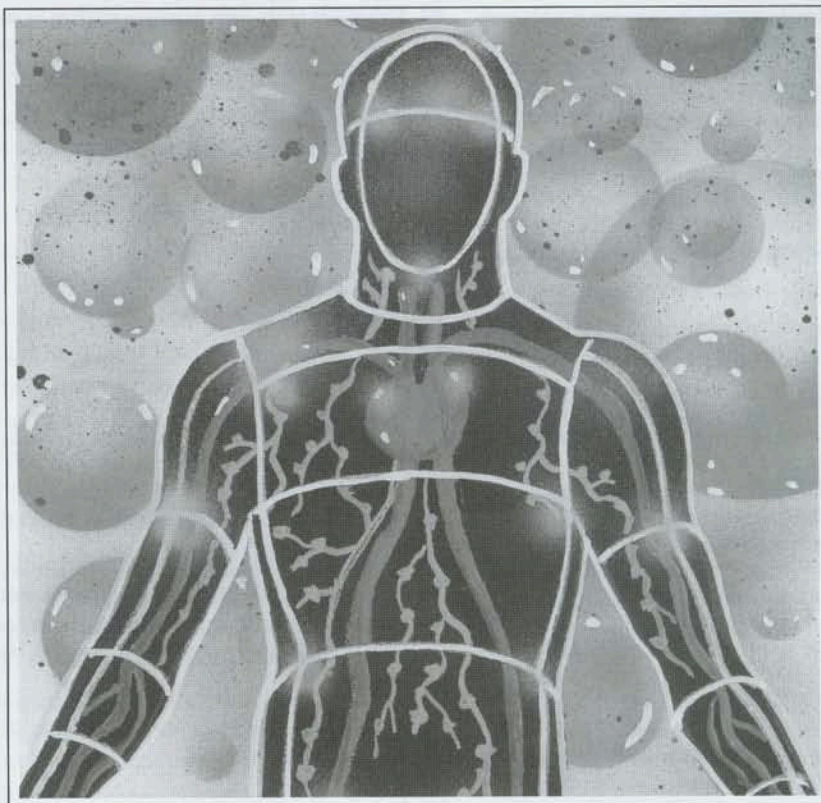


Part 2

AUTOIMMUNITY AND COFACTOR REPLACEMENT

by Russell Jaffe, M.D., Ph.D.



“A physician is obligated to consider more than a diseased organ, more even than the whole man—he must view the man in his world.”

—Harvey Cushing, M.D., U.S. neurosurgeon (1869-1939)

Editor's Note: The March/April issue of the *International Journal of Integrative Medicine*™ featured part 1 of Dr. Jaffe's two-part article on autoimmunity and biological response modifiers. In this article, Dr. Jaffe discusses the role of cofactor replacement as another approach to enhancing immune competence and protecting against autoimmune syndromes.

Among the often hidden consequences of immunologic reactions is the depletion of essential nutrients. This occurs because of the increased metabolic activity and acid reaction products that require buffering by renal excretory mechanisms. These acids are induced from increased consumption of coagulant-, complement, and kinin-related chemicals. These are consumed as the “infantry” of the immunologic defense responses.

The three groups of compounds most often required are minerals, antioxidants, and essential

fatty acids. The minerals are required to turn inert proenzymes into active biological catalysts.^{1,2} The antioxidants are needed to restore electron transport and to quench free-radical reactions.³ The essential fatty acids are required to build cell membranes.⁴

First, some general comments are provided about the importance of establishing and maintaining a proper nutrient assimilation,⁵⁻⁹ positive nitrogen balance, and nutrient repletion in immunocompromised people.¹⁰⁻¹²

RESTORING INTESTINAL INTEGRITY

Malabsorption and subsequent nutrient deficiencies stimulate glucocorticoid production. The resultant catabolism of muscle and lymphoid tissue provides abundant amino acids and energy for adaptation to the stressful situation, provided it does not last too long. Postulated physical and biochemical damage to the gastrointestinal tract by enteric pathogens might preclude successful dietary therapy with natural foodstuffs.

Elemental diets do not require digestion (but do require absorption, if given orally). They also do not contain potentially antigenic protein fragments found in partial protein hydrolysates, as well as whole foods incompletely digested. The glucose present in elemental diets should be readily absorbed and metabolized as an energy source. In animals, feeding of a 15% glucose solution abolished the test animal's response to glucocorticoids for 12 hours, probably by elevation of tissue cyclic guanylic acid (GMP), an antagonist to cyclic adenosine monophosphate (AMP).¹³

There is some concern about the acidosis linked to glucose metabolism in mineral-depleted hosts. However, this can be tempered by an evaporated whole cane juice that contains a full mineral complement (as 3-4% of total solids), with adequate chromium, manganese, vanadium, magnesium, and potassium to facilitate metabolism. This is suitable for oral administration in most people with nutrient assimilation blocks. We regularly use liquid nutrient diets, one or two days a week, in subjects who need to repair intestinal digestion and assimilation defects. They are then able to avoid the cost of ketosis and negative nitrogen balance, which may enhance viral activity. In addition, L-glutamine (20 - 40+ grams/day), or a combination of L-glutamine and pyridoxal alpha keto glutarate (PAK), can help repair mucosal integrity, as well as increase energy stores for gut, liver, muscle, and kidney use.

For some subjects, oral or intravenous hyperalimentation is essential for restoring intestinal integrity. Once this is restored, adequate nutrient assimilation can take place, and it becomes possible to provide higher tissue levels of substances than can be accomplished through the oral route. A typical course is 30 days, although 14 days may be sufficient, and at times 45 or more days may be required.

DRAWBACKS OF HIGH-PROTEIN DIETS

High-protein diets significantly enhance the adrenocortical stimulation elicited by stress conditions, but not under basal conditions in animals.¹⁴ If this observation is applicable to humans, one interpretation would be that in a stress state, high-protein diets accentuate adrenal responses, have acid residue from their metabolism, and enhance degradation of structural proteins. If this is the case, these diets are not recommended for people with AIDS, other immunologic impairment, autoimmune conditions, or other chronic viral states.

Protein consumption of 60 ± 20 grams daily results in sufficient protein for tissue replacement and repair, without the untoward consequences of excess protein consumption (>100 grams daily). High-protein, high-fat diets are surprisingly common, particularly in people who develop chronic viral syndromes or autoimmune conditions.

Moderately low-protein diets with adequate calories enhance growth hormone production. In animals, growth hormone administration completely abolished susceptibility to opportunistic infections caused by exogenous adrenocorticotrophic hormone (ACTH) or cortisol excess.¹⁵

Diets of this sort increase production of somatotrophic, growth-promoting hormones. Selye first described the protective effects of somatotrophic hormone against the catabolic effects and susceptibility to infection caused by cortisol excess.¹⁶ Some have hypothesized that rebound from immunological depression can be attributed to sustained elevation in growth hormone and thyroid hormones, which enhance lymphocyte proliferation.¹⁷

Growth hormone (HGH) and growth hormone homologues are obligatory factors in recovery of immune function following distress. They directly antagonize the lymphocyte effects of corticosteroids. Moderate-protein diets, such as those recommended, increase HGH release. Therefore, this may be a simple, indirect way of elevating HGH levels, and perhaps other anabolic factors as well.

ASSESSING NUTRITIONAL STATUS

How do we provide vigorous nutritional therapy to avoid the catabolic effects of negative nitrogen balance, while avoiding high-protein diets for subjects under stressful conditions? Generally, this is most easily accomplished through a whole-foods diet, with 55% complex carbohydrate, 20% protein, and 25% fat (particularly monounsaturated oils and essential fatty acids). This is particularly important for people with significantly disordered digestive microbial ecology (from colonization with fermentative yeasts, pathogenic microbes, and other parasites). These individuals are subjected to elevated levels of vasoactive, neuroactive, immunosuppressive, and antigenic polypeptide fragments because of impaired protein digestion and increased mucosal membrane permeability.

Mineral status can be determined through tissue mineral analysis.¹⁸⁻²⁰ Alternatively, therapeutic trials of mineral-rich dietary sources can be utilized.

Microbiologic or enzymatic assays can determine antioxidant deficiencies.²¹⁻²³ The phosphatides containing choline and ethanolamine are important for maintaining cell membrane fluidity. A more fluid membrane is more easily deformable, more resilient to circulating forces,

...IN A STRESS STATE, HIGH-
PROTEIN DIETS ACCENTUATE
ADRENAL RESPONSES,
HAVE ACID RESIDUE FROM
THEIR METABOLISM, AND
ENHANCE DEGRADATION OF
STRUCTURAL PROTEINS.

more able to internalize absorbed antigens for lysosomal destruction, and more resistant to viral binding and replication.²⁴ It is increasingly recognized that clinical needs may not be revealed by routine serum tests of, for example, cobalamin²⁵ or minerals.²⁶

MINERALS AND IMMUNOLOGIC INTEGRITY

A variety of minerals are important in maintaining immunologic integrity. Zinc and magnesium are particularly well-studied examples, especially as they relate to AIDS. Zinc deficiency reproduces many of the laboratory and clinical findings in AIDS, including depressed cellular immunity, particularly T4 function, killer T cell function, thymic involution,²⁷ and increased susceptibility to fungal and viral infections. Essential factor supplements, such as zinc, in aged patients is reported to improve immune responses in three respects:

1. Numbers of circulating lymphocytes,
2. Intracutaneous delayed hypersensitivity reactions, and
3. Specific antibody (IgG) production in response to injected antigens.²⁸

Another common problem in autoimmune and immunodeficiency patients is colonization by enteric fungi with elaborate immunosuppressive compounds, such as cyclosporin. The effects of cyclosporin have been proposed as a potentiating factor in AIDS.²⁹ Zinc administration is suggested as a logical therapy for this problem, since it both inhibits the production of gliotoxin in fungal cultures³⁰ and offers significant protection against formed mycotoxins.^{31,32} Yet another symptom frequently seen in AIDS patients, chronic diarrhea of unexplained etiology, may be secondary to zinc deficiency.

Measurements of zinc status are often unreliable indicators of clinical status.³³ A therapeutic trial of physiological amounts of zinc in the presence of the zinc-binding ligand polyconic acid³⁴ is one approach to determine its deficit status and clinical efficacy.

Other important minerals include magnesium, copper, iron, selenium, molybdenum, manganese, vanadium, and boron.³⁵⁻³⁷ Effective therapy requires pure, easily transported, biologically active, and properly balanced forms. The Krebs cycle intermediates (citrate, fumarate, and malate), ascorbate, and possibly picolinate, fill these requirements.

BENEFITS OF VITAMIN C

Among the antioxidants, tocopherol, ascorbate, glutathione, flavins, and cytochromes are most important. Bioflavonoids, particularly quercetin and possibly hesperidin, work synergistically to spare antioxidant consumption. In conditions of active viral replication, continuous therapeutic

amounts of antioxidants, for 30 or more consecutive days, may be essential to minimize viral control of cell machinery. For those who can, hourly consumption of ascorbate at tissue saturation levels is essential. For some, parenteral administration may be necessary to allow restoration of mucosal assimilation and to saturate tissue sites, such as the brain and bone marrow.³⁸

Let us look first at vitamin C as a representative antioxidant. The appropriate use of vitamin C supplementation in health and disease depends upon an accurate understanding of the relevant facts.³⁹⁻⁴¹ A few encouraging clinical observations have been made in AIDS and ARC.⁴³⁻⁴⁵

Ascorbate has a myriad of important functions within an organism and within a cell. Dozens of important functions of ascorbate relate to cell repair and division and energy production. Furthermore, ascorbate's antioxidant effects render toxins water-soluble and inert.

Vitamin C, reduced and crystallized in its native state, free of oxidized forms or contaminants, has virtually no toxic side effects. It has been given in dosages up to 300 grams per day, orally and intravenously, without complications.⁴⁶⁻⁵¹

Vitamin C in large doses is probably the most effective, lowest risk, general antiviral agent that exists.⁵²⁻⁵⁶ We especially recommend it in cases of chronic viral illness, including hepatitis,⁵⁷⁻⁶¹ mononucleosis with persisting fatigue, Epstein-Barr virus (EBV), cytomegalovirus (CMV), human immunodeficiency virus (HIV),^{62,63} syndromes such as systemic lupus erythematosus (SLE), and other autoimmune states such as Sjogren's (rheumatoid) syndrome.

Ascorbate is also beneficial against certain intestinal pathogens.⁶⁴ Recent work suggests a direct anti-HIV effect of therapeutic concentrations of ascorbate. These cell culture studies are based on quenching reverse transcriptase, a direct index of retroviral activity (personal communication).

In addition, ascorbate, taken at tissue saturation levels, strengthens immune system functioning.⁶⁵ We ask people to take vitamin C in the mixed ascorbate buffered mineral form rather than the ascorbic acid form. The neutral pH of the salts is preferable to the acidic form and much better tolerated in large doses. It also serves as a source for supplemental calcium, magnesium, potassium, and zinc.

It is recommended that people take ascorbate salts to tissue saturation. This refers to the amount that saturates absorption, just below the amount that results in gas, cramps, and/or diarrhea. This gastrointestinal "upset" represents saturation of the absorptive tissues so that no more ascorbate can be assimilated at that given moment.

Increased peristalsis moves digestion products through the gut more quickly. Improvements in gut bacteria quality are often accompanied by transient flatulence (gas). This is not harmful to the person—just uncomfortable.

Often gas, cramps, and diarrhea occur at rather low doses of ascorbate (below 10 grams). There are many possibilities for this, such as the body being so depleted that

AMONG THE ANTIOXIDANTS,
TOCOPHEROL, ASCORBATE,
GLUTATHIONE, FLAVINS,
AND CYTOCHROMES ARE
MOST IMPORTANT.

1. The ascorbate strengthens previously atonic intestinal motility,
2. A Herxheimer reaction occurs from die-off of harmful organisms in the gut, or
3. There exists a deficiency of two elements that aid ascorbate uptake and metabolism:
 - a. L-glutathione, reduced form (take 1% of ascorbate intake).
 - b. Bioflavonoids, such as quercetin/pycnogenol (take 5% of ascorbate intake).

This means 0.1 gram (100mg) of reduced L-glutathione and 0.5 grams (500mg) of quercetin/pycnogenol are required for each 10 grams of ascorbate ingested.

Pushing ascorbate to tissue saturation is important.^{66,67} Appropriate doses of ascorbate and other antioxidants effectively charge up the cellular electron pool, promote cellular healing and metabolism, purge the body of foreign invaders, and provide a base on which to build health.

Over a period of ascorbate use, people find that the required amount of ascorbate to achieve tissue saturation changes. For example, during stress or illness, much more may be needed because of increased cellular consumption than at other times. As health improves, tissue saturation levels typically decrease.⁶⁸⁻⁷³

IMPORTANCE OF OTHER ANTIOXIDANTS

Other antioxidants are also important. For example, tocopherol reduces oxidant and free-radical damage to cell membranes, thereby reducing cell turnover.⁷⁴⁻⁷⁹ Glutathione, flavins (such as riboflavin), and cytochromes (such as coenzyme Q) help maintain the electron shuttle that produces high energy compounds for the cell. Quercetin

reduces basophil degranulation^{80,81} and histamine release.⁸²⁻⁸⁴ It also dampens the inflammatory response directly by modulating certain key enzymes, including lipooxygenase, phospholipases, and nucleotide diesterases.⁸⁵⁻⁸⁸ Onions, ginger, and the allyl sulfides found in garlic may also be useful.⁸⁹⁻⁹¹

OVER A PERIOD OF ASCORBATE USE, PEOPLE FIND THAT THE REQUIRED AMOUNT OF ASCORBATE TO ACHIEVE TISSUE SATURATION CHANGES.

REFERENCES

1. Cousins RJ: Toward a molecular understanding of zinc metabolism. *Clin Physiol Biochem* 4:20-30, 1986.
2. Miquel J, Quintanilha AT, Weber H: *Handbook of Free Radicals and Antioxidants in Biomedicine, Vol I, II, III*. Boca Raton: CRC Press, 1989.
3. Warburg O: On the origin of cancer cells. *Science* 123:309, 1956.
4. Shinitzky M (ed): *Physiology of Membrane Fluidity, Vol I & II*. Boca Raton: CRC Press, 1984.
5. Chandra RK, Jain VK: Does nutritional deficiency predispose to acquired immune deficiency syndrome? *Nut Res* 4:537-543, 1984.
6. Kotler DP, et al: Body composition studies in patients with acquired immune deficiency syndrome. *Am J Clin Nutr* 42:1255-1265, 1985.
7. Gross RL, et al: The role of nutrition in immunologic function. *Phys Rev* 60:188-302, 1980.
8. Watson RR: Nutrition and immunity. *Mod Med of Aust* 33-36, 1982.
9. Robinson CH, Lawler MR: *Normal and Therapeutic Nutrition*. Boston: Macmillan, 1982.

10. Chandra, op. cit.
11. Goodhart RS, Shils ME: *Modern Nutrition in Health and Disease*. Philadelphia: Lea and Febiger, 1980.
12. Aggett PJ: Physiology and metabolism of essential trace elements: an outline. *Clinics in Endo and Meta* 14:513-543, 1985.
13. Honoune J, et al. *Arch Biochem Biophys* 148:180, 1972.
14. Moya F, et al. *Endocrin* 42:223-229, 1948.
15. Selye H. *Can Med Assoc J* 64:489, 1951.
16. Ibid.
17. Baroni CD, et al. *Immunology* 21:455-461, 1971.
18. Aggett, op. cit.
19. Brown AC, Crouse RG: *Hair Trace Elements in Human Disease*. New York: Praeger, 1980.
20. Baker H, Frank O: A superior functional test for vitamin assays. In: Yanick P, Jaffe RM (eds): *Clinical Chemistry and Nutritional Guidebook*. Hamlin: EPP, 1988.
21. Ibid.
22. Blass JP, Gibson GE: Abnormality of a thiamine-requiring enzyme in patients with Wernicke-Korsakoff syndrome. *N Engl J Med* 297:1367-1370, 1977.
23. Schwartz RA, Gross M, Lonsdale D, et al: Transketolase activity in psychiatric patients. *J Clin Psych* 40:427-429, 1979.
24. Shinitzky, op. cit.
25. Lindenbaum J, Heaton EB, Savage DG, Brust JCM, Garrett, TJ, Podell ER, Marcell PD, Stabler SP, Allen RH: Neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia and macrocytosis. *N Engl J Med* 318:1720-1728, 1988.
26. Beisel WR: Single nutrients and immunity. *Am J Clin Nutr* 35 (Supp):417-468, 1982.
27. DePasquale-Jardieu P, Fraker PJ. *Immunology* 124(6):2650-2655, 1980.
28. Duchateau J, et al. *Am J Med* 70:1001, 1981.
29. Eichner RD, Mullbacher A. *Aust J Exp Biol Med Sci* 62:479-484, 1984.
30. Menzel AEO, et al. *J Biol Chem* 152:419-429, 1943.
31. Allen JG, Masters HG. *Aust Vet J* 56:168-171, 1980.
32. Towers NR, Smith BL. *N Z Vet J* 26:199-202, 1978.
33. Deuster P: Personal communication.
34. Krieger I, Evans GJ. *Ped* 96(1):32-35, 1980.
35. Rosenberg IH, Solomons NW: Biological availability of minerals and trace elements: a nutritional overview. *Am J Clin Nutr* 35:781-782, 1982.
36. Sunderman Jr, FW: Trace elements. In: Brown SS, Mitchell FL, Young DS (eds): *Chemical Diagnosis of Disease*. 1979, pp.1009-1038.
37. Finch CA, Hueber H: Perspectives in iron metabolism. *N Engl J Med* 306:1520-1528, 1982.
38. Anderson R: Ascorbic acid and immune function: mechanism of immune stimulation. In: Counsell, Hornig (eds): *Vitamin C*. App Sci Pub, 1981.
39. Klenner F: Massive doses of vitamin C and viral diseases. *J Southern Med and Surg* 101:209-214, 1949.
40. Dalton W: Massive doses of vitamin C in the treatment of viral diseases. *J Ind State Med Assn* 55:1151-1154, 1962.
41. Cheraskin E: *The Vitamin C Controversy*. Wichita: Biocommunications Press, 1988.
42. Brichthope I, Fitzgerald P: *AIDS Fighters*. New Canaan: Keats Pub, 1988.
43. Jaffe R: Immune reconstitution protocol, pub 111. Health Studies Collegium, 1986.
44. Cathcart RF: Vitamin C in the treatment of acquired immune deficiency syndrome (AIDS). *Med Hypothesis* 14:423-433, 1984.
45. Dalton, op. cit.
46. Cheraskin, op. cit.
47. Brichthope, op. cit.
48. Jaffe, op. cit.
49. Hornig D, et al: *The Safety of High Vitamin C Intakes*. App Sci Pub, 1981.
50. Cheraskin E, Ringsdorf WM, Sisely EL: *The Vitamin C Connection*. Thorsens Press, 1983.
51. Lewin S: *Vitamin C: Its Molecular Biology and Medical Potential*. London: Academic Press, 1976.
52. Cheraskin, op. cit.
53. Cheraskin, Ringsdorf, op. cit.
54. Lewin, op. cit.
55. Murata A: Viricidal activity of vitamin C: vitamin C for prevention and treatment of viral diseases. *Proc Cong of Int'l Assn of Micro Soc* 3:432-442, 1975.
56. Baetgen D: Results of treatment of epidemic hepatitis in children with high doses of ascorbic acid in the years 1957-1959. *Medizinische Monatschrift* 15:30-36, 1961.
57. Cheraskin, op. cit.
58. Baur H, Staub H: Hepatitis therapy with infusions of ascorbic acid. *Schweiz Med Wochenschrift* 84:594-600, 1954.

59. Calleja HP, Brooks RH: Acute hepatitis treated with high doses of vitamin C. *Ohio State Medical Journal* 8:821-823, 1960.
60. Kirchmair H, Kirsch B: Treatment of epidemic hepatitis in childhood with high doses of ascorbic acid. *Medizinische Monatschrift* 11:353-357, 1957.
61. Morishige F, Murata A: Vitamin C For prophylaxis of viral hepatitis B in transfused patients. *J Int'l Acad Prev Med* 5:54-58, 1978.
62. Jaffe, op. cit.
63. BRIGHTHOPE IE: AIDS: Remissions using nutrient therapies and megadose intravenous ascorbate. *Int'l Clin Nut Rev* 13:53-75, 1987.
64. Rawal BD, McKay G, Blackhall MI: Inhibition of *Pseudomonas aeruginosa* by ascorbic acid acting singly and in combination with antimicrobials: in vitro and in vivo studies. *Med J Aust* 1:169, 1974.
65. Kennes B, Dumont I, Brohee D, Hubert C, Neve P: Effect of vitamin C supplements on cell-mediated immunity in old people. *Gerontology* 29:305, 1983.
66. Jaffe, op. cit.
67. Cathcart, op. cit.
68. Cheraskin, op. cit.
69. BRIGHTHOPE, op. cit.
70. Jaffe, op. cit.
71. Stone I: *The Healing Factor: Vitamin C Against Disease*. New York: Grosset and Dunlap, 1972.
72. Baumgartner WA: *Anti-Oxidants: Cancer and the Immune Response*. New York: Raven Press, 1979.
73. Cathcart, op. cit.
74. BRIGHTHOPE, op. cit.
75. Jaffe, op. cit.
76. Stone, op. cit.
77. Baumgartner, op. cit.
78. Cathcart, op. cit.
79. Belfield WO, Zucker WO: *The Healthy Cat Book*. New York: McGraw Hill, 1983.
80. Middleton E, Drzewiecki G: Naturally occurring flavonoids and human basophil histamine release. *Int Arch Allergy App Immunol* 77:155-157, 1985.
81. Foreman JC: Mast cells and the actions of flavonoids. *J Allergy Clin Immunol* 73:769-774, 1984.
82. Amella M, et al: Inhibition of mast cell histamine release by flavonoids and bioflavonoids. *Planta Medica* 51:16-20, 1985.
83. Pearce F, et al: Mucosal mast cells, III. Effect of quercetin and other flavonoids on antigen induced histamine secretion from rat intestinal mast cells. *J Allergy Clin Immunol* 73:819-823, 1984.
84. Middleton Jr E, Drzewiecki G: Flavonoid inhibition of human basophil histamine release stimulated by various agents. *Biochem Pharm* 33:3333, 1984.
85. Pearce, op. cit.
86. Middleton, op. cit.
87. Yoshiomoto T, et al: Flavonoids: potent inhibitors of arachidonate 5-lipoxygenase. *Experientia* 40:184-185, 1974.
88. Slover HT: Tocopherols in foods and fats. *Lipids* 6:291, 1971.
89. Ibid.
90. Block E: The chemistry of garlic and onions. *Sci Am* 252:114, 1985.
91. Cray EJ, Smyrna G, McCarty M: Potential clinical applications for high dose nutritional antioxidants. *Med Hypoth* 13:77-98, 1984.



Russell Jaffe, M.D., Ph.D., is director of Seramune Physicians Lab and a Fellow of the Health Studies Collegium. He is a scientific fellow of the American College of Allergy, Asthma and Immunology (ACAAI). Dr. Jaffe is also program director for the International and American Association for Clinical Nutrition (IAACN).

THIS REPRINT PROVIDED COMPLIMENTS OF:

ELISA/ACT
BIOTECHNOLOGIES LLC
14 Pidgeon Hill Drive, Suite 300
Sterling, VA 20165
Tel: 703.450.2980 • 800.553.5472
Fax: 703.450.2981