

# Vitamin C and the Treatment of Cancer: Part I

## Abstracts and Commentary from the Scientific Literature

by Gary Null, PhD; Howard Robins, DPM; Mark Tanenbaum, DPM; and Patrick Jennings, Editor

### Why Review the Scientific Literature?

Proper basic nutrition is an essential foundation for health, but there's a growing awareness that it's not enough. One has only to consider the high disease rates in our society – infectious diseases are now the third largest killer in the US as well as the first in the world, and our rates of cancer, arthritis, and mental illness are not abating – to realize that we have to go beyond basic nutrition in combating disease. It's time to look at supplemental nutrients in a serious light, in order to better understand their role in helping our natural immune defenses prevent disease, and in altering the course of disease as well.

People talk about orthodox medicine and alternative medicine as if there's a great divide between the two, but there's really no need for such a dichotomy. The bottom line in healing and in maintaining health is really the question, *What works?* and we should feel free to ask it in evaluating the offerings of both realms, and to combine the best of both. After all, the evidence that something works – not the label you give it – is the important factor in evaluating whether a given treatment, or mode of prevention, is of value.

Following is a review of the scientific literature as it pertains to the impact of vitamin C on cancer. The questions, *What works?* and *How might it be applied?* were the motivational ones behind this review. As this one does, each review will include only well-designed studies from peer-reviewed journals. Original journal citations are given, along with capsule descriptions of the original scientific abstracts.

In other words, what follows is not anecdotal evidence; it is scientific evidence. We can now move beyond the stage of allowing quackbusters, apologists for special interest groups, and other adherents of the flat-earth school of intellectual inquiry to maintain that there's no evidence of the disease-fighting value of nutrients. Because, quite simply, there is, and here it is.

This review article notes that approximately 90 studies have been done on the role of vitamin C in cancer prevention, with most finding statistically significant effects. Protective effects have been shown for cancers of the pancreas, oral cavity, stomach, esophagus, cervix, rectum, breast, and lung.

– G. Block, et al., Epidemiologic Evidence Regarding Vitamin C and Cancer, *American Journal of Clinical Nutrition*, 54 (6 Suppl), December 1991, p. 1310S-1314S.

Daily supplementation of 1g of vitamin C decreased the amount of chromosome damage induced in lymphocytes by an exposure to bleomycin during the last 5 h of cell culture. The authors suggest a similar assay for genetic instability might be helpful in detecting heterozygotes for chromosome-breakage syndromes and recommend considering dietary and lifestyle factors when interpreting results from this bleomycin assay and related assays for genetic instability.

– H. Pohl and J.A. Reidy, Vitamin C Intake Influences the Bleomycin-induced Chromosome Damage Assay: Implications for Detection of Cancer Susceptibility and Chromosome Breakage Syndromes, *Mutat Research*, 224(2), October 1989, p. 247-252.

A ternary antioxidant vitamin mix consisting of ascorbic acid, alpha-tocopherol and lecithin as well as a rosemary extract with carnosic acid and carnosol as the two major active ingredients were shown to exhibit strong antimutagenic effects in Ames tester strain TA102. Ascorbic acid was held responsible for this inhibitory property in the vitamin mix, while carnosic acid was identified as the antimutagenic agent in the rosemary extract. The authors conclude that these antioxidants might exhibit anticarcinogenic properties.

– M. Minnuni, et al., Natural Antioxidants as Inhibitors of Oxygen Species Induced Mutagenicity, *Mutat Research*, 269(2), October 1992, p. 193-200.

A mixture of ascorbic acid and cupric sulfate significantly inhibited human mammary tumor growth in mice when administered orally, while the administration of either alone did not. The activity of D-isoascorbic acid was similar to that of ascorbic acid. The authors suggest ascorbic acid's antitumor activity was due to its chemical properties rather than the metabolism of ascorbic acid as a vitamin.

– C.S. Tsao, Inhibiting Effect of Ascorbic Acid on the Growth of Human Mammary Tumor Xenografts, *American Journal of Clinical Nutrition*, 54 (6 Suppl), December 1991, p. 1274S-1280S.

In this study, vitamin C was shown to decrease kidney tumor incidence by approximately 50% in Syrian hamsters, lower the concentration of diethylstilbesterol-4',4"-quinone, the genotoxic metabolite of diethylstilbesterol, in vitro and in hamsters treated with stilbene, and decreases the levels in hamsters of DES-DNA adducts formed by the quinone metabolite. Noting that estrogens may spawn tumors by their metabolic oxidation to corresponding quinone metabolites, the authors argue that vitamin C may inhibit the formation of tumors by decreasing concentrations of quinone metabolites and their DNA adducts.

– J.G. Liehr, Vitamin C Reduces the Incidence and Severity of Renal Tumors Induced by Estradiol or Diethylstilbesterol, *American Journal of Clinical Nutrition*, 54 (6 Suppl), December 1991, p. 1256S-1260S.

This paper reports on the results of two large-scale studies of L-ascorbic acid in the food on tumor-free survival in mice. The first found that increasing ascorbic acid in the diet significantly delayed the development of spontaneous mammary tumors, with the median age at first tumor at 124.9 weeks in the highest-dose ascorbate group and 82.5 wk in ad libitum controls. The proportion of mice with tumors was also reduced. The second discovered a significant effect of ascorbate in delaying the onset and reducing the incidence of malignant lesions. Approximately five times the number of mice developed lesions in the zero-ascorbate as in the high-ascorbate group after 20 weeks of administration.

– L. Pauling, Effect of Ascorbic Acid on Incidence of Spontaneous Mammary Tumors and UV-Light-Induced Skin Tumors in Mice, *American Journal of Clinical Nutrition*, 54 (6 Suppl), December 1991, p. 1252S-1255S.

Ascorbate stabilizes the normal state of the avian tendon cell by reducing Rous sarcoma virus production and promoting the synthesis of differentiated proteins which allows the virus to coexist within the cell rather than completely take it over.

– R.I. Schwarz, Ascorbate Stabilizes the Differentiated State and Reduces the Ability of Rous Sarcoma Virus to Replicate and to Uniformly Transform Cell Cultures, *American Journal of Clinical Nutrition*, 54 (6 Suppl), December 1991, p. 1247S-1251S.

Noting theories that ascorbic acid might lower the risk of gastric cancer by preventing their formation within gastric juice, the authors measured both gastric juice ascorbic and total vitamin C in subjects and found that ascorbic acid is secreted into the gastric lumen so that gastric juices are frequently higher than concentrations in plasma. Gastric pathology affects this secretion, leading to values in gastric juice that are lower than plasma levels.

– C.J. Schorah, et al., Gastric Juice Ascorbic Acid: Effects of Disease and Implications for Gastric Carcinogenesis, *American Journal of Clinical Nutrition*, 53 (1 Suppl), January 1991, p. 287S-293S.

This case-control study evaluated the association between specific substances of the diet and invasive cervical cancer in four Latin American countries. Vitamin C was shown to significantly decrease the risk of invasive cervical cancer, as was the case with beta-carotene and other carotenoids. These results are consistent with those from other studies suggesting a protective role for vitamin C in the development of invasive cervical cancer.

– R. Herrero, et al., A Case-Control Study of Nutrient Status and Invasive Cervical Cancer: I. Dietary Indicators, *American Journal of Epidemiology*, 134 (11), December 1, 1991, p. 1335-13465.

2,974 men participating in the third examination of the prospective Basel Study in 1971-1973 were measured for plasma antioxidant vitamins A, C, and E, and carotene. Low mean plasma levels of carotene adjusted for cholesterol and of vitamin C was associated with overall mortality from cancer. Lower mean vitamin C levels were found to increase the risks of stomach cancer and gastrointestinal cancer in older subjects. In light of these results for vitamin C, in combination with those of the other vitamins studied, the authors conclude that low levels of antioxidants are associated with an increased risk of mortality from numerous cancers.

– H.B. Stahelin, et al., Plasma Antioxidant Vitamins and Subsequent Cancer Mortality in the 12-year Follow-up of the Prospective Basel Study, *American Journal of Epidemiology*, 133(8), April 15, 1991, p. 766-775.

Inverse relationships were found between intake of carotenoids, vitamin E, and vitamin C and the incidence of lung cancer among nonsmokers in a 20 year follow-up study of 4,538 initially cancer-free Finnish men. The authors suggest that increased intake of these nutrients may protect against the development of lung cancer among nonsmokers.

– P. Knekt, et al., Dietary Antioxidants and the Risk of Lung Cancer, *American Journal of Epidemiology*, 134(5), September 1, 1991, p. 471-479.

NAC administered in doses from 0.1 to 10 mmol/L reduced the number of mutagenic-induced breaks per cell in a range from 23% to 73%. In a dose range from 0.01 to 1 mmol/L, ascorbic acid reduced chromosomal breakage by 21% to 58%. These results illustrate NAC and ascorbic acid's protective effects mediated in vitro against mutagen-induced chromosomal damage. The difference in occurrence of head and neck cancer between population with varying diets may be explained by related in vivo phenomenon.

– Z. Trizna, et al., Effects of N-acetyl-L-cysteine and Ascorbic Acid on Mutagen-induced Chromosomal Sensitivity in Patients with Head and Neck Cancers, *American Journal of Surgery* 162(4), October 1991, p. 294-298.

Results of this placebo-controlled study found that powdered chow supplemented with 7%/wt ascorbic acid significantly reduced 1,2-dimethylhydrazine-induced tumor formation in rats.

– T.A. Colacchio and V.A. Memoli, Chemoprevention of Colorectal Neoplasms: Ascorbic Acid and Beta-Carotene, *Arch Surg* (1986 Dec) 121(12), Dec. 1986, p. 1421-1444.

One hundred fifty-eight samples from 139 lung-cancer patients were examined with respect to levels of plasma and buffy-coat vitamin C. Diet dependent hypovitaminosis C tended to be present in the majority of samples and proved capable of being increased by oral supplementation. Assays demonstrated that tumors had a greater vitamin C content than normal lung tissue.

– H.M. Anthony and C.J. Schorah, Severe Hypovitaminosis C in Lung-Cancer Patients: The Utilization of Vitamin C in Surgical Repair and Lymphocyte-Related Host Resistance, *British Journal of Cancer*, 46(3), Sept. 1982, p. 354-367.

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Beta carotene and ascorbic acid were shown to persistently protect against colorectal cancer in this case-controlled study of 828 patients with colon cancer and 498 patients with rectal cancer in Northern Italy.

- M. Ferraroni, et al., Selected Micronutrient Intake and the Risk of Colorectal Cancer, *British Journal of Cancer*, 70(6), December 1994, p. 1150-1155.

Vitamin C supplement use was shown to be inversely related to bladder and colon cancer in women in an 8 year follow-up study beginning in 1981 of 11,580 residents of a retirement community initially free from cancer.

- A. Shibata, et al., Intake of Vegetables, Fruits, Beta-Carotene, Vitamin C and Vitamin Supplements and Cancer Incidence Among the Elderly: A Prospective Study, *British Journal of Cancer* (1992 Oct) 66(4), Oct. 1992, p. 673-679.

This double-blind, placebo-controlled study examined the relationship between ascorbic acid and large bowel adenomas. 3 g/day of ascorbic acid reduced polyp area in the treatment group at nine months of follow-up and resulted in a trend toward the decrease in both area and number of rectal polyps midway through the trial.

- H.J. Bussey, et al., A Randomized Trial of Ascorbic Acid in Polyposis Coli, *Cancer*, 50(7), October 1, 1982, p. 1434-1439.

Human neoplastic cell lines MCF-7 (breast carcinoma), KB (oral epidermal carcinoma), and AN3-CA (endometrial adenocarcinoma) were studied relative to the effects of in vivo administration either in combination or alone of sodium ascorbate (vitamin C) and 2-methyl-1,4-naphthoquinone (vitamin K3). When administered separately, vitamin C or K3 showed a growth inhibiting effect but only at high concentrations (5.10(3)  $\mu\text{mol/l}$  and 10(5)  $\text{nmol/l}$ , respectively). When administered in combination both vitamin showed a synergistic inhibition of cell growth at 10 to 50 times lower concentrations. The addition of catalase to the culture medium containing vitamins C and K3 totally suppressed this tumor cell growth inhibitory effect. The authors argue this suggests an excessive production of hydrogen peroxide as being implied in mechanisms responsible for the tumor cell growth inhibitory effects.

- V. Noto, et al., Effects of Sodium Ascorbate (Vitamin C) and 2-methyl-1,4-Naphthoquinone (Vitamin K3) Treatment on Human Tumor Cell Growth in Vitro. I. Synergism of Combined Vitamin C and K3 Action, *Cancer*, 63(5), March 2, 1989, p. 901-906.

In this hospital based, case-control study of lung cancer, a strong protective effect for squamous and small cell carcinoma was associated with dietary vitamin C intake based on data obtained from food frequency questionnaires.

- E.T. Fontham, et al., Dietary Vitamins A and C and Lung Cancer Risk in Louisiana, *Cancer*, 62(10), November 15, 1988, p. 2267-2273.

The effects of 6-hydroxydopamine (6-OHDA) and H<sub>2</sub>O<sub>2</sub> on metabolic parameters critical for cell survival were examined in cells with low and high ferritin content in the presence and absence of ascorbate in this study. Human neuroblastoma SK-N-SH cells were pretreated with 100  $\mu\text{M}$  FeSO<sub>4</sub> and 10  $\mu\text{M}$  desferrioxamine, respectively, for 24 hours yielding cells with different ferritin contents. The most pronounced effects were in ferritin-rich cells and in the presence of ascorbic acid. Using isolated CCC PM2 DNA, 6-OHDA and ascorbic acid caused strand breaks that were prevented in the presence of mannitol or desferriothiocine. H<sub>2</sub>O<sub>2</sub>-mediated strand breaks were observed only in the presence of ascorbic acid. The authors suggest their data along with the results of previous studies, suggests that high dosages of ascorbic acid continuously applied may be an effective new approach in neuroblastoma therapy.

- G. Bruchelt, et al., Ascorbic Acid Enhances the Effects of 6-Hydroxydopamine and H<sub>2</sub>O<sub>2</sub> on Iron-Dependent DNA Strand Breaks and Related Processes in the Neuroblastoma Cell Line SK-N-SH, *Cancer Research*, 51(22), November 15, 1991, p. 6066-6072.

In this study, mice were fed one of three diets both with and without sodium ascorbate (30 mg/ml) in the drinking water starting 2 weeks before inoculation of 10(6) melanoma cells. Mice fed the purified diet experienced inhibited tumor growth in some cases, while it had no effect on others in the commercial diet group, ascorbate stimulated tumor growth. In mice fed the deficient diet, ascorbate inhibited tumor growth and survival was increased by 82%. Unlike mice fed the commercial diet, drug treatment reduced growth significantly in mice fed the purified diet and moderately increased their survival. Drug activity was enhanced and the survival of tumor bearing mice increased by 73% as well in the deficient diet group. Drug and ascorbate therapy combined resulted in mice fed the purified diet experiencing smaller tumors and living 55% longer than controls. Deficient diet fed mice who were administered the same combination experienced slowed tumor growth and their survival time was increased 123%.

- H.F. Pierson and G.G. Meadows, Sodium Ascorbate Enhancement of Carbidopa-Levodopa Methyl Ester Antitumor Activity Against Pigmented B16 Melanoma," *Cancer Res*, 43(5), 1983, p. 2047-2051.

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This study involving patients with acute nonlymphocytic leukemia found that the numbers of leukemic bone marrow cell colonies grown in culture were decreased 21% of control in 7/28 patients by adding 0.3 milliM of L-ascorbic acid to the culture medium. Concentrations of L-ascorbic acid as low as 0.1 milliM was capable of suppressing the leukemic cell colony in cultures of both leukemic and normal marrow cells. However, 1 milliM of L-ascorbic acid was required for suppression of normal myeloid colonies. Based on their results, the authors argue that the achieved suppression was a specific effect of L-ascorbic acid and was not due to its oxidation-reduction potential or pH change since normal hemopoietic cells were not suppressed while leukemic cells were selectively affected at an L-ascorbic acid concentration attainable in vivo.

- C.H.J. Park, et al., Growth Suppression of Human Leukemic Cells in Vitro by L-Ascorbic Acid, *Cancer Research*, 40(4), 1980, p. 1062-1065.

This in vitro study on the effects of L-ascorbic acid (LAA) on the growth of human leukemic colony-forming cells (L-CFC) demonstrated that L-CFC growth suppression by LAA is observed in one-sixth of leukemic patients, L-CFC enhancement in one-third of patients, and that L-CFC growth enhancement is a significant discovery with a biological mechanism as the basis.

- C.H. Park, Biological Nature of the Effect of Ascorbic Acids on the Growth of Human Leukemic Cells, *Cancer Research*, 45(8), August 1985, p. 3969-3973.

Eighty-one patients with premalignant lesions of the oral cavity were given 30 mg of beta-carotene, 1000 mg of ascorbic acid, and 800 IU of alpha tocopherol daily for nine months; 55.6% experienced either complete or partial clinical resolution of their lesions. Based on these findings, the authors recommend the use of antioxidant supplements as a treatment for oral premalignant lesions.

- G. Kaugars, et al., Serum and Tissue Antioxidant Levels in Supplemented Patients with Premalignant Oral Lesions (Meeting abstract), *FASEB Journal*, 7(4), 1993, A519.

This study examined levels of vitamin C and ascorbic acid in the gastric juice of 77 patients suffering from dyspepsia. Gastric concentrations of vitamin C and ascorbic acid were significantly lower in chronic gastritis patients and patients with hypochlorhydria were found to have particularly low levels of ascorbic acid concentrations.

- G.M. Sobala, et al., Ascorbic Acid in the Human Stomach, *Gastroenterology*, 97(2), August 1989, p. 357-363.

In this placebo-controlled study, vitamin supplementation was examined in relation to its effects on cell kinetics in uninvolved rectal mucosa patients with colorectal adenomas. Vitamins A, C, and E were administered to 20 subjects 6 months after complete polypectomy. Results indicate that supplementation was successful in reducing abnormalities in cell kinetics that may indicate a precancerous condition.

- G.M. Paganelli, et al., Effect of Vitamin A, C and E Supplementation on Rectal Cell Proliferation in Patients with Colorectal Adenomas, *Journal of the National Cancer Institute*, 84(1), January 1, 1992, p. 47-51.

In this case-control study of 117 in situ cervical patients, plasma vitamin C was found to reduce the risk of cancer by 60%.

- K.E. Brock, et al., Nutrients in Diet and Plasma and Risk of In Situ Cervical Cancer, *Journal of the National Cancer Institute*, 80(8), June 15, 1988, p. 580-585.

This case-control study of 419 colon and rectal cancer patients found that dietary vitamin C intake resulted in reduced risk of rectal cancer in women.

- J.D. Potter and A.J. McMichael, Diet and Cancer of the Colon and Rectum: A Case-Control Study, *Journal of the National Cancer Institute*, 76(4), April 1986, p. 557-569.

Noting that the use of ascorbate to treat cancer began in 1971, this case-control study involved over 300 patients with cancer who received 2.5 g of vitamin C four times a day in combination with standard surgical treatment and radiotherapy (a few cases of chemotherapy). Two hundred sixty-six patients with incurable cancer were found to benefit significantly from the vitamin C therapy which was shown to have significant benefits for those suffering from cancer of the stomach and colon, while there was a similar trend for those with cancer of the bladder. Based on their results, the authors conclude that ascorbate in high doses can improve survival in certain types of cancer.

- L. Moffat, et al., High Dose Ascorbate Therapy and Cancer, *NFRC Cancer Research Association Symposium*, (2), 1983, p. 343-256.

This study found that large amounts of vitamin C administered in drinking water reduced benzo(a)pyrene (BP) induced tumors in mice, resulting in an extended survival time for those animals exposed to the carcinogen.

- G. Kallistratos, et al., The Prophylactic and Therapeutic Effect of Vitamin C on Experimental Malignant Tumors, *NFRC Cancer Research Association Symposium*, (2), 1983, p. 221-242.

This review article on the effects of vitamins A, C, E, and selenium on cancer cites research pointing to ascorbic acid's ability to prevent formation of nitrosamine and other N-nitroso compounds. Studies also show supplementation with vitamin C can inhibit skin, nose, kidney, lung and tracheal cancer.

- D.F. Birt, Update on the Effects of Vitamins A, C, and E and Selenium on Carcinogenesis, *Proc Soc Exp Biol Med*, 183(3), December 1986, p. 311-320.

The administration of ascorbic acid (0.1-20 micrograms/ml for the first week) was found to suppress X-ray induced transformation of C3H10T1/2 cells in a concentration-dependent manner after irradiation. Cells initiated by radiation remained vulnerable to ascorbic acid up until the moment of morphological phenotype expression. Based on these findings, the authors postulate that expression of the neoplastically transformed phenotype is promoted by reactive oxygen species and peroxy radicals generated in cells during the whole assay period and they suggest their data might be helpful as a guide for chemopreventive efforts against radiation carcinogenesis.

- M. Yasukawa, et al., Radiation-induced Neoplastic Transformation of C3H10T1/2 Cells is Suppressed by Ascorbic Acid, *Radiation Research*, 120(3), December 1989 p. 456-467.

This study found that pretreatment of tumor target cells in vitro with a combination of interferon and ascorbate resulted in a 71% increase in growth inhibition of target cells compared to inhibition with interferon by itself. Administration of ascorbate alone showed minimal effect on tumor target cell growth in human monocytes.

- M.J. Skeen, et al., Synergy of Interferon and Ascorbic Acid in Stimulating Human Monocyte Cytostasis Against Tumor Target Cells, *Rev Latinoam Oncology Clin*, 13(4), 1981, p. 9-14.

This study found that a 4 mg/kg body wt/week dose of cisplatin supplemented with a 200 mg/alternated day dose of vitamin E and a 200 mg/day dose of vitamin C given to rats increased cisplatin's therapeutic potential in the treatment of oral cancer compared to the administration of cisplatin alone.

- D.K. Sharma, Amylase Activity of the Malignant Rat Salivary Gland after Cisplatin, Vitamin E and C Treatment, *Third International Congress on Engineered Oral Cancer*, January 22-25, 1994, Madras, India, 1994.

Vitamin C (35 mg/kg) ingestion has been shown to result in a reduction in DNA single strand breaks induced by ionizing radiation in human lymphocytes, as indicated by a significant decrease in overall comet length in both unirradiated control and the dose response to ionizing radiation damage. The effect was found to persist for up to six hours.

- C.F. Arlett, et al., The Modulation of DNA Damage in Human Lymphocytes by Dietary Vitamin C Supplementation, *Molecular Mechanisms in Radiation Mutagenesis and Carcinogenesis*, April 19-22, 1993, Doorwerth, The Netherlands.

Patients with oral leukoplakia were administered 30 mg of beta-carotene, 1000 mg of ascorbic acid, and 800 IU of alpha-tocopherol per day for 9 months. 55.6% of the 81 patients who completed the study showed either partial or complete clinical resolution of their oral lesions.

- G. Kaugars, et al., The Role of Antioxidants in the Treatment of Oral Leukoplakia, *CCPC-93: Second International Cancer Chemo Prevention Conf.*, April 28-30, 1993, Berlin, Germany, p. 65.

Twenty-four lung cancer and 35 bladder cancer patients were treated with doses of 5 g/day of ascorbic acid. Results suggest that such high doses are useful in correcting low haematic levels of vitamin C and in increasing the defense reactions in patients suffering from these types of cancer.

- A.M. Greco, et al., Study of Blood Vitamin C in Lung and Bladder Cancer Patients Before and After Treatment with Ascorbic Acid: A Preliminary Report, *Acta Vitaminol Enzymol*, 4(1-2), 1982, p. 155-162.

This review article points out that vitamin C's role in preventing cancer has been discussed in the literature for over 50 years and cites studies which suggest that foods rich in vitamin C are associated with lower risks of stomach cancer and cancer of the esophagus. Ascorbic acid had been demonstrated to interact with a number of tumor-inducing compounds, such as precursors of N-nitroso compounds to prevent tumors. Animal and in vivo studies have also shown ascorbic acid disrupts tumor promotion. Based on a review of the existing evidence, the authors conclude that vitamin C can inhibit the formation of some types of cancer.

- B.E. Glatthaar, et al., The Role of Ascorbic Acid in Carcinogenesis, *Adv Exp Med Biol*, 206, 1986, p. 357-377.

The administration of flavone, quercetin, and fisetin either alone, or in combination with ascorbic acid, were studied for their effects on the growth of human squamous cell carcinoma cell line (HTB 43) in vitro. When combined with ascorbic acid (2 micrograms/ml), fisetin and quercetin (2 micrograms/ml of either) impaired cell growth in 72 hours significantly. Ascorbic acid administered alone had no effect, nor did it when in combination with flavone.

- C. Kandaswami, et al., Ascorbic Acid-enhanced Antiproliferative Effect of Flavonoids on Squamous Cell Carcinoma in Vitro, *Anticancer Drugs*, 4(1), February 1993, p. 91-96.

This review article on the relationship between vitamin C, vitamin E, and cancer cites studies which suggest that the consumption of foods containing vitamin C is related to a reduced risk of esophageal and stomach cancer. Supplementation with vitamin C has been shown to inhibit nerve, lung, kidney, and skin cancer. Studies have also shown vitamin C is capable of inhibiting tumor cell growth and carcinogen-induced DNA damage. In vitro and animal studies have demonstrated that vitamin C inhibits the formation of carcinogenic nitrosamines.

- L.H. Chen, et al., Vitamin C, Vitamin E and Cancer, *Anticancer Research*, 8(4), July-August 1988, p. 739-748.

Previous research has shown ascorbic acid to be cytotoxic to neuroblastoma cells in vitro and in vivo. In this study, ascorbic acid proved to be more cytotoxic than dehydroascorbic acid in neuroblastoma SK-N-SH cells. It was also discovered that uptake of [14C] ascorbic acid and [14C] dehydroascorbic acid was impaired by glutathione and diethiothreitol. [14C] Dehydroascorbic acid was partially reduced to [14C] ascorbic acid once inside the cell. The authors argue that their results add support to previous beliefs that ascorbic acid acts as a pro-oxidant inside neuroblastoma cells and they recommend the use of ascorbic acid in treating neuroblastoma.

- S.L. Baader, et al., Uptake and Cytotoxicity of Ascorbic Acid and Dehydroascorbic Acid in Neuroblastoma (SK-N-SH) and Neuroectodermal (SK-N-LO) Cells, *Anticancer*, 14(1A), January-February 1994 p. 221-227.

L-ascorbate and its oxidative product dehydroascorbate have been shown to be lethal or cytotoxic to fast-growing malignant cells while being less toxic to nonmalignant cells. Similar effects were seen with D-ascorbate and D-isoascorbate. Additional studies on the viability of treated cells have found that the effect on cell growth was a result of ascorbate's direct killing action rather than being cytostatic in nature.

- P.Y. Leung, et al., Cytotoxic Effect of Ascorbate and its Derivatives on Cultured Malignant and Nonmalignant Cell Lines, *Anticancer Research*, 13(2), March-April 1993, p. 475-480.

Sodium benzyldeneascorbate (SBA) dose dependently induced degeneration of 3'-methyl-4-dimethylaminoazobenzene-induced hepatocellular carcinoma in rats. At the same time, it did not significantly induce fibrosis in the liver, lymphocyte infiltration, nor damage the gross morphology of spleen and kidney cells. The authors suggest such findings may point to an antitumor action of SBA by way of induction of apoptosis in the tumor.

- H. Sakagami, et al., Effect of Sodium Benzyldeneascorbate on Chemically-Induced Tumors in Rats, *Anticancer Research*, 13(1), January-February 1993, p. 65-71.

This long term study found that ascorbic acid (administered via drinking water) resulted in the suppression of gastric tumor development in rats.

- S. Dittrich, et al. [Effects of Nitrate and Ascorbic Acid on Carcinogenesis in the Operated Rat Stomach], *Arch Geschwulstforsch*, 58(4), 1988, p. 235-242.

Noting the radioprotective effect of ascorbic acid on patients with head and neck cancer, this paper recommends the oral administration of ascorbic acid for patients suffering from these conditions.

- R. Garcia-Alejo Hernandez, et al., [Radioprotective Effect of Ascorbic Acid on Oral Structures in Patients with Cancer of the Head and Neck], *Av Odontostomatol*, 5(7), September 1989, p. 469-472.

This study found that doses of 2mM of ascorbic acid had a strong cytotoxic effect on neuroblastoma, osteosarcoma, rhabdomyosarcoma and retinoblastoma cells cultured in vitro. Ascorbic acid administered at 0.2 2mM continue to be cytotoxic for neuroblastoma, osteosarcoma and retinoblastoma cells, but stimulates the growth of rhabdomyosarcoma cells.

- M.A. Medina, et al., Ascorbic Acid is Cytotoxic for Pediatric Tumor Cells Cultured in Vitro, *Biochem Mol Biol Int*, 34(5), November 1994, p. 871-874.

The administration of parahydroxyphenyllactic acid (5 mg, sc 2x/wk) in combination with ascorbic acid (250 mg/100 ml in drinking water) increased the latent period of tumor development in C57BL mice exposed to tyroxine metabolites. Animals administered the same dose of parahydroxyphenyllactic acid without ascorbic acid developed bladder precancer and experienced no anti-tumor effects.

- N.A. Khar'kovskaia, et al., [Effect of Ascorbic Acid on the Carcinogenic Activity of P-Hydroxyphenyllactic Acid], *Bull Eksp Biol Med*, 92(1), 1982, p. 64-66.

Ten micrograms/ml of L-ascorbic acid increased alkaline phosphatase activity in the osteoblastlike rat osteosarcoma cell line, UMR-106, 6 hours after the addition of 100 micrograms/ml of ascorbic acid to the medium. The response of cAMP to both PTH and PGE1 was potentiated by 100 micrograms/ml ascorbic acid treatment of the cells. The increasing concentrations of ascorbic acid also inhibited cell growth, and significantly reduced the number of colonies formed by the cell grown in soft agar. Such results suggest the differentiation of osteoblasts may be effected by the presence of ascorbic acid.

- T. Sugimoto, et al., Effects of Ascorbic Acid on Alkaline Phosphatase Activity and Hormone Responsiveness in the Osteoblastic Osteosarcoma Cell Line UMR-106, *Calcif Tissue Int*, 39(3) September 1986, p. 171-174.

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➤ This study examined the relationship between hyperthermia and ascorbic acid on DNA synthesis in Ehrlich ascites tumor cells. When 75 microM of ascorbic acid was administered to cells at a low density of 5 x 10<sup>3</sup>/ml for 1 hour, DNA synthesis was inhibited at 37°C. Treatment at 42° significantly enhanced the inhibition. In the absence of ascorbic acid, DNA synthesis failed to be inhibited. Treatment with 75 microM ascorbic acid and hyperthermia at 42°C in cells transplanted into mice also prolonged the survival time relative to untreated cells. Based on these findings, the authors recommend that ascorbic acid and hyperthermia be considered for the treatment of cancer.

- K. Kageyama, et al., Enhanced Inhibitory Effects of Hyperthermia Combined with Ascorbic Acid on DNA synthesis in Ehrlich Ascites Tumor Cells Grown at a Low Cell Density, *Cancer Biochem Biophys*, 14(4), January 1995, p. 273-280.

In this case-control study of 723 gastric cancer patients, significant protective effects were found between ascorbic acid and the risk of developing the disease.

- C. La Vecchia, et al., Selected Micronutrient Intake and the Risk of Gastric Cancer, *Cancer Epidemiol Biomarkers Prevention*, 3(5), July-August 1994, p. 393-398.

An inverse association was found between dietary vitamin C and cervical intraepithelial neoplasia (CIN) in this case-control study of biopsy confirmed CIN patients.

- J. VanEenwyk, et al., Folate, Vitamin C, and Cervical Intraepithelial Neoplasia, *Cancer Epidemiol Biomarkers Prevention*, 1(2), January-February 1992, p. 119-124.

In examining the effects of ascorbic acid on in vitro multiplication of ascites tumor cells (ATP C+), of fibroblast-like cells and hepatocytes from chick embryos, the authors found that ATP C+ cells were the most vulnerable to ascorbic acid's toxic effects and hepatocytes the least. Catalase greatly decreased the damage ATP C+ cells suffered from exposure to ascorbic acid. These findings led the authors to propose that the inhibition of cell multiplication by ascorbic acid is the result of the H<sub>2</sub>O<sub>2</sub> formed by its oxidation and that those cells most resistant to its toxic effects have the greatest amount of catalase.

- F.S. Liotti, et al., Antagonism Between Catalase and Ascorbic Acid in Control of Normal and Neoplastic Cell Multiplication, *Cancer Letters*, 33(1), October 1986, p. 99-106.

This study examined the effects of nitric oxide and ascorbate on the control human brain tumor cells. Results indicated that combining nitroprusside and ascorbate may be an effective approach for treating brain tumors.

- Y.S. Lee and R.D. Wurster, Potentiation of Anti-Proliferative Effect of Nitroprusside by Ascorbate in Human Brain Tumor Cells, *Cancer Letter*, 78(1-3), April 1, 1994, p. 19-23.

This study found that daily doses of 2 mg/ml of ascorbic acid administered over a period of 16 weeks significantly inhibited cervical cancer induced by methylcholanthrene in mice.

- P. Das, et al., Influence of Ascorbic Acid on MCA-induced Carcinogenesis in the Uterine Cervix of Mice, *Cancer Letters*, 72(1-2), August 16, 1993, p. 121-125.

This study found that the cytotoxic effects of ascorbic acid on two sensitive lymphocyte tumor and cell lines were time and dose dependent. The authors suggest that the existence of lymphocyte lines with differing sensitivities to ascorbic acid might be considered a useful model in the study of vitamin C's action on cancer cells.

- T.L. Kao, et al., Inhibitory Effects of Ascorbic Acid on Growth of Leukemic and Lymphoma Cell Lines, *Cancer Letters*, 70(1-2), June 15, 1993, p. 101-106.

This study found vitamin C to have a distinct inhibitory effect on the mutational specificity of 6 antineoplastic drugs. Such results, the authors argue, are significant with respect to the clinical prevention of tumors.

- Z.Z. Zhao and M.T. Huang, [A Study of Vitamin Inhibition on the Mutagenicity of the Antineoplastic Drugs], *Chung Hua Yu Fang I Hsueh Tsa Chih*, 26(5), September 1992, p. 291-293.

Noting that DES or estradiol-treated male Syrian hamsters supplemented with vitamin C have been shown to inhibit renal carcinogenesis, the effects of administered vitamin C on a series of biochemical markers of kidney carcinogenesis was studied. Results indicate that vitamin C inhibits estrogen-induced carcinogenesis by decreasing concentrations of estrogen quinone metabolites and their DNA adducts.

- J.G. Liehr, et al., Mechanism of Inhibition of Estrogen-Induced Renal Carcinogenesis in Male Syrian Hamsters by Vitamin C, *Carcinogenesis*, 10(11), November 1989, p. 1983-1988.

Forty-three patients were treated with oral supplementation of vitamin C. Treatment with vitamin C in patients with normal gastric mucosa resulted in elevation of intragastric ascorbate levels in all cases. Vitamin C supplementation decreased gastric mucosal DNA damage in 28 of the 43 patients which suggests that it may provide a protective role against the onset of gastric cancer.

- G.W. Dyke, et al., Effect of Vitamin C Supplementation on Gastric Mucosal DNA Damage, *Carcinogenesis*, 15(2), p. 291-295.

Noting that chromium metal salts are thought to be human carcinogens, and that lead chromate has been shown to be tumorigenic, genotoxic and clastogenic; this study demonstrated that a nontoxic dose of vitamin C blocked uptake of ionic chromium and eliminated the clastogenic activity of particles in cells treated with lead chromate particles.

- J.P. Wise, et al., Inhibition of Lead Chromate Clastogenesis by Ascorbate: Relationship to Particle Dissolution and Uptake, *Carcinogenesis*, 14(3), March 1993, p. 429-434.

This study found a positive relationship between human exposure to nitrosamines and the risk of esophageal cancer mortality. Vitamin C reduced the amount of gastric N-nitrosamines in the stomach and thus may be considered of potential value in the prevention of esophageal cancer.

- W.X. Yang, [Exposure Level of N-nitrosamines in the Gastric Juice and its Inhibition by Vitamin C in High Risk Areas of Esophageal Cancer], *Chung Hua Chung Liu Tsa Chih*, 14(6), November 1992, p. 407-410.

Rats fed a diet including vitamins A, C, E, and selenium compounds followed by aflatoxin B treatment for a period of 24 months remained free of cancer whereas the majority of controls not fed the vitamins developed liver cancer during the same period. Based on these results, the authors suggest liver cancer can be inhibited with the intake of vitamins by inducing hepatic microsomal enzymes that metabolize aflatoxins to noncarcinogenic products.

- H.S. Nyandieka and J. Wakhisis, The Impact of Vitamins A, C, E and Selenium Compound on Prevention of Liver Cancer in Rats, *East African Medical Journal*, 70(3), March 1993, p. 151-153.

### Part 2 to follow

#### Correspondence:

Gary Null, PhD  
P.O. Box 918 Planetarium Station  
New York, New York 10024 USA  
212-799-1246

Gary Null, PhD, award-winning investigative reporter has authored 50 books on health and nutrition, as well as numerous articles published in leading magazines. Dr. Null holds a PhD in human nutrition and public health science from the Union Graduate School. Former publisher of *Natural Living Newsletter*, the current *Gary Null's Natural Living Journal* reports on healthy alternatives in today's medicine, nutrition and lifestyle choices, ten times a year, and is available by calling 516-547-7177. Null hosts a nationally syndicated radio show, *Natural Living*, from New York City. Call 212-799-1246 for a radio listing in your area.