THE ROLE OF FREE RADICALS IN THE AGING PROCESS: A REVIEW ARTICLE

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OUTLINE

I. INTRODUCTION

American society, with its get-the-job-done attitude, expects a fast solution to every problem. This mentality has seeped into the medical model, which people expect to provide quick-and-easy solutions to their health problems. In some cases the medical community can indeed supply that type of quick cure. Penicillin, for example, certainly does its job to kill some bacteria. But the success of penicillin has also fueled the mentality that for every disease there is a magic bullet to cure it.

This puts a burden on the physician to deliver better and faster magic bullets. At the same time it downplays the importance of each person's natural resistance to ailments and disease. If more focus were put on this issue, we would learn to work with the body's wisdom and to support its natural ability to resist a bacterium or virus through the defense system. Zinc, for example, plays a major role in the body's production of immune system cells such as T-lymphocytes. Thus, providing the body with a physiological mineral such as zinc would strengthen its natural defense apparatus.

The concept of building our natural resistance has become extremely vital in recent years as we become more aware of the damage that can be caused by infectious agents other than bacteria, including viruses, yeast, and parasites. All of these must be viewed as an interaction between the person and his or her environment.

However, we also need to address another type of invader — the "free radicals" that attack us at a biochemical level. Free radicals are molecules that have an unpaired electron, which makes them capable of damaging cells, tissues, and organs. These dangerous molecules can weaken many vital aspects of body functioning, including our cardiovascular, neurological and immune systems.

For many people the idea that biochemical invaders may be altering their health and immunity is difficult to grasp. After all, these miniscule invaders affect the molecules of our cells and are not directly visible to us. By contrast the impact of invaders such as bacteria may be easier to observe because we can quickly see their results: a bacterial exudate on the tonsils, a virus manifest as a herpes blister, or a yeast overgrowth that causes a vaginal discharge or thrush infection in the mouth.

Free radicals, though less visible, can be every bit as harmful to our health. In fact a growing body of research shows that free radicals contribute to the aging process and to a long list if disorders, including heart disease and cancer, which now rank as two of the leading killers in our society.[1-19]

To understand how this damage occurs, we must look at the molecular events that take place in the body. Here a silent oxygen battle is waged between the "prooxdiants" (free radicals) and the "antioxidants" (certain nutrients), whose job it is to neutralize free radicals.

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This discussion takes us far beyond the organs and glands of the immune system – and even beyond the cellular aspects of immunity. By considering the functions of molecules, the building blocks of our cells, we can gain a deeper understanding of how to protect the body from oxygen-related damage and optimize its immune performance.

II. BODY DEFENSES AGAINST FREE RADICALS

We must continually strive to balance the events taking place in the molecules of our bodies. Fortunately nature has given us a way to achieve this balance: The body's built-in mechanism for handling free radicals consist of antioxidant enzymes, hormones, and nutrients that remove radicals before they can cause cellular damage.[20-31]

The antioxidant enzymes include two forms of superoxide dismutase (SOD), as well as glutathione, and catalase. SOD needs either manganese or a copper-zinc combination to do its work, depending on its location in the cell. Glutathione peroxidase requires selenium as its cofactor nutrient. And catalase depends on iron to carry out its antioxidant functions.[32]

Likewise, antioxidant vitamins act as "scavengers" to remove various forms of free radicals from the body and prevent new ones from being formed. These potent nutrients include vitamin C, vitamin E, and beta-carotene (a precursor to vitamin A). In addition to trapping free radicals, all three of these antioxidants can "quench" the highly reactive singlet oxygen.[33] In essence they absorb the molecule's altered energy state, thereby returning it to normal without harming the system.[34]

III. FREE RADICAL BODY DAMAGE

In recent years a variety of degenerative diseases have been linked to free-radical activity. These diseases get their start in the biochemical processes of the body, during which free radicals can damage cells and tissues.[35, 36, 37, 38] In *The Antioxidants*, Richard A. Passwater, Ph.D., identifies four basic types of damage caused by free radicals that will lead to the chronic diseases so prevalent today, including arthritis, neurological disorders, and cancer. The basic types of biochemical damage include:[39]

III.1. Lipid Peroxidation

When free radicals attack the polyunsaturated fats on the body, the fatty acids become rancid and can produce even more free radicals.

III.2. Cross-linking

Free radicals may alter the structure of DNA and protein molecules by causing them to fuse together. This cross-linking inhibits the molecules's ability to function in the body.

III.3. Cell Membrane Damage

The cell membrane serves as a filter to the surrounding environment. Free radicals can cause direct damage to the structure of this filtering system, thereby impairing the cell's ability to absorb certain nutrients and eliminate waste products.

III.4. Lysosome Damage

The lysosomes within our cells contain powerful digestive enzymes. But free radicals can destroy the lysosomes, allowing these enzymes to escape and "eat" important compounds within the cell.

What do these types of damage have in common? They occur in regions of the body that are rich in electrons, such as DNA, proteins, and polyunsaturated fatty acids. These biological molecules are rich in electrons because they contain unsaturated bonds, or what a chemist would call double bonds. The double bonds become the site of all biochemical activity of free radicals.[40]

IV. DISORDERS RELATED TO FREE RADICALS

With an understanding of the biochemical mechanisms of free radicals, it is easier to see how the progression of this damage could lead to different diseases, depending on which cells and tissues are being attacked. Lipid-peroxide activity, for example, may eventually lead to coronary artery disease. And as Diplock points out, in-vitro studies also show that the body's free-radical generating systems may damage the structure of DNA. This damage could be a major contributor to cancer development.[41]

At this point a variety of serious disorders have been linked to free-radical pathology. According to Dr. Bland, among others, these conditions include cancer, coronary heart disease, diabetes, cataracts, alcohol-induced liver damage, adverse drug reactions, immune hypersensitivity, cardiac toxicity to adriamycin (a chemotherapeutic drug), arthritic tissue damage,

inflammatory bowel disorders, Parkinson's disease, neurological degeneration, senile dementia, chronic brain disease, and traumatic inflammation.[42-52]

What's more the aging process itself may be associated with free-radical activity. Dr. Richard Passwater, a prominent researcher, explains the connections as follows: Free radicals impair or destroy healthy cells. Eventually the cumulative loss of active cells can lead to a loss of the "reserve function" in various organs, or the amount of energy held in reserve for functioning beyond the body's daily needs.

In a nutshell the loss of reserve function and the aging process are one and the same. "The stability of the aging living systems becomes progressively impaired by chemical reactions. not the passage of time," states Passwater. "If we can control the rate of these deleterious reactions, then we can control the advance of physiological aging."[53]

V. FREE RADICALS AFFECT THE IMMUNE SYSTEM

There are two sides to the story on the immune system and free radicals. On the one hand, a variety of immune system cells, including neutrophils, monocytes, and macrophages, can generate free radicals in the body. According to Dr. Lonsdale, the neutrophils depend on the mechanisms in order to kill bacteria. This is one example of the body's legitimate need for free radicals.[54]

The flip side of this scenario, however, is the adverse effect free radicals can have on the immune response. When free radicals damage cell membranes, for example, the immune system cannot function properly. The reason: Its communication system depends on cell membranes, where the receptors for interleukins, hormones, and immunoglobulins are placed. Also, two types of immunoglobulin help the phagocyte cells to "eat" foreign invaders by fixing an invader on the phagocyte's surface. A damaged cell membrane impairs this crucial immune response.[55]

VI. ASSISTING THE BODY'S DEFENSE MECHANISMS

The foods we eat are our first line of defense against free radicals because they provide the body with nutritional support. We must obtain an adequate supply of vitamins that contribute to the body's defenses against oxidant imbalance, as well as the cofactor minerals that fuel our antioxidant enzyme systems. "The quality of and quantity of nutrition emerge as the most important factors within human control," states Dr. Lonsdale.

For many people, however, the nutritional failings of the American diet as well as the onslaught of stressors may produce excess free-radical activity and a deficiency in the antioxidants needed to remove them. This negative balance is called free-radical pathology.

To achieve the proper oxygen balance, which is an integral part of the optimal health, the cellular metabolism must be able to neutralize the input of toxic free radicals with the antioxidant-enzyme complex. This is no easy task in our modern industrial society, regardless of whether you live in an urban or a rural area. We burn gasoline, oil, and coal; operate garbage disposal plants; and spray our foods with pesticides. All of these affect the quality of our oxygen.

The ability of your cells to produce sufficient quantities of the antioxidant enzymes depends upon your nutritional status, genetics, and age. In a healthy young person who is not subjected to stressors, for example, the cells may produce sufficient amounts of enzymes to neutralize the free radicals that are normal by-products of oxygen metabolism. But when stressors enter the picture – which include chemicals, physical trauma, infections, emotional stress, and even poor nutrition – free radicals will be produced beyond the normal levels. The body's ability to synthesize antioxidant enzymes also declines with age. In the process our natural scavenger activities decrease as well.[56]

In this case the essential balance is off and the free-radical activity overwhelms the body's antioxidant capabilities. To reestablish the proper balance, we must reduce the amount of stressors on the body and assist the natural defense mechanisms by supplying the antioxidants needed to defend the body against this pervasive damage.[57-61]

VII. MOLECULAR STRESS: OXIDANTS VERSUS ANTIOXIDANTS

In today's environment the molecular events in the body are generating much interest because the problems related to "oxygen stress" occur at that level[62]. As a society we have experienced an increase in allergies and chemical sensitivities of all kinds, in part because the level of oxygen stressors has also increased. The aging process may also be caused in

part by oxygen stress. The key to understanding this oxygen battle is to study the molecular level of immune functioning.

Majid Ali, M.D. believes the answers to our many questions about the disease process lie in the molecules of our cells. In "Intravenous Nutrient Protocols in Molecular Medicine," Dr. Ali defines human biology as "an ever-changing kaleidoscope of molecular mosaics." He divides these mosaics into two camps: The molecular events that preserve the integrity of cells, issues, and organs also preserve health; the molecular dynamics that injure cells and tissues also cause disease[63].

Dr. Ali presents an interesting hypothesis: The interaction between oxygen and free radicals not only fuels disease but also plays a key physiological role in the aging process. Indeed, he believes the quality of our "redox reaction," the process by which we neutralize oxidative actions, determines the life span of a species. The redox reaction affects both metabolism and the extent to which tissues are poisoned by oxidants.

For each of us the oxidant-versus-antioxidant status moves along a continuum. Dr. Ali believes that degenerative diseases and premature aging essentially result from accelerated "molecular burnout." In essence that means the redox homeostasis is a battlefield for the war between oxidative stress (free radicals) and the antioxidant potential of the tissues. In this battle the body is attempting to correct the oxidative poisoning.[64-68]

The ultimate issue is one of injury and repair. The body must defend itself from molecular injury and perform oxidative repair. All of this occurs at the molecular level, as a battle between energy forces. Dr. Ali uses the term *aging oxidative molecules* to describe the molecules that cause or facilitate physiologic changes in the aging and injury process, which is prompted by infectious or environmental agents. On the other side of the battlefield are the "life-span molecules," which counter the aging molecules and protect us from molecular injury.

In short the oxygen forces in the body are engaged in an ongoing struggle. The cells and tissues require oxygen to sustain themselves, but excessive oxygen will cause injury. Oxidation is part of the energy-giving process; the "reductive" actions that counterbalance such inquiry require the use of energy. If the body starts to lose the battle, disorders such as arthritis and arterioscleroris may develop. Experimental and patient-related data illustrate this relationship, says Dr. Ali. The heart muscle, for example, has served as a laboratory to explore the concept of oxidative stress versus antioxidant protection.

What are the mechanisms of aging? According to one widely held theory, aging results from the free-radical activity that is caused in part by the process of oxidation.[69,70,71,72] Another thoery maintains that aging is caused by the cross-linkage of proteins, says Dr. Ali. But this theory may not be so distinct from the first, since cross-linking also results from an oxidation injury. Both theories seem to imply that if the oxidative process is not properly controlled, the entire system deteriorates that much faster. Conversely we can sustain health if the oxidative processes are regulated.

Accelerated oxidative molecular injury creates a chain reaction of negative events. In the earliest stages these events include enzyme inactivation, cell membrane disturbances, plasma membrane peroxidation, and protein cross-linking. Beyond that, at an intermediate level, molecular injury causes toxin-gene-enzyme-immune phenomena, including a deficiency of vital minerals, toxicity to heavy metals, and autoimmune injury. The late-stage events are the ones we currently understand best – structural injuries at the subcellular, cellular, and tissue level[73].

To prevent this chain reaction, our first priority must be to preserve the structure and function of cells, which in turn helps to preserve the functioning of tissues and organs. But this will require a new approach to medicine, one that focuses on the molecular dynamics that lead to the injuries described here. As Dr. Ali points out, this is no small shift in perspective. Moving from a cellular level to a molecular level will require a breakthrough in medical thinking like the one that occurred in 1858, when a book called *Cellular Pathology* shifted the primary focus of medicine from organs and tissues to cells.

Today medicine still emphasizes the functioning of cells and tissues, rather than the concept of molecular pathology. With a focus on "molecular medicine," says Dr. Ali, we could develop a better understanding of genetics, the body's molecular defense pathways, the effects of environmental toxins on molecular events, the functioning of enzymes, and immune impairment.

The enzymes SOD, catalase, and glutathione peroxidase defend against oxidant damage at an intracellular level, while vitamin C provides extracellular protection. The hydrophobic cell membrane compartment also needs fat-soluble nutrients, primarily vitamin E and carotene, for antioxidant defense. In addition our molecular defenses and cellular health depend upon the integrity of the plasma membrane and the oxidative enzyme systems in the mitochondria of the cell, which protect the electron-transfer events. Diseases get their start when the electron-transfer defenses do not function properly.

Indeed the greatest threat to our survival today comes from toxic chemicals, heavy metals, and daily oxidative stress on the body systems. These stressors now outrank the infectious agents that plagued us in the late 1800s and focused our attention on the "microbial threat." The health problems of our times – allergies, chronic fatigue, chronic headaches, environmentally induced illnesses, chronic viral infections, hypoglycemia, and immune disorders – all share the common denominator of oxidative molecular injury[74].

VIII. CATARACTS: A MODEL OF THE AGING PROCESS

There's no denying that aging is a major issue in our society. Who wouldn't want to declare war on the aging process and prevent it from affecting their lives in destructive ways? For that reason theories about how aging takes place always prove interesting. But much of this scientific work, including many theories on aging, requires more research. In the coming years further research may bolster the underlying premises of these and similar theories.

In the meantime the practical aspects of aging continue to plague us, lowering the quality of life for many people in their later years. Rather than leave this discussion at a general and philosophical level, we want to look at how certain nutrients relate to one specific aspect of aging – the formation of cataracts. This type of vision impairment is an excellent model of the aging process; not only is it an extremely important issue among the aged population, but cataracts are a measurable and well-studied problem.

Here we summarize the work of Paul F. Jacques and Allen Taylor in "Micronutrients and Age-Related Cataracts," which explores the role various nutrients play in reducing the risk of cataracts and protecting against the oxidative processes that contribute to many aspects of the aging process[75]. As Jacques and Taylor point out, senile cataracts are "the leading cause of preventable blindness in the world." Each year some 400,000 people develop cataracts; in the United States alone 20 percent of people between ages sixty-five and seventy-five, and 45 percent of those over seventy-five, suffer from cataracts and vision impairment.

As we age, both structural and biochemical events contribute to the formation cataracts. The epithelial cells of the lens (which transmits and focuses light rays on the retina of the eye) from fiber cells throughout life. These cells start at the lens equator and travel inward. Eventually, say the authors, the old fibers become more dehydrated and compressed in the center of the lens. The gelatin-like substance of the lens has a refraction index that prevents light from scattering. This substance consists of 65 percent water and 35 percent protein. According to Jacques and Taylor, changes in the lens will alter the refraction index, allowing more light to scatter and lens to become clouded. This opacity is called a cataract.

In studying cataracts, then, one must consider the elements that affect the protein in the lens, such as exposure to light, oxygen, the products of normal aging, and environmental factors. These factors can cause protein aggregation and precipitation, both of which are linked to a greater level of water-insoluble protein in old lenses or those with cataracts. When cataracts form, the process by which protein becomes insoluble seems to be accelerated, say the authors.

A number of risk factors have been associated with senile cataracts, which make up the majority of lens opacities. Among those factors are ultraviolet radiation and infrared, ionizing and microwave radiation. The risk of senile cataracts has also been correlated with demographic factors such as gender, blood pressure, blood sugar, education, occupation, and vital capacity.

Beyond those basic risk factors, there is much research data relating the development of cataracts to reduce levels of certain micronutrients, according to Jacques and Taylor. The lens, for example, needs certain enzymes to help protect it against the effects of oxidation, which has been strongly correlated with cataract formation. In the young lens the antioxidant defense mechanisms will keep free radicals and photooxdiation in check. As we age, however, this

activity may fall off and lead to the oxidation of lens proteins.

The lens depends on three enzymes for its protection against oxidation: the glutathione redox cycle, SOD, and catalase. Also, a number of familiar nutrients, including vitamin C and vitamin E, help to fuel the glutathione enzyme system. Due to the link between cataracts and the process of oxidation, much of the research in this area has centered on these nutrients because they have antioxidant properties.

What follows is a brief summary of experimental and epidemiological evidence that correlates the levels of vitamin C and E with the risk of cataracts:

VIII.1. Vitamin C (ascorbate)

Compared with normal lenses, older lenses and lenses with cataracts have low ascorbate levels. In six animal studies conducted between 1978 and 1986, ascorbate was found to delay the formation of cataracts or protect the lens against various types of damage[76].

Beyond that, epidemiological studies have found an increased risk of cataracts in people with low ascorbate levels.[77,78,79,80,81] In one of these studies, for example, researcher J. Robertson compared the risk of senile cataracts among people who took regular ascorbate acid supplements (300-600 mg per day) and those who did not. The cataract risk for supplement users was only 30 percent of that for non-supplement users[82]. In another study by the same author, 175 cataract patients were compared with 175 individually matched cataract free controls. Results showed that consumption of supplementary vitamin C and vitamin E was significantly higher among controls[83].

The authors note, however, that a large study in India reported mixed results on the ascorbate-cataract connection. With a given increase in the plasma ascorbate level, there was a 90 percent jump in the risk of posterior subcapsular and nuclear cataracts. But at the same *lower* levels of an antioxidant index that factored in plasma ascorbate increased the risk of these same cataracts[84].

VIII.2. Vitamin E (tocopherol)

This nutrient, which is the primary fat-soluble antioxidant, prevents photoperoxidation of the lens lipids. As with other parts of the body, the integrity of the cell membranes in the lens must be preserved. Tocopherol seems to stabilize and protect cell membranes. A number of studies also show that this nutrient will retard cataractlike changes to the lens by various cataractogenic agents, including glucose, galactose, sorbitol, ionizing radiation, and steroids and other cataractogenic drugs.[85-93]

In Robertson's study on the relationship between vitamin C status and cataracts, it was also found that people who took an average of 400 I.U. of vitamin E each day had 40 percent of the risk of senile cataracts as those who did not take supplements. A study by Jacques, however, did not find any difference in the cataract risk for people with low, moderate, or high levels of tocopherol in the plasma.

Based on their research Jacques and Taylor conclude that senile cataracts are a common problem among the aged population, but not an inevitable one. The formation of cataracts appears to stem, in part, from damage to the lens protein by the process of oxidation. And research shows that antioxidant nutrients can slow down various types of cataractlike injuries. As a result, they say, the existing data establishing a connection between the risk of senile cataract and micronutrient intake provides a foundation for future Work in this area.

References

1. Cutler, R.G., Antioxidants and Aging, American Journal of Clinical Nutrition, 53(1 Suppl), January 1991, p. 373S-379S.
2. Roth, E., Oxygen Free Radicals and Their Clinical Implications, Acta Chir Hung, 36(1-4), 1997, p. 302-305.
3. Manso, C., [Aging and Free Radicals], Acta Med Port, 5(2), February 1992, p. 87-90.
4. Fielding, R.A. & Meydani, M., Exercise, Free Radical Generation, and Aging, ging, 9(1-2), February-April 1997, p. 12-18.
5. Knight, J.A., The Process and Theories of Aging, Ann Clin Lab Sci, 25(1), January-February 1995, p. 1-12.
6. Leeuwenburgh, C., et al., Caloric Restriction Attenuates Dityrosine Cross-linking of Cardiac and Skeletal Muscle Proteins in Aging Mice, Arch Biochem Biophys, 346(1), October 1, 1997, p. 74-80.
7. Edamatsu, R., et al., The Spin-trap N-tert-alpha-phenyl-butylnitrone Prolongs the Life Span of the Senescence Accelerated Mouse, Biochem Biophys Res Commun, 211(3), June 26, 1995, p. 847-849.
8. Sohal, R.S., et al., Biochemical Correlates of Longevity in Two Closely Related Rodent Species, Biochem Biophys Res Commun, 196(1), October 15, 1993, p. 7-11.
9. de Grey, A.D., A Proposed Refinement of the Mitochondrial Free Radical Theory of Aging, *Bioessays*, 19(2), February 1997, p. 161-166
10. Nohl, H., Involvement of Free Radicals in Ageing: A Consequence or Cause of Senescence, Br Med Bull, 49(3), July 1993, p. 653-667.
11. Ceballos-Picot, I., et al., Cellular Clones and Transgenic Mice Overexpressing Copper-zinc Superoxide Dismutase: Models for the Study of Free

Radical Metabolism and Aging, EXS, 62, 1992, p. 89-98.
12. Shi, L., et al., Alterations in Free Radical Activity in Aging Drosophila, Exp Gerontol, 29(5), September-October 1994, p. 575-684.
13. Ku, H.H., et al., Relationship Between Mitochondrial Superoxide and Hydrogen Peroxide Production and Longevity of Mammalian Species, Free Radic Biol Med, 15(6), December 1993, p. 621-627.
14. Pacifici R.E. & Davies, K.J., Protein, Lipid and DNA Repair Systems in Oxidative Stress: The Free-Radical Theory of Aging Revisited, Gerontology, 37(1-3), 1991, p. 166-180.
15. Perez-Campo, R., et al., The Rate of Free Radical Production as a Determinant of the Rate of Aging: Evidence from the Comparative Approach, J Comp Physiol, 168(3), April 1998, p. 149-158.
16. Muscari, C., et al., Role of Reactive Oxygen Species in Cardiovascular Aging, Mol Cell Biochem, 160-161, July-August 1996, p. 159-166.
17. Fleming, J.E., et al., Role of Oxidative Stress in Drosophila Aging, Mutat Res, 275(3-6), September 1992, p. 267-279.
18. Kendler, B.S., Free Radicals in Health and Disease: Implications for Primary Health Care Providers, Nurse Pract, 20(7), July 1995, p. 29-43.
19. Butterfield, D.A., et al., Free Radical Oxidation of Brain Proteins in Accelerated Senescence and Its Modulation by N-tert-butyl-alpha-phenylnitrone, Proc Natl Acad Sci, 94(2), January 21, 1997, p. 674-678.
20. Monti, D., et al., Apoptosis--programmed Cell Death: A Role in the Aging Process? American Journal of Clinical Nutrition, 55(6 Suppl), June 1992, p. 1208S-1214S.
21. Reiter, R.J., Pineal Function During Aging: Attenuation of the Melatonin Rhythm and its Neurobiological Consequences, Acta Neurobiol Exp (Warsz), 54(Suppl), 994, p. 31-39.
22. Reiter, R.J., Oxygen Radical Detoxification Processes During Aging: The Functional Importance of Melatonin, Aging, 7(5), October 1995, p. 340-351.
23. Vina, J., et al., Effect of Aging on Glutathione Metabolism. Protection by Antioxidants, EXS, 62, 1992, p. 136-144.
24. Pierrefiche, G. & Laborit, H., Oxygen Free Radicals, Melatonin, and Aging, Exp Gerontol, 30(3-4), May-August 1995, p. 213-227.
25. Reiter, R.J., Oxidative Processes and Antioxidative Defense Mechanisms in the Aging Brain, FASEB Journal, 9(7), April 1995, p. 526-533.
26. Lopez-Torres, M., et al., Simultaneous Induction of Sod, Glutathione Reductase, GSH, and Ascorbate in Liver and Kidney Correlates with Survival During Aging, Free Radic Biol Med, 15(2), August 1993, p. 133-142.
27. Machlin, L.J. & Bendich, A., Free Radical Tissue Damage: Protective Role of Antioxidant Nutrients, *FASEB Journal*, 1(6), December 1987, p. 441-445.
28. Bendich, A., Symposium Conclusions: Biological Actions of Carotenoids, Journal of Nutrition, 119(1), January 1989, p. 135-136.
29. Bendich, A., Carotenoids and the Immune Response, Journal of Nutrition, 119(1), January 1989, p. 112-115.
30. Bendich, A., Biological Function of Carotenoids, Carotenoids in Human Health. February 6-9, 1993, San Diego, CA, A6.
31. Diplock, A.T., Will the 'Good Fairies' Please Prove to Us that Vitamin E Lessens Human Degenerative Disease? Free Radical Research, 27(5), November 1997, p. 511-532.
32. Bendich, A., Antioxidant Micronutrients and Immune Responses, Micronutrients and Immune Function, A, Bendich and R.K. Chandra (eds.), Annals New York Academy of Sciences, New York, 1990, 171.
33. Bendich, A., Antioxidant Micronutrients and Immune Responses, Micronutrients and Immune Function, A, Bendich and R.K. Chandra (eds.), Annals New York Academy of Sciences, New York, 1990, p. 175.
34. Diplock, A.T., Antioxidant Nutrients and Disease Prevention, American Journal of Clinical Nutrition, 53, 1991, p. 190S.
35. de Haan, J.B., et al., Cu/Zn Superoxide Dismutase mRNA and Enzyme Activity, and Susceptibility to Lipid Peroxidation, Increases with Aging in Murine Brains, Brain Res Mol Brain Res, 13(3), April 1992, p. 179-187.
36. Stadtman, E.R., et al., Protein Modification in Aging, EXS, 62, 1992, p. 64-72.
37. Cestaro, B., et al., Free Radicals, Atherosclerosis, Ageing and Related Dysmetabolic Pathologies: Biochemical and Molecular Aspects, European Journal Cancer Prevention, 6(Suppl 1), March 1997, p. S25-S30.
38. Bhagwat, V.R., Relationship of Erythrocyte Superoxide Dismutase, Serum Lipid Peroxides and Age, Indian Journal of Med Sci, 51(2), February 1997, p. 45-51.
39. Passwater, Richard A., The Antioxidants: The Nutrients that Guard Us Against Cancer, Heart Disease, Arthritis and Allergies – and Even Slow the Aging Process, New Canaan, CT: Keats Publishing Inc.,1985, p. 2.
40. Bland, Jeffrey, The Nutritional Effects of Free Radical Pathology, 1986/A Year in Nutritional Medicine Monograph, New Canaan, *CT*: Keats Publishing Inc., 1986, p. 12-13.
41. Diplock, A.T., Antioxidant Nutrients and Disease Prevention, American Journal of Clinical Nutrition, 53, 1991, p. 190S.
42. Bland, Jeffrey, The Nutritional Effects of Free Radical Pathology, 1986/A Year in Nutritional Medicine Monograph, New Canaan, *CT*: Keats Publishing Inc., 1986, p. 14.
43. Ward, J., Free Radicals, Antioxidants and Preventive Geriatrics, Aust Fam Physician, 23(7), July 1994, p. 1297-1305.
44. Florence, T.M., The Role of Free Radicals in Disease, Aust N Z J Ophthalmol, 23(1), February 1995, p. 3-7.
45. Henrotin, Y., et al., Active Oxygen Species, Articular Inflammation and Cartilage Damage, EXS, 62, 1992, p. 308-322.
46. Scarfiotti, C., et al., Free Radicals, Atherosclerosis, Ageing, and Related Dysmetabolic Pathologies: Pathological and Clinical Aspects, European Journal of Cancer Prevention, 6(Suppl 1), March 1997, p. S31-S36.
47. Hunt, J.V. & Wolff, S.P., Oxidative Glycation and Free Radical Production: A Causal Mechanism of Diabetic Complications, Free Radic Res Commun, 12-13(Pt 1), 1991, p. 115-123.
48. Marzatico, F. & Café, C., Oxygen Radicals and Other Toxic Oxygen Metabolites as Key Mediators of the Central Nervous System Tissue Injury, Funct Neurol, 8(1), January-February 1993, p. 51-66.
49. Preuss, H.G., Effects of Glucose/Insulin Perturbations on Aging and Chronic Disorders of Aging: The Evidence, Journal of the American College of Nutrition, 16(5), October 1997, p. 397-403.
50. Stohs, S.J., The Role of Free Radicals in Toxicity and Disease, J Basic Clin Physiol Pharmacol, 6(3-4), 1995,pg. 205-228.
51. Richter, C., Reactive Oxygen and DNA Damage in Mitochondria, Mutat Res, 275(3-6), September 1992, p. 249-255.
52. Sack, C.A., et al., Antioxidant Treatment with Phenyl-alpha-tert-butyl nitrone (PBN) Improves the Cognitive Performance and Survival of Aging Rats, Neurosci Letters, 205(3), March 1, 1996, p. 181-184.
53. Passwater, Richard A., The Antioxidants: The Nutrients that Guard Us Against Cancer, Heart Disease, Arthritis and Allergies – and Even Slow the Aging Process, New Canaan, CT: Keats Publishing Inc.,1985, p. 19.

54 Lonsdale, Derrick, Free Oxygen Radicals and Disease, 1986/A Year in Nutritional Medicine Monograph, New Canaan, CT: Keats Publishing Inc., 1986, p. 5-6.

55 Bendich, A., Antioxidant Micronutrients and Immune Responses, Micronutrients and Immune Function, A, Bendich and R.K. Chandra (eds.), Annals New York Academy of Sciences, New York, 1990, p. 170

56. Bradford, R. & Allen, H., Antioxidant Enzymes, Agents and Mechanisms, Robert W. Bradford Research Institute, Chula Vista, California.

57 Barnett, Y.A., Nutrition and the Ageing Process, British Journal Biomed Sci, 51(3), September 1994, p. 278-287.

58. Ward, J.A., Should Antioxidant Vitamins be Routinely Recommended for Older People? Drugs Aging, 12(3), March 1998, p. 169-175.

59 Emerit, I., Free Radicals and Aging of the Skin, EXS, 62, 1992, p. 328-341.

60. Sharma, P., et al., Consequences of Aging on Mitochondrial Respiratory Chain Enzymes in Cultured Human Fibroblasts Treated with Ascorbate, Gerontology, 44(2), 1998, p. 78-84.

61. Diplock, A.T., Safety of Antioxidant Vitamins and Beta-carotene, American Journal of Clinical Nutrition, 62(6 Suppl), December 1995, p. 1510S-1516S.

62 Wei, Y.H., Oxidative Stress and Mitochondrial DNA Mutations in Human Aging, Proc Soc Exp Biol Med, 217(1), January 1998, p. 53-63.

63 Ali, Majid, Nutritional Medicine: Principles and Practice, Institute of Preventive Medicine, Denville, NJ., 1991.

64 Harman, D. & Eddy, D.E., Free Radical Theory of Aging: Effects of adding Antioxidants to Maternal Mouse Diet on the Life Span of their Offspring, Second Experiment, Age, 1, 1978, p. 162.

65. Tolmasoff, J., Ono, T. & Cutler, R., Superoxide Dismutase: Correlation with Life Span and Specific Metabolic Rate in Primate Species, Proceedings of the National Academy of Sciences, 77, 1980, p. 2777.

66. Miquel, J., et al., Antioxidants, Metabolic Rate and Aging in Drosophilia, Arch Gerontol. Geriatr, 1(2), 1982, p. 59.

67 Cutler, R.G., Peroxide-producing of Tissues: Inverse Correlation with Longevity of Mammalian Species, Proceedings of the National Academy of Sciences, 82, 1985, p. 4798.

68 Cross, C.E.,Halliwell, B., Borsih, E. et al., Oxygen radicals and human diseaseAnnals of Internal Medicine, 1987;107:526-545107, 1987, p.526.

69 Beckman, K.B. & Ames, B.N., The Free Radical Theory of Aging Matures, Physiol Rev, 78(2), April 1998, p. 547-581.

70 Harman, D., Free Radical Involvement in Aging. Pathophysiology and Therapeutic Implications, Drugs Aging, 3(1), January-February 1993, p. 60-80.

71 Harman, D., Extending Functional Life Span, Exp Gerontol, 33(1-2), January-March 1998, p. 95-112.

72 Harman, D., Aging and Oxidative Stress, J Int Fed Clin Chem, 10(1), March 1998, p. 24-27.

73 Ali, Majid, Molecular Basis of Environmental Illness, Syllabus of the American Academy of Environmental Medicine, Denver, CO., 1991.

74. Ali M. Spontaneity of Oxidation in Nature and Aging. Monograph, Teaneck, New Jersey, 1983.

75. Jacques, Paul F. & Taylor, Allen, Micronutrients and Age-Related Cataracts, in Micronutrients in Health and in Disease Prevention, Bendich, A. & Butterworth, C.E., (eds.), Marcel Dekker, New York, 1991, p. 359-379.

76 Jacques, Paul F. & Taylor, Allen, Micronutrients and Age-Related Cataracts, in Micronutrients in Health and in Disease Prevention, Bendich, A. & Butterworth, C.E., (eds.), Marcel Dekker, New York, 1991, p. 367.

77 Jacques, P.F., et al., Antioxidant Status in Persons with and without Senile Cataract, Arch Opthalmol, 106(3), March 1988, p. 337-340.

78 Jacques, P.F. & Chylack, L.T., Epidemiologic Evidence of a Role for the Antioxidant Vitamins and Carotenoids in Cataract Prevention, American Journal of Clinical Nutrition, 53(1 Suppl), January 1991, p. 352S-355S.

79. Gerster, H., Antioxidant Vitamins in Cataract Prevention, Z Ernahrungswiss, 28(1), March 1989, p. 56-75.

80. Jacques, P.F., et al., Long-term Vitamin C Supplement Use and Prevalence of Early Age-Related Lens Opacities, American Journal of Clinical Nutrition, 66(4), October 1997, p. 911-916.

81. Weber, P., et al., Vitamin C and Human Health – A Review of Recent Data Relevant to Human Requirements, Int J Vitam Nutr Res, 66(1), 1996, p. 19-30.

82. Robertson, J., Donner, A.P., & Trevithick, J.R., Vitamin E Intake and Risk of Cataracts in Humans, Annals of the New York Academy of Sciences, 570, 1989, p. 372-382.

83. Robertson, J.M., et al., A Possible Role for Vitamin C and E in Cataract Prevention, American Journal of Clinical Nutrition, 53(1 Suppl), January 1991, p. 346-351S.

84. Mohan, M., et al., India-US Case-control Study of Age-related Cataracts, Arch Ophthalmol, 107, 1989, p. 670-676.

85. Jacques, Paul F. & Taylor, Allen, Micronutrients and Age-Related Cataracts, in Micronutrients in Health and in Disease Prevention, Bendich, A. & Butterworth, C.E., (eds.), Marcel Dekker, New York, 1991, p.368-369.

86. Hattori, H., et al., [Effect of Vitamin E-containing Liposome on Experimental Sugar Cataract] Nippon Ganka Gakkai Zasshi, 93(1), January 1989, p. 97-102.

87. Knekt, P., et al., Serum Antioxidant Vitamins and Risk of Cataract, British Medical Journal, 305(6866), December 5, 1992, p. 1392-1394.

88. Varma, S.D., Scientific Basis for Medical Therapy of Cataracts by Antioxidants, American Journal of Clinical Nutrition, 53(1 Suppl), January 1991, p. 335S-345S.

89. Rouhiainen, P., et al., Association Between Low Plasma Vitamin E Concentration and Progression of Early Cortical Lens Opacities, American Journal of Epidemiology, 144(5), September 1, 1996, p. 496-500.

90. Ohta, Y., et al., Preventive Action of Vitamin E-containing Liposomes on Cataractogenesis in Young Adult Rats Fed a 25% Galactose Diet, J Ocul Pharmacol Ther, 13(6), December 1997, p. 537-550.

91. Kohima, M., et al., Inhibition of Steroid-induced Cataract in Rat Eyes by Administration of Vitamin E-Opthalmic Solution, Opthalmic Res, 28(Supp 2), 1996, p. 64-71.

92. Ohta, Y., et al., Anticataract of Vitamin E: Its Estimation Using an in Vitro Steroid Cataract Model, Opthalmic Res, 28(Suppl 2), 1996, p. 16-25.

93. Leske, M.C., et al., Antioxidant Vitamins and Nuclear Opacities: The Longitudinal Study of Cataract, Opthalmology, 105(5), May 1998, p. 831-836.

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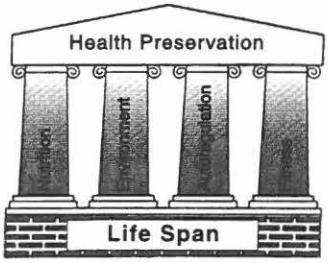

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