Scientific Rationale for EDTA Chelation Therapy

Mechanism of Action

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ABSTRACT: The widely accepted free-radical theory gave us a unified scientific explanation for many diverse benefits following EDTA chelation therapy. Newer concepts of cell-senescence and apoptosis, together with an insight into homocysteine and cholesterol metabolism expand our knowledge, leading to a broader, more comprehensive understanding. The mechanism of action must explain why full benefit occurs several months after chelation is administered and why that improvement persists for months and years thereafter. EDTA has its effect by binding, redistributing and removing metallic ions. Realignment of essential trace elements with augmentation of vital metalloenzymes may be as important as elimination of free radical catalysts and toxic heavy metals. Pulsitile increases in parathormone using disodium EDTA may cause lasting improvements in calcium metabolism, with benefits experienced months after each infusion (not possible with calcium EDTA).

INTRODUCTION--RESEARCH SHOWING SAFETY AND EFFECTIVENESS

The use of chelation therapy with intravenous ethylenediaminetetraacetate (EDTA) for the treatment of atherosclerosis is rapidly increasing worldwide. This practice, which began more than four decades ago, accelerates each year. Dozens clinical studies have been published to document safety and effectiveness of intravenous EDTA for treatment of occlusive atherosclerotic arterial disease and age-related degenerative diseases.(1-89) A very important basis for the scientific rational of this therapy is thus the fact that it has been proven effective over and over again in clinical practice. More than one million patients have received more than twenty million infusions with no serious adverse effects--when administered following the approved Protocol. Many years ago

reports of kidney damage and other adverse events resulted from excessive doses of EDTA, infused too rapidly (more than 50 mg/Kg/day or infused more rapidly than 16.6 mg/min).

Excessive dose-rates of infusion, especially in the presence of preexisting kidney disease or heavy metal toxicity, were responsible for occasional reports of nephrotoxicity.(64-74) No adverse effect on kidneys has been reported when the currently approved protocol has been correctly followed.(72-74)

Research with laboratory animals provides further support for the effectiveness of EDTA chelation therapy.(77-83)

There has never been a scientific study of EDTA chelation that did not show effectiveness, although there have been reports in which positive data were erroneously interpreted as negative. Reports of negative or adverse results from EDTA chelation following the currently approved protocol have been either editorial comments and letters to the editor written by opponents of this therapy or seriously flawed attempts to discredit chelation with biased and unscientific interpretation of data--sometimes by cardiovascular surgeons who freely admit their bias.(75,84-89)

In the last ten years, a small cluster of studies has sprouted up in the medical literature purporting to demonstrate that EDTA chelation is not effective in treatment of cardiovascular disease. Although flawed and imperfect, those studies in actuality provide only positive support for chelation. Their negative conclusions are not supported by the data.

The Danish Study

The most controversial and oft cited study of that type was done in Denmark. It was the handiwork of a group of Danish cardiovascular surgeons who freely admitted their opposition to chelation. Results of that study were published in two medical journals, the Journal of Internal Medicine and the American Journal of Surgery.(84-85) Adverse conclusions were also widely publicized in the news media.

The surgeons who conducted that study followed 153 patients suffering from intermittent claudication. The patients had such severely compromised circulation in their lower extremities that walking a city block or less would cause them to stop with pain. An endpoint measured for this study was their maximal walking distance

(MWD)--the very longest distance that they could walk before pain of claudication brought them to a halt. Patients were equally divided into an EDTA group and a placebo group. In the pre-treatment phase, the EDTA group averaged walking 119 meters before pain stopped them; the placebo group was less limited at the outset and averaged 157 meters.

Treatment was either 20 intravenous infusions of disodium EDTA or 20 infusions of a simple salt solution, depending on their group. Although the study was alleged to be double-blinded (neither patients nor researchers were supposed to know who received placebo and who received EDTA), the researchers later admitted that they broke the code well before the post-treatment final evaluation

Both groups showed improvement, and the investigators concluded that the improvement was not statistically significant. This Danish study turned many people against chelation; but, in rather short order, the integrity of the study was called into question. It was learned that the researchers had violated their own double-blind protocol. Not only did they themselves know before the end of the study who was receiving EDTA and who placebo, they had also revealed this information to many of the test subjects. Before the study was over more than 64 percent of the subjects were aware of which treatment they had received. This was highly questionable from an ethical and scientific standpoint.

One important aspect of the Danish study is the startling fact that the patients who were given EDTA were much sicker than the patients treated with a placebo. Therefore, the improvements the EDTA group made were harder earned and more significant. The researchers (who candidly admitted that they undertook the study to convince the Danish government's medical insurance NOT TO PAY for chelation) either never noticed that aspect or felt reluctant to reveal it. The evidence is seen in the pre-treatment MWDs, 119 meters for the EDTA group and 157 meters for the placebo group.

Still more significant was the standard deviations The plus or minus 38 meters SD for EDTA patients versus the plus or minus 266 meters SD for the placebo group represents an enormous variation in walking capacity that is heavily biased in favor of the placebo group. Those standard deviations show that some placebo patients must have walked half a mile before stopping. The placebo group’s claudication was therefore markedly less severe, and the EDTA group was much more severely diseased. The design of the study was obviously biased

against EDTA chelation from the outset.

Yet, when the six-month study was completed the mean MWD in the EDTA group increased by 51.3 percent, from 119 to 180 meters, while the mean MWD in the placebo group increased only 23.6 percent, from 157 to 194 meters. The chelation group's improvement was therefore more than twice as great as the placebo group's, even though the chelation group was significantly sicker at the outset. This is a positive study, supporting the usefulness of EDTA chelation. The authors' published negative conclusions are not supported by the data.

The New Zealand Study

Another study--also conducted by cardiovascular surgeons--was done at the Otago Medical School in Dunedin, New Zealand, two years after the Danish study. The subjects of this study were also suffering from intermittent claudication. The subjects were divided into two groups, the EDTA group and the control group. The study extended to three months after 20 infusions of either EDTA or a placebo were given. The authors concluded that EDTA chelation had been ineffective. Once again, that conclusion was unsupported by their data.(86-87)

Absolute walking distance in the EDTA group increased by 25.9 percent; while in the placebo group, it increased by 14.8 percent. The difference was not considered statistically significant. The study, however had only 17 subjects in the placebo group. One of the placebo patients was what the statisticians call an "outlier," whose results differ strikingly from everyone else in the group. This patient's walking distance increased by almost 500 meters. All of the statistical gain in the placebo group was due to this one individual's progress. Without him, the placebo group's distance actually decreased.

This illustrates the perils of a small study. The 25 percent gain in the EDTA group compared to no gain in the placebo group would have been very significant statistically.

In addition, the New Zealand researchers did concede that improvement in artery pulsatility (pulse intensity) in the EDTA group's worse leg improved enough to reach statistical significance ($p<0.001$).

A 25.9 percent improvement in walking is by no means minor and would attract notice if the agent had been a patentable drug. Even that level of improvement is not representative of the much greater

improvements claudication patients normally experience after chelation. The below expected improvement seen in this study can be explained by smoking. Eighty-six percent of the chelated subjects were smokers. Although they were advised to quit smoking when the study began, how many of them actually complied is not known.

The Heidelberg Study

Another study that was carried out with an erroneous negative conclusion is the “Heidelberg Trial,” funded by the German pharmaceutical company Thiemann, AG in the early 1980s. A group of patients with intermittent claudication were given 20 infusions of EDTA and compared with a so-called “placebo” group which was actually given bencyclan, a pharmacologically active vasodilating and antiplatelet agent owned by Thiemann.

From a practical commercial standpoint, Thiemann’s action was bizarre. If EDTA did well in the trial, Thiemann’s well-established drug could only suffer. Nonetheless, the trial went forward and was reported in 1985 at the 7th International Congress on Arteriosclerosis in Melbourne, Australia.(87) Immediately following 20 infusions of EDTA the trial subjects’ pain-free walking distance increased by 70 percent. By contrast, patients receiving bencyclan increased their pain-free walking distance by 76 percent. The difference between these two results was not statistically significant, but another result was. Twelve weeks after the series of infusions was completed, the EDTA patients’ average pain-free walking distance had continued to increase, going up to 182 percent. No further improvement had occurred in the patients receiving bencyclan. Those percentages were never published.(87)

An informal report from Thiemann mentioned only the 70 and 76 percent figures. Press releases stated that chelation was no better than a placebo, but failed to mention that the “placebo” was a drug that had been proven effective in the treatment of intermittent claudication. Thiemann never released the actual data on which the Heidelberg Trial based its conclusions, but some German scientists who had access to it, and who were disturbed at the deception they were witnessing, chose to reveal the complete raw data to members of the American scientific community.

The complete data showed that four patients in the EDTA group experienced more than a 1,000-meter increase in their pain-free

walking distance following treatment. That highly significant data from those four patients mysteriously disappeared before the final results were made public. Thiemann had a legal right under terms of their contract to edit the final results and to interpret the data in any way that suited them. A subsequent analysis of the data, with the four deleted patients included, showed an average increase in walking distance of 400 percent in the EDTA treated group--five times the 76 percent increase of the group receiving bencyclan.(89)

The Kitchell-Meltzer Reappraisal

A dark moment for chelation research occurred in 1963, when Drs. J.R. Kitchell and L.E. Meltzer co-authored an article reassessing their support for EDTA chelation.

Although it was hardly in widespread use in 1963, chelation had not been controversial. Beginning in 1953, Norman E. Clarke, Sr., M.D., a prominent cardiologist and Chief of Research at the Providence Hospital in Detroit, began using EDTA chelation to treat coronary artery disease. In 1956 he treated 20 patients suffering from heart disease with angina pectoris. He reported that 19 of the 20 patients who received EDTA had a "remarkable improvement" in symptoms.(1)

Soon other physicians became interested, among them Kitchell and Meltzer, at Presbyterian Hospital in Philadelphia. From 1959 to 1963, Kitchell and Meltzer reported good results treating cardiovascular diseases with EDTA. Their early reports were all very positive.(7,10,14)

In April of 1963, shortly after their last favorable report, Kitchell and Meltzer published a "reappraisal" article in the American Journal of Cardiology that questioned chelation's value.(75)

In that reappraisal, they reported on ten of the original patients they had treated for cardiovascular disease, plus another 28 patients that were treated subsequently. Patients in their study were all severely ill. The authors state, " . . . we selected ten patients referred to us because of severe angina. The patients had previously been treated with most of the accepted methods, and their inclusion in this study resulted from wholly unsuccessful courses. Each of the patients was considered disabled at the start of therapy." This was therefore a high-risk group of very sick patients, who had not improved with any other form of therapy.

Seventy-one percent of patients treated had subjective improvement of symptoms, 64 percent had objective improvement of measured exercise tolerance three months after receiving 20 chelation treatments, and 46 percent showed improved electrocardiographic patterns. Kitchell and Meltzer concluded that chelation was not effective because some patients eventually regressed long after treatment. However, considering the poor health of the patients, some eventual worsening would be expected with any treatment. Eighteen months following therapy, 46 percent of the patients remained improved. The results were very favorable, even though the authors' interpretation was not.

Kitchell and Meltzer's reappraisal article was largely responsible for termination of hospital-based, academic research into chelation as a treatment for cardiovascular disease. Rather than analyzing the data for themselves, many physicians simply accepted the flawed conclusion at face value. We will probably never know what prompted those early researchers to change their position so abruptly. We can only speculate that it was an unrealistic expectation that the emergence of bypass surgery would be a final solution.

EDTA'S ONLY ACTION IS TO ALTER DISTRIBUTION OF METALS IN THE BODY

Intravenous EDTA enters and exits the body very rapidly. In less than one hour, half has been excreted in the urine unchanged except for metal ions it attracts enroute. Half-life in the body with normal renal function is approximately 45 minutes.

EDTA does not otherwise enter chemically into metabolic pathways. The EDTA molecule is not degraded or altered. Its only action in the body is to rapidly and reversibly attract, chelate and redistribute metal ions, or remove them from the body. When EDTA binds a specific metal, and subsequently encounters another ligand (a metalloenzyme, for example) with stronger affinity, that metal ion is dropped and another is substituted. In that way a shuffling and redistribution may occur without actual removal from the body. To be plausible, a scientific rationale for mechanism of action must be based on that type of activity, and must also explain why full benefit does not occur for several months after therapy.

Cellular metabolism relies on 50,000 or more different enzyme catalysts, many of which are metalloenzymes, requiring the presence

of a specific metallic trace element for activity. In excess, all essentials trace elements are toxic, poisoning those enzymes. As discussed below, nutritional trace elements can increase to potentially toxic levels in diseased tissues. Realignment of essential trace elements with augmentation of vital metalloenzymes may be as important to benefit as elimination of free radical catalysts and toxic heavy metals.

One nutritional element, iron, accumulates with age to act as a catalyst of oxygen radical proliferation, commonly referred to as free radicals. Free radical pathology is a causative factor in age-related diseases. EDTA has a high affinity for that potentially catalytic form of iron, and removes it from the body.

A number of heavy metals are toxins with no known metabolic function, such as lead and cadmium. They poison enzyme activity directly. EDTA also removes those metals from the body.

It is not yet known which action is most responsible for clinical benefit. Most likely, it is a synergistic combination. In light of recent scientific advances, a number of theoretical possibilities will now be discussed in more detail.

Cell-Senescence Model of Aging and Trace Metals

The cell-senescence model (sometimes called the telomere theory) of aging is hypothesized to underlie almost all aspects of age-related disease, including atherosclerotic cardiovascular disease.(90,91,92) As cells continuously die and are replaced with daughter cells, accuracy of gene expression progressively deteriorates. Replacement cells, produced by cell division and DNA replication, grow increasingly weaker. With each replication, accuracy is lost and subsequent generations of cells reflect that deterioration.

Telomeres on chromosomes shorten with each successive cell division, eventually becoming spent. After 50 divisions, cells reach the so-called Hayflick limit; telomeres become fully depleted and those depleted cells lose their ability to divide further. Without telomere replacement, cell death results.

There is more to the story that that. Progressive telomere shortening throughout life also correlates with cell senescence, leading to gradual but progressive deterioration through multiple generations of daughter cells. When cell deterioration is sufficient to cause impairment in organ

function, age-related disease results. Cells also divide and heal more slowly with each successive division.

It was once thought that only the absolute limit of cell division was important, when telomere length was totally depleted. We now know that as cells divide and telomeres shorten, cumulative inaccuracies in DNA replication cause progressive deterioration of gene expression. This results in cell senescence.

Two types of cells that do not senesce are germ cells and cancer cells, both of which contain telomerase, an enzyme that restores telomeres with each division. They are thus called immortal cells. If other types of cells, such as fibroblasts, are genetically modified in culture to contain telomerase, they also become immortal and do not senesce. Cell senescence is not only reversed, but aging ceases in cells that produce telomerase, even after 400 or more subsequent divisions.(93)

Endothelial cells in blood vessel walls, lacking telomerase, therefore deteriorate with each cell division.(94) With progressive telomere shortening, cell division and replacement slows and the healing process is retarded. Replacement endothelium becomes increasingly weaker and defective with each division. Cells subjected to frequent trauma and injury divide more frequently and therefore age more rapidly.

When endothelial cells are injured and replaced by adjacent cells, daughter cells are produced to fill in the gap. Damage to endothelia occurs with sheer stress at points of bifurcation, from hypertension, infection, toxins, tobacco byproducts, hyperglycemia, oxygen radicals, oxidized LDL cholesterol, and autoimmune processes. Endothelial cells become most disrupted at points of greatest stress, and divide most frequently at precisely those locations where atherosclerosis prevails. The cell senescence model thus accommodates and provides a broadened explanation for all known risk factors of atherosclerosis.

Senescent endothelial cells divide at a progressively slower rate and are progressively less effective at closing breaches in arterial walls. The resulting exposure of denuded subendothelial tissues triggers a cascade of events that encompasses all other theories of causation: monocytes and platelets are attracted and adhere to damaged areas; monocytes transform into macrophages; a variety of trophic factors and mitogenic factors, including cytokines and platelet-derived growth factor, are released locally; smooth muscle cells proliferate; oxidized

lipids accumulate in macrophages; and, eventually this enlarging plaque calcifies or ulcerates.

An underlying cause of this chain of events is now postulated to be the progressive telomere shortening in endothelial cells at points where they are most often called upon to divide. This occurs at arterial sites most subject to damage and therefore to plaque formation.

Cell types that divide frequently throughout life are precisely those cells that show decline with age. Skin cells and cells in hair follicles are frequently replaced throughout life. Resulting deterioration is plainly visible to the naked eye, to the extent that a close estimate of chronological age can be made at a glance. Cell types that divide frequently throughout life and therefore age at predictable rates include chondrocytes, fibroblasts, keratinocytes, microglia, hepatocytes, and lymphocytes. Associated DNA mutations and diminished immune function can act as initiating events in cancer.

Rare or absent division of neuronal cells seems to contradict this theory, since brain function so often declines with age. Astrocytes in the brain, however, continue to divide throughout life and are prominent in the early inflammatory stages of Alzheimer's dementia. Neurons make up only 10 percent of brain cells.

The cell senescence model supports a conclusion that cell division and telomere shortening are central to cell senescence, and thus to diseases of aging.

To help explain the benefits of EDTA within the cell senescence model, it is only necessary to consider the extensive biochemical pathways involved in cell division and replication require a very large number of metalloenzymes--as many as ten thousand or more different metalloenzymes. For example, DNA-dependent RNA polymerase, an enzyme involved at an early stage of cell replication, is zinc-dependent. Other enzymes needed for cell replication require the entire spectrum of essential nutritional minerals and trace elements. EDTA has its only known effect on those metallic ions--binding, redistributing and removing them.

Frustaci and coworkers in Italy recently published data showing that essential trace elements accumulate to potentially toxic levels in diseased tissues. Essential elements all have the potential to be toxic in excess. Ischemic myocardium accumulates a spectrum of essential,

nutritional trace elements to high levels, when compared with myocardial cells of healthy, young control subjects: cobalt increases 500 percent; chromium increases 520 percent; iron increases 400 percent; and zinc increases 280 percent.(95) Metallic trace elements have a narrow margin between normal and toxic levels.

Three- to four-fold intracellular elevations with ischemia may poison cellular metabolism. Toxic metals also increase in ischemic myocardium, but less than the essential elements. It is thus possible that EDTA chelation therapy benefits by restoring a more normal distribution of essential metallic elements within the body. This action may be as important or even more so than enhanced renal excretion of toxic meals. We are still not sure of the most important mechanism of action.

Apoptosis (Programmed Cell Death) and Trace Metals

When intracellular stresses reach a critical threshold, permeability transition pores (PTP) open in mitochondrial membranes and holocytochrome-C is released. The combination of holocytochrome-C with d-ATP then triggers cellular damage and death. That process is termed apoptosis. Cells become increasingly susceptible to apoptosis with each successive DNA replication and cell division, adding support to the cell-senescence model introduced above. When free oxygen radicals reach high enough levels, apoptosis occurs. Formation of a specific protein, called BAX protein, also opens the PTP, and triggers apoptosis.(96,97) Synthesis of BAX protein depends on enzymes that require trace elements as cofactors. Metals in excess can poison metabolism at many different points or trigger apoptosis directly. Every step in the process of apoptosis involves metal-sensitivite enzymes, and it is on those metals that EDTA has its only known action.

Free Radical Causes of Degenerative Disease

The field of free radical biochemistry is as revolutionary and profound in its implications for medicine as the germ theory was for the science of microbiology. It has created a new paradigm for viewing the disease process. Emerging knowledge in this field gives us a compelling scientific rationale for treatment and prevention of major causes of long-term disability and death with EDTA chelation therapy.(98-107)

Detection and direct measurement of free radicals has only recently

been possible.(108-110) Although not yet fully understood, recent discoveries in the field of free radical pathology, in combination with the cell senescent model and apoptosis, lead to a coherent and elegant scientific explanation for many of the reported benefits following EDTA chelation therapy.

Properly administered intravenous EDTA, together with a program of applied clinical nutrition and modification of health-destroying habits, act synergistically to prevent free radical damage.

What are Free Radicals?

A free radical is a molecular fragment with an unpaired electron in its outer orbital ring, causing it to be highly oxidative, unstable, and to react instantaneously with other substances in its vicinity.(111,112) The half-life of biologically active free radicals is measured in microseconds.(100) Within a few millionths of a second, free radicals have the potential to react with and damage nearby molecules and cell membranes. Such reactions can then produce an explosive cascade of free radicals in a multiplying effect--a literal chain-reaction of damage.(98,101,102,109,113,114)

Free radicals react aggressively with molecules to create other aberrant compounds. Harmful effects of high-energy ionizing radiation (ultraviolet light, x-rays, gamma rays, nuclear radiation, and cosmic radiation) are similarly caused by the free radicals produced in living tissues when photons of radiation knock electrons out of orbiting pairs.(105,115-119)

In a similar way, free oxygen radicals in cells produce damaging lipid peroxides, oxyarachidonate and oxycholesterol products.(98,119-122) Oxidized cholesterol is toxic and contributes to atherosclerosis. Lipid peroxides can trigger chain reactions, accelerating a further cascade of damaging free radical reactions. Protection against free radicals is achieved from dietary, supplemental and endogenous antioxidants.(98,99,101,102,103,106,121,123,124)

Ongoing free radical reactions in normal cellular metabolism occur continuously in all cells of the body and are necessary for health.(98-103,105-107,125-128) Mitochondrial oxidative phosphorylation produces free radicals during the ongoing production and storage of energy as adenosine triphosphate (ATP) from mitochondrial oxydation. These normal and essential free radical reactions are contained and

damage is prevented if adequate antioxidant protection is available. The highly reactive free radicals continuously produced within healthy human cells include hydroxyl radicals, superoxide radicals, and excited or singlet-state oxygen radicals. They are commonly referred to collectively as "free oxygen radicals," or often as simply "free radicals."(99-107)

When free radicals react in the body they in turn produce other highly reactive molecules, including hydrogen peroxide, lipid peroxide, and other peroxides. Peroxides are metastable, highly reactive, corrosive molecules and also react rapidly, producing additional organic radicals in surrounding tissues.(111,112)

To prevent uncontrolled propagation of free radicals, cells normally contain a dozen or more antioxidant control systems that regulate the many necessary and desirable free radicals present.(98-106,109,110,116,121,123,129-134) Those control mechanisms include endogenous enzymes, such as catalase, superoxide dismutase, and glutathione peroxidase. Free radical regulation also depends on nutritional antioxidants such as vitamins C and E, beta-carotene, coenzyme Q-10, and the trace element selenium. In fact, almost all vitamins, including the B vitamins, play a role in antioxidant protection.

When functioning properly, antioxidant systems suppress and control excessive free radical production, allowing oxidative energy metabolism to proceed normally without cellular or molecular damage. When those control systems are weakened, free radicals multiply out of control, much like a nuclear chain reaction, disrupting cell membranes, damaging enzymes, interfering with both active and passive transport across cell membranes, and causing mutagenic damage to nuclear DNA. This is one cause of cancer.(102,109,113,114,120,121,135,136)

Concentration of the free radical control enzyme, superoxide dismutase (SOD), in mammals is directly proportional to life span. Humans have the highest concentrations of SOD. SOD is the fifth most prevalent protein in the human body.(101,102) Elephants, parrots and other long-lived species also have high levels. Thus, life expectancy seems to be highly dependent on effective free radical regulation.

Nonenzymatic free radical scavengers are stoichiometrically consumed on a one-to-one ratio when neutralizing free radicals. These include

beta-carotene (provitamin A), vitamin E, vitamin C, glutathione, cysteine, methionine, tyrosine, cholesterol, some corticosteroids, and selenium. Once neutralized, other vitamins and enzymes are necessary to restore antioxidant activity, but they must all be present in adequate amounts.

Enzymes involved in free radical protection are proteins, but also require nutritional metallic trace elements or vitamins as co-enzymes. For example, copper, zinc, and manganese are all essential for superoxide dismutase activity; selenium is essential for glutathione peroxidase; and iron is necessary for catalase and some forms of peroxidase. Tens of thousands of different enzymes in the body depend on vitamins, trace elements and minerals to function. Optimum dietary intake of those nutrients is therefore necessary for protection against free-radical mediated, age related diseases. Recent epidemiological studies show that it is difficult to receive optimal amounts from food alone, without supplementation.

Identifying Free Radicals

Free radicals exist in very low, steady-state concentrations. They rarely reach levels high enough for direct analysis.(98,102) Sophisticated instruments have only recently become available that allow us to recognize the importance and extent of free radical damage in tissues. Electron paramagnetic resonance spectroscopy (EPR) is one type of technology now used.(109,110) Free radicals can be estimated most easily, and perhaps even more accurately, by analyzing end-products of free radical reactions, using gas chromatography, mass spectroscopy, and high-performance liquid chromatography. Cross-linkages between molecules, damaged collagen, lipid peroxides, oxyarachidonate, oxidized cholesterol, lipofuscin, ceroid, and increased pigment can all be caused by free radical reactions. Those substances can more easily be measured.(98,101,102,110,137,138)

By sifting through the molecular wreckage left in the wake of evanescent free oxygen radicals, it thus becomes possible to indirectly estimate the type and extent of ongoing free radical reactions. For example, free radical damage in the brain and central nervous system (CNS) can be assessed by the rate of cholesterol depletion. Cholesterol is not otherwise metabolized in the nervous system. The only way for cholesterol to decrease in the CNS is through oxidation caused by free radicals. Cholesterol acts as an antioxidant and is consumed in the process.(101,102,139,140)

Cholesterol Metabolism

As a free radical scavenger, cholesterol is liberally disbursed throughout cell walls and lipid membranes in the body. Contrary to the popular notion that cholesterol is harmful, it actually protects cell membranes--if it has not previously become oxidized in the process of neutralizing a potentially harmful free radical.(110,139) Unoxidized cholesterol is one of the body's important antioxidant defenses. Some of the cholesterol-derived steroid hormones, including glucocorticosteroids, dehydroepiandrosterone (DHEA), pregnenolone, testosterone, progesterone, and estrogen, can also function as free radical scavengers.(110) Those substances decline steadily with age, inversely related to the incidence of age-associated diseases.

Cholesterol is a precursor to vitamin D. Vitamin D is normally produced in the skin by exposure of cholesterol to ultraviolet radiation from sunlight. Without cholesterol, vitamin D deficiency may occur. Ultraviolet light is a form of ionizing radiation that can also produce free radicals in the skin, leading to sunburn and skin cancer. Unoxidized cholesterol and other antioxidants act to protect the skin.

Total body cholesterol (approximated by measuring blood levels of cholesterol) is derived primarily from cholesterol synthesis within the liver, not from dietary intake.(102) Plasma cholesterol levels increase with free radical stress. Elevation of plasma or serum cholesterol can act as an indicator of exposure to excessive free radicals and increased risk of atherosclerosis and apoptosis. Also, as cholesterol becomes oxidized, in the form of low-density lipoprotein (LDL) cholesterol, LDL receptor sites in the liver and elsewhere are altered, causing increased hepatic synthesis of endogenous cholesterol. An increase in cholesterol thus appears to be a normal physiologic response to free radical stress. Cholesterol is synthesized in the body as needed, and the need is greater to protect those at risk. In Western cultures, where atherosclerosis, cancer, and other free radical mediated diseases are epidemic, blood cholesterol levels commonly increase with age. A problem occurs, however, when the increased cholesterol becomes oxidized, producing its own form of cellular toxicity.

After encountering and neutralizing a free radical, cholesterol is oxidized as LDL cholesterol. In oxidized LDL form, cholesterol is toxic to blood vessel walls. If antioxidant protection is diminished, or if free radical production exceeds the threshold of tolerance, oxidized LDL cholesterol thus contributes to atherosclerosis.

A recent multi-country study in Europe, funded by the World Health Organization, showed that low blood levels of vitamin E are statistically 100 times more significant as a predictor of coronary heart disease than are high blood levels of cholesterol.(141). In another report, all published autopsy studies that correlated the extent of atheromatous arterial plaque with levels of blood cholesterol were reviewed. Surgical specimens removed at the time of bypass surgery were also analyzed. After eliminating data from those few individuals with a hereditary form of extremely high cholesterol (above 400 mg/dL), no correlation was found between blood cholesterol levels and the severity of atherosclerosis.(142) The author stated that prior studies falsely concluded that blood cholesterol levels correlated with atherosclerosis because of failure to eliminate those occasional individuals with extremely high cholesterol caused by a lethal genetic mutation.

Less than one half of one percent of the population has a hereditary trait for dangerously high cholesterol. People with that genetic disease have blood cholesterol levels above 400 mg/dL, sometimes much higher. They commonly suffer premature death from atherosclerosis, despite aggressive pharmacological therapy to lower cholesterol. The statements in this section do not apply to people in that group.

Free radicals oxidize cholesterol into a variety of break-down products.(98,100,101,102,110,143,144) Oxidized cholesterol is bound selectively to low-density lipoproteins, referred to as LDL cholesterol, while unoxidized (antioxidant) cholesterol is predominately bound to high density lipoproteins, HDL cholesterol.(101,102) Oxidized cholesterol, bound to small, dense lipoprotein molecules are especially toxic to cells.

Laboratory research at the Cleveland Clinic demonstrated that both EDTA and the antioxidant glutathione prevent LDL cholesterol from becoming toxic.(143)

Oxidized forms of cholesterol possess varying toxicities. (98,102,143-146) Some of those substances have vitamin D activity, which can cause localized vitamin D toxicity in tissues and macrophages.(144) Abnormal calcium deposits in tissues and blood vessel walls may to some extent be caused by localized vitamin D activity at toxic levels.

Free radicals also cause tissue calcification by damaging the integrity of cell membranes, causing leaks in cell walls, and by damaging enzymatic cell-wall transport pumps. If the calcium pump is weakened,

or if cell wall integrity is damaged, the calcium pump becomes unable to remove calcium as it leaks in. Intracellular calcium accumulates, causing malfunction and eventually cell death. X-rays of older people commonly show dense calcium deposits in soft tissues that do not normally have that bony appearance. A similar weakening of the sodium pump in cell walls allows an increase of intracellular sodium, leading to swelling of the cell, edema, and eventual cell lysis.

Dietary restrictions of cholesterol and prescription drugs to reduce blood cholesterol have, in some ways, been counterproductive, because the antioxidant role of cholesterol has not been widely recognized. Natural, unoxidized cholesterol is widely dispersed in cell membranes as a protective factor against atherosclerosis, cancer, and other free-radical induced diseases. In this form, cholesterol is not the harmful substance we have been told. Cholesterol is a fat, and dietary cholesterol is consumed in fatty foods. Restriction of dietary cholesterol necessarily results in simultaneous reduction of total dietary fats. Research studies which allegedly show benefit from low-cholesterol diets may have only reflected benefit from reduction in excessive dietary fat and the accompanying lipid peroxides and oxidized cholesterol.

It is not widely known that cholesterol-lowering drugs also have antioxidant and antiplatelet activity.(147) Those drugs also produce significant toxicity and cost much more than antioxidant nutritional supplements.

Free radicals cause damage by oxidation. Fats, especially unsaturated fats, are highly susceptible to oxidation, in the same way that cooking fats and oils can easily catch fire on the stove. They ignite (oxidize) easily and burn vigorously. All cells and intracellular organelles are enveloped in easily oxidized layers of unsaturated fat. Damaging oxidation of those fatty cellular and intracellular membranes by free radicals can be prevented in three ways:

1) By "fire-proofing" lipid membranes with nutritional anti-oxidants;

2) By depriving the fire of fuel by partially restricting dietary fats; and

3) By removing metallic catalysts of free radical proliferation with EDTA chelation therapy (as described in detail below).

These three strategies used together can act synergistically to reverse and slow diseases of aging.

A statistical correlation has been reported between low blood cholesterol and increased risk of cancer.(148) Cancer is caused in part by free radical damage to nuclear material and chromosomes. Free radicals act as both primary initiators and subsequent promoters of malignant change. If adequate unoxidized cholesterol is not present to provide antioxidant activity for nuclear membranes and DNA, an important defense against mutation and cancer can be lost. High fat diets, rich in lipid peroxides, are known to increase the risk of cancer.(98,101,102) However, if antioxidant defenses are reinforced, dietary fats can be protected against and rendered more useful for energy.

Homocysteine Metabolism

Homocysteine can contribute to atherosclerosis in several ways. The higher the homocysteine level, the greater the risk. Free radical production and oxidative stress occur during homocysteine metabolism. (149-153) Homocysteine is a metabolite of methionine, and is normally oxidized by free radicals to become homocysteic acid, a potent stimulator of cell growth and multiplication. (154) In this way, oxidative breakdown of homocysteine can induce proliferation of smooth muscle cells in arterial walls and promote growth of atherosclerotic plaques.(155)

Metabolic pathways of homocysteine that cause damage to blood vessel walls involve release of hydrogen peroxide, superoxide radical, and inhibition of glutathione peroxidase.(156) Homocysteine increases the tendency for blood clotting.(157) In addition, homocysteine can speed oxidation of cholesterol, which then becomes bound to small dense LDL particles and is taken up by macrophages to become foam cells in plaque. (158)

Damage to blood vessel walls from elevated homocysteine thus leads to accelerated plaque growth, followed by cholesterol and lipid deposition.(159) Clinical and epidemiological research have shown that atherosclerosis throughout the body correlates directly with blood levels of homocysteine. Elevated homocysteine is a powerful and independent risk factor, as strong or stronger than other well-documented risk factors. (150-152)

Fortunately, there is an easy solution--vitamin supplementation. Homocysteine is metabolized by enzymes that require vitamins B-6, B-12 and folate as cofactors.(160-161) Increased intake of those vitamins reduces homocysteine levels and atherosclerosis.(162,169) With daily supplementation of B-complex vitamins containing 800 mcg per day of folate, five mg or more of vitamin B-6, and 50 mcg or more of vitamin B-12, even those individuals with a familial trait for excessive homocysteine can correct and prevent potential problems.(162-166)

Essential Free Radical Reactions

Life cannot exist without a balance of carefully regulated free radical reactions. Life in the presence of oxygen requires antioxidant protection--fire proofing, if you will. Cellular respiration involves transfer of electrons across mitochondrial membranes within cells. For every such electron, a superoxide radical is produced. Antioxidants must be present prevent damage to vital intracellular structures during this process. Humans cannot utilize food for fuel without such ongoing oxidation-reduction reactions, which in turn produce free radicals as a byproduct. Oxygen is breathed in through the lungs and transported in the blood to every cell in the body, where oxidation reactions produce life-supporting energy. Red blood cells also produce free radicals during the binding and release of oxygen and carbon dioxide by hemoglobin.

Superoxide radicals are released during oxidative phosphorylation of ATP. Cellular protection from those superoxide radicals is provided by mitochondrial superoxide dismutase(SOD), a manganese-containing enzyme. The average American diet contains suboptimal amounts of manganese.(170) SOD in the cytoplasm of cells requires both zinc and copper for activity. Those trace elements are also marginal to deficient in the average American diet.(170) If the integrity of cell membranes is not protected by adequate SOD, then the activity of other vital enzymes contained within those cell membranes will be compromised.(171)

The metabolic degradation of many chemicals, including most prescription drugs, artificial colorings and flavorings, petrochemicals, and inhaled fumes, takes place in the endoplasmic reticulum of cells, most importantly in the liver. That detoxification process releases hydroxyl free radicals and peroxides.(98,101,102,125-127) Glutathione peroxidase, vitamin C, and a wide variety other antioxidants must be present in adequate supply to prevent chain

reactions of damaging free radicals Drugs and other chemical exposures thus cause increased production of free radicals, which may then exceed the threshold of antioxidant protection.(98,101,102) The resulting excess of free radicals can also multiply further, in a chain reaction, magnifying the damage by up to a million times or more.(98,102)

Synthesis of prostaglandins and leukotrienes from unsaturated fatty acids also involves release of free radicals.(102,106,128) Lacking sufficient antioxidant protection, prostaglandin production becomes unbalanced. Thromboxane increases and prostacyclin decreases in the presence of lipid peroxides.(98,101,102) Thromboxane is associated with atherosclerosis while prostacyclin acts to prevent arterial plaque.

Leukocytes and macrophages normally produce free radicals. Disease-causing organisms and foreign material are ingested and destroyed by free radicals during phagocytosis. Leukocytes use free radicals much like "bullets" against an invading army.(172,173) Antioxidants localize and limit the damage caused by those free radicals. If antioxidant protection is exceeded, free radicals migrate into adjacent tissues and produce inflammation, manifested by redness, heat, pain and swelling.

Without antioxidant enzymes, we would die very quickly. And antioxidant defenses decease with age.(98,101,102) An extreme example of accelerated aging is the disease known as progeria, caused by hereditary absence of free-radical protective enzymes. Within ten to fifteen years after birth, a victim of that genetic mutation can experience every aspect of the aging process, including wrinkled, dried, and sagging skin, baldness, bent and frail body, arthritis, and advanced cardiovascular disease. Administration of antioxidant supplementation has successfully slowed one form of progeria. Heredity determines each individual's unique resistance to free radical mediated disease. Familial differences therefore result in a wide variation in tolerance to dietary and life-style stresses that increase free radical production.

Oxygen Toxicity

The process leading to free radical pathology is often referred to as "oxidative stress." Ground state or unexcited atmospheric oxygen has the unique property of being both a free radical generator and a free radical scavenger.(98,102,174,175) Although a liter of normal atmospheric air on a sunny day contains over one billion hydroxyl

radicals,(122) oxygen at normal physiologic concentrations in living tissues neutralizes more free radicals than it produces.(176) When oxygen concentration falls below normal, as occurs with diseased arteries and ischemia, oxygen becomes a net contributor to free radical production.(101,102,177)

Oxygen in excessive concentrations for prolonged periods of time can cause toxicity and even death, primarily by free radical damage to the lungs and brain. Under proper conditions, however, intermittent high-pressure oxygen, administered for short periods in a hyperbaric chamber, can stimulate an adaptive increase of intracellular superoxide dismutase, an enzymatic antioxidant.(175,178) Too much or too little oxygen can be equally harmful. Hyperbaric oxygen should be administered in short, pulsitile exposures, to stimulate an adaptive increase in antioxidant defenses without causing harm. **Hyperbaric oxygen therapy** enhances the benefits of EDTA chelation therapy.

Protection Against Oxygen Free Radicals

Normal oxygenation of tissues strengthens defense against free radicals. Aerobic exercise stimulates blood flow and improves oxygenation. Improved oxygenation during exercise thus acts to protect against free radicals and reduces free radical related disease.

Antioxidant metalloenzymes require trace elements to function. Mitochondrial SOD contains three atoms of manganese. Each molecule of cytoplasmic SOD contains two atoms of zinc and one atom of copper. Each molecule of glutathione peroxidase contains four atoms of selenium. Catalase and peroxidase contain iron. Elemental selenium is an antioxidant, independent of its function as an enzyme co-factor.(102)

The human body lacks an intrinsic defense against a major destructive free radical precursor--excited state singlet oxygen. When superoxide radicals exceed a concentration that can be neutralized by SOD, they spontaneously convert to singlet oxygen. Polynuclear aromatic hydrocarbons and aldehydes, found in tobacco tar and tobacco combustion, produce singlet oxygen. The most important protection against singlet oxygen is dietary intake of beta-carotene; a precursor form of vitamin A.(179-183) Epidemiological evidence correlates increased dietary beta carotene with reduced incidence of cancer. Fully formed retinoid vitamin A lacks that protective activity.(101,102)

When beta-carotene is inactivated by free radicals it must be re-activated by other antioxidants, including vitamin C. Vitamin C is inactivated in the process. Cigarette smoke depletes vitamin C. If smokers are given beta-carotene, the oxidized beta-carotene further depletes vitamin C and other antioxidants. It is therefore important to supplement with a full spectrum of antioxidants and micronutrients simultaneously. In one study, an increase in lung cancer was reported when beta-carotene alone was given to smokers. If beta-carotene and vitamin C are not supplemented simultaneously, beta-carotene alone might worsen a preexisting deficiency of vitamin C. That would explain the seemingly paradoxical report of increased cancer with beta-carotene supplementation. Many different antioxidants work together in harmony. An antioxidant is inactivated when it encounters a free radical, and must in turn be reactivated by the next antioxidant in a cascade--a multi-step process.(184-187) All antioxidants must be present simultaneously for optimal protection.

Vitamin E (tocopherol), vitamin C (ascorbate), beta-carotene, glutathione, selenium-containing glutathione peroxidase, riboflavin, niacin, and a spectrum of other antioxidants are all interrelated in a recycling process that protects against free radicals. If all of those antioxidants are present in optimum amounts, they are continuously recycled back into their active forms, after being inactivated by free radicals.

The process proceeds as follows: vitamin E and beta-carotene neutralize a free radical by becoming oxidized to tocopherol quinone and oxidized beta-carotene. Tocopherol quinone and oxidized beta-carotene are returned to their antioxidant forms of vitamin E (tocopherol) or reduced beta-carotene by vitamin C or co-enzyme Q-10, which are oxidized in the process. Oxidized vitamin C is dehydroascorbate. Interestingly, the ratio of ascorbate to dehydroascorbate diminishes progressively with age and no species survives when that ratio falls below one to one.(102) A protective ratio can be restored and maintained despite advancing age with supplementation.

Inactive vitamin C (dehydroascorbate) is reactivated by reduced glutathione, which in turn is recycled by glutathione peroxidase (containing selenium). Glutathione peroxidase is returned to its active form by the vitamin-B2-dependent (riboflavin-dependent) enzyme, glutathione reductase. Glutathione reductase is reactivated by a vitamin-B3-dependent (niacin-dependent) enzyme, NADH, which is oxidized to become NAD. NAD is then metabolized in an elaborate

electron transport system, passed from step to step down the carboxylic acid (Kreb's) cycle. Potentially destructive energy originating as a free radical is thus redirected to useful metabolism. Subsequent steps in energy metabolism require virtually every nutritional vitamin, mineral and trace element.

This stairstep cascade of oxidation-reduction pathways demonstrates that each component depends on an adequate supp1y of all other components in the chain.(124) A chain is only as strong as its weakest link. This interdependence explains the sometimes-equivocal results reported from clinical trials supplementing just one vitamin or antioxidant. For years medical scientists have been conducting research by supplementing with only vitamin E, beta-carotene, selenium, or vitamin C. Although results were often positive(180-182), benefits would have been much greater had a full spectrum of essential nutrients been supplemented simultaneously.(184-188) When free radical production exceeds the neutralizing capacity of this antioxidant system, serious damage to cell membranes, protein molecules, and nuclear material (DNA) results.(98,101,102,111,119,121,123)

A comprehensive understanding of free radical defenses provides a rationale for nutritional supplementation with a full range of vitamins and trace elements, in safe amounts and in proper physiologic ratios. Although large amounts of water-soluble vitamins are rapidly excreted, transient elevations in tissues are nevertheless achieved following ingestion, which saturate tissues and provide additional.(102)

An 18-year nutritional study involving thousands of adults, published by researchers at the University of California, Los Angeles, showed that daily intake of a multiple vitamin-mineral supplement containing at least 500 mg of vitamin C could extend average life expectancy by up to six years.(189)

Increased Production of Free Radicals

If free radicals in living tissues exceed safe levels, the result is cell destruction, malignant mutation, tumor growth, damage to enzymes, and inflammation, all of which manifest clinically as symptoms of age-related, chronic degenerative diseases. Each uncontrolled free radical has the potential to multiply by up to a million-fold in a chain reaction, much like a nuclear reaction.(98,101,102,111,119,121,123)

Dietary fats, especially polyunsaturated fats, are potential sources of pathological free radicals. Double bonds on unsaturated fatty acids combine very readily with oxygen to produce lipid peroxides. This may occur both within the body after consumption and while exposed to atmospheric oxygen prior to consumption.

Lipid peroxidation begins when fats and oils are exposed to air, and is speeded by heat. That oxidation process is catalyzed and hence accelerated greatly by metallic ions, especially unbound iron. For example, peanuts crushed to make peanut butter are rich in iron, which is released into the oil when the peanut is disrupted. Iron is a potent catalyst of lipid peroxidation and increases the speed of rancidity of peanut oil by up to a million fold. Oxidized fats and oils are commonly called rancid; however, extensive peroxidation can exist in some oils without a detectable rancid odor or taste.(102) Lipid peroxidation commonly occurs during the manufacture of many foods and cooking oils.(102)

The more unsaturated the fatty acids in oil, the more readily peroxidation will occur. The rate of peroxidation is logarithmically proportional to the square of the number of unsaturated bonds in each molecule. Factors that increase the rate of peroxidation include heat, oxygen, light, and presence of unbound catalytic metallic elements.(102,119) Oils prepared in the dark, at low temperatures, in an atmosphere of pure nitrogen, and with added fat-soluble antioxidants such as vitamin E, would be best for nutritional use.(102) Such oils are not commercially feasible. The alternative is to consume oil-containing foods, such as nuts and seeds, in their natural state, without crushing until chewed and swallowed. Dietary supplementation with insurance doses of antioxidants can help to prevent free radical damage in the body, even when oxidized fats and oils are eaten.

Unsaturated vegetable oils commonly contain trace amounts of iron and other catalytic metals. Such oils are routinely subjected to heat and atmospheric oxygen when foods are fried. That creates a perilous combination. Hence, the admonition to limit consumption of fried foods. Oils used in the manufacture of salad dressings, such as mayonnaise, often contain high concentrations of lipid peroxides. The poorest quality oils are commonly used to produce commercial food products of that type because heavy seasoning masks rancidity.(102)

Hydrogenation of vegetable oils during the manufacture of margarine and shortenings used in baking results in cis- to trans-isomerization. Trans-isomerization alters the three-dimensional configuration of

dietary fatty acid molecules from their normal "cis" coils to straightened "trans" configurations. Trans-fatty acids are then incorporated into cell membranes in the place of natural cis forms, weakening the membrane structure and impairing function of imbedded phospholipid-dependent enzymes.(101,102,218,219) Substrate recognition by enzymes used to synthesize cell membranes is not able to distinguish between these two forms.(102)

Phospholipids that compose cell membranes are easily damaged by free radicals, as already explained. Dietary intake of peroxidized fats can initiate that process. The prostaglandin precursors, arachidonic and linoleic acids, are depleted when that occurs, as measured by gas chromatography.(101,102) Cell membranes containing trans-fatty acids exhibit impaired fluidity and increased permeability, which interfere with trans-membrane movement of sodium, potassium, calcium, magnesium, and other substances. Receptors on the cell surface for insulin and other hormones are disrupted.(98,101,102) Damage from trans-isomerization of fatty acids is cumulative with lipid peroxidation.(98,101,102)

Very little attention has been paid to the more important qualities of dietary fats and oils. Emphasis has mistakenly been placed on the ratio of saturated to unsaturated fatty acids, irrespective of lipid peroxidation and trans-isomerization. Contrary to conventional wisdom, unsaturated fats are more toxic than saturated fats.(102) Margarine contains far more peroxides and trans-fatty acids than butter. Moderation of intake of all fats and oils is desirable.(102) It has been shown epidemiologically that margarine consumption is a risk factor for heart disease, contrary to advertisements for preventive benefit.(192)

The quantity and quality of dietary fat is as important or more so than the ratio of unsaturated to saturated fatty acids.(98,101,102) If dietary fats and oils are obtained from fresh, whole, unfractionated, and unprocessed foods, they will be minimally oxidized and will produce healthy cell membranes, with normal cis-fatty acid configurations. They will enhance a normal balance of prostaglandins. Although fully saturated fats are not as easily oxidized, all animal fats contain some unsaturated fatty acids and cholesterol, both of which are subject to oxidation. Animal experiments have shown that as little as one percent of dietary cholesterol consumed in oxidized form can contribute to atherosclerosis. Supplemental antioxidants reduce that risk. (144,145,193)

How much dietary fat and oil can one tolerate without risk? Evidence indicates that between 25 to 35 percent of dietary calories as fat can be both safe and nutritious, if attention is paid to the quality and source of the fat, as described above; and if supplemental vitamins, minerals, and trace elements are taken.(101,102) The more oxidized the fats, the less well they are tolerated. In the United States, an average of 45 percent of dietary calories are consumed as fat, mostly of poor quality, with no consideration for rancidity or trans-isomerization. Half the population takes little or nothing in the way of nutritional supplements. Lipid peroxidation occurs much more slowly when foods are frozen.(102)

Free radical damage contributes to senility, dementia, and other nervous system diseases, including Alzheimer's and Parkinson's syndromes. The brain and spinal cord contain the highest concentration of fats of any organ. The central nervous system is very rich in highly unsaturated arachadonic and docosahexanoic acids. Because the rate of lipid peroxidation increases exponentially with the number of unsaturated carbon-carbon double bonds, docosahexanoic and arachadonic acids oxidize many times more readily than most other lipids. The brain and spinal cord therefore require added antioxidant protection.

To provide that extra protection, vitamin C is concentrated in the brain by metabolically active pumps in the blood-brain barrier. Ascorbate is 100 times more concentrated in the brain and spinal cord than in other organs.(102) Two ascorbate pumps operate in series. The first increases the concentration ten-fold from blood to cerebrospinal fluid. A second pump concentrates vitamin C by another factor of ten between cerebrospinal fluid and the subdural space. The disappearance rate of vitamin C from spinal fluid can be used to indicate the extent of damage and subsequent lipid peroxidation following ischemia or trauma to the central nervous system.(194,195)

Experimental spinal cord injuries in animals have been used to show benefit from treatments based on free radical protection. A minor contusion to the spinal cord results in rapid breakdown of unsaturated fatty acid sheaths surrounding nerve pathways. Following a contusion, capillaries leak blood. Erythrocytes hemolyze, releasing iron. Iron is a very potent catalyst and reacts with oxygen extraordinarily well to increase the rate of lipid peroxidation.(102) Spinal cord injury has been contained and the chain reaction of oxidative damage and inflammation that occurs has been reversed experimentally in animals by: 1) The spinal cord has be exposed and irrigated with a potent free

radical scavenger, such as dimethyl sulfoxide (DMSO); and 2) iron and copper catalysts have been inactivated by bathing the injured area in a weak chelating solution containing EDTA.(102,109,140,191,196-198)

Intravenous DMSO in large doses has been reported to prevent paralysis and permanent damage following spinal cord and brain injuries. Results thus far indicate that if treatment is begun within the first thirty minutes, or at most within the first two hours, the outcome is much better than would otherwise have been expected.(199-214)

Chelation therapy with EDTA combined with dietary fat restriction have been reported to temporarily alleviate multiple sclerosis (MS).(34,215,216) MS victims experience degeneration of the fatty myelin sheaths which insulate nerve pathways in the brain and spinal cord. Although lipid peroxidation may be only one link in the chain of cause and effect, it is sometimes possible to slow this devastating disease by using treatments that reduce free radical pathology.

Tobacco and Alcohol

Habitual use of tobacco and excessive alcohol can cause diseases and premature death. Alcohol can cause damage and scarring to the liver and cancer in the mouth and digestive organs.(217) Alcohol is metabolized to acetaldehyde, which is a potent free radical precursor. Acetaldehyde is closely related to formaldehyde (embalming fluid), and causes cross-linkages of connective tissue by free radical reactions (similar to the process of tanning leather).(101,102,218,219) Alcoholic cirrhosis of the liver might therefore be considered quite literally a form of predeath embalming.

Tobacco smoke contains polynuclear aromatic hydrocarbons--potent precursors of free radicals. Those substances can overwhelm the body's free radical defenses and trigger the onset of cancer, atherosclerosis and other age-related degenerative diseases.(220) Processed tobacco also contains cadmium, a heavy metal ten times more toxic than lead, which acts as a catalyst of free radical reactions and displaces zinc in metallo-activated enzymes.

Cell Membranes

Every cell in the body is enveloped in a film of fat molecules, which form bipolar phospholipid membranes. Spanning those membranes are large proteins, enzymes, molecular pumps, and receptors for various

hormones and peptides. Cell membranes are metabolically very active and have characteristics of a viscous fluid. They are constantly changing. Cell membranes have one-way permeability to substances that must be kept out of or inside of cells. The water-soluble, polar ends of phospholipid molecules line up on the inner and outer surfaces, bathed in aqueous fluids. The fat-soluble, nonpolar tails point toward the center of the membrane, intertwining with fatty tails of similar molecules extending inward from the opposite surface, traversing the interior of the membrane. The normal, curly, cis-configuration of phospholipids allows them to wrap around each other and also to grasp cell-wall proteins, enzymes and other constituents within the membrane, holding them in proper position. The cis-curvature of naturally occurring lipids is therefore essential to integrity and metabolic activity of cell membranes.(98,101,102) Hydrogenation and free radical oxidation isomerize fats from cis to trans, leading to malfunction.

Unoxidized cholesterol is widely disbursed within lipid membranes and acts as an antioxidant.(102) Oxidized dietary cholesterol produced by food processing offers no such protection and can be atherogenic.(102,144) When free radicals occur in the vicinity of a cell, unoxidized cholesterol, vitamin C, vitamin E, coenzyme Q-10, and the entire array of anti-oxidant defenses are needed to prevent damage.

Large enzymatic proteins span the full thickness of cell walls to act as metabolically active "pumps". They are bathed in plasma on the exterior and extend to the cytoplasm within the cell. One such pump keeps sodium ions out of the cell and potassium within--against a large diffusion gradient in the opposite direction. Another keeps calcium out and magnesium in. Cellular organelles, including mitochondria, lysosomes, endoplasmic reticuli, Golgi bodies, and nuclear DNA are also enveloped in bipolar lipid membranes that contain energy-dependent transport mechanisms. Mitochondrial membranes are protected by coenzyme Q-10, an antioxidant necessary for safe energy production. Mitochondria are the power plants of cells. They continually produce free radicals during transport of electrons in the essential process of oxidative phosphorylation. Damage to mitochondria leads to premature aging. A spectrum of antioxidant defenses is necessary to prevent those necessary free radicals from damaging mitochondria.(98,101,102)

Cell wall receptors for neurotransmitters, insulin, hormones, and hundreds of oligopeptide regulators are susceptible to damage by free radicals. The calcium-magnesium and sodium-potassium pumps

become progressively weakened with age, allowing calcium and sodium enter cells excessively. Free radicals damage nuclear membranes. They alter nuclear pores and chromosomes, and cause mutations--leading to impairment of protein synthesis and cell replication. Free radical mutations of DNA can thus trigger uncontrolled cell division and cancer.

Free radicals increase the activity of guanylate cyclase, an enzyme that can stimulate uncontrolled cell multiplication.

Lymphoid tissues are rich in unsaturated fatty acids, and free radical damage can therefore cause immunologic abnormalities.(102) The immune system may subsequently attack the body's own tissues in so-called autoimmune diseases or it may weaken and fail to recognize and destroy disease-causing organisms and malignant cells.(98,101,102,106)

Calcium Metabolism

Free radical damage to the calcium-magnesium pump allows excessive calcium to diffuse into the cell. Calcium is 10,000 times more concentrated outside the cell than inside. The calcium pump must constantly work against this gradient. The reverse is true of magnesium. If the pump cannot prevent calcium from leaking into cells, and keep magnesium from leaking out, the cell becomes poisoned and soon dies.

Calcium activates phospholipase-A2 in cells, which cleaves arachadonic acid from membrane phospholipids. Increased levels of arachadonic acid can in turn create an imbalance of prostaglandins and leukotrienes, creating more free radicals in the process.(101,102) Leukotrienes are potent mediators of inflammation and attract leukocytes. Leukocytes, as noted previously, release superoxide free radicals during phagocytosis. Leukocytes, stimulated by leukotrienes, can overpower local antioxidant defenses, causing inflammation and damage to surrounding tissues.(101,102,227) Small capillaries and arterioles then dilate, causing edema and leakage of erythrocytes through blood vessel walls. Platelets produce microthrombi. Erythrocytes hemolyze, releasing free iron, which catalyzes accelerated oxidative damage to adjacent tissues. This results in an inflammatory chain reaction, beyond normal control mechanisms.

Free radical damage allows calcium to leak into smooth muscle cells in

arterial walls. Calcium binds to calmodulin, activating myosin kinase, which in turn phosphorylates myosin. Myosin and actin constrict, causing the muscle cells to shorten. By this mechanism, excess calcium within arterial smooth muscle cells cause spasm. The same occurs in cells of the myocardium. When muscle fibers encircling arteries constrict, blood flow is reduced. Calcium channel blockers relieve symptoms by slowing abnormal entry of calcium into cells, but they do not correct the underlying cause of the problem--free radical disruption of cell membranes.(101,102,222)

Myocardial cells are weakened by excessive intracellular calcium, lowering the efficiency of oxygen utilization and placing an extra burden on an already impaired coronary artery system. If a coronary (or other) artery is partially occluded by atherosclerotic plaque, a small amount of spasm superimposed on a preexisting partial blockage will cause ischemia. Thromboxane and serotonin are released by platelets in the presence of free radicals.(101,102) Thromboxane and serotonin also cause arterial spasm. A myocardial infarction can be caused by spasm alone, even with coronary arteries that are completely free from plaque.(223)

Excessive intracellular calcium can also be caused by other factors. Ionized plasma calcium, the metabolically active fraction not bound to protein, slowly increases with age. The higher the concentration of ionized calcium outside a cell, the harder the calcium pump must work to prevent excessive calcium from leaking in. Naturally occurring calcium channel antagonists can slow the calcium influx. These include dietary magnesium, manganese, and potassium. Magnesium and manganese intakes are suboptimal in the average American diet.(170) Diets are rarely deficient in potassium, but an excessively high ratio of dietary sodium to potassium is common, allowing excessive sodium to diffuse into cells, weakening metabolism. Depletion of potassium and magnesium caused by diuretic therapy can potentiate this problem.

The efficiency of energy metabolism can be impaired by stress. Stress increases circulating catecholamines and inhibits production of ATPase. The calcium and sodium pumps both require ATPase. Cells lose potassium and magnesium and retain calcium and sodium at a greater rate under stress because of relative inhibition of both magnesium-calcium ATPase and sodium-potassium ATPase.

Catecholamines produce free radicals when they are metabolized.(101,102) If free radicals in the central nervous system exceed defenses, stress-related catecholamines cause free radical

damage to neuron receptors. That is a partial explanation for stress-related psychiatric disorders. Breakdown products of dopamine, a catecholamine neurotransmitter, can also cause free radical damage to neuronal receptor sites in the brain. That is hypothesized to be one factor in the causation of Parkinson's syndrome, and some types of schizophrenia.(224) Neuronal receptors for norepinephrine can also be damaged by free radicals, contributing to depression. Heart disease has also been shown to result from catecholamine-induced free radicals.(225)

In recent animal experiments, primates subjected to stress were found to have an increased incidence of atherosclerosis, even when fed a diet that would otherwise have been protective. Increased free radical pathology related to increased catecholamines provides one explanation.

Dementia of the Alzheimer's type is thought by some authorities to be caused by free radicals damage to brain cells.(204) Arrest or improvement in that condition has been reported following treatment with deferoxamine, an iron and aluminum chelating agent.(226) EDTA also binds to iron and aluminum very effectively. Free, unbound iron is a potent catalyst of lipid peroxidation. Accumulations of aluminum, combined with lipid and protein breakdown pigments, are found in brains affected by both Parkinson's and Alzheimer's, although it is not known whether those are late events instead of causative factors--much like the accumulation of calcium and cholesterol in arterial plaque.

It was once hypothesized that EDTA chelation therapy had its major beneficial effect on calcium metabolism. It now seems that calcium is just one link in the chain of cause and effect. EDTA can influence calcium metabolism in many ways, but direct action on calcium is not adequate to explain all of the benefits following chelation. Disodium EDTA removes calcium from atherosclerotic plaque and improves calcium metabolism, (which is the reason disodium EDTA is used (and not calcium EDTA) to treat cardiovascular and age related diseases.

EDTA lowers ionized plasma calcium during infusion. In response, the body attempts to maintain homeostasis by producing parathormone.(227) The intermittent three- to four-hour pulses of increased parathormone caused by EDTA infusion can have a measurable effect on bone metabolism.(228) Frost’s concept of bone metabolism, known as the Basic Multicellular Unit (BMU) theory, is accepted by some experts.(229) The BMU theory helps to explain the

causes and treatment of osteoporosis and osteopenia.

The BMU is a group of metabolically active cells that control the turnover of approximately 0.1 cubic millimeter of bone tissue. When a BMU is activated, it goes through a cycle consisting of an initial three to four weeks of bone absorption (osteoclastic phase) followed by a two- to three-month period of new bone reformation (osteoblastic phase). Net increase or decrease in bone density at the end of the that three- to four-month cycle depends on the rate and completeness of bone turnover. Hormone regulation of BMUs also involves calcitonin, growth hormone, thyroxin, and adrenal corticosteroids, but parathormone remains the most important controlling factor.(228)

Chronic high levels of parathormone cause net bone destruction; but brief pulsatile increases in parathormone, as occur during intravenous EDTA chelation therapy, can result in increased of new bone formation.(230) EDTA chelation therapy does not add to osteoporosis, and if anything, may do the opposite.(52)

Postmenopausal women who are not supplemented with estrogen experience a large increase in follicular stimulating hormone (FSH). Elevated FSH interferes with new bone formation by BMU cells and is regarded as a contributing factor in postmenopausal osteoporosis.(231)

Anabolic activation of BMUs by pulsatile parathormone secretion provides one hypothesis for delayed benefit following chelation, although probably of minor importance relative to other mechanisms of action.

In their original studies, Meltzer and Kitchell used EDTA to treat ten men who were severely disabled by heart disease and suffered from intractable angina. After approximately twenty infusions of EDTA, therapy was discontinued because of initially disappointing results. Three months later, nine out of ten patients returned to report marked relief of angina, despite no change in their life styles, such as altering smoking or nutritional habits.(7) This three-month delay for full benefit has remained a consistent observation by chelating physicians over more than four decades. That delay suggests that EDTA corrects a metabolic derangement, allowing subsequent healing to occur with time.

Before free radical pathology was discovered, it was hypothesized that

removal of calcium from atherosclerotic plaque and from molecular crosslinkages would explain benefits seen from chelation. Crosslinkages increase with age and include disulfide bonds caused by free radical reactions, and intermolecular bridging by divalent cations, such as calcium, lead, cadmium, aluminum, and other metals. EDTA can displace those metals. Chelation can also remove abnormal disulfide cross linkages. Reduction of crosslinking between molecules acts to restore elasticity of vascular walls and other tissues that is lost with age and to reactivate enzymes.(36,37)

Improvements in blood flow may not be detectable on arteriograms, despite marked clinical improvement. Research shows that arteriograms are limited, and can only measure the diameter of an artery to within plus or minus 20 percent (as discussed in chapter 16). Although counterintuitive, it is nonetheless true that with smooth, laminar blood flow, a mere 19 percent increase in the diameter of an artery will double the flow of blood. In a plaque-filled vessel with turbulent flow, less than 10 percent increase in diameter will double blood flow. This can be proved using Poiseuille's Law of hemodynamics, found in textbooks of medial physiology.

In an organ with compromised circulation, a 25 percent increase in blood flow could bring significant functional improvement and relieve symptoms. Less than 5 percent increase in arterial diameter would do that. Changes in diameter of that small magnitude cannot be detected on either arteriograms or ultrasound imaging.

EDTA CHELATION THERAPY

Free radical control

EDTA can greatly reduce the production of free radicals.(102,143,232) It is not possible for free radical reactions to be catalyzed by metallic ions in the presence of EDTA. Traces of unbound metallic ions are necessary as catalysts for uncontrolled proliferation of free radicals in tissues. EDTA binds those ionic metals, making them chemically inert and rapidly removing them from the body. The amount of metal ions necessary to catalyze lipid peroxidation is so miniscule that the tiny traces remaining in distilled water can initiate and accelerate those reactions.(102,176) Metals incorporated into metallic enzymes are tightly bound and not accessible to EDTA. Some essential elements are briefly removed, however, and require supplementation for replacement.

To catalyze lipid peroxidation, a metallic ion must easily change electrical valence by one unit. Two essential nutritional elements, iron and copper, are potentially the most potent catalysts of lipid peroxidation, although copper is not prevalent enough in the body to be clinically important in that regard. With age, catalytic iron accumulates adjacent to phospholipid cell membranes, in joint fluid, and in cerebrospinal fluid. It is released into tissues following trauma and ischemia. This unbound form of extracellular iron causes free radical tissue damage, evidenced clinically as inflammation.(110,119,121,233-238)

Toxic Heavy Metals

EDTA has long been the accepted treatment for lead poisoning. Lead and other toxic heavy metals can impede metabolism in a variety of ways. Poisonous metals such as lead, mercury, and cadmium react avidly with sulfur-containing amino acids on protein molecules. When lead reacts with sulfur on the cysteine or methionine moiety of an enzyme, enzyme activity is reduced or destroyed. Lead also competitively displaces zinc in zinc-dependent enzymes. Chelation therapy reactivates enzymes by removing those toxic metals. The average concentration of lead in human bones has increased by approximately one thousand fold since the Industrial Revolution.(239) Bone lead is in equilibrium with other vital organs and is released into the circulation with a fever and under stress, increasing toxicity when it can be least tolerated.(240)

Lead destroys the antioxidant properties of glutathione and glutathione peroxidase. Lead reacts vigorously with sulfur-containing glutathione and prevents it from neutralizing free radicals. As previously described, reduced glutathione is an essential antioxidant in the recycling of vitamins E and C and glutathione peroxidase. Lead therefore impairs the free radical protective activity of the subsequent cascade of steps in antioxidant protection.

Lead reacts with selenium even more avidly than sulfur, inactivating the selenium-containing enzyme, glutathione peroxidase. In addition to performing its role in the antioxidant recycling system, selenium protects directly against lipid peroxides. Other toxic heavy metals also inactivate glutathione peroxidase. Testing for levels of toxic metals, as well as clinical evaluation for adequacy of essential trace elements, is routinely done during patient evaluation of patients prior to chelation therapy.(170,241-266)

EDTA cannot easily chelate metallic ions when they are tightly bound within metal-containing enzymes or to specific metal-binding proteins. On the other hand, when metals accumulate in unbound form, and are able to act as catalysts of uncontrolled lipid peroxidation or metabolic poisons, EDTA can easily bind and inactivate them. Iron accumulates with age and in abnormal locations, where it greatly accelerates free radical damage.(34,233-238) EDTA binds much more tightly to iron and other potential free radical catalysts than it does to calcium. EDTA will only bind calcium if those other metal ions are not present.(34)

Iron accumulates more slowly in women during the childbearing years because of monthly menstrual blood loss. Because of that hemoglobin iron loss, younger women have more protection against atherosclerosis. That protection is lost at menopause. Body iron stores, as reflected by serum ferritin and transferrin saturation, accumulate in men four times more rapidly after adolescence than in premenopausal women.(267) The risk of atherosclerosis is also four times greater in men in this same age group. Data from the Framingham study show that two years after a hysterectomy, a woman's risk for cardiovascular disease becomes equal to a man's, with or without hormone replacement. This occurs even if the ovaries are not removed.(268-270) Those data imply that slower buildup of tissue iron is responsible for reduced atherosclerosis in premenopausal women.(271) Periodic donation of blood to the blood bank also significantly prolongs life.(272) The fact that iron is a potent catalyst of lipid peroxidation provides a link between these clinical and epidemiologic findings. EDTA has a very high affinity for unbound iron and rapidly removes it from the body.

The affinity of EDTA to bind various metals at physiologic pH, in order of decreasing stability, is listed below. In the presence of a more tightly bound metal, EDTA releases metals lower in the series and binds to the metal for which it has a greater affinity.(273)

Chromium 2+ Iron 3+ Mercury 2+ Copper 2+ Lead 2+ Zinc 2+ Cadmium 2+ Cobalt 2+ Aluminum 3+ Iron 2+ Manganese 2+ Calcium 2+ Magnesium 2+

In clinical practice, chromium, mercury and copper are not removed in any significant amount by EDTA--evidence that those essential metals are more tightly bound by natural ligands in the body than by EDTA.

Magnesium is a calcium antagonist and is relatively deficient in many

chelation patients. Magnesium is the metallic ion least likely to be removed by EDTA. In fact, EDTA is usually administered as magnesium-EDTA, which provides an efficient delivery system that increases magnesium stores and reduces likelihood of pain at the infusion site.

Lasting inhibition of disease-causing free radicals by EDTA offers an explanation for data from Switzerland, which documented a 90 percent reduction in deaths from cancer in a large group of patients who were chelated and then carefully followed over an eighteen-year period. Chelation patients were compared with a statistically matched control group. Death rate from cancer was ten times greater in the untreated group, compared to the death rate of patients who had previously been treated with EDTA chelation ($p=0.002$).(38) A greatly reduced incidence of cardiovascular deaths was also observed following chelation. One common denominator of both cancer and atherosclerosis is free radical oxidative damage to molecules.(98,101,102) Calcium-EDTA was administered in that study, which precludes any direct effect on calcium metabolism as an explanation for outcomes. Removal of free radical catalysts seems one likely explanation. Demopoulos first proposed that chelation be used to control free radical pathology.(102,121) He also pointed out that many antioxidants have chelating properties.(98)

EDTA increases the efficiency of mitochondrial oxidative phosphorylation and improves myocardial function, quite independently of any effect on arterial blood flow.(274) Treatment with deferoxamine, an iron chelator, has been shown to improve cardiac function in patients with increased iron stores.(275) In addition, removal of iron with deferoxamine reduces inflammatory responses in animal experiments.(276) Sullivan has suggested that periodic donation of blood be studied as a way to reduce the risk of atherosclerosis in men and postmenopausal women.(271-272)

By reducing damage from free radicals, EDTA chelation therapy can support normal healing. The time required for healing of damaged tissues gives us another explanation for the time lapse of several months following chelation before full benefit is achieved. By correcting an underlying cause of the disease process, and allowing time for subsequent healing, tretment with EDTA seems far superior to the mere suppression of symptoms achieved with so many other therapies.

Chelation and Atherosclerosis

When an injury results in bleeding, homeostatic mechanisms quickly stop the flow of blood to prevent hemorrhage and death. This regulation of blood loss is under the control of a complex array of mechanisms, including hormones, prostaglandins, fibrin, and thromboplastin. Prostaglandins are produced and degraded continuously and very rapidly in endothelial cells and platelets. Prostaglandins have a half-life measured in seconds and must be constantly synthesized at a controlled rate and with a proper ratio between their various subtypes to maintain normal blood flow.

The two most important prostaglandins in that regard are prostacyclin and thromboxane. Prostacyclin reduces the adhesiveness of platelets, facilitating free flow of blood cells and plasma, and reducing the tendency for fibrin deposition and thrombus formation. Prostacyclin relaxes encircling muscle fibers in artery walls, reducing spasm. Thromboxane does the opposite. It causes intense spasm in blood vessel walls and stimulates platelets to adhere.(277) In oversimplified terms, thromboxane may be considered as undesirable and prostacyclin as desirable. In actual fact, a proper balance must be maintained to protect against injury and hemorrhage, on the one hand, and to maintain normal circulation, on the other.

Synthesis of prostacyclin is greatly inhibited by lipid peroxides and free radicals, while thromboxane production remains unaffected. If lipid peroxides are present, either from dietary intake of peroxidized fats and oils or from nearby peroxidation of lipid cell membranes, less prostacyclin is produced to balance the effects of thromboxane. (101,102,278)

Ongoing damage to vascular endothelium occurs continuously in response to hemodynamic stresses. Damage may also be caused by disordered immunity or bacteria. With good health, minor vascular injuries are rapidly healed, initiated by a layer of platelets that coat the disrupted surface with a protective blanket.(145) If free radical protection is inadequate and local controls have been overtaxed, the local increase of free radicals blocks the production of prostacyclin. Without prostacyclin, thromboxane is unopposed and causes the injured area of the arterial wall to attract platelets abnormally. This causes platelets to increasingly stick to each other. Platelets thus aggregate and the growing layer of platelets traps leukocytes, which in turn produce more free radicals. A network of fibrin and microthrombi is formed, and erythrocytes become trapped. Some of the erythrocytes hemolyze, causing iron to be released. Catalytic iron then produces a further explosive increase in free radical oxidation, oxidizing any

cholesterol present and damaging phospholipids in cell membranes. Prostacyclin production continues to be inhibited for some distance along the blood vessel.

The resulting spread of free radicals can damage nuclear material in arterial cells, causing mutation and uncontrolled cell replication. Lipid peroxides increase the activity of guanylate cyclase, which speeds mitosis.(98,101,102) Platelets release growth factors. This sequence of events can produce an atheroma, an enlarging tumor consisting of mutated, rapidly multiplying, multipotential cells that have lost their high degree of differentiation and specialized function. Atheroma cells produce substantial amounts of connective tissue, collagen, and elastin. They also act as macrophages, ingesting cellular debris and oxidized cholesterol. The monoclonal theory of atheroma formation first proposed by Benditt(279) accurately fits these known facts, further elucidated by the cell senescence concept discussed above. Cholesterol is oxidized by free radical activity, and some cholesterol oxidation products ingested by atheroma cells have vitamin D activity.(144)

We have thus far explained how intracellular calcium increases abnormally because of free radical damage to homeostatic mechanisms. Localized excesses of vitamin D activity are caused by free radical oxidation of cholesterol, analogous to the way sunlight creates vitamin D from cholesterol on the skin. Localized increases in vitamin D activity further accelerate calcium accumulation as plaques grow. Calcium and cholesterol deposition do not occur until late in the process of atheroma formation. In its role as an antioxidant, cholesterol acts to protect against further free radical damage, but becomes oxidized in the process. Some cholesterol is even synthesized within atheroma cells.(280)

Oxidized cholesterol and cholesterol esters thus accumulate within plaque. The plaque gradually expands to exceed its blood supply and ulcerates. When ulceration occurs, the central core of the plaque degenerates into an amorphous fibro-fatty mass containing varying amounts of calcium, cholesterol, connective tissue, and cellular debris. This necrotic core can rupture, releasing embolic showers of plaque debris. Free radicals continue to suppress prostacyclin, causing further aggregation of platelets. Platelets release high concentrations of thromboxane and serotonin, contributing to arterial spasm and ischemia.

Symptomatic ischemia does not usually occur until a blood vessel

becomes 75 percent occluded. A meal laden with peroxidized fats can cause a sudden free radical insult, triggering an abrupt increase in spasm or even an acute thrombosis, superimposed on a partial occlusion, producing an infarction.

Cell damage of this type may occur in any part of the body. Cells swell and die as membranes become leaky and damaged. Membrane pump mechanisms become uncoupled or disabled. DNA damage results in mutations, atheromata, and cancer.(98,101,102) Lymphoid tissues and other cells of the immune system become damaged.(98,101,102) Tissues become stiffer and lose flexibility as cross-linkages occur in connective tissue, elastin, and protein molecules.

Tissues damaged in this way age more rapidly and associated organ functions deteriorate. Joints become hypertrophic, inflamed, and deformed with arthritis. Leukotriene production and prostaglandin imbalances cause inflammatory change in joints and other organs. Lysosomes rupture, releasing proteolytic enzymes that further devastate cells. Lysosomes have been called the cells' digestive organs and, when disrupted, produce cellular autodigestion. Free radicals inactivate selenium, creating inert selenium compounds and resulting in relative selenium deficiency. Cancer patients excrete selenium in amounts up to five times the normal rate, just when they need it the most.(170)

Antibody production and cellular immunity are impaired by free radicals. Cells of the immune system are especially rich in unsaturated fats and are therefore more vulnerable to free radical damage. Oxidized cholesterol and lipid peroxides are potent immunosuppressants. (101,102,106,144) Antigenic substances and malignant cells, which would otherwise be neutralized, can overwhelm a weakened immune system. Intact food molecules, that leak across the gut wall undigested, are poorly tolerated.(281-283) Adverse reactions to specific foods (so-called “food allergies”) may occur appear. Normal free radical reactions in macrophages during phagocytosis of antigens proliferate out of control and cause inflammation. Adverse reactions may then be triggered by a variety of nutritious foods and environmental exposures to which the immune system becomes sensitized. This is an increasingly common cause of symptoms. Avoidance of sensitizing foods and other trigger factors are often necessary to control symptoms.(284-288)

Antigenic properties and toxins released by Candida albicans, a yeast normally present in the body in small numbers, can overwhelm a

weakened immune system--further provoked following use of antibiotics.(289-295). A struggling immune system may become over-reactive in other areas, attacking healthy tissues, leading to so-called autoimmune syndromes.

Atheroma and Cancer: Both are Tumors

The development of cancer can take decades from the initiating event to the onset of symptoms. If cancer-promoting factors are removed, free radical damage can be repaired and healing will be supported by a nutritious diet, antioxidant supplementation, and prudent lifestyle. In the early stages, malignant cells have the ability to transform back into a normal, benign state. For example, smokers who stop the use of tobacco have approximately the same risk of cancer ten years later as those who never smoked.(102)

Atherosclerotic plaque is actually a benign tumor, an atheroma, somewhat analogous to cancer. It does not metastasize. It kills in another way by expanding in place to occlude the flow of blood. An atheroma may regress with time, if causative factors are removed. Free radical pathology is the common denominator for both atherosclerosis and cancer.

A Treatment Strategy for Diseases of Aging

(1) Diet

Dietary fats and oils are best limited to 35 percent or less of total calories.(101,102) Consumption of fats and lipids that have been processed, exposed to air, heated, hydrogenated, or otherwise altered should be avoided when practical. Consumption of refined carbohydrates that are depleted of trace elements (white flour, white rice, and sugar) should be minimized. Total caloric intake should be moderated to maintain weight within 20 percent of ideal body weight. The use of excessive tale salt should be avoided. Diets should contain ample amounts of fiber-rich whole grains, fresh fruits, and vegetables. Patients suffering with chronic debilitating diseases must be stricter with diet. Clinical improvement involves a healing process, sometimes requiring months or years to complete.

(2) Nutritional Supplements

A scientifically balanced regimen of supplemental nutrients reinforces

endogenous antioxidant defenses. It is not possible to receive optimal quantities of those nutrients from food alone. Supplemental antioxidants and vitamins should include vitamins E, C, B-1, B-2, B-3, B-6, B-12, folate, pantothenate, PABA, beta-carotene, coenzyme Q-10, and N-acetyl cysteine, plus a spectrum of minerals and trace elements including magnesium, zinc, copper, selenium, manganese, chromium, boron, and vanadium.(170) Trace elements can be toxic if taken to excess and iron supplementation in the absence of deficiency will speed free radical damage. Iron should be supplemented only to treat deficiency states, confirmed by low serum ferritin and transferrin saturation.(271,296) Trace element supplementation should be under the supervision of a health care professional knowledgeable in nutrition. Dietary histories and biochemical testing allow supplementation to be tailored to the needs of each individual.(170,241-266,296,297)

(3) Modification of Health-Destroying Habits

Tobacco: It is best to eliminate the use of tobacco altogether, but, if that is not possible, a marked reduction in exposure would be helpful. This applies to cigarettes, pipe tobacco, cigars, snuff, and chewing tobacco. Tobacco causes problems, even without combustion. Free radical precursors are absorbed from tobacco through the lining of the mouth and nose, even without inhaling smoke. A relatively healthy adult with supplemental intake of antioxidants may tolerate a small exposure to tobacco without an increased risk of cancer, but even a small amount increases the risk of atherosclerosis.(298)

Alcohol: Many patients suffering with debilitating chronic disease discover for themselves that alcohol is not well tolerated. For those individuals, complete avoidance is advisable. A healthy adult should be able to tolerate and detoxify up to two ounces of pure ethanol per twenty-four hours (up to four eight-ounce glasses of beer, four small glasses of wine, or two shot glasses of hard liquor at most). That amount may be consumed in twenty-four hours without exceeding a healthy person’s capacity to metabolize the alcohol and neutralize the resulting free radicals.(101,102) But with daily use, tolerance may be lost.

(4) Physical Exercise

Moderate physical exercise, even a brisk forty-five minute walk several times per week will improve efficient utilization of oxygen. More

vigorous aerobic exercise results in proportionately greater benefits. Lactate accumulates up to twice normal levels in tissues during endurance exercise.(299) Lactate has proven chelating properties, and it is possible that some of the benefits of exercise may result from internal chelating effects of lactate.(37)

(5) EDTA Chelation Therapy

The use of EDTA to restore the balance and distribution of essential metallic elements, while at the same time removing toxic heavy metals and catalytic free iron, has been shown to slow or arrest progression of diseases of aging. Other benefits of chelation occur from uncoupling of disulfide and metallic cross-linkages between molecules, by normalization of calcium metabolism, by reactivation of enzymes poisoned by lead and other toxic metals, and by restoration of normal prostacyclin production along blood vessel walls. Lasting benefits follow a series of intravenous EDTA infusions, plus nutritional supplementation and lifestyle improvements.

This well-documented, safe, and effective therapy deserves widespread recognition and acceptance.

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