*– Patient Education –*

# The Antioxidant Enzymes

by Gary Null, Ph.D.

While vitamins and minerals have captured all the limelight in the nutritional arena, the enzymes in our bodies are the real workhorses of biochemistry. In and of themselves, vitamins and minerals serve a limited biochemical function. Their real power comes from their role as "coenzymes" and "cofactors," in which they attach to an enzyme and activate it. Without an enzyme to link up with, many of the vitamins and minerals to which we assign such beneficial properties would be useless.

The enzymes we need are manufactured by our DNA. They act as catalysts, making possible all the thousands of biochemical reactions that fuel the body. Just as certain vitamins serve as both coenzymes and antioxidants, certain enzymes serve as both catalysts and free radical scavengers. Three enzymes, in particular, have proven enormous antioxidant properties: glutathione peroxidase, superoxide dismutase (SOD) and catalase.

All three of these enzymes are found *inside* the cell, where they deactivate free radicals as they are formed. According to Dr. Derrick Lonsdale, these antioxidant enzymes "are divided into two main classes known as 'preventives' and 'chain breakers'." Glutathione and catalase are preventive enzymes; they reduce hydroperoxides to nonradical components. SOD is a chain-breaking enzyme because it traps peroxy radicals and stops the chain reaction by which many free radicals are born.[1]

All of the antioxidant enzymes (there are two forms each of glutathione and SOD) need a mineral cofactor to function. Hence, their name "metalloenzymes." These minerals include zinc, copper, manganese, selenium and iron. The enzyme-mineral partnership is essential to the body's battle against free radicals and other oxidation products. A deficiency in any of these minerals could mean that the antioxidant defense mechanism is not performing up to speed. As Anthony Diplock explains in the *American Journal of Clinical Nutrition*, this deficiency could set the stage for the initiation of the disease process.[2]

On the other hand, these minerals only join the antioxidant battle when they work in conjunction with an enzyme. What's more, large quantities of such minerals do not necessarily make an enzyme more effective, says Adrianne Bendich in "Antioxidant Micronutrients and Immune Responses." An enzyme has a saturation point, and once that point is reached the remaining mineral supply will not boost its functioning.[3]

In recent years, as the antioxidant enzymes have been studied more closely, researchers have discovered that they can help to prevent a host of chronic and degenerative disorders, from coronary heart disease and arthritis to neurological damage and cancer. What we now realize is that the body's primary defense against free radicals comes not from vitamins and minerals but from our enzyme systems. The body, in its innate intelligence, has strategically placed these enzymes in the cells to provide us with optimal protection. Let's look at how each of the enzymes—and their mineral cofactors—contributes to our body's defenses.

### Glutathione Peroxidase

Glutathione, which comes in two forms, is a major contributor to our defense systems. It has the important job of rounding up certain types of free radicals and deactivating them before they can damage cells. When a hydrogen peroxide free radical is formed, for example, glutathione will reduce it to water in either the mitochondria or the cytosolic compartments of the cell. In short, it puts hydrogen peroxide out of action before it can transform into an even more dangerous free radical, the hydroxyl radical.

Glutathione also scavenges lipid peroxides, the free radicals that are formed when oxygen radicals (such as singlet oxygen and the hydroxyl radical) attack the unsaturated fats of our cell membranes. The resulting process, called lipid peroxidation, damages the phospholipids contained in the cell membrane, says Dr. Lonsdale. This damage sets off a chain reaction of adverse events. The cell membrane loses two essential fatty acids, arachidonic and linoleic acids. Eventually, the permeability of the cell increases, leading to an imbalance of minerals such as sodium, potassium, calcium and magnesium.[4]

Glutathione is the primary constituent of the antioxidant defenses in the lung, heart, liver and blood cells, according to Jeffrey Bland, Ph.D. But the enzyme does not work alone. It needs the mineral selenium to function efficiently. When selenium is deficient, free radical pathology in the body may accelerate. Therefore, the relationship between glutathione and selenium is a vital component of the body's defenses. "Increased glutathione levels, along with optimal selenium and riboflavin status, are essential in optimizing the body's free radical antioxidant protection system," states Dr. Bland.[5]

He also points out that glutathione is known to work synergistically with vitamins C and E. As mentioned glutathione and ascorbic acid rejuvenate the fat-soluble Vitamin E. In the lungs, both Vitamin C and glutathione battle oxidizing environmental pollutants, such as ozone and nitrogen dioxide. More important, glutathione itself needs sulphur amino acids such as cysteine to function properly. Diets low in sulfur-containing amino acids, then, may impair the body's ability to respond to oxygen radicals. To insure the proper functioning of glutathione, says Dr. Bland, "a proper balance should be achieved between sulfur amino acids in the diet, tocopherol and ascorbate."[6]

In recent years, a number of studies have looked at glutathione's ability to protect various parts of the body from damage. Here's a quick summary of the study results:

*Liver.* In a study of elderly men, glutathione was tested as a protective agent against liver disease. While the results were not "particularly brilliant," said the researchers, all patients showed improvement in their clinical condition and laboratory findings.[7] Two other studies examined glutathione's effect on alcohol-induced liver damage (the level of glutathione is reduced by heavy alcohol consumption). In the first study, large doses of glutathione over a two-week period improved the enzyme

pattern in the liver function of 33 chronic alcoholics.[8] In the second, patients who received 300 mg of glutathione for 30 days showed a much greater improvement in their liver function indices than did patients who received 10 mg of vitamin K instead.[9]

*Lung.* Glutathione may play a role in protecting the lung from oxidant damage as well. The toxic effects of such damage are accelerated when the level of glutathione is reduced, leading to increased damage of cells and membranes, pulmonary edema and mortality. In several studies, a precursor to glutathione (such as N-acetyl cysteine) offered significant protection against certain toxins in the lung. In one case, the lethal effects of 100% oxygen were reduced in rats by 65%.[10]

*Brain.* In a study of rats, both oxidized and reduced glutathione were protective against the damage caused by neurotoxicity. The results suggest that glutathione acts on certain receptors in the brain. The overstimulation of these receptors has been implicated in disorders such as stroke, trauma and various neurodegenerative conditions.[11] Another study found that glutathione and its related amino acids—cysteine and glycine— worked as an anti-convulsant by significantly reducing the duration of seizures in rats.[12]

*Heart.* Again, researchers used rats to investigate glutathione's ability to protect the heart from delayed cardiomyopathy. In the study, large doses of the enzyme partially prevented certain effects of cardiotoxicity. According to the researchers, the data indirectly supports the theory that oxidative damage contributes to this toxicity and indicates that glutathione may be an important factor in heart protection.[13]

*Stomach.* In this study, the administration of oxidized glutathione improved the survival rate and decreased the symptoms of gastrointestinal distress of rats that were irradiated with X rays to the abdomen.[14]

**Superoxide Dismutase and Catalase**

Much like glutathione, the superoxide dismutase (SOD) enzyme system launches a direct attack against reactive oxygen molecules in the body. Its target is the superoxide anion free radical, which helps form the hydroxyl radical if it is not deactivated. SOD intervenes in the free radical chain reaction by demoting the superoxide radical to hydrogen peroxide. At this point, the enzyme catalase takes over the battle and reduces hydrogen peroxide to oxygen and water. This process totally defeats the superoxide radical.[15]

In essence, then, SOD is on the front lines of our free radical defenses. As Dr. Bland points out, the most toxic free radical is not superoxide anion, but the hydroxyl radical that it may help to create. "If superoxide is properly quenched by SOD, it reduces the potential for hydroxyl radical generation," he states.[16] The hydroxyl radical is especially reactive because, unlike other free radicals, it can steal

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an electron from virtually *any* of the organic molecules in its immediate area. This strong reactivity allows the hydroxyl radical to react with DNA, lipids, proteins and the vital components of the cell.

Again, both SOD and catalase are dependent on mineral cofactors. SOD has special mineral requirements; it may need either manganese or a copper/zinc combination depending on its form. When SOD works in the mitochondria of the cell, it requires manganese; when SOD patrols the cytoplasm, on the other hand, it requires both copper and zinc. Catalase, which is found in the peroxisomes, requires iron for its functioning.[17]

Since the discovery of SOD in the early 1970s, much work has been done to study its protective effects in the body. One particular area of research interest is "reperfusion injury," in which the oxygen supply to an organ is cut off and then allowed to reflow. The reintroduction of oxygen causes a burst of free radical activity. It is this activity, not the oxygen deprivation, that can lead to disorders such as heart attacks and arrhythmias, states Dr. Bland. SOD and catalase seem to counteract this oxidant overload and protect the tissues from such damage.[18]

In addition to the heart, many other organs may benefit from the protective effects of SOD. What follows is a summary of the research that continues to come in on SOD and catalase:

*Heart.* Many recent animal studies show that SOD provides protection to the heart or the cardiovascular system when free radicals are released during reperfusion injury.[19-24] Some nuances in such studies are worth noting, however. Since SOD has a short half-life in the body, one group of researchers bypassed this problem by coupling the enzyme with a longer-lasting substance, polyethylene glycol. This combination offered sustained protection against heart damage.[25] Another study found that SOD was ineffective on its own. But when the enzyme was administered along with a prostacyclin, the two agents combined provided significant myocardial protection.[26]

Finally, one analysis of SOD's use in ischemic injuries concluded that the enzyme's effectiveness can vary considerably depending on the type of SOD in question and the source of the enzyme. As the researchers state, "All superoxide dismutases are equal but some are more equal than others." Bovine copper-SOD and Escherichia Coli manganese-SOD functioned especially well; but yeast copper-SOD and the homologous rat copper-SOD were completely ineffective.[27]

Other studies have focused on the combined use of SOD and catalase in guarding the heart from reperfusion-induced damage. These experiments, too, found that the enzymes could inhibit the free radical damage that accompanies reperfusion or ischemic injury.[28-30] However, one study concluded that SOD and catalase "may serve only to delay rather than prevent myocardial infarction."[31] Another study of diabetic animals found that SOD and catalase seemed to benefit the heart primarily by increasing the production of prostacyclin (the non-diabetic hearts did not benefit from the treatment).[32]

*Brain.* The brain and nervous system also can suffer from oxygen deprivation. But in a number of animal studies, SOD was protective against free radical damage to the nervous system.[33-35] Several experiments found that SOD improved the functioning of nerves that were previously damaged.[36,37] As with the heart, one study shows that the combination of SOD and catalase reduced ischemic brain injury.[38]

*Lung.* In other animal studies, SOD guarded against lung injury from oxygen radicals. In one case, the researchers concluded that "SOD was effective in preventing warm ischemic damage even in the deflated lung."[39] In another, the role of oxygen radicals in influenza infection was explored. The study found that a modified form of SOD "led not only to an increase in the survival rate but also to a delay in deaths."[40] Likewise, a modified form of SOD inhibited evolving fibrosis in the lungs.[41]

*Miscellaneous.* In addition to the heart, brain and lungs, a growing list of body organs and systems may benefit from SOD's antioxidant properties. These include the kidney, liver, eyes, ears, digestive tract and joints, all of which have been aided by the enzyme in recent studies.[42-47] Based on these results, researchers are speculating that the disease process in many organs may share a common pathogenesis — the runaway assault of free radicals on the body systems.

**Selenium: The Cofactor Mineral**

An analysis of antioxidant enzymes would be incomplete without a closer look at their mineral cofactors, including zinc, selenium, iron, copper and manganese. While all of these minerals are important to body functioning, selenium could be considered the David of the micronutrient world — a mineral capable of going to battle against such Goliaths as cancer and heart disease.

As consumers, we do not put much thought into the status of our selenium intake. After all, it's easy to take some of the trace minerals contained in our foods for granted. But the importance of selenium in our diet has become increasingly clear since the 1960s, when research on selenium began to unearth more data about its role in maintaining optimal health. The small-but-mighty selenium seems to gain such power through its partnership with glutathione peroxidase in combatting free radical activity.

Selenium deficiency, for example, has been strongly correlated with two diseases that afflict children—cystic fibrosis and Keshan disease. Selenium deficiency was first suggested as a factor in cystic fibrosis in 1979. According to Dr. Bland, researcher J.D. Wallach believed this disease was related to a deficiency of selenium or vitamin E in the mother during pregnancy or an acquired deficiency during infancy. At the time, Wallach's theory was roundly ignored by the medical community due to a lack of evidence. But researchers later found that children with cystic fibrosis do indeed have low levels of selenium, says Bland, independent of a vitamin E deficiency.[48]

With Keshan disease, on the other hand, it is the heart that suffers from a selenium deficiency. As far back as the 1940s, this relationship was noted in a large study of children and young women in an area of China that has low levels of selenium in the soil. In 1980, reports Bland, a study of selenium supplementation in water indicated that the mineral could inhibit Keshan disease. Other research into selenium's role in preventing this disease have focused on its link to glutathione peroxidase.[49]

In addition, selenium is known to work synergistically with vitamin E. According to Dr. Lonsdale, this relationship allows selenium to deactivate free radicals in the fatty acids. Selenium and vitamin E are so complementary, in fact, that the level of each nutrient in our body will affect our need for the other. "The amount of selenium required in the diet is inversely related to the dietary level of vitamin E and the two nutrients have mutually sparing effects upon the biological needs for both," states Lonsdale.[50]

Much of the research on selenium concerns its protective effects against cancer. The mineral may achieve this protection through a variety of functions in the body, according to Richard A. Passwater, Ph.D. These include its ability to stimulate the immune response, combat free radicals, detoxify environmental carcinogens, protect the liver and maintain cellular respiration.

Passwater, a pioneer in selenium research, points to hundreds of studies as evidence of the link between selenium and cancer risk. As he states in *Selenium Update*: "The evidence for a prophylactic role for selenium is without a doubt stronger than for any other factor, including the nutrient beta-carotene, dietary fiber, crucifers or any other food factor recommended as potential cancer-preventive agents by the American Cancer Society, National Cancer Institute and other official bodies."[51]

A handful of studies conducted between 1983 and 1985, adds Passwater, established a solid connection between the incidence of cancer and selenium levels in the body. In one such study, for example, people were ranked according to their blood selenium levels. Those in the lowest fifth of these levels had twice the rate of cancer as people in the top fifth. Similarly, another study found that people in the bottom tenth of blood selenium levels had six times the rate of cancer as those with the highest selenium levels. And in a study that considered both selenium and vitamin E levels, the incidence of cancer was 11 times higher for people in the lowest third of vitamin E levels who also were low in selenium.[52]

Animal studies have since explored the anticancer effects of selenium, with positive results. Researcher L.Q. Wang, for example, conducted a study of liver cancer in which rats that received selenium-supplemented water showed no carcinogenetic changes. Among the group of rats that did not receive selenium, 61% developed liver carcinoma. Wang has also found that selenium's preventive properties are greater at 3 pmm than at 6 ppm. In fact, some evidence of toxicity was present in the group that received 6 ppm of selenium in water.[53-55]

In a comprehensive analysis of selenium's chemopreventive properties, G. Hocman reached the following conclusions about the link between selenium and cancer: A daily intake of selenium prevents the attack of certain carcinogens; people with low blood selenium levels are at greater risk of cancer than those with high levels; selenium's ability to prevent cancer can be attributed, in large part, to its antioxidant properties; and the amount of selenium needed to optimize cancer protection is 150 mcg to 300 mcg per day.[56]

While selenium's role in cancer prevention has been well established, its direct effect on our immune system is not entirely understood. A number of studies have shown, however, that selenium can help to protect the body against certain types of viruses and bacteria. One three-year study, for example, explored selenium's ability to prevent infectious hepatitis. More than 20,000 people in the Jiangsu Province of China received daily selenium supplements; the incidence of hepatitis in these people was significantly lower than in control subjects.[57]

In animal experiments, selenium has proved to be protective against such diseases as influenza and lupus.[58,59] In "Micronutrients and Immune Functions," Rangit Kumar Chandra also reports that selenium can increase the vaccine-induced immunity to malaria and enhance protection against parasitemia. In addition, a selenium deficiency may lead to a depressed immune response and decreased microbicidal activity.[60]

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## References


1. Derrick Lonsdale, "Free Oxygen Radicals and Disease," *1986/A Year In Nutritional Medicine Monograph*, Keats Publishing Inc., New Canaan, Conn., 1986, p. 13.
2. Anthony T. Diplock, "Antioxidant Nutrients and Disease Prevention: An Overview," *American Journal of Clinical Nutrition*; 1991; 53:190S.
3. Adrianne Bendich, "Antioxidant Micronutrients and Immune Responses," *Micronutrients and Immune Functions*, A. Bendich and R.K. Chandra (eds.) New York Academy of Sciences, 1990, p. 172.
4. Free Oxygen Radicals and Disease, p. 11.
5. Jeffrey Bland, Ph.D., "The Nutritional Effects of Free Radical Pathology," *1986/A Year in Nutritional Medicine*; Keats Publishing Inc., New Canaan, Conn.; 1986; p. 12.
6. Ibid, p. 15-16.
7. E. Del Nero et al., "Therapeutic Use of Glutathione," *Clin. Ter.*; February 15, 1990; 132(3); p. 167-71.
8. E.A. Nardi et al., "High-Dose Reduced Glutathione in the Therapy of Alcoholic Hepatopathy," *Clin. Ter.*; January 15 1991; 136(1); p.
9. G. Bresci et al., "The Use of Reduced Glutathione in Alcoholic Hepatopathy," *Minera. Med.*; November 1991; 82(11); p. 753-5.
10. C.E. Patterson and R.A. Rhoades, "Protective Role of Sulfhydryl Reagents in Oxidant Lung Injury," *Exp. Lung Res.*; 1988; 14 Suppl.; p. 1005-19.
11. D.I. Levy et al., "Glutathione Prevents N-Methyl-D-Asparate Receptor-Mediated Neurotoxicity," *Neuroreport*; June 1991; 2(6); p. 345-7.
12. A. Pinelli et al., "Anti-Convulsant Effects by Reduced Glutathione and Related Amino Acids in Rats Treated with Isoniazid," *Toxicology*; January 1988; 48(1); p. 103-7.
13. F. Villani et al., "Prevention of Doxorubicin-Induced Cardiomyopathy by Reduced Glutathione," *Cancer Chemother. Pharmacol.*; 1991; 28(5); p. 365-9.
14. S.P. Grozdov, "Effect of Glutathione on the Course of Radiation Sickness with a Marked Gastrointestinal Syndrome and the Effectiveness of Parenteral Feeding in an Experiment," *Radiobiologiia*; September-October 1987; 27(5); p. 657062.
15. Bendich, p. 171-172.
16. Bland, p. 22.
17. Bendich, p. 170-71.
18. Bland, p. 5-6.
19. T. Yamakawa et al., "Effects of Polyoxyethylene-Modified Superoxide Dismutase on Reperfusion-Induced Arrhythmias in Isolated and Guinea-Pig Hearts," *J. Mol. Cell. Cardiol.*; May 1989; 21(5); p. 441-52.
20. K. Bando et al., "Extended Cardiopulmonary Preservation for Heart-Lung Transplantation: A Comparative Study of Superoxide Dismutase," *J. Heart Transplant*; January-February 1989; 8(1); p. 59-66.
21. N. Aoki et al., "Cardioprotective Actions of Human Superoxide Dismutase in Two Reperfusion Models of Mayocardial Ischaemia in the Rat," *Br. J. Pharmacol.*; November 1988; 95(3); p. 735-40.
22. J.T. Flaherty, "Myocardial Injury Mediated by Oxygen Free Radicals," *Am. J. Med.*; September 30, 1991; 91(3C); p. 79S-85S.
23. M.C. Oz et al., "Hydroxyethyl Strach Macromolecule and Superoxide Dismutase Effects on Myocardial Reperfusion Injury," *Am. J. Surg.*; July 1991; 162(1); p. 59-62.
24. J.L. Mehta et al., "Superoxide Dismutase Decreases Reperfusion Arrhythmias and Preserves Myocardial Function During Thrombolysis with Tissue Plasminogen Activator," *J. Cardiovas. Pharmacol.*; July 1990; 16(1); p. 122-20.
25. B.A. Freeman, "Superoxide Dismutase conjugated to Polyethylene Glycol Provides Sustained Protection Against Myocardial Ischemia/ Reperfusion Injury in Canine Heart," *Circ. Res.*; November 1988; 63(5); p. 944059.
26. X.L. Ma et al., "Low Doses of Superoxide Dismutase and a Stable Prostacyclin Analogue Protect in Myocardial Ischemia and Reperfusion," *J. Am. Coll. Cardiol.*; January 1992; 19(1); p. 197 204.
27. G. Jadot and A.M. Michelson, "Comparative Anti-Inflammatory Activity of Different Superoxide Dismutases and Liposomal SOD in Ischemia," *Free Radic. Res. Commun.*; 1987; 3(6); p. 389-94.
28. D. Hou et al., "Prevention of Myocardial Reperfusion Injury with Free Radical Scavengers: An Experimental Study," *Chin. Med. J.* (Engl.); October 1989; 102(10); p. 768-73.
29. Y. Nishikawa et al., "The Effect of Superoxide Dismutase and Catalase on Myocardial Reperfusion Injury in the Isolated Rat Heart," *Jpn. J. Surg.*; July 1991; 21(4); p. 423-32.
30. D.J. Chambers et al., "Free Radical and Cardioplegia: Free Radical Scavengers Improve Postischemic Function of Rat Myocardium," *Eur. J. Cardiothorac Surg.*; 1987; 1(1); p. 37-35.
31. T. Miura et al., "Effect of Superoxide Dismutase plus Catalase on Myocardial Infarct Size in Rabbits," *Can. J. Cardiol.*; November December 1988; 4(8); p. 407-11.
32. G.M. Pieper, "Superoxide Dismutase Plus Catalase Improves Post Ischemic Recovery in the Diabetic Heart," *Cardiovasc. Res.*; December 1988; 22(12); p. 916-26.
33. O. Uyama et al., "Protective Effects of Human Recombinant Superoxide Dismutase on Transient Ischemic Injury of CAl Neurons in Gerbils," *Stroke*; January 1992; 23(1); p. 75-81.
34. S. Imaizumi et al., "Liposome-Entrapped Superoxide Dismutase Ameliorates Infarct Volume in Focal Cerebral Ischemia," *Acta. Neurochir. Suppl.* (Wien); 1990; 51; p. 236-8.
35. N. Matsumiya et al., "Conjugated Superoxide Dismutase Reduces Extent of Caudate Injury After Transient Focal Ischemia in Cats," *Stroke*; September 1991; 22(9); p. 1193-200.
36. A.M. Michelson et al., "Treatment of Brain Trauma with Liposomal Superoxide Dismutase," *Free Radic. Res. Commun.*; 1988; 4(4); p. 209-24.
37. J.M. Roda et al., "Prevention of Cerebral Ischaemic Reperfusion Injury by Intra-Arterial Administration of Superoxide Dismutase in the Rat," *Neurol. Res.*; September 1991, 13 (3); p. 160-3.
38. T.H. Liu, "Polyethylene Glycol-Conjugated Superoxide Dismutase and Catalase Reduce Ischemic Brain Injury," *Am. J. Physiol.*; February 1989; 256(2 Pt. 2); p. H589-93.
39. C. Yamashita et al., "Experimental Studies on the Effects of Superoxide Dismutase on Warm Ischemic-Reperfusion Injury of the Lung," *Nippon Kyobu. Jeka. Gakkai. Zasshi.*; November 1991; 39(11); p. 2002-5.
40. B.P. Sharonov et al., "The Effective Use of Superoxide Dismutase from Human Erythrocytes in the Late Stages of Experimental Influenza Infection," *Vopr. Virusol.*; November-December 1991; 36(6); p. 477-80.
41. A.V. Maksimenko et al., "Anti-Fibrotic Effects of Aldehyde Dextran Modified Superoxide Dismutase in Experimental Silicosis," *Biull. Eksp. Biol. Med.*; September 1991; 112(9); p. 265-7.
42. J. Schneider et al., "Equieffective Protection by Human and Bovine SOD Against Renal Reperfusion Damage in Rats," *Basic Life Sci.*; 1988; Vol. 49; p. 891-4.
43. D. Nakae et al., "Liposome-Encapsulated Superoxide Dismutase Prevents Liver Necrosis Induced by Acetaminophen," *Am. J. Pathol.*; April 1990; 130(4); p. 787-95.
44. M.E. Szabo et al., "Free Radical-Mediated Effects in Reperfusion Injury: A histologic Study with Superoxide Dismutase and EGB 761 in Rat Retina," *Ophthalmic Res.*; 1991; 23(4); p. 225 34.
45. M.D. Seidman, et al., "The protective effects of allopurinol and superoxide dismutase-polyethylene glycol on ischemic and reperfusion-induced cochlear damage," *Otolayngol. Head. Neck. Surg.*; September 1991; 105(3); p. 457-63.
46. M. Hirota et al., "Inhibition of Stress-Induced Gastric Mucosal Injury by a Long-Acting Superoxide Dismutase that Circulates Bound to Albumin," *Arch. Biochem. Biophys.*; August 1. 1990: 280(2); p. 269-73.
47. P. Richard et al., "Open Clinical Study of Liposomal Superoxide Dismutase in Severe Rheumatoid Arthritis: Study of a Series of Seven Cases," *Therapie*; July-August 1989; 44(4); p. 291-5.
49. Ibid, p. 11-12.
50. Lonsdale, p. 14.
51. Richard A. Passwater, Ph.D., *Selenium Update: How it protects Against Cancer. Heart Disease. Arthritis and Aging*, Keats Publishing Inc., New Canaan, Conn.; 1987; p. 5.
52. Ibid, p. 6.
53. L.Q. Wang, "The Study of Aflatoxin Bl-Induced Hepatocarcinogenesis of Rats and Mechanism of Selenium's Inhibitory Effect on Carcinogenesis," *Chung. Hua. Yu. Fang. I. Rsueh. Tsa. Chih.*; September 1989; 23 (5); p. 289092.
54. D.N. Lei and L.Q. Wang et al., "Effect of Selenium on Aflatoxin Hepatocarcinogenesis in the Rat," *Biomed. Environ. Sci.*; March 1990; 3(1); p. 65-80.
55. L.Q. Wang, "The Effect of Selenium on Hepatocarcinogenesis of Rats Induced by Aflatoxin Bl," *Chung. Hua. Ping. Li. Hsueh. Tsa. Chih.*; Mareh 1990; 19(1); p. 46-9.
56. G. Hocman, "Chemoprevention of Cancer: Selenium," *Int. J. Biochem.*; 1988; 20(2); p. 123-32.
57. S.Y. Yu et al., "Chemoprevention Trial of Human Hepatitis with Selenium Supplementation in China," *Biol. Trace Elem. Res.*; April May 1989; 20(12); p. 15-22.
58. I.I. Ablullaev et al., "Effect of Sodium Selenite and its Combination with Remantadine on the Synthesis of Virus-Specific Polypeptides in a Cell Culture Infected with Influenza A Virus," *Vopr. Virusol*; November-December 1988; 33(6); p. 676-80.
59. J.R. Odell et al., "Improved Survival in Murine Lupus as the Result of Selenium Supplementation," *Clin. Exp. Immunol.*; August 1988; 73(2); p. 322-7.
60. Rangit Kumar Chandra, "Micronutrients in Immune Functions: An Overview," *Annals New York Academy of Sciences.*


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