left forearm just below the base of your left hand. Then rock your left thumb back and forth and gently press down over the small depression in your forearm, and bingo – you have your pulse. You should be able to note rate (number of beats or "pulses" per minute) and rhythm (regular rate or irregular rate). Rate and rhythm together immediately tell you how your heart is behaving. An irregular (beat to beat) variation in pulse is highly suggestive of atrial fibrillation, the most common abnormal heart rhythm in older patients. Likewise, a very slow regular beat (sometimes as low as 30 beats in a minute) may indicate complete heart block, which might require a pacemaker. This conduction disturbance is also very common as we age, and for those two reasons, know your pulse! This is very important to measure during exercise, and for cool down after exercise; the general "rule of thumb" being that the quicker your pulse rate falls toward normal, the better your heart.

Now you have simple and simply elegant ways to assess fluid and salt, and heart function, the thumb print in the lower leg for edema, and the fingerprint on the lower forearm for heart rate and rhythm.

Falls

It should be no surprise to any of you that a fall in an elderly person can be life changing. A broken hip or femur, a broken pelvis, forearm or shoulder, a concussion or a brain hematoma can be the immediate result of a fall when, in fact, 50% to 60% of falls can be prevented by a "no fall policy." What is such a policy? It is the policy which says that you will do everything necessary from head to foot to prevent a fall. And we mean head to foot prevention because when you fall, all of you falls, head to foot.

Old age and dementia, even early dementia, bring increasing difficulty with depth perception, spatial and location judgment and balance, either because vision is declining or the balance mechanism in the inner ear is "off balance," or the brain cannot properly process the input from the eyes and ears, or send out proper instructions to correct imbalance (a problem in the cerebellum).

Obviously, visual, hearing and balance assessment is essential, preferably by a professional for eye care and a physical therapist for balance, but there are some useful tricks of the trade. Practice getting up from the chair or bed with arms folded in front of you (with a helper initially). Walk briskly with arms folded, rotate 360° and check your stability. Practice straight line walking or try to cross one leg over to the other side, and vice a versa, as you walk to check balanced gait. While standing "write" a large "X" on the floor with one foot, then with the other. A well formed "X" both ways is a good balance and stability test as is going up and down a single step repeatedly and quickly (you can use a step box from a fitness center). Remember, dehydration makes all of these worse.

Inner ear balance exercises are also useful. The easiest is simply moving your chin from shoulder to shoulder repeatedly and check for dizziness or vertigo. Another is rotating your head as around a small circle repeatedly. This will give you a vertigo baseline, which can be confirmed by immediately trying your straight line walk right after. REMEMBER UNLESS YOU ARE IN SHAPE, BALANCED AND HAVE DONE THESE MANEUVERS BEFORE, DO NOT TRY THESE UNSUPERVISED. Once you are cleared for these, incorporate them into your exercise routine. Incidentally, swimming is a fantastic way to do these and improve balance, gait and "anti-vertigo."

Note that while balance is a "head" thing, stability is a "foot" thing. We cannot tell you how many falls are occasioned by bad footwear and poor foot mechanics coupled with weather events, wet flooring or poor carpeting, all the worse when exiting a bath or shower, or descending stairs.

Footwear is for safety. Comfortable, well-fitted footwear, with orthotic support for most, is essential. Then it is a matter of safe walking which means heels first on carpets, and toe first on wet surfaces, the "toe touch" means that you test the surface for skidding and slipping with one foot out, especially exiting bath or shower (where sufficient support bars are in place for you, and if they are not put this down and go out and get them!). As a general rule, heel first walking is actually safer and will tighten the abdominal and back muscles better.

Arch supports are an essential part of footwear not only for balance and fall safety, but for back pain relief as well. Numerous are the reports from grateful back sufferers who went orthotic and found amazing relief of symptoms. Orthotics will place the body in proper biomechanics, alignment for stability and balance while easing foot, back and even neck pain for many of you.

The third factor in falls and balance is related to orthostatic (standing) drop in blood pressure, as we discussed in the "Dehydration" section above. Three other "conditions" can contribute to a perilous fall risk from orthostatic drop, and they are:

1. Severe anemia from any cause but especially from occult (you don't know it is happening) blood loss.
2. After weight loss from dieting, surgery or infections, especially if you are on blood pressure reduction medications and the doses are not lowered consistent with your weight loss. If your weight drops, your blood pressure will drop. So you might have to drop your blood pressure prescription – another reason for a blood pressure monitor at home, not simply for blood pressure but for orthostatic drop and fall risk and gait and balance issues.
3. Peripheral nerve damage (neuropathy) or damage to the autonomic nervous system (A.N.S.) from certain neuro disorders such as Parkinson's Disease (A.N.S. trouble can precede tremor or stiffness). Diabetes, especially if it is Insulin dependent, and certain drugs that interfere with A.N.S. function such as alpha blockers for prostrate enlargement and some classes of blood pressure drugs.

Syncope

Syncope is a sudden loss of consciousness from any position usually lasting less than 30 seconds, but on occasion as long as 2-3 minutes. Rarely that might include vagal asystote when the heart simply stops beating. In any case, the same suspects are the rule: first is orthostatic hypotension with blood pressure drop sufficient to cause the subject to "black out," usually due to dehydration, excessive blood pressure medication, anemia or autonomic dysregulation, as in peripheral neuropathy, diabetes or Parkinson's Disease. Inadequate fluid intake leads the list in our experience. This is especially critical in patients with dementia who do not know they are thirsty. Job #1 as a caregiver is to make sure your loved one is taking in sufficient fluids throughout the day (and sometimes at nigh as well). Weight loss from any cause will increase the risk of orthostatic hypotension, and this will be worsened by failure to reduce water pills (diuretics) or blood pressure medications. Keep in mind that the commonly used drugs for memory (e.g., Aricept) or for prostate difficulty (e.g., Hytrin) can also cause low blood pressure. As weight loss of significant degree is common in Alzheimer's Disease and other ND diseases, standing blood pressure checks are essential to monitor for orthostatic drops. Many elderly patients have occult bleeding; they lose blood slowly and no one observes blood loss, or the bone marrow begins to fail to produce adequate blood cells. Either way, significant anemia can go undetected until a syncopal event. Patients should get blood counts three times a year as a routine practice, and more frequently if they are on medications that thin the blood or may cause occult bleeding (arthritis medications).

To summarize, the elderly or patients with Alzheimer's Disease have high risk for orthostatic syncope by a combination of factors, and these must be accounted for when treating blood pressure. Home blood pressure monitoring is essential. We cannot emphasize enough the need to begin this as early as possible to intercept and correct the risk before a syncopal fall brings a broken pelvis or head injury (possible brain hemorrhage) to your loved one. (See page 51, 52)

We will briefly mention several less common causes of syncope because they must be on your short list. The first is heart block, where the pulse shows dramatically and patients black out from a drop in blood flow to the brain. The second problem is neurocardiogenic syncope, so called because of "mixed" signals being sent from the heart to the pulse and blood pressure sensors in the brain. The important thing to note about this disorder is that the syncopal events can occur while one is driving, eating or watching television. There is often no orthostatic

component to those events and as they may occur infrequently this very treatable disorder is missed. A special tilt table study may be needed to diagnose this disorder.

A third cause of unusual syncope is a severe blockage either in the valve that empties the left side of the heart, the aortic valve or from overgrowth of the muscle below it (hypertrophic cardiomyopathy). While common, these rarely cause syncope because they are usually detected by echocardiogram. With any unexplained syncope, especially first event syncope, an echocardiogram must be part of the evaluation and perhaps a tilt table study.

Confusion

Confusion is usually a sudden, or within days, alteration in mental status. Dementia is a chronic state of cognitive impairment. Delirium is acute or sub-acute confusion with complete disconnect from reality, usually with hallucinations (verbal or visual) and delusions (imagining people or things that are not present). The confusion list is long but the common alerts when confusion begins are:

1. Medications, especially pain killers, sleepers, anti-anxiety and depression medications.
2. Infections in the elderly may cause weakness and confusion without fever. The most common infections to do this are urinary tract infections (prostate, bladder or kidney) and pneumonia (see "Infections" section), but any infection or sepsis (blood infection) can do this.
3. Vascular events, especially transient ischemic attack (T.I.A.) to brain, the onset of heart failure with low oxygen delivery to the brain, stroke, or cardiac arrhythmia that also reduces oxygen delivery, such as new onset Atrial Fibrillation, especially in the background of heart or lung disease.
4. In the setting of gradually worsening confusion, always consider:
    a. Anemia, Low sodium, dehydration
    b. Hypothyroidism (low thyroid) or rarely, hyperthyroidism*
    c. Significant renal disease or liver disease (simple measurement of Bun for renal, or Ammonia (NHH) level, respectively
    d. Head injury with gradual development of blood clot over the brain (subdural hematoma)

e. Brain tumor

f. Pernicious anemia (B_{12} deficiency) especially in the elderly

g. Always consider dehydration and electrolyte imbalance

*Elderly patients with overactive thyroid may be "apathetic" and the only clue would be weight loss, or rapid pulse.

Sleep Disturbances

A few practical tips: The most important aspect of sleep is that you establish quality, patterned sleep. This means a regular schedule of sleeping and waking. Quality sleep means no excessive alcohol, food, or use of medications that can disturb sleep. It also means the regular use of CPAP or dental appliance if you have obstructive sleep apnea.

Organized sleep patterns can become easily disorganized and irregular with retirement, illness, depression or early dementia. It is essential that retirement or increasing age do not become a reason to stop daily exercise and activities. Remember the rule of sleep, a good night depends on a good day! Stay active, stay alert to changes in your sense of well being and stamina. If there are changes, get checked out.

Longstanding poor quality sleep and/or insufficient sleep are usually lifestyle problems and are very difficult to change. Many patients manage to do fairly well with very idiosyncratic sleep patterns by napping once or twice during the day, brief power naps even as brief as 10-15 minutes can be very beneficial. In any case, it might be necessary to have a thorough sleep evaluation in a sleep center to pinpoint possible causes and treatment. A sleep evaluation may be as important, or more important, than a heart evaluation.

There is invariably a background story to sleep for each of us, consequently, longstanding abnormal sleep patterns will be most often refractory to medication or sleep management therapies. If there is to be any success, even with mild sleep disturbance, it is essential to look at 1) meals, both content and time, 2) regular exercise, and 3) stress management. On the other hand, many patients with heart or lung disease and certain dementia patients will have both increased sleep requirements and disturbed sleep patterns. In fact as Alzheimer's Disease progresses, the sleep requirements can increase to 14-16 hours a day.

A final point: Most of the prescribed sleep aids ultimately do not aid, and over time only make the situation worse. Alcohol is one such sleep aid. Almost every "moderate" drinker (2 or more a day) has disturbed

sleep with early mid-sleep (3-4 hours) arousal as well as disturbed sleep quality. On the other hand, many patients report that a small amount of alcohol helps them fall asleep and stay asleep. No doubt in small amounts alcohol has a beneficial, calming and anti-anxiety effect and this may be its main benefit in sleep. Keep in mind that this is an individual situation, and will depend on medical, emotional or neurological factors as well.

Usually one of two general "patterns" of sleep emerges as we age, either less sleep or, with the dementias, especially Alzheimer's Disease, increasing sleep requirements. Patients with advanced Alzheimer's Disease typically sleep 10-12 ours (nightly) and an additional 4-6 hours (daytime). Our best advice on this for you in caring for a loved one with Alzheimer's Disease is to do nothing to change this because you can't. This is the disease and there is no treatment, even if you and the doctor are trying to restore quality sleep. Where there is a severe behavioral problem treatment with sedating doses of drugs will be needed, but other than managing aggressive behavior provides no benefit and will significantly increase sleep time in most patients.

Daytime naps, on the other hand, are part of our DNA. Even healthy, high functioning people benefit from brief power naps, and obviously in dementia it is not a matter of napping to boost function, but needing prolonged naps because brain cells are being lost in huge numbers. Here functionality is simply giving way to survival by sleeping.

"Sleepers"

The rule is most of the time to avoid them. The exceptions are:

1. for short-term stabilization
2. for anxiety induced sleep disorders
3. for patients already on long-term "sleepers" who are unable to wean. It is most often preferable to leave such patients on the medication as it is very difficult to restore quality, natural sleep in these patients. In any case their patterns of habituation are difficult to reverse, and need not be unless the medications present medical hazards.

Your job as caregiver is to stay alert to prescription patterns for patients with many specialists but no single medical coordinator. It is easy for them to get dosed inappropriately and the prescribed medications become the issue. The only rule about sleep, then, is that there is no fixed rule. Given the information about alcohol, drugs, exercise and

stress management, will usually establish an effective sleep-rest schedule most in sync with one's overall circadian rhythm.

A number of medications are available purporting to restore quality, restful sleep. By and large the claims are false. The medications might work for a period of time but either increasing doses are needed or the medications lose their effectiveness.

The second important rule here is to avoid all "medication wandering," moving from one sleep medication to the next in search of the best night's sleep. Likewise, "neither a borrower nor lender be." No trading or borrowing medications for any reason. This is a dangerous and common practice when insurances don't pay for the drug your friends or family members say is just the one you need; remember, not from them!

Sleepers may be appropriate for short periods (days to two weeks) for those situations where sleep loss is a greater risk to health than the sleep medications themselves. Medications such as Ativan or Xanax can be helpful if there is sleep dysregulation coupled with anxiety. These medications are in the benzodiazepine class of drugs which increase a neurotransmitter, GABA, that helps neutralize excitatory neurotransmitters. The net effect is a lessening of anxiety and motor activity and some sleep enhancements, but at the risk of daytime drowsiness and increased fall risk.

The better option if anxiety is not a component would be a small glass of red wine, or a small shot of cognac, port or some other low alcohol drink by volume. A small amount of alcohol can relax one to sleep without fragmenting sleep four hours later, and with less daytime issues the following day than with Ativan, Xanax or Ambien and related sleep medications.

Gastrointestinal (G.I.) Problems

G.I. problems are ageless. Nonetheless, aging brings a few wrinkles to some common disorders, the first being reflux disease (GERD). Patients with GERD at any age may have painless GERD but more so older patients who may not experience lower esophageal pain or burning but might have chronic cough, hoarseness, sinusitis, wheezing or asthma, or irregular heart beats. Any one of these symptoms, or multiples thereof, may signal that reflux is the cause and rather than the symptom it keeps leading to a separate diagnosis. In other words if reflex is treated, these symptoms are very likely to resolve. The diagnosis of reflux may require an upper endoscopy, but it certainly is appropriate to consider a two-week trial of an anti-reflux medication (e.g., Nexium or Prilosec)

if two or more symptoms are present, especially if they are cough and hoarseness, keeping in mind that larynx tumors can produce the same to symptoms. Likewise, reflux itself may not be primary GERD but reflux secondary to obstructive sleep apnea, or significant weight gain. In that case you may have to work back from symptoms such as cough and hoarseness, consider reflux but if there is no burning or pain or of you are experiencing severe breathing, severe snoring, and daytime fatigue, especially after weight gain, you may need to go straight to the sleep lab and not the endoscopy suite. Better yet, weight loss may fix everything!

Infection with the organism H. Pylori may be an issue and this can be tested by your physician. We do not recommend an empirical trial of the antibiotic regime for this as the antibiotic combination may impose risk of Clostridium Difficle ("C Diff") infection. Actually, C Diff colitis is not an infection from outside but massive overgrowth of this bacteria in our colon purged of good bacteria by antibiotic therapy or chemotherapy or contact with a carrier (see below: Diarrheal Illness).

Lactose Intolerance and Gluten Sensitivity increase with age, either of which (and they do occur together as well) can produce unexplained gas, bloating, indigestion and abdominal discomfort, even weight loss (gluten – Celiac Disease). We mention these as two commonly overlooked disorders the symptoms of which while nonspecific should suggest the simple changes in diet that will ameliorate them. More rarely, elderly patients, especially after long-term use of anti-acid drugs, can have general bacteria overgrown with similar symptoms.

We mention ischemic bowel disease as another problem as we age, especially if vascular disease, including peripheral (legs) vascular disease is present. Patients have vague to significant abdominal pain after eating (abdominal angina) which can be misdiagnosed or neglected for many months, or until an acute blockage occurs. While we have not seen this in any of our research patients, we remind you caregivers that your loved one with Alzheimer's Disease may be less able to express the symptoms of abdominal angina but may inexplicably begin to eat less and lose weight at an accelerated pace. Keep "abdominal angina" in mind if that happens, keeping in mind also that abdominal angina may actually be cardiac angina.

We previously mentioned C Diff colitis and we want to alert you to the increasing risk for your loved one (or you), acquiring this during hospital or nursing home stays, either by contact with C Diff spores (C Diff is in the family of bacteria that causes tetanus and the once infamous diphtheria). In any case, the widespread use of antibiotics in hospitals has made C Diff a primary hospital hazard infection, as it is if

you or your loved one has received antibiotic therapy for any reason, in or out of the hospital, even for a brief period of time. Diarrhea, bloody diarrhea, fever and toxicity on an increasing scale of severity may occur weeks after the hospital stay or antibiotic therapy. It is a growing risk and deserves your consideration and your doctor's attention at the first symptom if either hospitalization or antibiotic therapy was previously in the picture. It might also be well considered to ask your doctor to cover for C Diff "prophylactically" depending on risk potential, even though good studies of such use of Flagyl or Vancomycin, the drugs used to heal C Diff after symptom onset, are lacking. Probiotics, on the other hand, are readily available without prescription (and in the dairy section of the market) and may provide some protection against C Diff and help in diverticulosis, irritable bowel and chronic constipation.

The beneficial probiotic bacteria are found in high quality, high protein Greek yogurt. Among the probiotics identified as important for colon health and perhaps for treatment are members of the family Bifidobacterius or Saccharomyces (S) Boulardii, S. Bulgarigus, Lactobacillus Casei and L. Rhamnosus. In addition certain natural foods serve as efficient prebiotics which provide a beneficial milieu for maintaining probiotic health (for example, barley, oats, psillium, high quality fiber foods, legumes and beans). In general, vegetables, fruits, grains and nuts assist this. We recommend that all hospital or nursing home patients eat yogurt daily in addition to anyone of any age on any antibiotic for any reason, period!

Another common disorder is an incarcerated hernia in the inguinal area. These hernias may slip in and out, partially obstructing the bowel so that pain, nausea and vomiting, especially if intermittent and mild, may be overlooked until a true medical emergency occurs. We know that patients with more advanced Alzheimer's Disease are unlikely to report either pain or mild to moderate symptoms. Think about an obstructing hernia if you see these symptoms, and examine gently the inguinal hernia for tenderness or swelling, and call the doctor!

Constipation is such a common and potentially difficult problem in the elderly, especially with autonomic dysfunction, as in Parkinson's Disease or in Alzheimer's Disease with inactivity. The wisest course is to always anticipate it will happen and begin dietary changes long before. Chronic dehydration is the number one enemy followed by medication, recovery from surgery and intermittent partial intestinal blockage. Fluids, especially soup broth and copious water intake are essential. Dietary fibers are important such as whole grains, especially flax seed, oatmeal and unprocessed miller's bran, veggies, fruit and yogurt

(if no lactose intolerance; if so, it is okay to add lactaid). Walking, of course, and as much time upright as possible are equally important but sometimes are not possible. Manual disimpaction is an unpleasant but necessary skill that must be part of care giving when the problem develops, keeping in mind that five or more days without relief requires professional evaluation.

Urinary incontinence in men is usually due to prostate disease and "overflow" from a partially blocked bladder outlet. Incontinence is also common after stroke, with Parkinson's Disease and dementia, and can also present as sudden urge incontinence as in woman, in either case relates to "instability" in the bladder. Other than the overflow incontinence due to the prostate, the other forms of incontinence can be treated with bladder training and Kegel exercises (pelvic muscle contractions) or with medical therapy for sudden urge or stress (cough, bending, lifting) incontinence. Keep in mind one very important point, the bladder is not a reservoir. It is a muscle pump and it works better after it is filled. So even with incontinence you need to hydrate for all the reasons we have mentioned. The common mistake of drinking less because of incontinence is a mistake.

Anxiety and Depression

Anxiety and depression are more difficult to gauge in elderly patients or in patients with early to moderate Alzheimer's Disease where the capacity for emotional content thinking is still present but increasingly disabled. One of the reasons why the diagnosis of depression is more difficult in these situations is the natural development of reserve as we age. Sometimes detachment or "apathy," so called, which might be a sign of depression, may actually be the sign of the person's relief at no longer feeling the need to engage the chaos of the Internet age. One can literally be twittered to madness. Isn't it much better to simply drop out? Call it apathy if you must, but it is much more likely it is a necessary psychic tool for emotional self-preservation. On the other hand, indifference to matters of personal or family significance may reflect real depression or repressed anger.

Apathy is a hallmark of progressive Alzheimer's Disease and may be as much a blessing in one sense as it is a measure of disease in another, because "apathy" here is not a conscious decision to remove oneself emotionally; it is a forced retreat, if you will. Nonetheless, in earlier stages of Alzheimer's Disease this apathy, so called, may be responsive to Aricept or other acetylcholine boosters and help the patient to re-engage. In fact, such a response is likely diagnostic of apathy rather than

depression which Aricept would not be expected to help. Insofar as depression may be an issue in Alzheimer's Disease, antidepressant drugs are less likely to be helpful for two reasons: 1) apathy was mistaken for depression and less "target" neurotransmitters (e.g., Serotonin or Nor-Epi) may be available. This might be the reason why the older antidepressant, such as Elavil, may be helpful in some cases.

Anxiety in the elderly and in Alzheimer's Disease patients is equally difficult to diagnose if its main manifestation is agitation since agitation is a hallmark of progressing Alzheimer's Disease. Virtually all of our research patients exhibit this in the earlier "stages," likely due to their awareness of ongoing decline and their frustration with their increasing inability to recall, react or interact. The agitation is appropriate and unless it is destabilizing at home or in public, we advise sympathetic guidance instead of sedating drugs.

Interestingly, a recent N.I.H. review suggests that the antidepressant Celexa may be helpful here, working at least as effectively as the more aggressive mood stabilizer, Risperdol. Likewise, the benzodiazepine class (Ativan, Xanax) can be effective at low doses, with their added benefit of anti-anxiety and sleep aid effect in some patients (see Medication discussion below).

We must point out something very important to all of you. There is always much to worry about and much that will sadden us. Is it the wisest thing to always look at worry and anxiety, or sadness, simply as mental health categories? If that is how we receive them, that is how we will respond to them, as therapeutic problems. But if these moods and conditions indicate something more profound, they become opportunities for more authentic dialogue. The philosopher Martin Buber called these occasions the "I and thou" which speaks to the soul. Carl Jung, a famous psychoanalyst and contemporary of Buber, once said that in the last half of his life as a psychoanalyst he believed that each of the persons who came to him was suffering from a "disorder of the soul" and the psychological symptoms were only an incomplete reflection on the deeper questions. If religious faith is part of your loved one's story then make that part of the "treatment plan," especially where there is anxiety, depression, fear or anger.

Medication Alerts

Tylenol	All Tylenol/Acetaminophen recommended maximum doses are at least twice what is acceptable in elderly patients because of the toxic effect on the liver. We recommend no Tylenol.

NSAIDS	Non-steroid anti-inflammatory Drugs (e.g., Motrin, Aleve, Advil, etc.) affect the liver and kidneys but the highest risk is for G.I. bleeding, and is more toxic when used with Tylenol. NSAIDS also increase bleeding risk in the brain and G.I. tract when used with ASA and/or Plavix, which also increase bleeding risk.
Antibiotics	Main risk (other than allergic reaction) is appearance of drug resistance or development of C Diff. This is a great concern with antibiotics which target families of gram negative bacteria especially in G.I. or G.U. tract (e.g., Floroquinolones, Clindamycin, and cephalosporins). Overuse is a large problem. Use yogurt as probiotic.
Blood Pressure Medications	Alert for standing blood pressure and falls, changes in Na, K and renal function. If you take them you must monitor them and your own blood pressure – always with a standing measurement as well. All blood pressure medications can increase salt and water retention. Weight loss (e.g., after surgery) may drop your blood pressure, in which case you may need to drop your medication.
Ulcer and GERD Medications	Prolonged use increases risk for pneumonia and C Diff because the stomach acid looses its bacterial barrier effect; may worsen risk for osteoporosis and Iron deficiency as well. If you are on these medications and symptom free, ask your doctor about stopping.
Diabetic Medications	Especially long-acting sulfonylureas (e.g., Glyburide) can cause dangerously low blood sugar, especially early morning.
Diet "Weight Loss" Medications	Avoid any and all diet aids. Every diet medication which has been marketed has shown potentially serious side effects, including cardial arrhythmias, increased blood pressure and even stroke or heart attack.

Sleep Aids	May not aid and can increase fall risk, and lead to driving, work or recreation accidents. May decrease cognitive level, paradoxian effect of increased agitation, REM sleep disorders reported with Ambien and related medications. Alcohol in more than very modest doses (1 glass of wine or 1 bottle of beer) may worsen sleep.
Prostate Medications	Some of them can lower blood pressure and increase fall risk, especially when out of bed during the night.
Pain and Anti-Depression Medications	Sedating effects, paradoxical reactions, which increase agitation and suicidal thinking; must be prescribed and monitored responsibly by both patient and doctor. Combination use, or with pain medications or anti-seizure medications used for neuropathic pain, can present significant risk. Never combine these without first discussing with your doctor. There is a growing emphasis on topical compounded pain formulas, especially for neuropathic pain. Try these first.
Behavioral Control Rx in Alzheimer's Disease	Management of manic or aggressive behavior in Alzheimer's Disease can be accomplished but sometimes requires high doses of benzos (Ativan) or atypical antipsychosis (e.g., Risperdol, Seroquel), which will leave the patient quite sedated, more sleeping, more neglect of food, personal hygiene, etc. all of which can already be a problem. Sometimes the choice is necessary, but you will have to decide…not the doctor.
Appetite Boosters	Megace for appetite and special protein supplement usually have marginal benefit. A balanced natural diet is always preferred unless there is extreme weight or appetite loss and protein-caloric deficiency.

Statins	There is a marginal if any benefit after age 75 or 80 regarding life expectancy without risk/benefit recommendations unless there is a definite indication.
Osteoporosis	Same as Statins, above. The elderly see less benefit for primary prevention with fairly good T score. Risk of G.I. (esophagus) or bone necrosis and worse event first fracture. Recommend stop unless absolutely indicated.
Energy Drinks	Absolutely NOT!! They increase heart rate, increase blood pressure, and create sleep disturbances.
Decongestants	Nothing with phenylephrine or pseudoephedrine (Sudafed) because heart rate, blood pressure and sleep disorders are increased, just as with weight loss aids.
Hormonal Rx (e.g., testosterone growth hormone, etc.)	You are supposed to get old and tired. It is one thing to treat pathology with all of the hormones available. It's quite another thing to push physiology. The risk of blood clots, heart attacks, thick blood, even prostate cancer are real. Avoid these unless medically necessary. Remember, body protection always takes precedent over body building.

Give every one of your doctors your most updated medication list with notes of prior drug failures or side effects.

"Neither a borrower nor lender be." You thought that was about money….Wrong…it is about medications.

In general, the lowest dose for the shortest possible time compatible with the target effect.

Think of medication effect if any of the following occur: arthritis, skin rash, abnormal blood tests (e.g., liver, renal, etc.), diarrhea, constipation, new onset bleeding, confusion, headache, weakness, loss of appetite; actually anything.

Ask your doctor about gene tests for drug metabolism. Patients metabolize drugs with different speed so that doses of drugs such as Plavix, heart and psych drugs can be appropriately adjusted. The new science

of pharmacogenomics promises safer, less costly drug dosing by these means.

Last of all, we remind you again to remember you are fighting a disease not a patient. Your loved ones may hear you at times and try to follow your concerns and guidance. Or they will be unable or unwilling. You can never keep them perfectly safe, fully cooperative or make them connect their thinking to yours. If that is true for all of us without Alzheimer's, how much more so it is in Alzheimer's disease. If they won't use their walkers, hearing aids or safety devices, if they refuse their medication, if they stop seeing friends, even their doctors, if they become apathetic or contentious, whatever happens, do not make these issues "do or die" issues for you. You do what you can, and they do what they can, and that is all any of us can do. In the final analysis it is all imperfect, but that is good enough, and when your loved one is gone, your own memories of what you did will become a source of peace for you. You will be able to rest each night in the certain knowledge that in the most difficult time of your life you went beyond what you ever thought you could do, or endure, but you did, and you know better than most that, "We will be old, we will be infirm, but we will never be worth more."

A Note to the Adult Children of a Parent with Alzheimer's Disease

We end with a few thoughts for you as so many of you have asked us the same questions, "what are my chances?" and "what can I do?" The first important thing you did was read this book because we wrote it for you, comprehensive both in describing the disease and the preventive strategies you can undertake now, both in relation to the disease and to aging. As we have already noted, Alzheimer's is called a disease of aging. We can only say that the temporal association may not in the final analysis define the causes of the disease, not to speak of aging itself, as we discussed in Section I.

There are some new developments in imaging and spinal fluid biomarkers particularly that will be helpful in terms of better defining the probabilities for disease in a specific situation perhaps even decades earlier than we could have a decade ago, but with all of these developments we still have no specific therapies available, and no way of turning the data into a personal strategy for you beyond the general topics we have discussed.

First, we can tell you that no one can tell you what your chances are. Several serum biomarkers, most particularly for Apo Protein E_4, are a predictor of risk, perhaps threefold if a single copy of E_4, per-

haps tenfold if a double copy, but as with all predictors of risk, it is not a statement of your outcome. There are, however, spinal fluid protein measurements for amyloid protein AB_{1-42} and Tau protein which will be indicators of relative risk and even early disease depending on the levels. The problem is that both proteins are present in each one of us and the "exact" load which announces disease is still undefined.

More detailed assessment of inflammatory molecules in the spinal fluid will give an early and more precise indication of where you are in the spectrum from normal through mild cognitive impairment (which may be unsuspected but demonstrated by careful psychometric testing) to prodromal Alzheimer's disease (storm warning is up, the storm has not yet hit). The inflammatory markers are non-specific in that there are other neurological diseases that are driven by these, but in the context of your relationship to a patient with Alzheimer's disease may indicate something more specific for the future.

The PET Scan, especially with ultra sensitive contrast enhancement, gives a very good look at the hippocampus, the first brain area usually to be hit by Alzheimer's disease, especially the volume of the hippocampus and distribution of contrast. Nonetheless we do not yet have a large enough database of PET findings of normals, those with or without a family history and without obvious symptoms. PET "tracking" will not likely take on the frequency of mammography or MRI tracking for breast cancer since we do not yet know what time intervals are appropriate but PET is certainly a tool for you in the near future.

We have not said anything about specific interview-based testing but for many of you without symptoms a thorough evaluation of memory, short and long-term remote, comprehension, visual spatial, calculation, and personality dynamics are still the easiest and most practical way to get a peak inside your brain. Thorough testing in a reliable experienced center will detect subtle findings which <u>may or may not</u> be early warning signs.

All of these modalities used together promise to give you a reliable means of judging your risk for Alzheimer's disease, perhaps as far out as five years, but in no case will the data establish a specific date of onset or the length of time between onset and significant disease. Perhaps the data gathered with those modalities will provide more specifics about the onset of disease but your hope, our hope, is that it will give us tools to fashion early, pre-morbid interventions sooner. The problem, of course, is that we do not yet have an active to market disease modifying drug, although the hope is that immunotherapy with amyloid targeted antibodies will be available by late 2015 or early 2016.

The other point to keep in mind is that our growing sophistication in biomarker risk assessment will likewise prove to have the same "fluidity" as risk modeling in other diseases. Just as patients might follow a general pattern into Alzheimer's disease early symptoms are quite pleomorphic and timelines vary and so do the biomarkers. They will be neither absolute predictors of risk nor predictors of time to symptom stages. We are, after all, studying a disease of the brain which interrupts or short circuits the highest functions of memory and cognition, imagination and creativity, language and though, unique to each person in health and thus more so in disease.

The question for you is this, "should I do everything I can now to find out what's going to happen to me a decade or more from now?" The simple answer would be "yes", but the huge qualifier here is this, "what can we do about it?" We have already outlined quite thoroughly testing and monitoring for Alzheimer's disease and stroke, and the pathways common to so many other diseases. The modification of all of these generic risks should already long have been in your day planner because that is proven risk modification. Beyond that, however, the question distills to specific intervention and the answer is there is as yet no specific treatment other than research, there is no intervention. Why all the testing then? The answer is always the same, a need to know and the advancement of the general database. The other side of the casting of nets is this, you are likely to pull in anything, and so it is in medical screening. The more we look the more we find, and the more we do about what we find. The problem is that very often mass screening or high intensity individual screening, as in whole body CT imaging, as a way of early detection for many types of cancers wind up simply being the detection of ultimately harmless dots, blots and spots that everyone feels obliged to chase down and destroy. Most of these turn out to be artifacts or benign cysts we had for years, or old scars from remote infections or injuries. It would have been safer and cheaper not to have done the whole body CT and for most of us it is no longer performed. Is this the same thing that might happen with aggressive early detection of risk (not disease, but remote risk) for Alzheimer's disease? Yes, of course it will be once drug therapies are on the market and the temptation to do it very early is reinforced by the hope that we can stop it early.

In the meantime, which is today, you who are the children of a parent with Alzheimer's disease, do the very best thing you can do for you, and that is help care for and be there for your parent so that one day your loved ones will be there for you, whatever disease it is that comes for you.

There is, however, one promising change in strategy, more correctly, a new strategy, specifically aimed at you, the adult children of a par-

ent. Several of the pharmaceutical companies will be offering you, without symptoms of memory loss, even casual forgetfulness, or other early warning signs of disease, the opportunity to participate in research trials with some of the study drugs being used in current trials. The key element in deciding one's eligibility for entry into a study of this kind as a preemptive strike, if you will, rests in either spinal fluid measurements of target amyloid or tau, and various inflammatory markers. The other inclusion requirement will be a PET-isotope study targeting amyloid which must show an amyloid burden sufficient to indicate future risk and not a real time diagnosis of Alzheimer's disease. One or both of these measurements will be the specific criteria for inclusion, as the usual memory testing will not be of much help.

The exact numbers on spinal fluid analysis or readings on quantitative imaging are certainly not yet defined for disease specificity, so it is clear there will be no definitive changes in your case should you decide on one of these "pre-symptomatic" trials. In fact, part of the gain in this preemptive research will be the accumulated data on the correlation between the presymptomatic CSF, PET and biomarker changes and the timelines for the onset of symptoms, and the modifications in progression.

This is a new, welcomed strategy, but is even less precise than the already diagnosed patient protocols, which in themselves, do not offer precisely indexed criteria for specific stages of Alzheimer's disease (i.e., prodromal, mild-early, etc.). Keep this in mind, however, regarding preemptive treatment, it is not precisely prevention in the sense that we have used the term throughout the book (i.e., attacking early multiple risk factors to prevent the critical disease end points). The end points in the preemptive trials are still the culprit proteins, a much lower burden of protein, so that an intervention before diagnosis might prevent the proteins from attacking. In the ordinary sense of prevention, however, the goal would be to intercept pathways that lead to the evolution of these proteins (amyloid or tau) into their toxic reconfigurations (e.g., by modifying inflammation and oxidation, and epigenetic DNA methylation or histone acetylation). Those interventions are interventions at the starting gate. The protein attack strategy before diagnosis is intervention at the final stretch, but at least before the finish line (i.e., that critical mass of culprit proteins that preclude halting or slowing further disease progression). That, of course, is the critical question, what is a critical burden? And that is part of the new strategy to guard the brain before the attack. It is a hopeful approach, we just do not yet know if it will be effective, but that's the search in research!

We mean this "care" in a very specific way, especially in the cultural time of "managed care" by families, care from a distance through surrogates and agencies, with good management of bureaucracies. Nothing in your future will be more important than your own physical presence, hands-on care, and time spent, however limited because of work and distance. This is your mother or father, after all, who cared for you tirelessly at a time in your life before memory. Now they are in a time of their lives beyond memory. As best as you can, as intimately as you can, "honor thy father and thy mother."

QUESTIONS:

1. A caregiver needs:
   a. A support system
   b. To talk about experiences
   c. To say nothing to protect the patient's privacy
2. The caregiver must:
   a. Be available "24/7"
   b. Take breaks
   c. Be a relative
3. Patient and caregiver support can include:
   a. Clergy
   b. Doctors
   c. Anyone who wishes to help
4. Caregivers are at risk for depression:
   ❑ True ❑ False
5. The most common reasons for caregiver illness include:
   a. Stress
   b. Fatigue
   c. Pre-existing disease
6. Patient behaviors are:
   a. Not under their control
   b. Not personal
   c. Often treatable
7. If your spouse/patient is delusional or confused:
   a. Talk them out of it
   b. Say nothing
   c. Reassure them you are always with them
8. Anything that the patient wishes to do that is safe is okay:
   ❑ True ❑ False
9. Conversations "with" persons from long ago should be stopped:
   ❑ True ❑ False

Conclusion

THE ONCE AND FUTURE BRAIN

Neuroscience has matured over the last 25 years, building on a century of work in anatomy (architecture), physiology, (function) and cybernetics (integrated systems), the three aspects of brain. These advances have brought most of us to the belief that all thought and behavior is biologically driven, if not determined. Certainly, Alzheimer's disease is an impressive witness to this, as it delivers its destruction to all cognitive functions, even conscience and moral choice, by obliterating billions of neurons and thousands of miles of wiring. It is hard to argue against such evidence in favor of mind as brain. There is, however, other evidence which confutes this analysis; i.e. functional imaging which gives immediate "light-up" of brain centers as subject's emotions, intentions, fantasies, and concrete directed thinking take place instantaneously. How, one asks, do cells and electrical wiring drive such instantaneous thinking, or its immediate reversal, or the immediate replacement of thoughts by new thoughts which can conclude or contradict those which immediately preceded, just a nanosecond prior? How does "the program" of the three aspects of brain give up so many variables; artist or athlete, scientist or poet, or categories; Goodness, empathy and service, or crime, violence, and evil, sometimes in the same brain, the same person. Is the difference between Mother Theresa and Adolf Hitler a chemical difference, or the difference between Einstein and Picasso simply one of neuron selection?

There is an unbridgeable gulf between brain and mind. No doubt without brain there is no mind and no psyche, but that is all we can say. There is absolutely no scientific warrant for saying they are the same, no matter how similar all brains are in the three categories. If it were so, then it might also be said that the three aspects of the brain represent all of the instruments, all of the musicians, and all of the sounds of a symphony. But when we test this by putting all of the musicians in a room playing their respective instruments as closely in sync as they can, would they come together so perfectly that they would give us a symphony? Can all of these prodigies give us Beethoven's Ninth without Beethoven? This is the real question, and this is the reality; the difference between brain and mind, and the difference it means.

Nonetheless, neuroscience promises even more and soon, the fusion of nanotechnology and cell biology as part of the explosion and the power of artificial intelligence (AI) wherein the computer will outthink its maker.

There is other research in "directed" thinking, where test animals talk to each other by hardwired computer signaling, so that activities in one are "mirrored" by the second animal. The goal in either case of these "bio-brains" or "mirrorbrains" is to mimic mind the way robotics mimics human work. We have no doubt some of this will happen, as some of it already has happened, but we are still left with the ultimate separation between the machines and the mimics, and the minds who created them. There is in all of this wondrous technology a more astounding wonder, and we suppose it to be the final test of all things brain; replication is not creation!

You have learned much more about neurons, that they are the material substrates for all your intellectual, emotional, and psychic life, and how to defend against chemical hits to them. The most interesting thing about all of this, however, is another fact. Neurons only release chemical neurotransmitters, not thoughts. Yes, the neurons are essential to all of the things your mind does, there is no mind without matter, but matter cannot think.

A single neuron emits a measurably small amount of the memory chemical, acetylcholine, but acetylcholine is not a thought, not even a nano thought, or a tiny part of a thought. Thoughts, you see, are irreducible, they cannot be broken down biologically, even though they might be analyzed psychologically – but that's just thought thinking about thought ! Each and every thought, however irrational, is a complete entity even if it makes no sense at all. Consider, as well, that no multiplication of neurons even into the billions can produce a thought, they can only produce more chemical.

The easy definition of Alzheimer's disease is that it is a state of dementia substantially related to a decline in neurotransmitters and the accumulation of killer plaque, until such a patient no longer thinks coherently in a conscious, reflective sense (as far as we know). Nonetheless, that patient still has thoughts, they never stop, no matter how little they are verbalized, if at all. Remember, once again, it is impossible to be alive and thoughtless, until there is a brain death. Even patients in deep coma have thoughts, albeit completely unknown to them, and certainly to us. How else could they return to thinking again, and conscious thought life if they do emerge from coma?

So neurons are essential for everything human, all the powers of the mind. Yet, in the greatest contradiction in science, they are mindless, thoughtless, they are only chemicals. Something else is at work here in the brain and the mind, but as to what that might be, we leave you with your thoughts!

Dr. Mark Brody
Dr. Joseph Mauceri

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