The Use of Vitamin C with Chemotherapy in Cancer Treatment: An Annotated Bibliography

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"There are only three presently known examples in which an agent classifiable as an antioxidant has been shown to decrease effectiveness of... chemotherapy in vivo. The vast majority of both in vivo and in vitro studies have shown enhanced effectiveness of standard cancer therapies or a neutral effect on drug action."

–D.W. Lamson and M.S. Brignall, 2000.

Introduction

There is an ongoing controversy over the use of vitamin C in conjunction with chemotherapy. This writer has reviewed 44 scientific and other articles on the effectiveness of vitamin C alone, or with other vitamins, with chemotherapy. The purpose of this bibliography is to summarize these findings–international in scope–in chronological order. This paper presents 24 positive studies, 12 positive reviews, one neutral study, one negative study, two negative reviews and four responses to the latter. It then discusses these findings.

It is necessary to point out that, although the first two studies reviewed involve terminal cancer patients not undergoing chemotherapy, they appear here because they were the first, or among the first, major clinical trials conducted with high-dose vitamin C.

Positive Studies (Table 1)

Study 1. 1976

Cameron E, Pauling, L: Supplemental Ascorbate in the Supportive Treatment of Cancer: Prolongation of Survival Times in Terminal Human Cancer. *Proceedings of the National Academy of Sciences, USA,* Oct 1976; 73/10: 3685-3689.

Summary

Cameron and Pauling wrote: "There is increasing awareness that the progress of human cancer is determined to some extent by the natural resistance of the patient in his disease. Consequently there is growing recognition that improvement in the management of these patients could come from the development of practical supportive measures specifically designed to enhance host resistance to malignant invasive growth."

Since the authors believed "the free availability of ascorbic acid" to be an "important factor in host resistance", they conducted a clinical trial at the Vale of Leven District General Hospital in Scotland to test this theory.

In the study, 100 terminal cancer patients, many of whom had been treated with chemotherapy, were given supplemental ascorbate as part of their routine management. It was found that their survival times were much greater than a controlled group of 1,000 similar patients who had not received the supplemental ascorbate. The method of treatment was through daily high-dose (about 10g) intravenous administration for about 10 days and then continued orally. This treatment was applied after it had been considered by independent clinicians that continued conventional treatment "would offer no further benefit" to the patients involved.

There was no indication in the study that supplemental ascorbate did any harm to patients. On the contrary, life was both prolonged and enhanced by the administration of ascorbate which would have a positive effect on "the natural mechanisms of resistance." The treated group lived an average of more than 210 days compared with 50 days for the control group.

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Table 1. Positive studies.

1.	Cameron E, Pauling L:	Proc Natl Acad Sci, USA	1976; 73/10: 3685-3689.
2.	Cameron E, Pauling L:	Proc Natl Acad Sci, USA	1978; 75/9: 4538-4542.
3.	Murata A, Morishige F, Yamaguchi H:	Intl J Vit Nutr Res, Suppl	1982; 23: 101-113.
4.	Taper HS, De Gerlache J, Lans M, et al:	Intl J Canc	1987; 40: 575-579.
5.	Hoffer A, Pauling L:	J Orthomol Med	1990; 5/3: 143-154.
6.	Meadows GG, Pierson HF, Abdallah R:	Am J Clin Nutr	1991; 54: 1284S-1291S.
7.	Skimpo K, Nagatsu T, Yamada K, et al:	Am J Clin Nutr	1991; 54: 1298S-1301S.
8.	Hoffer A, Pauling L:	J Orthomol Med	1993; Vol. 8, No. 3, pp. 157-167.
9.	De Loecker W, Janssens J, Bonte J et al:	Anticanc Res	1993; 13: 103-106.
10.	Sarna S, Bhola RK:	Archivum Immunol Ther Exper	1993; 41: 327-333.
11.	Prasad KN, Hernandez C et al:	Nutri Canc	1994; 22/3: 233-245.
12.	Chiang CD, Song E, Yang VC, Chao CC:	Biochem J	1994; 301: 759-764.
13.	Hoffer A:	Townsend Lett Doct Patient	1996; Nov: 50-51.
14.	Kurbacher CM, Wagner U, Kolster B, et al:	Canc Lett	1996; 103:183-189.
15.	Chen Y, Li C, Liu Y:	Zhonghua Zhong Liu Za Zhi	1997; Sept19/5: 350-352.
16.	Roomi MW, House D, Eckert-Maksic M, et al:	Canc Lett	1998, Jan; 122/1-2: 93-99.
17.	Nakagawa K:	Cellular Mol Biol	2000; 46/8: 1375-1381.
18.	Reddy VG, Khanna N, Singh N:	Biochem Biophys Res Comm	2001; 282: 409-415.
19.	Blasiak J, Gloc E, Wozniak K, et al:	Chem-Biol Interact	2002; 140: 1-18.
20.	Catani MV, Costanzo A, Savini I, et al:	Biochem J	2002; 364: 441-447.
21.	Calderon PB, Cadrobbi J, Marques C, et al:	Medic Chem,	2002; 9/24: 2271-2285.
22.	Mantovani G, Maccio A, Madeddu C, et al:	J Environ Pathol, Toxicol, Oncol	2003; 22/1:17-28.
23.	Drisko JA, Chapman J, Hunter VJ:	J Am Coll Nutr	2003; 22/2: 118-123.
24.	Abdel Rehim WM, Sharaf IA, et al:	Arzneim-Forsch./Drug Res	2003; 53/3: 214-220.

Cameron and Pauling concluded " that there is strong evidence that treatment of patients in Scotland with terminal (untreatable) cancer with about 10 g of ascorbate (ascorbic acid, vitamin C) per day increases the survival time by the factor of about 3 for most of them and by at least 20 for a few (about 10%)."

Study 2. 1978

Cameron E, Pauling L: Supplemental Ascorbate in the Supportive Treatment of Cancer: Reevaluation of Prolongation of Survival Times in Terminal Human Cancer. *Proceedings of the National Academy of Sciences, USA,* Sept 1978; 75/9: 4538-4542.

Summary

In this study, Cameron and Pauling confirmed the results of their previous clinical trial (1976) after "several experienced investigators in [the] field" had raised questions about the selection of the control and treatment groups.

Using a new control group, not only were the previous results reconfirmed, but this study showed that "the increase in life expectancy of ascorbate-treated patients ... [was] found to be somewhat larger." Indeed, eight of the terminal cancer patients who were treated in 1976 were still living at the time of this study.

Cameron and Pauling concluded "again that there is strong evidence that treatment $^1/_4$ with about 10g of ascorbate per day increases [the patients'] survival significantly (by an average of about 300+ days)." Likewise, the quality of life was enhanced, and there was no indication of any harm done to the patients.

Study 3. 1982

Murata A, Morishige F, Yamaguchi H: Prolongation of Survival Times of Terminal Cancer Patients by Administration of Large Doses of Ascorbate. *International Journal for Vitamin and Nutrition Research Supplement,* 1982, Vol. 23, pp. 101-113.

Summary

This study by Murata et al. supports the conclusions of Cameron and Pauling (1976 and 1978) that high-dose ascorbic acid increases the life expectancy of terminal cancer patients and to a certain extent enhances their quality of life.

The clinical trial at the first (large) hospital was conducted between January 1973 and December 1977. It was involved of 99 patients–48 male and 51 female in two groups (high-dose and low-dose ascorbate) and without a control group. The high-dose group contained 55 patients who were provided with "5 g per day or more" and the low-dose group involved 44 patients who were given "4 g per day or less" of ascorbate. Other criteria were age–the average age being 60.5 years–and different types of cancer classed as nine primary and other, with stomach, lung and bronchus and uterus being the main tumors.

With regard to average survival time, the results "to April 1, 1980, for those still alive" were as follows: "None of the low-ascorbate patients survived more than 174 days, whereas 18 (33%) of the high-ascorbate patients" had an average of 620 days. "Three (6%) of the high-ascorbate patients were still alive: ...with cancer of the uterus ... breast and thymus .... These 3 patients were clinically well, but with no significant progression or regression in tumor; that is, the patients survived in symbiotic existence with their tumors."

These results were compared with an earlier period (1967-1972) when the patients either received no ascorbate or the administration of ascorbate was low, and the average survival time was also low.

For high-ascorbate patients who received between 5 and 29 g per day, the average survival time was 246 days–"5.6 times as long as the patients [who received] small doses of ascorbate." This group's average survival time was 43 days. "Three of the high-ascorbate patients were still alive, their average survival time being 1550 days on April 1, 1980.

Murata et al. concluded: "Ascorbate is especially effective for cancer of the uterus, whereas it gives smaller increase in survival times for cancer of the stomach and lung than for other kinds of cancer."

The authors added: "In many cancer patients, the administration of ascorbate seemed to improve the state of well-being, as measured by improved appetite, increased mental alertness, decreased requirement for pain-controlling drugs, and other clinical criteria."

A second smaller clinical trial was conducted between January 1975 and December 1979. It was comprised of 31 patients, with an average age of 66.8 years. The commonest cancer was that of the stomach. Fifteen male and 16 female were divided into two groups (high-dose and low-dose). There was also a control group. Both of the treated groups had six participants, while the controls numbered 19. The high-dose group was administered "5 to 30 g per day" of ascorbate and the low-dose group was given "0.5 to 3 g per day." Other criteria were the same as those at the trial at the large hospital.

Again Murata and coworkers noted ascorbate improved survival times. "None of the control patients survived more than 98 days, whereas 3 (50%) of the high-ascorbate patients (receiving 5 g per day or more) survived longer than 98 days, their average being 158 days. One of the high-ascorbate patients was still alive, with a survival of 215 days." The tumor (bladder) in this patient had decreased.

Average survival time for the controls was 48 days, while for the high-ascorbate patients it was 115 days - "2.4 times that of the controls." No comparison was made of

the average survival time for high-ascorbate and low-ascorbate patients and for low-ascorbate patients and controls, since the authors believed that "the value obtained would have little statistical significance because of [the] small numbers of the subjects."

In reference to ascorbate and pain control, the authors noted that pain control drugs were given mainly to the control and low-ascorbate groups as opposed to the high-ascorbate group.

Murata et al. concluded: "The results of the clinical trials conducted at the [two hospitals showed] that large doses of ascorbate [offered] some degree of benefit to advanced cancer patients, even though there were some defects in the methods."

The authors ended by explaining the reasons for their not conducting "a double-blind trial". They mentioned the impossibility of finding "matched pairs for comparison within" their small practice and cited "the effectiveness" of Cameron and Pauling's studies (1976 and 1978). "Moreover," they stated that as their "clinical experience increased, [they] felt it to be ethically wrong to withhold ascorbate in otherwise hopeless situations, merely for the sake of obtaining observations of dubious significance for statistical comparison." Beyond this, "no harmful long-term side effect was observed among the patients who received large doses of ascorbate."

Study 4. 1987

Taper HS, De Gerlache J, Lans M, Roberfroid M: Non-Toxic Potentiation of Cancer Chemotherapy by Combined C and K3 Vitamin Pre-Treatment. *International Journal of Cancer,* 1987; 40: 575-579.

Summary

Taper et al. investigated: "The influence on the survival of ascitic liver tumor (TLT)-bearing mice of combined vitamin C and K3 administered before or after a single i.p. dose of 6 different cytotoxic drugs, all commonly used in human cancer therapy."

The results of the study showed that (1) the vitamin treatment "produced a distinct chemotherapy-potentiating effect for all drugs examined, especially when injected before chemotherapy", and (2) the "treatment did not increase the general and organ toxicity that accompanies cancer chemotherapy."

"The main object of the potentiation of cancer therapy [as stated by Taper et al. was] to increase the cell-destructive action of cytotoxic drugs or radiation, if possible in a most selective, irreversible and non-toxic way. Such a potentiation might considerably increase the survival of cancer patients."

The authors continued: "Based on our previous observations, we hypothesized that DNase-reactivating compounds could act as potentiators of cancer therapy.... Among the different compounds examined, vitamin C (ascorbic acid or sodium ascorbate) exclusively activates acid DNase in a transplantable hepatoma whereas K3 (menadione sodium bisulfite) selectively and distinctly influences alkaline DNase."

This acid-alkaline observation was seen in an earlier study by Taper; still earlier, other investigators had made the same observation.

The test was conducted with 10 or 12 ascitic transplantable mouse liver tumor (TLT)-bearing mice, six cytotoxic drugs of varying dosage, vitamin C (1g/kg), vitamin K3 (10 mg/kg) and controls, The vitamins were administered i.p. before and after the chemotherapy. "Since the optimum time of therapeutic efficiency was not known, both vitamins were administered twice, 24 and 3 h[ours] before or after a single dose of chemotherapy." The observations re: mortality etc. were made on mice "considered as long-term survivors (LTS)–these were: "The mice which [had] survived 45 to 59 days after tumor transplantation and exhibited no external signs of tumor [and] were killed and autopsied."

The results were as follows: For CK3

alone, the increase in life span was (% ILS 45.79) as compared to the controls.

For CK3 and three drugs (cyclophosphamide, procarbazine hydrochloride and asparaginase), the administration of the vitamins before the chemotherapy increased "the therapeutic effect of [the] drugs alone, thus indicating a synergistic effect." It was further noted that both mean survival time (MST) and ILS were increased, with LTS only increasing for the first two mentioned drugs. Also, when CK3 was administered after the first drug, the "treatment appeared less efficient".

For CK3 and two drugs (vinblastine and adriamycin), the administration of the vitamins before the chemotherapy produced a higher effect than after the chemotherapy which was "consistently lower." In the case of the first drug, when the vitamins were administered after the chemotherapy, there was "no significant effect in any parameter, except a slight increase in LTS (+16%)." In the case of the second drug, when the vitamins were administered after the chemotherapy, three of the parameters were "significantly increased". The increases were: "MST (30.3), ILS (+70.2%) and LTS (40%)." On the other hand, when the vitamins were administered before both of the drugs, the "treatment was highly potentiating, since the ILS [for the first drug was] +87% [and for the second drug] +88.8% ..., and 50% of mice were LTS after both drugs."

For CK3 and 5-Fluorouracil, the administration of the vitamins was most effective both before and after the chemotherapy. When the drug was used alone, it "had an insignificant effect (slight increase of all parameters)". When CK3 was administered after the drug, the effect was "considerably increased." The parameters were: "ILS +73.1% [and] LTS + 20%". CK3 treatment before the drug "produced the greatest potentiating effect" which was plus or minus 143% ILS [and] plus or minus 60% LTS."

Another experiment was conducted to confirm the result that CK3 administered before the chemotherapy produced a better effect. Taper et al. wrote: "It appeared important to evaluate whether combined administration of both vitamins was required to produce the potentiation of tumor chemotherapy" as described.

The authors continued: "In order to investigate the effect of CK3 on the toxicity of the antineoplastic drugs, 2 more experiments were performed with cyclophosphamide." These experiments showed that "administration of CK3 before a single dose of 80 mg/kg of the drug did not increase loss of total body weight as compared to treatment with the cytotoxic drug alone. Other experiments, using higher doses of cyclophosphamide alone or together with CK3, gave similar results."

To conclude, Taper et al. stated: "Several hypothetical mechanisms may be involved in the action of vitamin C", among them the generation of H_2O_2 as reported by other investigators. Vitamin K3 may also generate H_2O_2 as reported by an investigator.

The authors continued: "The possible generation of peroxides followed by membrane lipid alteration, DNase activation and DNA destruction by combined vitamin C and K3 in catalase-deficient cancer cells might be involved in the mechanisms of this selective potentiation."

Finally, Taper et al. stated again: "The potentiating action of CK3 does not increase the general toxicity of cancer chemotherapy" and they saw no need for objection in the use of vitamin C and vitamin K3 with chemotherapy, although further research was needed.

Study 5. 1990

Hoffer A, Pauling L: Hardin Jones Biostatistical Analysis of Mortality Data for Cohorts of Cancer Patients with a Large Fraction Surviving at the Termination of the Study and a Comparison of Survival Times of Cancer Patients Receiving Large Regular Oral Doses of Vitamin C and Other Nutrients with Similar Patients not Receiving Those Doses. *Journal of Orthomolecular Medicine,* 1990; 5/3: 143-154.

Summary

Hoffer and Pauling used "the biostatistical analysis of mortality data for cohorts of cancer patients based on the Hardin Jones principle" as developed by Dr. Pauling in their clinical test of 134 patients. These patients were from Dr. Hoffer's practice and most of them had received chemotherapy.

The 134 patients were divided into three groups. Two of the groups were administered 3 to 40 g but "mostly" 12 g daily of vitamin C and other nutrients. The third group did not follow the regimen. The average age of the patients was 53.1. The authors stated: "An important reason for carrying out such a test is the determination of the mean survival times of the homogeneous subcohorts that compose the cohort being tested."

Hoffer and Pauling concluded from the results that "80% of the patients who followed the regimen [had] a probable survival time 21 times that of the controls ... or 13 times that of the controls ..., or, for all 81 patients, 16 times that of the 31 controls." (Originally there were 33; Moss (1999) said that one died and one was very ill.)

In response to questions raised about "the validity of the results presented in [the] paper", Hoffer and Pauling stated that although "the Hardin Jones principle has been discussed briefly in several books and papers during the last thirty years" only two writers addressed "any significant discussion of its general validity for homogeneous cohorts of cancer patients." Moreover, other methods suggested for use have been said by the authors to be "less powerful than the method that [they had] used". They believed that this method is an acceptable one as evidenced by the number of studies using it because of its "accuracy and reliability".

In addition, the authors noted that the results obtained in this study compare favourably with those associated with the use of high-dose ascorbic acid for terminal cancer patients by Cameron and Pauling (1976 and 1978). Once again there was no indication of harm caused by the administration of ascorbic acid.

Hoffer and Pauling concluded that their trial "will have value in calling to the attention of both physicians and patients the possibility that this regimen, as an adjunct to appropriate conventional therapy, may have great value."

Study 6. 1991

Meadows GG, Pierson HF, Abdallah R: Ascorbate in the Treatment of Experimental Transplanted Melanoma. *American Journal of Clinical Nutrition,* 1991; 54: 1284S-1291S.

Summary

In this study Meadows et al. showed: "Sodium ascorbate supplementation in drinking water inhibited subcutaneous tumor growth, enhanced levodopa methylester (LDME) chemotherapy, and increased survival of B16 melanoma-bearing mice."

This study compared basal and restricted diets either with sodium ascorbate or LDME alone, or in combination. These groups were matched to a control group. In mice on the basal diet:

(1) "Ascorbate had variable effects on tumor volume. Some tumors were sensitive whereas some were resistant to inhibition by ascorbate."

(2) "LDME treatment inhibited tumor growth during the treatment period and for 8 d[ays] after treatment was stopped. The tumor then began to grow, but the mean tumor volume never reached the level of the untreated group."

(3) "The greatest suppression of tumor growth was observed in the LDME plus ascorbate group, where ascorbate supplementation enhanced the growth-inhibitory effect of LDME."

Results were better for mice on the restricted diet. To quote the authors directly:

"The most pronounced growth-inhibi-

tory activity on B16 melanoma was obtained in mice fed the restricted diet. This diet alone greatly inhibited tumor growth. Ascorbate alone and in combination with LDME was more effective than LDME alone at retarding tumor growth, even though the differences were slight." In addition the authors noted that:

"Tumors generally were more invasive in untreated mice fed the basal diet than in mice fed the restricted diet." Beyond this: "The primary tumor masses from both dietary groups receiving ascorbate were smaller, more well defined and less invasive. Secondary tumor masses were encapsulated and the size of the tumors in mice fed the restricted diet was smaller."

Meadows and coworkers concluded:

"The combination of LDME and ascorbate reduced the size and distribution of secondary tumors with the greatest effect observed in mice fed the restricted diet."

In reference to survival time, the results for the basal diet group showed that survival time was similar with LDME, ascorbate and LDME plus ascorbate treatments. This increase in survival was "significantly different" from the controls. In contrast, the results for the restricted diet group showed that survival time was similar and greater with LDME and ascorbate treatment alone, but greatest for LDME and ascorbate treatment. These increases in survival time were also "significantly different" from the controls.

With regard to the mechanism that was involved in the activity of ascorbate, the authors stated: "Although the mechanism underlying this enhancement is unknown, it may be related in part to the almost threefold greater accumulation of ascorbate in tumors from mice fed the restricted diet compared with mice fed the basal diet."

Meadows and colleagues pointed out: "An important effect of ascorbate in all studies was the potentiation of the growth-inhibitory effects of LDME chemotherapy in mice fed either basal or restricted diets and bearing primary or experimental metastatic tumors. This modulating role is not without precedent and may be the most important role for ascorbate in treatment of metastatic disease."

The authors cautioned however: "Ascorbate should not be used indiscriminately as an adjunct to chemotherapy because it may abrogate the effect of some drugs" as reported by other investigators.

Meadows and coworkers concluded: "In summary, ascorbate alone has some inherent antitumor activity against primary B16 melanoma in vivo; however, it exhibited antimetastatic activity only in the presence of tryosine and phenylalanine restriction and/or LDME treatment. This adjuvant activity may also be important to the therapy of other cancers, and more studies are needed to evaluate this role for ascorbate."

Study 7. 1991

Skimpo K, Nagatsu T, Yamada K, Sato T, Niimi H, Shamoto M, Takeuchi T, Umezawa H, Fujita K: Ascorbic Acid and Adriamycin Toxicity, *American Journal of Clinical Nutrition,* 1991; 54: 1298S-1301S.

Summary

Skimpo et al. wrote: "Adriamycin (ADR) is effective against a wide range of human neoplasms. However, its clinical use is compromised by serious cardiac toxicity, possibly through induction of peroxidation in cardiac lipids."

In their study, the authors tested the effectiveness of ascorbic acid and two derivatives "in reducing ADR toxicity in mice and guinea pigs." At the same time, they observed the survival time of the animals citing an interest in the clinical trial of Cameron and Pauling (1976 and 1978). The results of the tests showed that the ascorbic acid and its derivatives can play a role in increased survival and in preventing cardiac toxicity in mice with leukemia and carcinoma. The tests were as follows:

(1) Five leukemia-bearing mice were administered ADR 5 mg/kg and ascorbate 2 g/kg for [12] days i.p. The test showed that the treatment "prolonged the life of [the] mice", and toxicity of ADR was reduced.

(2) Five carcinoma-bearing mice were tested in three parts: (1) ADR 0.5 mg/kg and ascorbate 2 g/kg for 12 days i.p., (2) ADR as above and the derivative (CV-3611) 50 mg/kg for the same time, and (3) the other derivative (ascorbyl palmitate) with the same dose and time as above. The tests showed that the treatment with both the derivatives also "prolonged the life of ... [the] mice". The toxicity of ADR was also reduced. In addition, only "ascorbyl palmitate had a tendency to potentiate the antitumor effect of ADR."

(3) Ten leukemia-bearing mice were administered two sets of ADR - "1 mg/kg" and 5 mg/kg and the same dose of ascorbate as above through the same method. The test showed an increase in survival - the effect was most marked at the higher dose of ADR (5 mg/kg), and toxicity of ADR was reduced

(4) Eleven carcinoma-bearing mice were tested in two parts: (1) ADR 15 mg/kg and CV-3611 430 mg/kg and (2) ADR as above and ascorbyl palmitate 1240 mg/kg. These doses were administered subcutaneously for seven days with the derivatives given before ADR and for 14 days after. For CV-3611, the survival time increased "significantly" while for ascorbyl palmitate, survival time increased "only slightly". Reduction in toxicity of ADR was observed for both.

(5) Another test was conducted on ten "normal guinea pigs, which, like humans, cannot synthesize ascorbic acid". In this test with ADR 0.5 mg/kg and ascorbate 143 mg/kg, survival time increased "significantly", and there was also a reduction in toxicity of ADR.

(6) With reference to lipid peroxide levels in mouse heart ADR toxicity, ascorbate or ascorbyl palmitate was used. "Ascorbate (2 g/kg) or ascorbyl palmitate (50 mg/kg) was administered intraperitoneally for 5 d[ays] before a single subcutaneous ADR (15 mg/kg) administration, and ascorbate or ascorbyl was continued for 5d[ays]." The test showed that ADR plus ascorbate "decreased the elevated lipid peroxide levels by ADR, significantly in the heart." ADR plus ascorbyl palmitate showed "similar results".

(7) The effects of ascorbate in cardiomyopathy in guinea pigs were measured by electron microscopy. This permitted the authors to learn that: "The earliest alterations of dilation of sarcoplasmic recticulum and tranverse tubular system and the appearance of a large number of cytoplasmic fat droplets, which were seen in cardiac tissue from guinea pigs receiving ADR, were apparently reduced in animals that were treated with ascorbate."

Skimpo and colleagues concluded: "Our results suggest that ascorbate and the derivatives may delay general toxicity of ADR and also prevent cardiac toxicity, possibly due to its activity as an antioxidant. Moreover, the ascorbate derivatives alone are likely to prolong the life of tumor-bearing animals."

Study 8. 1993

Hoffer A, Pauling L: Hardin Jones Biostatistical Analysis of Mortality Data for a Second Set of Cohorts of Cancer Patients with a Large Fraction Surviving at the Termination of the Study and a Comparison of Survival Times of Cancer Patients Receiving Large Regular Oral Doses of Vitamin C and Other Nutrients with Similar Patients not Receiving These Doses. *Journal of Orthomolecular Medicine,* 1993, Vol. 8, No. 3, pp. 157-167.

Summary

The purpose of this study was two-fold. Firstly, it was an extension of the study by Hoffer and Pauling (1990) but with a large number of cancer patients. Secondly, it was designed to allow comparisons with the studies of Cameron and Pauling (1976 and 1978) on the produced effectiveness of vi-

tamin C alone or in combination with other nutrients in the treatment of cancer.

This latter study involving 170 cancer patients produced similar results to the first study with 134 cancer patients. The participation rate in this second project was higher with 155 patients following the regimen and 15 choosing not to do so. The results showed that for the controlled group of 15, the mean survival time was 135 days - the same for the 1990 study. The treated-group of 155 in the designated sub-group, that of four specific types of cancers and other cancers, were analysed as being excellent and good responders.

The mean survival time of about 50% of the first sub-group was "greater than 5 years", and for the other 50% it was 630 days. The mean survival time for about 33% of the second sub-group was also "greater than 5 years" while for the remaining 67% it was 540 days.

According to the authors: "The main difference between the results of the Hoffer studies and the Cameron studies is that the fraction of excellent responders is about 4 times as great for the Hoffer regimen (50%..., 33%...) as for the Cameron regimen (10%). The good responders (about 60% for Hoffer, 90% for Cameron) seem to be benefitted by about the same amount (mean survival time 4 or 5 times the values for the controls)." They continued: "These differences suggest that an additional 30% of patients with advanced cancer may be "cured", (with survival times of five years, or more, after reaching an advanced stage of the disease) by following the more extensive orthomolecular regimen prescribed by Hoffer rather than only the vitamin C regimen prescribed by Cameron."

Hoffer and Pauling concluded that both "regimens have some value, often great value, for all cancer patients as an adjunct to appropriate conventional therapy." They recommended "that all cancer patients begin the orthomolecular regimen as early in the course of the disease as possible. The Hoffer regimen (varying somewhat from patient to patient), in addition to including fruits and vegetables in the diet, includes" the vitamins and minerals described in the 1990 study.

Study 9. 1993

De Loecker W, Janssens J, Bonte J, Taper HS: Effects of Sodium Ascorbate (Vitamin C) and 2-Methyl-1,4-naphthoquinone (Vitamin K3) Treatment on Human Tumor Cell Growth *in Vitro*. Synergism with Combined Chemotherapy Action. *Anticancer Research,* 1993; 13: 103-106.

Summary

De Loecker et al. reported that when vitamins C and K3 were combined with certain chemotherapeutic agents, "in well defined conditions" and dosage, the application resulted "in a synergistic effect on growth inhibition." It was further noted that when the vitamins reached "their own synergistic cytotoxicity levels [they] frequently [obscured] the additional synergistic levels attributable to the chemotherapeutic agents." However, it is believed that "less defined secondary mechanisms" than free radicals both of the vitamins and the chemotherapy may be "responsible for the observed stimulated cytotoxicity."

The authors cited previous work on the increased effectiveness of combined vitamins and chemotherapy application on hepatoma-bearing mice. In their own study the authors examined the "effects of a combined application of both vitamins together with chemotherapy on a human endometrium adenocarcinoma cell line."

This study consisted of a treated series and a controlled series both of which met certain criteria but with the application process differing. For example, when the test material reached what was termed "50% confluence stage" for the treated series, "the cells were exposed for 3 hours" to certain chemo-therapeutic agents and then to a combination of the two vitamins. For

the controlled series, after a certain confluence stage was reached, these cells "were only treated for 4 hours" with the chemotherapeutic agents "and for 1 hr" with the vitamins but not with a combination of the vitamins and chemotherapy.

The results showed that the effectiveness of the chemotherapy together with the vitamins was considerably greater than that of the chemotherapy alone.

De Loecker et al. concluded: "Although the specific characteristics of the different cytostatic drugs used have not been further explored or analyzed, it appears that to visualise any synergistic effects between chemotherapy and combined Vit C and K3 treatment *in vitro*, the therapeutic dose levels have to be adequately proportioned and adjusted in function of actual cell density to avoid either an insufficient effect or an undesired predominance of one kind of treatment pattern."

Study 10. 1993

Sarna S, Bhola RK: Chemo-Immunotherapeutical Studies on Dalton's Lymphoma in Mice Using Cisplatin and Ascorbic Acid: Synergistic Antitumor Effect *in Vivo* and *in Vitro. Archivum Immunologiae et Therapiae Experimentalis,* 1993; 41: 327-333.

Summary

Sarna et al. noted "the serious side effects" of high dose cisplatin treatment as reported in a review of the drug. The objective of the study then was "to find out the effects of ascorbic acid on enhancement of tumor growth inhibition induced by [a] low dose of cisplatin."

The method used was "direct treatment of tumor cells *in vivo* and *in vitro*." The test using Dalton's lymphoma mice treated with different doses of either cisplatin and ascorbic acid alone or in combination was conducted in two parts; namely, chemotherapeutical studies and chemoimmunotherapeutical studies. A controlled group of mice was used for comparison.

The results obtained from the chemotherapeutical studies were as follows:

For ascorbic acid alone: "When tumor bearing mice were treated with ascorbic acid (20 or 40 mg/kg x 4) a slight increase in their mean survival time compared to control mice was observed. Animals treated with [a] high dose of ascorbic acid (60 mg/kg x 4) failed to show significant increase in their life span; however, 20-25% [of the] animals appeared as tumor free survivors."

For cisplatin alone: A "dose of cisplatin (3 mg/kg) was able to prolong the survival time of the ... mice (life span increased to 166%)"-35 days without tumor free survivors.

For ascorbic acid and cisplatin: "Mice treated with cisplatin [as above] along with ascorbic acid 20 or 40 mg/kg x 4) showed increased mean survival time from 13 days in control to 50 days in treated animals." "Both [of] the concentrations of ascorbic acid in combination with cisplatin resulted in 40% tumor free survivors. Animals receiving 60 mg/kg of ascorbic acid with cisplatin survived beyond 60 days, 50% appeared as tumor free survivors without any sign of tumor and its reappearance, the rest of them died at a later stage prolonging their life span by 400%." The life span with 20 mg/kg and 40 mg/kg was prolonged by 287% and 275% respectively.

The results obtained from the chemoimmunotherapeutical studies were as follows:

For ascorbic acid alone: "Dalton's lymphoma cells ..., when incubated with different concentrations of ascorbic acid and injected into normal mice, developed tumor in all the animals similarly as in control mice. Mice receiving tumor cells, incubated with 25 μg/ml ascorbic acid showed 10-15 day increase in their life span; however, innoculation of tumor cells incubated with 50 μg/ml of ascorbic acid resulted in mean survival time of mice similar to the control." The mean survival time was: 20 days for the controls, 34.6 days for ascorbic acid 25 μg/ml and 21.6 days for ascorbic acid 50 μg/ml. "No tumor free as

well as 60/more than 60 day survivors were observed with either concentration."

For cisplatin alone: "Mice injected with cisplatin (5 or 10 μg/ml) incubated tumor cells showed significant increase in their survival time compared to the control." The latter concentration was more effective that the former resulting "in 70% 60-70 day survivors with 204% increase in their life span." The increase for the first concentration was 110%. "Both [concentrations] of cisplatin significantly enhanced the mean survival time of mice to 43 and 62 days respectively. No tumor free survivors were observed ... with either dose."

For ascorbic acid and cisplatin: "Tumor growth was significantly affected after injecting tumor cells incubated with cisplatin (5 μg/ml) along with 25 or 50 μg/ml of ascorbic acid. Up to 30% mice failed to develop tumor.... Even those mice which developed tumor exhibited significant increase in their mean survival time."

The tests were as follows: "Tumors cells incubated with cisplatin [as above] along with 50 μg/ml of ascorbic acid, when injected in mice resulted in 30%, 60/more than 60 day survivors apart from tumor free survivors."

"Mice injected ... with 10 μg/ml of cisplatin along with 25 μg/ml of ascorbic acid resulted in 20% tumor free survivors, the rest of them developed tumor with an increase in their mean survival time up to 48 days including 20% of 60 day survivors."

"Tumors cells incubated with cisplatin (10 μg/ml) along with ascorbic acid (50 μg/ml) when injected ... showed maximum survival time of mice up to 70 days without any tumor free survivors.... The mean survival time in this [latter] group of mice was 58 days which increased significantly compared to the control mice." As seen above, the control mice survived for 20 days. The result for cisplatin 5 μg/ml and ascorbic acid 25 μg/ml was not recorded, but the increase in mean survival time was 42.2 days.

In summary, Sarna et al. observed that in chemotherapeutical studies the "[m]ost effective dose [of usage] of ascorbic acid in combination with cisplatin was found to be 60 mg/kg which has given almost 100% tumor free survivors up to 65 days. About 50% mice further survived indefinitely like normal animals. Even low doses of ascorbic acid (20 or 40 mg/kg) were found to be effective in regressing tumor when combined with the subtherapeutical dose of cisplatin. This finding shows that ascorbic acid somehow increases the therapeutical potential of the low dose of cisplatin resulting in complete regression of tumor in most of the animals. The subtherapeutical dose of cisplatin alone resulted in an increase in the mean survival time of tumor bearing mice without any tumor free survivors." In chemo-immunotherapeutical studies:

"The tumor growth inhibition [by cisplatin alone] was further enhanced when vitamin C was combined with the low dose of cisplatin *in vitro*." The authors continued: "One of the causes of the enhancement of cisplatin induced tumor inhibition by vitamin C ... might be an increased uptake of cisplatin into the tumor cells" as reported "for vitamin E...."

In conclusion, Sarna et al. wrote that their present "studies suggest that cisplatin and ascorbic acid should be given together for combination therapy of Dalton's lymphoma in mice. Treatment with ascorbic acid under certain conditions enhances the tumor growth inhibition induced by cisplatin. Possible causes of the enhancement ... are: (i) modulation of permeability of tumor cell membrane by ascorbic acid which elevates the intratumor contents of ascorbic acid, (ii) increased uptake of cisplatin into tumor cells, (iii) increase of the efficiency of adduct formation in genomic DNA making less efficient the DNA repair of cell, thus rendering the cisplatin more effective as an antitumor agent." The authors ended by stating:

"In view of [their] studies the potential usefulness of ascorbic acid in the prevention and treatment of cancer should not be ignored."

Study 11. 1994

Prasad KN, Hernandez C, Edwards-Prasad J, Nelson J, Borus T, Robinson WA: Modification of the Effect of Tamoxifen, *cis*Platin, DTIC, and Interferon-α2b on Human Melanoma Cells in Culture by a Mixture of Vitamins. *Nutrition and Cancer,* 1994; 22/3: 233-245.

Summary

In this study vitamin C was one of the antioxidants used either alone or in combination to test its effectiveness both on the reduction of growth and the enhancement of the growth-inhibition of certain chemotherapeutic agents for human melanoma cancer.

The results showed that vitamin C (sodium ascorbate), when used alone "inhibited growth of melanoma cells ... without affecting the morphology" while in combination the growth inhibition was either more or significant.

With regard to the enhancement by vitamin C in conjunction with a chemotherapeutic agent, the results were as follows:

Vitamin Treatment with Tamoxifen: Vitamin C 100 μg/ml alone and vitamin C 50 μg/ml with three vitamins "increased the growth-inhibitory effect of tamoxifen," while vitamin C 100 μg/ml with three vitamins showed no significant change.

Vitamin Treatment with *cis*-platin: Vitamin C 100 μg/ml alone "increased the growth-inhibitory effect of *cis*-platin", vitamin C 100 μg/ml with three vitamins "enhanced the *cis*-platin effect" while vitamin C 50 μg/ml with three vitamins "also increased the *cis*-platin effect."

Vitamin Treatment with DTIC: Vitamin C 100 μg/ml alone "enhanced the growth-inhibitory effect of DTIC," vitamin C 100 μg/ml with three vitamins "did not result in further suppression of growth" while vitamin C 50 μg/ml with three vitamins "markedly enhanced the DTIC effect."

Vitamin Treatment with Interferon α2b

Vitamin C 100 μg/ml alone "enhanced the growth-inhibitory effect of interferon," vitamin C 100 μg/ml with three vitamins "enhanced the interferon effect" while vitamin C 50 μg/ml with three vitamins "significantly increased the interferon effect."

In summary, vitamin C 100 μg/ml with three vitamins and the four anti-cancer agents "reduced growth of melanoma cells by about 85%. This vitamin mixture in combination with cisplatin and interferon further reduced growth..., but in combination with DTIC or tamoxifen, no better effect was noted." Vitamin C 50 μg/ml with the same number of vitamins "markedly enhanced the growth-inhibitory effect of all chemotherapeutic agents."

The authors believed: "These results suggest that the addition of vitamin C, [and the other vitamins] at nontoxic doses of each vitamin may enhance the growth-inhibitory effect of currently used therapeutic agents on human melanoma cells in culture."

Prasad et al. suggested: "Another scientific rationale for using vitamins in combination with chemotherapeutic agents involves the reduction of toxicity of [these] agents on normal cells by vitamins. This rationale cannot be tested in tissue culture systems. However, several studies using individual vitamins showed that they can reduce tumor therapeutic agent-induced toxicity in animal models .... Vitamin C ... has been shown to reduce the adverse effects of some chemotherapeutic agents on normal cells in animals" as reported by other investigators.

The authors ended by stating: "The mechanism of action of vitamins in tumor therapy is not totally clear"; they then explained the mechanisms of action that may be involved in the effectiveness of vitamin C and other vitamins in cancer therapeutic agents' activity.

Study 12. 1994

Chiang CD, Song E, Yang VC, Chao CC: Ascorbic Acid increases Drug Accumulation and reverses Vincristine Resistance of Human Non-Small-Cell Lung-Cancer Cells. *Biochemical Journal,* 1994; 301: 759-764.

Summary

Chiang et al. "established a [vincristine] VCR-resistant subline from human lung-cancer PC-9 cells which displays a reduced drug accumulation". This resistant subline (PC-9/VCR) treated with cytotoxicity from a MTT dye assay showed a higher "increase in resistance to VCR" as opposed to the increases of other anti-cancer agents; for example, adriamycin and cisplatin. The addition of ascorbic acid enhanced the treatment of PC-9/VCR.

The authors wrote: "A reduced accumulation of VCR was demonstrated. Interestingly, the VCR resistance of the PC-9/VCR cell line was partially reversed by ascorbic acid, and the drug uptake was enhanced."

The results were as follows: "The effect of ascorbic acid on cellular response to VCR was measured by the MTT-dye assay. To eliminate complications from the modulating agent itself, a non-toxic or low cytotoxic concentration of ascorbic acid was used." While low concentrations of ascorbic acid "had no profound effect" on resistant cells, a high concentration did. "At 25 μg/ml, ascorbic acid slightly inhibited cell growth." In addition, a treatment with "25 μg/ml" ascorbic acid significantly lowered the resistant-cell proliferation. Lower concentrations of ascorbic acid were also effective in sensitizing VCR toxicity."

Chiang et al. concluded that "ascorbic acid effectively inhibited the resistance of PC-9/VCR cells to VCR" noting: "Although the exact mechanism whereby ascorbic acid sensitizes PC-9/VCR cells to VCR is not clear, it is possible that the drug-accumulation-associated membrane activity detected in this study is modulated by ascorbic acid through an oxidation mechanism."

The authors, after explaining the particular mechanism, suggested: "This novel mechanism of drug resistance may be an additional resistance pathway encountered in clinical cancer therapy."

Study 13. 1996

Hoffer A: One Patient's Recovery from Lymphoma. *Townsend Letter for Doctors & Patients,* 1996; Nov: 50-51.

Summary

Hoffer reported on the use of "megavitamin therapy of which ascorbic acid was the main and most important compound."

In this case of a man who had become very depressed as the result of "extreme hardship, torture, and malnutrition" as well as personal problems, and who developed a rare form of cancer, Hoffer administered a high dose of vitamin treatment.

The patient had undergone surgery, and chemotherapy had been started. At the same time Hoffer "increased his ascorbic acid to 12 grams daily", along with another vitamin and two minerals. Over the course of time the dosage of ascorbic acid was increased to 24 g daily" as radiation had also been applied. This vitamin treatment was effective in helping the regression of the "severe lymphoma". Throughout the whole period, the patient's personal problems had remained and he had continued to be depressed.

This patient survived "14 years after he first saw [Dr. Hoffer], 13 years after he was diagnosed." Hoffer noted that since this first case: He had "seen 19 patients with lymphoma ... who were treated by the same cancer clinic, and by [him], using the orthomolecular program."

The author continued: "Out of 13 male patients, six were alive after five years and two more will probably make it. An 80% five year cure rate is pretty good. One patient did not start the program. He lived 1.5 years. The six female lymphoma cases did not do nearly as well. Only one lived for one year. The starting time was always from the date they first saw me. This is a small series and indicates a trend. I have not been able to find any factor which distinguishes the two sexes. They received similar orthodox treatment and the same orthomolecular treatment."

Hoffer ended by noting:

"In an earlier report with Linus Pauling [1990 - described elsewhere in this presentation], we showed that in general every group of cancer patients given megavitamin treatment lived much longer than did their comparison group who were not given the benefit of these vitamins."

Study14. 1996

Kurbacher CM, Wagner U, Kolster B, Andreotti PE, Krebs D, Bruckner HW: Ascorbic Acid (Vitamin C) improves the Antineoplastic Activity of Doxorubicin, Cisplatin, and Paclitaxel in Human Breast Carcinoma Cells in Vitro. *Cancer Letters,* 1996; 103:183-189.

Summary

Kurbacher et al. used vitamin C (ascorbic acid) and three antineoplastic agents in a study of their effectiveness on "human breast carcinoma cell lines". The vitamin and each agent were tested alone and in combination. Vitamin C at certain levels "improved the cytotoxicity" of the three antineoplastic agents "significantly".

In the test with doxorubicin (DOX), it was found that vitamin C "both at nontoxic and at cytotoxic concentrations [produced] a consistently synergistic antineoplastic activity". The authors noted that "this effect might be related to the generation of free radicals which have been shown to have an impact on DOX-induced cell kill" in one of the cells tested as reported by other investigators.

It was found that the test with cisplatin (DDP) "produced synergistic cytotoxicity solely when the [vitamin] was added at cytotoxic concentrations, [which] might indicate that mechanisms other than those mediated by oxyradicals are more important for DDP-activity compared to DOX, at least in some breast tumors."

The last test, that with paclitaxel (Tx), showed "a significant potentiation of Tx activity induced by Vit C."

Kurbacher et al. ended by stating: "In conclusion, we were able to demonstrate that ascorbic acid is likely to potentiate three of the most active drugs for the treatment of [breast cancer]. Combination effects mostly were synergistic or at least additive. The mechanism by which Vit C is able to improve the cytostatics studied is not known at present and should be elucidated in further investigations. Due to the low toxicity of Vit C even at very high concentrations, combinations of ascorbic acid with cisplatin, doxorubicin, or paclitaxel seem to be attractive for the future treatment of breast cancer."

Study 15. 1997

Chen Y, Li C, LiuY: [Effect of Ascorbate on the Permeation and Photosensitizing Activity of Hematoporphyrin Derivative (HPD) in Tumor]. *Zhonghua Zhong Liu Za Zhi,* Sept, 1997; 19/5: 350-352.

Summary

The summary is extracted from an abstract as the article was written in Chinese.

Chen et al. tested "the depth of permeation and concentration" of the anticancer agent (HPD) alone or in combination with ascorbic acid in their examination of "photosensitizing effect."

The test with mice tumor of a certain size was conducted in three groups as follows:

In group I, HPD (PsD-007) 1 mg/ml was administered to the mice.

In group II, HPD (PsD-007) 1 mg/ml and ascorbic acid 20 mg/ml for 1 hour was administered to the mice.

Group III was used for comparison with HPD (PsD-007) 10 mg/ml alone, and the treatment "was injected intravenously to mice bearing tumor of similar size". The tumor was removed 24 hours later.

The examination through the photosensitizing of the three tumors showed that for groups I and II, "red fluorescence was mainly at the periphery of tumors that had been immersed in HPD whereas the fluo-

rescence was weaker and more evenly distributed in tumors that had received HPD i.v." A further comparison with HPD and other mixture and groups I and II of frozen material showed similar features. For example, the concentration of the new mixture - malondialdehyde (nmol/L) - "was higher in tumors that had been immersed in [HPD] plus ascorbate than in tumors immersed in [HDP] alone. Tumors of mice that had received PsD-007 i.v. had the lowest concentration of both PsD-007 and malondialdehyde."

Chen et al. concluded: "Ascorbate facilitates permeation of HPD into tumor and enhances the photodynamic effect of HPD."

Study 16. 1998

Roomi MW, House D, Eckert-Maksic M, Maksic ZB, Tsao CS: Growth Suppression of Malignant Leukemia Cell Line In Vitro by Ascorbic Acid (Vitamin C) and Its Derivatives. *Cancer Letters,* 1998; Jan; 122/ 1-2: 93-99.

Summary

Roomi et al. wrote: "Despite the various reports on [ascorbic acid] toxicity, no work has been reported underlying the critical chemical structural features for its activity. The present study addresses this question." The authors described two "moieties" of ascorbic acid (AA), and these compounds were tested on a murine leukemia cell line.

In addition to investigating the mechanism which was involved in the cytotoxicity of ascorbic acid, Roomi et al. looked at the "effect of modifying the structure to yield the maximum cytotoxic effect of tumor cell growth."

An observation of one of the tests suggested "that the cytotoxic effect of ascorbate was apparently not related to the metabolic or vitamin activities of ascorbate at the cellular level. Furthermore, studies on the viability of the treated cells indicated that the observed effect on cell growth was not cytostatic in nature but was the result of a direct cell killing action of ascorbate."

The results of the study demonstrated "that the critical underlying feature for AA cytotoxicity [was] the dihydroxy γ-crotonolactone ring [moiety]." The other moiety - ethylene glycol - was "not an important feature for its toxicity."

Roomi et al. concluded that the above compounds in addition to two others "could be potential candidates for human trials."

Study 17. 2000

Nakagawa K: Effect of Chemotherapy on Ascorbate and Ascorbyl Radical in Cerebrospinal Fluid and Serum of Acute Lymphoblastic Leukemia. *Cellular and Molecular Biology,* 2000; 46/8: 1375-1381.

Summary

The purpose of this study on ascorbate (ASA) and ascorbyl (ASR) was twofold. One section involved patients with "various human malaises" not having chemotherapy, and the other involved patients with acute lymphoblastic leukemia (ALL) treated with chemotherapy. This presentation reports on the latter part.

Nakagawa described an action of vitamin C by stating that ascorbate "reacts with short-lived free radicals such as OH radical and forms ascorbyl radical (ASR)." He continued: "The propagation of chain reactions initiated by the short-lived free radical can be minimized due to the relative stability of ASR. Steady state concentration of ASR in serum can be related to diseases and the treatments. Electron paramagnetic resonance (EPR) spectroscopy is a reliable technique to investigate free radicals." The author pointed out that studies had been done on "ASA or ASR" and "ASA in cerebrospinal fluid (CSF)". However, he stated: "details of ASR along with ASA in CSF and serum such as the effect of

medical treatment and dynamic aspects concerning ASA and ASR are not yet known."

In this study "to examine the effect of chemotherapy" on ASA and ASR in CSF and serum, the test comprised two groups of 73 acute lymphoblastic leukemia (ALL) patients. Group 1 with 57 ALL patients - 36 male and 21 female - were undergoing chemotherapy. Group 2 with 16 ALL patients - 12 male and 4 female - had followed chemotherapy. (This latter group was a type of control.) The average age of the groups was 9.7 years and 8.7 years respectively.

The results for group 1 (undergoing chemotherapy) showed: "ASA concentration in CSF was approximately two times higher than that in serum. ASR concentration in CSF was also higher than that in serum." Statistical analyses showed:

"The statistical values [were] consistent with that of ASA, which is in blood at first and becomes ASR. It [was] noted that ASR in CSF does not correlate with ASA in CSF. This correlation implies that oxidation of ASA in CSF may not interrelate with the subjects studied. However, ASR in serum has reasonable correlation with ASA in serum. This implies that oxidation of ASA in serum may be induced by the treatment."

The results for group 2 (following chemotherapy) showed: "Weak correlation ... [was] obtained for ASR in CSF and serum. No strong correlation for ASR and ASA in serum nor for ASA in CSF and serum was obtained."

The author continued: "These results were different from those for patients undergoing the treatment and may be attributed to remission."

In conclusion, Nakagawa stated: "The analyses showed that ASR and ASA in CSF and serum had good correlation for patients undergoing chemotherapy but not for patients after the therapy. The correlation for ASR and ASA suggests that ascorbate may play an important role during chemotherapy."

Study 18. 2001

Reddy VG, Khanna N, Singh N: Vitamin C augments Chemotherapeutic Response of Cervical Carcinoma HeLa Cells by stabilizing P53. *Biochemical and Biophysical Research Communications,* 2001; 282: 409-415.

Summary

Reddy et al. wrote: "Human Papilloma Virus (HPV) is associated in most instances with cervical cancer. The HPV oncoproteins target P53 protein [a tumour suppressor gene] for degradation, leading to deregulation of cell cycle."

The authors found that vitamin C through a downregulating action was shown to decrease one of the functions of HPV, and as a result stabilized P53. They also observed: "Accumulation of P53 and its target gene bax then sensitized HeLa cells to cell-cycle arrest, cell death/apoptosis induced by cisplatin, and etoposide."

For the downregulatng activity, low dose vitamin C (1 μM) was administered for various time periods (6 - 36 hrs) to the cell culture of human cervical carcinoma cell line (HeLa). This treatment was found to be non-toxic.

The test using vitamin C with the two anti-cancer agents showed that "cisplatin treatment (2-10 μM) for 48 h[ours] in Hela cells primed with vitamin C (1 μM) for 24 to 36 h[ours] resulted in increased cell death.... Flow cytometric analysis showed that the percentage apoptosis increased from 13.7% with cisplatin alone, to 18.9, 32.6, and 49.23% after vitamin C priming for 12, 24, and 36 h[ours], respectively...." Similar results were observed with vitamin C (1 μM) and etoposide (2 μM) for 36 hours.

In summary, Reddy et al. stated: "The cause for poor responsiveness to chemotherapy lies in the etiopathogenesis of cervical cancer i.e., HPV infection and loss of tumor suppressor gene function due to inactivation of P53 [and another].

The restoration of P53 levels could be a potential strategy to increase chemoresponsiveness. However, there are conflicting reports regarding the role of P53 and chemosensitivity" as reported by other investigators. The authors continued: "Different authors have adopted different strategies... [to] stabilize P53 levels. We selected vitamin C based on the fact that it prevents the development of CIN to cervical cancer and decreases methylcholanthrene (MCA) induced cervical cancer in mice" as reported by other investigators. Reddy et al. continued: "Vitamin C at low doses was seen to... increase in p53 protein... but was not sufficient to induce apoptosis"-thus its augmenting capability.

With regard to cisplatin, Reddy et al. stated: "Cisplatin, the single most active drug against cervical cancer, was found to produce maximum addictive affect *in vitro* on vitamin C pretreatment." The authors also stated: "Another important finding of our study was that the combination of high doses of vitamin C and cisplatin could decrease the effect of chemotherapy." They added: "Our findings suggest that priming with low dose of vitamin C can have a significant additive effect particularly with low dose of *in vivo* achievable chemotherapeutic drugs, as shown by increased apoptosis."

In conclusion, Reddy et al. stated: "Increasing drug sensitivity of cervical carcinoma cells by stabilizing P53 using vitamin C is a novel approach and has potential clinical relevance."

Study 19. 2002

Blasiak J, Gloc E, Wozniak K, Mlynarski W, Stolarska M, Skorski T, Majsterek I: Genotoxicity of Idarubicin and its Modulation by Vitamins C and E and Amifostine. *Chemico-Biological Interactions*, 2002; 140: 1-18.

Summary

Blasiak et al. stated in this minireview of treatment with antioxidants and chemotherapy: "Genotoxicity of anticancer drugs in non-tumor cells is of special significance due to the possibility of inducing secondary tumors. It is therefore important to determine genotoxic potential of a drug, which is to be used in chemotherapy." They cited other investigators in considering DNA damage "as essential markers of genotoxicity."

The authors noted: "Idarubicin is an anthracycline anticancer drug used in haematological malignancies. The main side effect of idarubicin is free-radicals based cardiotoxicity."

Blasiak et al. stated: "Because diet of patients receiving chemotherapy can be easily supplemented with vitamins, it is reasonable to check whether these vitamins, ..., can suppress the adverse effects of anticancer drugs." The authors cited studies which "indicated profitable activity of vitamins against side effects of cisplatin, DOX and other anticancer drugs."

For example, it was reported that (1) "vitamin C can promote the removal of oxidative DNA damage from the DNA and/or nucleotide pool, through the upregulation of repair enzymes," and (2) it "can cause strand breaks and base modifications in DNA via the production of hydroxyl radicals or lipid alkoxyl radicals by reaction of the reduced metal ions with hydrogen peroxide or lipid hydroxy-peroxides."

Blasiak et al. stated that in their study, they "investigated DNA-damaging potential of idarubicin in normal human peripheral blood lymphocytes using the alkaline single cell gel electrophoresis (comet assay)." A further study sought to discover "mechanisms underlying genotoxicity of idarubicin", and to this end a test was conducted to check "the ability of vitamins C and E and amifostine to modulate DNA-damaging effect exerted by the drug."

The tests were conducted with normal human lymphocytes and murine transformed (cancer) cells.

With regard to normal human lymphocytes, which were treated with the drug in the presence and absence of the vitamins, the result showed that vitamin C (sodium ascorbate) 10 μM "significantly de-

creased the mean % tail DNA of the cells exposed to idarubicin at all tested concentrations of the drug" - thus being effective with normal cells. On the other hand, the same dose of sodium ascorbate "had no influence on [the] murine ... transformed cells" - thus not being effective with cancer cells. The authors had noted that the latter cells "can be treated as model cells of human acute myelogenous leukemia." To conclude, Blasiak et al. stated:

(1) "Our experimental data [indicated] that idarubicin can generate damage to DNA in intact normal human peripheral blood lymphocytes. It is likely, that the damage is caused by oxygen radicals generated by idarubicin; DNA methylation by the drug can also contribute to the damage."

(2) "Our results [indicated] that not only cardiotoxicity but also genotoxicity and in consequence induction of secondary malignancies should be taken into account as diverse side effects of idarubicin."

(3) "Genotoxicity of idarubicin may be considered as the origin of its anticancer activity, but the genotoxic effect exerted by the drug on normal cells should not surpass the effect on cancer cells."

(4) "Vitamin C can be considered as protective agents against DNA damage in normal cells in persons receiving idarubicin-based chemotherapy, but the use of vitamin E cannot be recommended and at least needs further research."

Study 20. 2002

Catani MV, Costanzo A, Savini I, Levrero M, De Laurenzi V, Wang JYJ, Melino G, Avigliano L: Ascorbate Up-Regulates MLH1 (Mut L Homologue-1) and P73: Implications for the Cellular Response to DNA Damage. *Biochemical Journal,* 2002; 364: 441-447.

Summary

Catani et al. stated as reported by other investigators: "The cellular response to DNA damage requires activation of MLH1, which can co-operate with the tumour-suppressor *p53* gene to promote cell cycle arrest and cell death."

In this study using cell culture, the authors "investigated the ascorbate-mediated up-regulation of the *MLH1* gene, as an involvement of ascorbate in the regulation of DNA repair enzymes [as] has been postulated."

Their results showed "for the first time, that this antioxidant vitamin positively regulates the apoptotic cascade primed by MLH1 in response to DNA damage" as reported by other investigators. MLH1 was shown to modulate "the effectiveness" of cisplatin when used in conjunction with ascorbate. "Ascorbate, by increasing the cellular content of MLH1, improves the cellular response to DNA damage. Indeed, induction of increased *MLH1* gene expression by DNA damage allows faster c-Abl [pathway] activation; thereafter, increased p73 activation (which is also regulated by ascorbate) could be achieved."

In conclusion, Catani et al. stated that "biochemical mechanisms accounting for this activity are not fully understood." However, the authors suggested that "both the anti-carcinogenic and anti-cancer activities of ascorbate might be explained by modulation of *MLH1* gene expression. The chemopreventive activity may be attributed to the ability of ascorbate to act as a radical scavenger and also to prime, through induction of *MLH1* and *p73* gene expression, the apoptotic programme in DNA-damaged cells, which otherwise would proceed towards tumorigenic progression. By modulating *MLH1* gene expression, ascorbate can also enhance the anti-neoplastic activity of several drugs: in our experimental model, ascorbate, used in combination with cisplatin, increased the apoptosis of tumour cells." Catani et al. noted that their results compared with the results of other investigators; namely, Sarna and Bhola (1993) as seen elsewhere in this annotated bibliography.

Finally the authors stated that "combined therapy with ascorbate and DNA-damaging drugs (such as cisplatin) may allow the same pharmacological effectiveness to be attained with lower doses of the chemotherapeutic agent, with a consequent reduction in collateral effects."

Study 21. 2002

Calderon PB, Cadrobbi J, Marques C, Hong-Ngoc N, Jamison JM, Gilloteaux J, Summers JL, Taper HS: Potential Therapeutic Application of the Association of Vitamins C and K3 in Cancer Treatment. *Current Medicinal Chemistry,* 2002; 9/24: 2271-2285.

Summary

Calderon et al. stated: "Oxidative stress can stimulate growth, trigger apoptosis, or cause necrosis depending upon the dose and the exposure time of the oxidizing agent."

The authors continued: "A large body of evidence supports the idea that oxidative stress induced by redox cycling of vitamins C and K3 in association surpasses cancer cellular defense systems and results in cell death, The molecular mechanisms underlying such a process are, however, still unknown. Indeed, several types of cell death may be produced, namely autoschizis, apoptosis and necrosis."

The method which Calderon et al. studied in the treatment of cancer cell death was the use of combined C-K3 treatment with chemotherapy. Some abbreviations are ILS–increase in life span and MST -mean survival time.

The authors stated that "the oxidative stress induced by redox cycling of these vitamins make cancer cells - which are deficient in antioxidants enzymes [as reported by other investigators]-more sensitive to the antitumoral compound." They continued: "Indeed, it has been reported that the loss of redox homeostasis either by vitamin C or by vitamin K3, results in cell death by apoptosis. Due to the close relationship between apoptosis and oxidative stress, the increase in the intracellular levels of hydrogen peroxide (H_2O_2) was thought to be the explanation for the cytotoxicity of the combined vitamins"; vitamin K3 can also "produce reactive oxygen species."

One of the following tests was similar to that described in Taper et al. (1987)– Taper, as indicated, is one of the authors here. The results of the *in vivo* tests are as follows:

(1) C and K3 alone and C plus K3: Twelve ascitic TLT-bearing mine were administered i.p. with C 1 g/kg and K3 10 mg/kg alone or in combination. A control group was used for comparison. The test showed that the combined treatment of CK3 resulted in a mean survival time of "23.1 days as compared to 15.8 days" for the control group. The vitamins alone did not "have any significant effect on the life span" of the mice.

(2) Cyclophosphamide alone and CK3 plus Cyclophosphamide: The number of mice and the dose of the vitamins were the same as above, and the drug treatment was i.p. 80 mg/kg. The result for cyclophosphamide alone was similar to CK3 alone, whereas that for CK3 plus cyclophosphamide showed a much higher increase in life span over the controls. "The cyclophosphamide alone increased the MST from 16.8 days in untreated mice to 20.6 days (ILS=23%). The effect of CK3 on cyclophosphamide treatment resulted in an increased MST and ILS of 26.8 days and 59.5% respectively."

(3) Vincristine (Oncovin®) alone and CK3 plus Vincristine (Oncovin®): In this test, the number of mice was ten and the dose of the vitamins was the same as above. The drug treatment was i.p. 0.3 mg/kg or 1.0 mg/kg. The result showed that the first dose of oncovin had a "MST of 19.0 days and CK3 alone a MST of 22.5

days (as compared to 18.5 days in untreated animals)". In contrast "CK3 before injection of oncovin [increased] the MST to 36.5 days, that is an ILS of 97.3%."

In summary, "CK3-treatment selectively potentiated tumor chemotherapy, [and] produced sensitization of tumors resistant to some drugs," among other effects not particular to this work.

With regard to the mechanism involved in CK3 activity, Calderon et al. noted: "One of the main questions raised by the selective activity of CK3 against cancer cells concerns the mechanisms conditioning the cell death." Among the mechanisms for this activity may be the generation of H_2O_2 by both vitamins as noted in Taper et al. (1987). Here, Calderon et al. stated that they "have formulated the hypothesis that H_2O_2 is the major reactive oxygen species involved in the cell death by combined vitamins C and K3. The experimental evidence supporting such hypothesis" was then explained.

To conclude, Calderon et al. proposed "the association of vitamins C and K3 as an adjuvant cancer therapy which may be introduced into human cancer therapy without any change in the classical anticancer protocols, and without any supplementary risk for patients." The authors added: "Such adjuvant cancer therapy..., will not produce any supplementary risk ... but, on the contrary it will lead to beneficial effects of clinical cancer treatment."

Study 22. 2003

Mantovani G, Maccio A, Madeddu C, Mura L, Massa E, Gramignano G, Lusso MR, Murgia V, Camboni P, Ferreli L: Reactive Oxygen Species, Antioxidant Mechanisms, and Serum Cytokine Levels in Cancer Patients: Impact of an Antioxidant Treatment. *Journal of Environmental Pathology, Toxicology and Oncology,* 2003; 22/1:17-28.

Summary

"The main goal" of this study by Mantovani et al. "was to verify if the administration of different antioxidant agents, given either orally or i.v. to cancer patients, is feasible and effective - that is, if it reduces the blood levels of ROS [reactive oxygen species] and increases antioxidant enzymes."

"ROS play both positive and negative roles in vivo." The negative role is associated among others with the production of oxidative stress (OS), which in its turn is associated with certain degenerative diseases such as cancer.

The measuring tool used in this study was "the most important clinical index of disease progression - namely, the Eastern Cooperative Oncology Group (ECOG) Performance Status (PS)." The study of 28 patients was conducted in five groups with a selection of antioxidants administered individually for 10 days with limited chemotherapy involvement. The results for the group which was administered a vitamin A-E-C mixture showed that this mixture was "effective in reducing reactive oxygen species levels," as well as having "the additional effect of increasing glutathione peroxidase activity" (GPx - antioxidant enzyme).

The test comprised of 28 advanced-stage cancer patients, 10 male and 18 female, who had eight different tumors and who met certain characteristics of age, height and weight. Two of the patients had been on a chemotherapy regimen at least two weeks prior to the study. A controlled group comprised 20 healthy individuals with similar physical characteristics. The measuring tool was the "WHO - approved ECOG-PS scale." A number of tests using different parameters including the single antioxidants and the combined vitamin mixture in the five groups was conducted. The controlled group was not tested with the individual antioxidants. Of the five groups, the vitamin

A-E-C group was termed Arm 5. This arm was comprised of four females only and were designated by the number 1 of the ECOG PS, classified as stage III (1) and IV (3) patients and had breast (1), lung (1), melanoma (1) and myeloma (1) cancers. The treatment administered orally per day for 10 days was vitamin A 30,000 IU, vitamin E 70 mg and vitamin C 500 mg.

The results of the test at baseline and after for Arm 5 (A-E-C treatment) showed that the "blood levels of ROS decreased significantly" with the treatment. (Three of the other arms also showed this decrease.) With regard to GPx (antioxidant enzyme) activity, Arm 5 showed the lowest increase of the arms.

With regard to safety (in the different tests), Mantovani et al. stated: "The administration of antioxidant agents has been proven safe: no adverse events were recorded except in one patient who, after amifostine administration, had a short episode of orthostatic hypotension, which cleared up spontaneously in a few minutes. The compliance to the antioxidant treatment was very high, and no patient was withdrawn from or refused to continue treatment."

In reference to Arm 5 (A-E-C treatment), Mantovani et al. stated that these antioxidants "have ... been shown to be effective at [their] institution and in several of the articles cited." They noted that a further study on the impact of antioxidants on reactive oxygen species among others has been "accepted for publication." (A note pertaining to that study follows this summary.)

The authors continued that antioxidants "have different mechanisms of action", and that "numerous recent data [have] demonstrated that antioxidant agents are effective in reducing the OS [oxidative stress], and they even have an impact on cancer progression." They referred to a study with vitamin C alone or in combination where the effect on oxidative stress had been shown.

In their conclusion however, Mantovani et al., based on the results of this study did not suggest the vitamin combination as a "best treatment" as they did for three of the antioxidants. They had stated in the same paragraph that a number of factors was required to reach a "best antioxidant treatment". Finally, the authors stated that their "results warrant further investigation with an adequately large clinical trial to test the hypothesis that the supplementation of antioxidant agents may mitigate oxidative stress in cancer patients, occurring either spontaneously or enhanced by treatment with cisplatin or other oxidative damage-inducing drugs" as reported by other investigators.

A Note

The anticipated follow-up on further study of the A+C+E treatment was not forthcoming as that treatment was not among the combined antioxidant treatments of the phase II study below. A phase III study mentioned in the earlier article "is soon to be activated at [the authors'] institution."

Mantovani G, Maccio A, Madeddu C, Mura L, Gramignano G, Lusso MR, Murgia V, Camboni P, Ferreli L, Mocci M, Massa E: The Impact of Different Antioxidant Agents Alone or in Combination on Reactive Oxygen Species, Antioxidant Enzymes and Cytokines in a Series of Advanced Cancer Patients at Different Sites: Correlation with Disease Progression. *Free Radical Research,* 2003; 37/2: 213-223.

Study 23. 2003

Drisko JA, Chapman J, Hunter VJ: The Use of Antioxidants with First-Line Chemotherapy in Two Cases of Ovarian Cancer. *Journal of the American College of Nutrition,* 2003; 22/2: 118-123.

Summary

Drisko et al. stated: "Because of poor overall survival in advanced ovarian malignancies, patients often turn to alternative therapies despite controversy surrounding their use. Currently, the majority of cancer patients combine some form of complementary and alternative medicine with conventional therapies. Of these therapies, antioxidants, added to chemotherapy, are a frequent choice." Vitamin C is among the antioxidants used.

In this study, the authors reported on "two cases of advanced ovarian cancer where antioxidants were added adjunctively to chemotherapy without adversely effecting outcome or survival." The study was observed as Case 1 and Case 2 because as will be seen, the patients' procedures were not the same in all respects.

Case 1: This patient was 55 years old who had undergone surgery and was found to have what is called Stage IIIC papillary serous adenocarcinoma of the ovary. After the surgery, the patient began a combined oral antioxidant treatment. This treatment "included vitamin E (1,200 IU), coenzyme Q10 (300 mg), vitamin C (9,000 mg), beta-carotene (mixed carotenoids, 25 mg), and vitamin A (10,000 IU)." Then the patient received the first cycle of chemotherapy. This application consisted of "standard carboplatin (AUC 6) and pacilitaxel (175 mg/m2) chemotherapy for a total of six cycles". The next procedure was a treatment of intravenous vitamin C. This application of ascorbic acid began with "15 grams and increased to 60 grams per infusion given twice weekly."

Drisko et al. continued: "The 60-gram ascorbic acid infusions were given two times per week during the six cycles of consolidation chemotherapy, after which the patient continued the 60-gram ascorbic acid infusion once per week. This dose and schedule was continued for one year, after which the patient chose to reduce the frequency of the infusion to every 10 to 14 days." They continued: "The patient is currently over 40 months from initial diagnosis and remains on ascorbic acid infusions. She has had several CT scans, as well as a PET scan, all of which remain negative for disease. Her CA-125 remains normal at a value of 8.8."

Case 2: This patient was 60 years old who also had undergone surgery and was found to have what is called Stage IIIC mixed papillary serous and seromucinous adenocarcinoma of the ovary. Three months after surgery, because of a problem involving a respiratory condition, this patient also began a combined oral antioxidant treatment. This treatment consisted of "ascorbic acid (3,000 mg/day), vitamin E (1,200 IU/day) and beta-carotene (25 mg/day) and vitamin A (5,000 IU/day)" but no coenzyme Q10. Then the patient also received the first cycle of chemotherapy. This application consisted of "carboplatin (AUC 6) and paclitaxel (135 mg/m2) for six cycles". The next procedure for this patient differed from that of the other patient because:

"After the completion of her first course of chemotherapy, the patient was found to have disease in the pelvis.... The patient declined consolidation chemotherapy, instead opting for continuation of oral antioxidants and initiation of parenteral ascorbic acid infusions." The intravenous ascorbic acid application was the same as for patient 1 - "15 grams and increasing to 60 grams per infusion."

Drisko et al. continued: "The patient [then] had daily 60-gram ascorbic acid infusions for one week and then began twice weekly infusions, which continues to date 36 months post-diagnosis. Although further diagnostic imaging was declined, physical examination has remained normal. Her most recent CA-125 is 5, and she is over three years out from diagnosis."

With regard to side effects of chemotherapy, Drisko et al. observed from the results:

(1) "Both patients were monitored for

toxicity, and neither patient had grade three or four toxicity that limited completion of six cycles of front-line chemotherapy."

(2) "Both patients had mild, self-limited nausea."

(3) "Patient 1 noted the onset of numbness and tingling of both hands and feet during the first course of chemotherapy, but prior to the institution of parenteral ascorbic acid."

(4) "Patient 1 also complained of the onset of fatigue, increased shortness of breath and peripheral edema during the first course of chemotherapy, but prior to the introduction of intravenous ascorbic acid."

(5) "Neither patient demonstrated hematologic toxicity, including neutropenia or thrombocytopenia" or "required colony-stimulating factors. There was no evidence for febrile neutropenia or infection."

(6) Neither patient "demonstrated elevated renal or liver enzymes."

The only concern was the cardiac problem which was resolved with other treatment.

Finally, Drisko et al. stated, after reviewing a number of studies on the use of antioxidants with chemotherapy:

"Despite the fact that chemotherapy-induced formation of free radicals is well demonstrated, chemotherapy-induced cytotoxicity in general does not seem to depend on formation of reactive oxygen species; thus, the concept that antioxidants are contraindicated during most chemotherapy regimens is no longer valid. In fact, as demonstrated with the reported cases, antioxidants when added adjunctively to chemotherapy may improve the efficacy of chemotherapy and may prove to be safe." The authors noted that a further study based on "the positive results" of this study is underway at their institution.

Study 24. 2003

Abdel Rehim WM, Sharaf IA, Hishmat M, El-Toukhy MA, Abo Rawash N, Fouad HN: Antioxidant Capacity in *Fasciola hepatica* Patients Before and After Treatment with Triclabendazole Alone or in Combination with Ascorbic Acid (Vitamin C) and Tocofersolan (Vitamin E). *Arzneim.-Forsch./ Drug Res.,* 2003; 53/3: 214-220.

Summary

Abdel Rehim et al. noted: "In Egypt, an increasing prevalence of human fascioliasis was observed in the last 20 years", and according to other investigators a new drug, triclabendazole, "has recently been registered in Egypt for the treatment of human fascioliasis."

The authors stated: "The aim of the present study was to investigate the effect of triclabendazole (...) therapy alone or in combination with ascorbic acid (vitamin C, ...) and tocofersolan (vitamin E, ...), in *Fasciola hepatica* patients, on Lipo-peroxidation (LPO) and blood antioxidant capacity."

The clinical test was conducted with 32 *Fasciola hepatica* patients both male and female who had an average age of 28 years old. They were grouped as 16 acute and 16 chronic patients. These two groups in turn were grouped in two subgroups of eight patients each. It was in these subgroups that the clinical test was observed along with a controlled group of ten healthy subjects both male and female of the same average age.

"One subgroup was given two consecutive oral doses each of 10 mg/kg body weight of trilabendazole suspension and the other received vitamin C (1000 mg/day) and vitamin E (600 mg/day) for two months, together with the same dose of triclabendazole given to the first subgroup."

Five biochemical parameters were used for the test: (1) serum lipid peroxide, (2) erythrocyte lipid peroxide, (3) reduced glutathione (GSH), (4) glutathione peroxidase (GPx) and (5) superoxide dismutase (SOD).

The results showed that the combined treatment with the drug and vitamins was more effective than the drug alone. The

test also showed that a statistical correlation between the biochemical parameters was either positive or negative.

Abdel Rehim et al. observed the following:

For Lipid Peroxides-"The results obtained in the present study revealed a significant increase in the levels of lipid peroxides expressed as MDA [malonyl dialdehyde] of both serum and erythrocyte in chronic and acute *Fasciola* patients before and after triclabendazole treatment alone or in combination with vitamins as compared to the corresponding control levels." The authors also observed: "In the group of chronic *Fasciola* patients ..., the levels of MDA were significantly decreased as compared to the corresponding values after triclabendazole treatment". They continued, as reported by other investigators, that "this may be due to the reduction in oxidative stress induced by the free radical scavenging effect of vitamins C and E with a consequent improvement of patient's antioxidant capacity."

For Reduced Glutathione-"In the present study, there was a significant decrease in the level of glutathione content in chronic and acute *Fasciola* patients before and after triclabendazole alone or in combination with vitamins as compared to the corresponding control level." With regard to both groups of patients, the authors observed, as reported by an investigator:

"The significant decrease in blood glutathione peroxidase enzymatic activity in all *Fasciola* patients compared to controls could be partly due to the reduction of glutathione itself where glutathione peroxidase (GPx) functions together with glutathione to exert its effect."

For Glutathione Peroxidase and Superoxide Dismutase-"The activities of GPx and SOD were significantly higher in all *Fasciola* patients treated with triclabendazole and vitamins when compared with those of patients treated with triclabendazole alone." The authors continued: "This could be explained on the basis of increased antioxidant capacity of these patients exerted by vitamins C and E supplementation."

Lastly, in reference to the statistical correlation, Abdel Rehim et al. stated: "A highly positive correlation was observed between GSH and SOD, and between GSH, GPx and SOD and between serum and erythrocyte lipid peroxides ..., while a significant negative correlation was found between lipid peroxides and GSH, GPx and SOD...."

Finally, Abdel Rehim concluded: "The significant improvement of SOD and GPx activities and in lipid peroxide levels after vitamins supplementation as compared to their corresponding values after treatment with triclabendazole alone could be explained on the basis of the potent action of these vitamins in protection against oxidative damage."

This summary brings to an end the section on positive studies.

Positive Reviews (Table 2)

Review 1. 1993

Hoffer A: Orthomolecular Oncology. In Quillin P; Williams RW (eds.). *Adjuvant Nutrition in Cancer Treatment,* 1992 Symposium Proceedings, Cancer Treatment Research Foundation, Arlington Heights, Illinois, USA, 1993.

Summary

Hoffer wrote: "Orthomolecular oncology is the treatment of cancer by the provision of the optimal molecular environment for the body, especially the optimal concentrations of substances normally present in the human body. This does not mean that this treatment is an alternative or is antagonistic to standard therapy using toxic drugs in sublethal doses (xenobiotics). In my opinion, the optimum treatment for cancer today, imperfect as it is, is orthomolecular therapy combined with xenobiotic therapy."

In this article, Hoffer reported on the 1990 Hoffer and Pauling study mentioned

Table 2. Positive reviews.

1. Hoffer A:	Orthomolecular Oncology. Adjuvant Nutrition in Cancer Treatment	1992 In Quillin, P and Williams, RW (eds.). Symposium Proc, Cancer. Treatment Res Foundation. Illinois, USA, 1993.
2. Moss RW:	Questioning Chemotherapy	1995; Equinox Press, NY.
3. Prasad KN, Kumar A, Kochupillai V, et al:	J Amer Coll Nutr	1999; 18/1: 13-25.
4. Simone CB, Simone NL, et al:	Intl J Integr Med	1999; 1: 20-24.
5. Moss RW:	Cancer Therapy: The Independent Consumer's Guide to Non-Toxic Treatment and Prevention	1999; Equinox Press, NY.
6. Lamson DW, Brignall MS:	Altern Med Rev	1999; 4/5: 304-329.
7. Conklin KA:	Nutr Canc	2000; 37/1: 1-18.
8. Hoffer A:	Vitamin C and Cancer	2000; Quarry Press Inc., ON.
9. Lamson DW, Brignall MS:	Altern Med Rev	2000; 5/2: 152-163.
10. Drisko JA, Chapman J, Hunter, VJ:	Gynec Oncol	2003; 88/3: 434-439.
11. Tamayo C, Richardson MA:	Alternat Ther	2003; May/June/9/3: 94-102.
12. Houston R:	Townsend Lett Doctors Patients	2003; June/239: 104-106.

in the above section. Following that study, as a result of a possible concern by "critics" regarding "validity", another study was conducted for comparison. (The writer does not know the date of the study as it was not mentioned before. However, it may be 1990 or shortly thereafter as the results were known before 1992 as per below.) That study comprised the 101 original treated patients and 19 untreated patients from the original 33 controls (14 of whom had died).

With regard to survival time, the result of this comparison study showed: "The difference in outcome between these two groups [remained] large. In the first year, 75% of the group not on the orthomolecular program died, and at the end of five years only 5% were alive. From the orthomolecular group, 25% died by the end of the first year, and at the end of the 5th year 39% were alive. By January 1, 1992, 41 patients were still alive. The average duration of life from the time I first saw them until this date was 49 months, compared with 15 months for the group treated with xenobiotic therapy only."

These results supported the investigators' "conclusion that orthomolecular treatment combined with xenobiotic treatment is much superior to xenobiotic therapy alone." However, Hoffer stated: "As a clinician who has worked with patients for 42 years, I still think the original control group [of 33] is the sounder one to use scientifically." The author continued:

"Twenty patients out of 59 (34%) survived 8 years. They were first seen between 1978 and 1984. From the remaining 75, seen between 1985 and 1988, 22 (29%) survived 4 years. This suggests that over the four years this group will also yield a 25% 8-year survival."

Finally, with regard to quality of life, the results of the 1990 study showed that the mineral-vitamin treatment enhanced the life of the patients. Here, Hoffer elaborated on that enhancement. He stated:

"It is difficult to measure quality of life, but it is relatively easy to find out whether the patients and their families were more comfortable, suffered less

pain, and remained more functional.... I have not had a single complaint from my patients that they suffered more pain and discomfort. This contrasts strongly with xenobiotic therapy, which is characterized by severe discomfort of many kinds, nausea, fatigue of long duration, loss of hair, etc. Orthomolecular therapy tends to decrease the discomfort caused by xenobiotic therapy. This is also difficult to quantify, but I believe my patients were telling me what really happened when they reported that they were able to tolerate radiation and chemotherapy better." Hoffer added: "Their surgeons often were surprised by their rapid recovery from surgery." He noted: "They were discharged very quickly from the hospital."

Review 2. 1995

Moss RW: *Questioning Chemotherapy.* Equinox Press, New York, 1995, chapter 9.

Summary

One of the topics examined by this book is the quality of life that results from the use of chemotherapy and non-toxic substances alone or in combination. Antioxidants, including vitamin C, used in conjunction with chemotherapy have been found to enhance the life of cancer patients.

Moss cited two studies which showed vitamin C's effectiveness:

(1) "vitamin C increased the cell-killing ability of chemotherapy [Block 1991]."

(2) vitamin C "blocked heart damage associated with the drugs doxorubicin (Adriamycin) and interleukin - 2 [Skimpo 1991]" - seen elsewhere in this presentation as well.

Moss quotes Linus Pauling [1987]: 'Vitamin C ... controls to a considerable extent the disagreeable side effects of the cytotoxic chemotherapeutic agents, such as nausea and loss of hair, and that benefit seems to add its value to that of the chemotherapeutic agent.'

Finally, with regard to the concern of some doctors that "by reducing toxic side effects one may inadvertently decrease the effectiveness of cytotoxic drugs", Moss cited Simone (1994). The latter reported that there are "dozens of studies suggesting an enhanced killing of cancer cells by adding vitamin supplements, especially antioxidants to chemotherapy."

Review 3. 1999

Prasad KN, Kumar A, Kochupillai V, Cole WC: High Doses of Multiple Antioxidant Vitamins: Essential Ingredients in Improving the Efficacy of Standard Cancer Therapy. *Journal of the American College of Nutrition,* 1999; 18/1: 13-25.

Summary

Prasad et al. wrote: "Numerous articles and several reviews have been published on the role of antioxidants, and diet and lifestyle modifications in cancer prevention. However, the potential role of these factors in the management of human cancer have been largely ignored."

The authors also stated: "The efficacy of standard tumor therapy (...chemotherapy...) has reached a plateau." They continued by noting: "The lack of enthusiasm among clinical oncologists for using high doses of antioxidant vitamins in combination with ... chemotherapy is primarily based on fear that antioxidant vitamins may protect both normal and cancer cells against free radicals which are generated by ... most chemotherapeutic agents. Several *in vitro* and some *in vivo* studies suggest that such concerns are not valid."

Prasad et al. continued: "Based on results of our studies and others, we proposed a hypothesis that supplementation with high doses of multiple antioxidant vitamins, together with diet modification and lifestyle changes may improve the efficacy of standard ... cancer therapies by reducing their toxicity on normal cells and by enhancing their growth-inhibitory effects

(...) on cancer cells." The authors continued: "This review will discuss whether or not the above hypothesis can be supported by published ... clinical results."

With regard to the use of multiple antioxidants with chemotherapy, the authors stated: "Several *in vitro* studies have revealed that vitamin C [as reported by many investigators] ... enhance[s] the growth inhibitory effect of most of the currently used chemotherapeutic agents on some cancer cells." An example was cited with sodium ascorbate and 5-Fluorouracil which showed that the vitamin enhanced the anti-tumor effect of the chemotherapy. The authors noted: "The extent of [the] enhancement depends on the dose and form of vitamin, the dose and type of chemotherapeutic agent and the type of tumor cells."

Prasad et al. also noted: "The effect of individual antioxidant vitamins in combination with ... chemotherapeutic agents has not been tested in human tumors *in vivo* in a systematic manner." The authors continued: "Most standard therapeutic agents mediate their effects, in part, by generating free radicals which damage both normal and cancer cells. Therefore, clinical oncologists fear that the use of high doses of antioxidant vitamins during standard cancer therapy might be harmful since they might protect both normal and cancer cells against free radical damage produced by tumor therapeutic agents. The available experimental data suggest that such fear has no scientific basis."

The authors cited examples including that of vitamin C above that demonstrated clearly: " ... antioxidants do not protect cancer cells against free radical and growth-inhibitory effects of standard therapy. On the contrary, they enhance its growth-inhibitory effects on tumor cells, but protect normal cells against its adverse effects." The study by Prasad et al. (1994) with combined vitamins and chemotherapy was also noted.

With reference to toxicity, Prasad et al. stated: "The second part of our proposed hypothesis is that antioxidant vitamins in combination with standard therapeutic agents may reduce the toxicity of these agents on normal cells. Several studies using animal models (...) support this hypothesis"- vitamin C is among them. For example, the authors cited a study of vitamin C plus adriamycin (similar to Skimpo 1991) which showed that the vitamin reduced "the adverse effects of adriamycin on normal animal cells." While in combination with other vitamins, it reduced "bleomycin-induced chromosomal breakage" as reported by other investigators.

"Based on the data ... and safety issues," Prasad et al. recommended certain combined supplements for use "during and after standard therapy". The formula consisted of the following: "Multiple antioxidant vitamins including B-vitamins and appropriate minerals but without iron, copper and manganese, since these three minerals interact with vitamin C to produce free radicals".

"Additional 8 grams of vitamin C in the form of calcium ascorbate", as the use of "10 g or more have been used in human cancer treatment without toxicity" as has been reported. Extra vitamin E and B-carotene made up the formula.

The authors explained that calcium ascorbate was selected over sodium ascorbate because the latter at high doses has been reported to have particular side effects. They also explained the reasons for selecting the other nutrients and their particular doses, and they described the treatment procedure.

In addition, Prasad and coworkers point out: "A low fat (...) and high fiber (...) diet should be continued during and after standard treatment."

To conclude, Prasad et al. stated: "The proposed recommendations ... will test our hypothesis that vitamin supplements, diet, and lifestyle modifications may markedly improve the efficacy of stand-

ard ... therapies by enhancing their growth-inhibitory effects selectively on tumor cells, and by reducing their toxicity to normal cells." The authors added: "The proposed recommendation ... may also reduce the risk of second malignancies, which are being detected at increased rates among survivors of standard cancer treatment."

Review 4. 1999

Simone CB, Simone NL, Simone II CB: Nutrients and Cancer Treatment. *International Journal of Integrative Medicine,* 1999; 1: 20-24.

Summary

Simone et al. noted: "Cellular studies, animal studies, and human studies demonstrate that vitamins A, E, C, and K, beta-carotene, and selenium, as single agents or in combination, all protect against the toxicity of adriamycin and enhance its cancer-killing effects."

With regard to cellular and animal studies, the authors continued: "*In vitro* cellular studies and animal studies have used vitamins C [and other nutrients] - as single agents or in combination - given concomitantly with chemotherapy, or tamoxifen, or interferon alpha-2b, or radiation, or combinations of these modalities. They all show the same effect: Increased tumor killing and increased protection of normal tissues."

In reference to the effectiveness of antioxidants as anti-cancer agents, Simone et al. stated:

"Antioxidants protect normal cells and other tissues by fighting free radicals and the oxidative reaction that free radicals cause." Vitamin C is among these antioxidants.

Finally, the authors, as their contribution to cancer treatment, recommend a program consisting of 22 vitamins, minerals and other nutrients - "Dr. Simone's Recommended Nutrients/Dosages."

Review 5. 1999

Moss RW: Cancer Therapy: *The Independent Consumer's Guide to Non-Toxic Treatment and Prevention.* Equinox Press, New York, 1999.

Summary

The purpose of Moss' book is two-fold: (1) "to provide the person with cancer [and future cancer patients] with useful information on cancer alternatives", and (2) "to aid the patient to better exercise freedom of choice in medical care." To this end, the author presented "nearly 100 non-toxic and less-toxic treatments for cancer" and their "effectiveness and safety" as cited in "nearly 1000 references" from international scientific journals. Treatment with vitamin C alone or in combination with chemotherapy is among the methods used.

The following treatments using vitamin C alone or in combination were shown to work "well in conjunction with conventional treatments, by either enhancing their cell-killing power or decreasing toxic side effects."

Moss cited studies by Hoffer and Pauling 1990 and 1993 re: combined vitamin-mineral treatment and survival time, Meadows et al. 1991 re: vitamin C and cell-killing and side effects and Skimpo et. al. 1991 re: vitamin C and toxicity of adriamycin. All the cited studies are reviewed elsewhere in this publication.

To conclude, Moss acknowledged the toxicity of high dose vitamin C "under certain circumstances" but noted that by reducing the dosage or changing to another form, the "symptoms can be relieved". Therefore, he continued, "vitamin C appears to be a very non-toxic substance, which most people can take in large amounts for long periods of time without harm."

Review 6. 1999

Lamson DW, Brignall MS: Antioxidants in Cancer Therapy: Their Actions and Interactions with Oncologic Therapies. *Alternative Medicine Review,* 1999; 4/5: 304-329.

Summary

In this review, Lamson and Brignall presented summaries of the use of antioxidants alone in cancer therapy and as an adjunct to chemotherapy. The authors acknowledged the concern of investigators that antioxidants might "decrease the effectiveness" of chemotherapeutic agents. However, they noted that it had been demonstrated - with a few exceptions - that certain antioxidants including vitamin C were effective with chemotherapy. The review also provided an extensive bibliography.

Lamson and Brignall reported on the following studies: Taper et al. 1987 re: vitamin C plus vitamin K3 given before chemotherapy which showed that the combined vitamin treatment "increased survival and the effect of several chemotherapeutic agents (...) in a murine ascitic liver tumor model." It was shown that the C+K3 treatment "did not increase the toxicity of these agents to healthy tissue." A certain characteristic of the models showed the antioxidants to be more effective than that of the "cytotoxic treatment alone, suggesting an immune-stimulating action of the vitamins."

Skimpo et al. 1991 re: vitamin C plus doxorubicin (adriamycin) which showed that the combination "led to a reduction in the toxicity seen with doxorubicin alone in mice and guinea pigs"

Chiang et al. 1994 re: vitamin C plus vincristine whereby the vitamin was "shown to increase the drug accumulation and decrease resistance to [it] in human non-small-cell lung cancer cells in vitro. An ascorbic acid-sensitive uptake mechanism was theorized to explain these results."

Wells et al. 1995 re: enhancement by vitamin C in "doxorubicin resistance in human breast cancer cell lines already known to be resistant" as opposed to those that are not.

Kurbacher et al. 1996 re: three chemotherapeutic agents and vitamin C in which the vitamin "at non-cytotoxic concentrations (...) increased the activity of doxorubicin, cisplatin, and paclitaxel in human-breast carcinoma cells in vitro." Doxorubicin had the greatest activity. Lamson and Brignall noted that from these results, the study's authors noted "that since vitamin C has already shown an ability to reduce the cardiotoxicity of doxorubicin, ascorbic acid and doxorubicin are an attractive future treatment for breast cancer."

In conclusion, Lamson and Brignall recommended that the time has come "to research the role of [antioxidants] in conventional oncologic treatment, rather than dismiss them as a class based on theoretical concerns."

Review 7. 2000

Conklin KA: Dietary Antioxidants During Cancer Chemotherapy: Impact on Chemotherapeutic Effectiveness and Development of Side Effects. *Nutrition and Cancer,* 2000; 37/1: 1-18.

Summary

Conklin wrote: "Chemotherapy has long been a cornerstone of cancer therapy. Although extensive research is done on the development of more effective and less toxic antineoplastic agents, much less attention has been paid to factors that may enhance the effectiveness of existing drugs. Nutritional factors may hold a key to enhancing the anticancer effects of chemotherapy and to reducing or preventing certain chemotherapy-induced side effects."

The author noted: "Administration of antineoplastic agents results in oxidative stress, i.e., the production of free radicals and other reactive oxygen species (ROS). Oxidative stress reduces the rate of cell proliferation, and that occurring during chemotherapy may interfere with the cytotoxic effects of antineoplastic drugs, which depend on rapid proliferation of cancer cells for optimal activity. Antioxidants detoxify ROS and may enhance the anticancer effects of chemotherapy."

The author added: "ROS also contribute

to side effects that occur only with individual agents, such as doxorubicin-induced cardiotoxicity, cisplatin-induced nephrotoxicity, and bleomycin-induced pulmonary fibrosis. Antioxidants can reduce or prevent many of these side effects, and for some supplements the protective effect results from activities other than their antioxidant properties."

"This review considers a limited number of dietary supplements that have antioxidant properties or influence cellular antioxidant systems. The emphasis of the review is on those antioxidant supplements that have been most studied with respect to effects on antineoplastic responsiveness or reduction of chemotherapy-induced side effects." Vitamin C is among these supplements.

In reference to vitamin C and chemotherapy, Conklin reported on several studies, most of them described in this publication.

For example the author cited *in vitro* studies which showed that vitamin C (1) enhanced "the cytotoxic activity of doxorubicin, cisplatin, paclitaxel, dacarbazine, and bleomycin." (2) increased "drug accumulation" and "partially [reversed] vincristine resistance of human non-small-cell lung cancer cells." (3) the author also noted: "Animal studies have shown that vitamin C at 500 mg/kg and 1,000 mg/kg [enhanced] the chemotherapeutic effect of cyclophosphamide, vinblastine, 5-FU, procarbazine, ... (BCNU), and doxorubicin, although other studies found that vitamin C was without effect on the activity of doxorubicin when vitamin C was administered at 2 g/kg/day to mice or 835 mg/kg/day to guinea pigs." (4) "In mice and guinea pigs, 2,000 mg/kg/day of vitamin C prevented doxorubicin-induced lipid peroxidation and reduced the acute cardiotoxic effect of doxorubicin." (5) "Protection against chemotherapy-induced mutagenesis by vitamin C has been demonstrated in cultured human lymphoblastoid cell lines and peripheral blood lymphocytes and after intraperitoneal administration of 3, 5, and 7 g/kg of vitamin C in mitomycin C-treated mice."

The author also reported on a clinical study that compared treatment with 100 mg or 1,000 mg of vitamin C as follows: "Protection against chemotherapy-induced mutagenesis has been found by Pohl and Reddy [1989] after oral administration of vitamin C to human volunteers. These investigators cultured lymphocytes from 10 volunteers two weeks before and two weeks after daily administration of 100 or 1,000 mg of vitamin C and assessed bleomycin-induced chromosomal damage in each of the cultures. Supplementation with 1,000 mg of vitamin C significantly reduced the chromosomal damage, suggesting that vitamin C may reduce the risk of chemotherapy-induced carcinogenesis. Although supplementation with 100 mg of vitamin C reduced chromosomal damage, the difference did not reach statistical significance."

In conclusion, Conklin stated: "Dietary supplementation with antioxidants may provide a safe and effective means of enhancing the response to cancer chemotherapy." The author continued: "Vitamin E may prove to be an important nutrient for enhancing antineoplastic activity because of its role in preventing lipid peroxidation, thus maintaining the rapid rate of proliferation of cancer cells. Other antioxidants may be important because of their antioxidant properties". With regard to vitamin C, the author did not mention it specifically, but as reported in the studies above, it seems to fit into the "other" category because of its protection "against lipid peroxidation" and its enhancing and reduction of toxicity activities as reported in the studies above.

Conklin also noted the probable improved quality of life with dietary supplements after chemotherapy. The author wrote:

"Quality of life of patients after chemotherapy may be improved by dietary supplementation with antioxidants that reduce

or prevent chemotherapy-induced side effects." He continued: "Although approved cytoprotectants are available" as reported by another investigator, "these agents are not without adverse effects." He continued: "In contrast, certain dietary antioxidants, in doses that are without adverse effects, can ameliorate some side effects of cancer chemotherapy." Only coenzyme Q10 in reference to "cardiotoxicity" was mentioned for this activity.

Conklin ended by stating that "much more work is needed to establish a clear role for the use of dietary supplements as an adjunct to cancer chemotherapy."

Review 8 . 2000

Hoffer A: *Vitamin C and Cancer*. Quarry Press Inc., Kingston, ON, 2000.

Summary

Hoffer wrote that this book "is a collaborative work with Linus Pauling" who originated it, "because of his great interest in vitamin C and cancer". However, the author stated:

"In spite of his immense prestige, Linus Pauling could not find a publisher who would publish our book." He continued: "We should have anticipated this response because the Proceedings of the National Academy of Science[s] ..., had rejected our first paper."

The reason that Linus Pauling's name was not given as co-author is that, as Dr. Hoffer stated, by the time a publisher was found "it was too late to have Dr Pauling participate in the final editing of the book, for he died soon after. After he died I assumed that I could still co-author this book with him, but certain complications made this impossible."

The purpose of this book is to detail the results of the 1990 Hoffer and Pauling study by "offering the reader the complete case histories" of that study. The author also elaborated on the quality of life of his cancer patients. It is this latter that is summarized here.

The main parts of the presentation are set out under the following chapter headings: New Hope for Cancer Patients; Clinical Nutrition for Treating and Preventing Cancer; Clinical Studies of the Value of Orthomolecular Treatment; Case Histories.

Hoffer, in recognising "the fears of some critics," stated that "this book is not an attack on the medical profession and the use of the standard methods for treating cancer, which include surgery, radiation, and chemotherapy. Rather, we have attempted to redress the imbalance that exists today between these xenobiotic or drug treatments and nutritional or orthomolecular therapy." He continued:

"It is necessary to let the public know that complementary treatment is available and to alert the press that they should pay as much attention to the newer developments in this field as they do to the standard approaches. It is an attempt to bring nutrition back into medicine, restoring the role it played for hundred of years."

The new hope is in the survival and quality of life of cancer patients through the use of megavitamins including vitamin C alone, or in combination "as an adjunct to appropriate conventional therapy." Hoffer pointed out:

"An important word in this statement is the adjective 'appropriate'. If there is good evidence that the proposed conventional therapy has been found to be sufficiently effective in the treatment of other patients with the same kind of cancer to outbalance the disagreeable side effects of the treatment, then the patient should give serious consideration to the possibility of accepting the treatment, but if there is no such evidence, then the patient should reject the proposed therapy."

Orthomolecular treatment as a complement to chemotherapy has been shown to increase survival time and reduce the side effects of some drugs for certain cancers. The Hoffer regimen was outlined in the 1993 Hoffer and Pauling study as de-

scribed elsewhere in this document.

Hoffer also pointed out: "Oncologists are beginning to emphasize the importance of considering duration and quality of life in measuring response to treatment. Tumor shrinkage alone is no longer considered an adequate measure" and he quoted a Toronto oncologist who agreed with this view.

The author further expounded on the quality of life as seen in his patients by detailing an example. Finally, he reiterated the benefits of orthomolecular treatment with regard to quality of life, side effects from chemotherapy and the program's palatability. He noted that only those patients who were suffering from severe side effects of chemotherapy, or other associated condition could not follow the regimen.

In conclusion, Hoffer stated: "Orthomolecular therapy provides a step forward in the battle against cancer which must be fully explored. There can be no logical reason today why most of the research funds should go only toward the examination of more chemotherapy and more ways of giving radiation. There must be a major expansion into the use of orthomolecular therapy to sort out the variables and to determine how to improve the therapeutic outcome of treatment."

In Hoffer's overall conclusion to the chapter (Clinical Studies of the Value of Orthomolecular Treatment), the last word was for his friend, colleague and collaborator, Dr. Linus Pauling, when he wrote:

"Enterprising medical schools should establish chairs in Orthomolecular Oncology, perhaps called the Linus Pauling Chair of Orthomolecular Oncology."

Review 9. 2000

Lamson DW, Brignall MS: Antioxidants and Cancer Therapy II: Quick Reference Guide. *Alternative Medicine Review,* 2000, Vol. 5, No. 2, pp. 152-163.

Summary

Lamson and Brignall explained:

"This guide is meant to be a companion to [their] previous review on effects of antioxidant supplementation during cancer therapy. Widespread use of antioxidant compounds make this an area of increasing interest to oncologists as well as other physicians; hence, the attempt to reduce the findings of a lengthy report to a manageable guide."

The authors continued: "Reducing complicated interactions to a single sentence can be an oversimplification. In may instances the effect of an antioxidant compound with a certain therapeutic agent may be specific to a particular tumor type, or may vary with dosage of both antioxidant and chemotherapy. This guide is best used as a means of quickly identifying which antioxidants are likely to be indicated or contraindicated with a particular therapeutic agent."

Lastly, the authors summarized in tables a number of studies, some of which are seen elsewhere in this presentation.

Lamson and Brignall reported on six studies for vitamin C alone or in combination with other vitamins in conjunction with chemotherapy: five studies were positive and one study was negative. The results were as follows:

Positive

(1) Vitamin C in combination "increased [the] therapeutic effect" of cyclophosphamide, doxorubicin, 5-fluorouracil and vincristine (Taper et al. 1987).

(2) Vitamin C "decreased [the] toxicity" of doxorubicin (Skimpo et al. 1991). The authors noted that 'decreased toxicity' referred "to effect on healthy tissue."

(3) Vitamin C "increased [the] cytotoxic effect" of paclitaxel and cisplatin, as well as in human breast CA [carcinoma] cells of doxorubicin (Kurbacher et al. 1996).

(4) Vitamin C "increased [the] cytotoxic effect" of vincristine (Chiang et al. 1994).

(5) Vitamins C in combination "increased [the] cytotoxic effect" of tamoxifen (Prasad et al. 1994).

Negative

(1) Vitamin C - "ascorbic acid 2-phosphate found no change in drug-sensitive cells and decreased effect in resistant lines of doxorubicin (adriamycin)" (Wells et al. 1995).

Lamson and Brignall concluded by stating:"There are only three presently known examples in which an agent classifiable as an antioxidant has been shown to decrease effectiveness of ... chemotherapy in vivo. The vast majority of both in vivo and in vitro studies have shown enhanced effectiveness of standard cancer therapies or a neutral effect on drug action."

Review 10. 2003

Drisko JA, Chapman J, Hunter VJ: The Use of Antioxidant Therapies During Chemotherapy. *Gynecologic Oncology,* March 2003, Vol. 88, Issue 3, pp. 434-439.

Summary

Drisko et al. wrote: "At the present time, many cancer patients combine some form of complementary and alternative medicine therapies with their conventional therapies. The most common choice of these therapies is the use of antioxidants."

This article is a review of four antioxidants including vitamin C.

The authors noted: "While it is accepted that antioxidants are useful in the reduction of adverse effects of chemotherapy, the prevailing opinion is that antioxidants reduce the effectiveness of chemotherapy and radiation therapy's neoplastic toxicity [five sources]. However, there is evidence that antioxidants may also be a choice for therapeutic intervention alongside chemotherapy with demonstrated benefit in tumor size reduction and/increased longevity [twelve sources]."

They continued: "Despite the theoretical concern that antioxidant therapies interfere with chemotherapy ... by lowering oxidative damage, evidence supporting this mechanism is currently lacking [one source]. In fact, antioxidants act as therapeutic biologic response modifiers and are able to directly induce apoptosis in already established neoplastic cells [five sources]. There is also supportive evidence that antioxidants enhance antitumor effects of chemotherapy in vitro and in vivo [five sources]." Lastly, the authors noted: "It is now recognized that chemotherapy kills tumor cells not by damaging essential biological functions but by initiating programmed cellular responses" and that "mutations that interfere with apoptosis may produce tumor chemotherapy resistance [two sources]."

In reference to vitamin C, Drisko et al. reported from 24 references on the vitamin which showed both positive and negative results of vitamin C alone, or in combination with other vitamins used with chemotherapy, among other descriptions. Three of the studies are reviewed elsewhere in this document.

Drisko et al. concluded: "Currently, evidence is growing that antioxidants may provide some benefit when combined with certain types of chemotherapy. Because of the potential for positive benefits, a randomized controlled trial evaluating the safety and efficacy of adding antioxidants to chemotherapy in newly diagnosed ovarian cancer is underway at the University of Kansas Medical Center."

Review 11, 2003

Tamayo C, Richardson MA: Vitamin C as a Cancer Treatment: State of the Science and Recommendations for Research. *Alternative Therapies,* 2003; May/June/9/3: 94-102.

Summary

Tamayo and Richardson stated: "The rise in the use of dietary supplements and herbal medications by patients makes it

imperative to reevaluate the past findings of clinical studies. Among unconventional approaches, high-dose vitamin C is one of the most widely used and studied, yet controversial approaches."

The authors continued: "High doses of vitamin C and other naturally occurring substances are used in orthomolecular medicine as described by the renowned chemist Linus Pauling." They continued, according to one of the main proponents of orthomolecular medicine: "The primary aim of this approach is to establish an optimal molecular environment, yet the benefits remain unproven and the approach discouraged" by other authors.

"This paper summarizes the evidence for the anti-tumor activity of vitamin C and reviews the biological plausibility supporting the use of high dose vitamin C as a cancer treatment." Most of the material for this study came from a 1999 Montreal workshop, at which the objective among others, was to "assess the evidence of megadoses of vitamin C alone or with other agents as a cancer treatment." The findings of this assessment are described here.

By way of introduction, Tamayo et al. briefly recalled an early work by Ewan Cameron, MD, who "used high doses of vitamin C to treat advanced, untreatable cancer in Scotland."

The authors noted: "In 1971, Dr. Cameron conducted a Phase I-II study in patients with advanced, untreatable malignancies and evaluated fifty consecutive cases for minimal/no response growth retardation, cytostasis, tumor regression, or tumor hemorrhage/necrosis" as reported in his 1974 study with Linus Pauling.

Tamayo and Richardson continued: "Approximately 4% of patients had been previously treated with chemotherapy and considered unlikely to respond to standard treatment" as reported in a 1993 book by Cameron and Pauling. This book also outlined positive effects including "reduced tumor progression".

The present authors continued: "The clinical responses in Scotland suggested a biological basis for further investigation in several cancers. Subsequently, two retrospective studies [1978 and l979 - Cameron and Pauling] compared survival for patients with vitamin C with that of patients treated with conventional treatment and who were matched on gender, age, tumor diagnosis, and clinical stage. Both studies demonstrated significantly improved survival with vitamin C."Thereafter, Tamayo and Richardson continued: "Increased interest in vitamin C resulted in two randomized, double-blind controlled trials of high dose oral vitamin C that were conducted at the Mayo Clinic. The 1979 study included patients with a variety of advanced cancers [Creagan et al.] and a 1985 trial included patients with advanced colon cancer [Moertel et al.]. Neither found vitamin C beneficial." However, it was stated by the original investigators (Cameron and Pauling) that the two afore-mentioned studies were not identical to theirs. Following this controversy, "rational guidelines for testing biological agents such as vitamin C have been developed, and new information has emerged [ten sources]."

Finally, by way of introduction and with regard to safety and toxicity, Tamayo and Richardson noted:

"Although data about the effect of high vitamin C concentrations in modifying or enhancing biochemical or molecular function in human tissues is limited, it seems that high doses are safe and lack deleterious toxic effects." Two authors reported that very high doses - in excess of 2,000 mg "may result in nausea and diarrhea."

Tamayo and Richardson summarized the findings of the evidence of high dose vitamin C used alone or in combination with chemotherapy in point form. The material for the latter is presented in like manner.

The suggested "mechanisms of action for vitamin C ... with conventional chemotherapy"

based on several studies were as follows:
Enhanced cytotoxicity of conventional chemotherapy [seven sources]
Potentiation of chemotherapy ... with vitamin K3 [four sources]
[Modulation] and potentiation when combined with [other vitamins] of cytostatic agents (...) [one source]
Increased cisplatin-induced apoptosis [one source]
Reduction of toxicity for select chemotherapy (...) [three sources]
[P]revention of adriamycin cardiotoxicity in mice, [one source] and idarubicin genotoxicity and induction of secondary malignancies [two sources]
Reversal of cellular resistance to chemotherapeutic agents [two sources] in MCF-7 breast [one source] and melanoma cells [one source] Many of the above studies are seen elsewhere in this presentation.

Finally, Tamayo and Richardson cited the 1990 Hoffer and Pauling study using orthomolecular medicine, which is also detailed in this presentation, as appearing "to enhance the effectiveness of the conventional treatment [one source]."

To conclude, Tamayo and Richardson stated: "The value of vitamin C as a cancer treatment, alone or in combination with other nutrients, will only be established with scientific studies to determine effectiveness, if any, and appropriate clinical indications and dosages." The authors continued: Phase I and II studies as well as Phase III investigations are necessary given the plausible evidence from case reports, basic research, and the limitations of prior Phase III research. The types of clinical studies and mechanism of action studies" to be investigated was then described.

Review 12, 2003

Houston R: Two Anticancer Mechanisms of Vitamins in Humans: A Review. *Townsend Letter for Doctors & Patients,* 2003; June/239: 104-106.

Summary

In this review Houston noted:

"Recent literature explains why vitamin C has been both successful and unsuccessful at extending the life of cancer patients. Vitamin C at 10,000 mg/day was effective in the form of sodium ascorbate but not as dry ascorbic acid. The ascorbate solution oxidizes to dehydroascorbate that readily and preferably enters cancer cells and kills them." The author continued: "However, Abram Hoffer achieved excellent results with ascorbic acid."

Houston referred to a publication (2001), by a John Boik, which "lists seven traits that distinguish cancer." Also listed were "some natural compounds [including vitamin C] that are or probably are therapeutic."

Houston quoted Boik in reference to Hoffer and Pauling 1990, described in Hoffer 2000: 'My central thesis is that the most successful cancer therapies will be those that target all of these primary events involved in cancer cell survival'.

The author also noted the clinical trials of Cameron mentioned in Cameron and Pauling's book (1993) and Morishige et al. (1982) in the use of high dose vitamin C. He also noted studies by Tsao et al. (1988) and Agus et al. (1999) with regard to the sodium ascorbate derivative, dehydroascorbate (DHK), and its activity in cancer cell-killing. "Normal cells can control the intake of vitamin C." The author also mentioned the criticism by Creagan et al. (1979) and Moertel et al. (1985) of the 1976 Cameron and Pauling study. Lastly, Houston mentioned the positive review of Lamson and Brignall (2000) of the use of vitamin C with chemotherapy. The author reported:

"High-dose vitamin C can become an oxidizer and kill cancer by a free radical mechanism. Radiation and chemotherapy kill cancer by the same mechanism but also kill normal cells." Two of the above studies and the review are presented elsewhere in this publication.

In summary, Houston stated: "The sin-

gle, non-randomized clinical test by Hoffer is not scientific proof." However he acknowledged that patients are concerned with usability, safety, contraindication and helpfulness. He added:

"Hospitals and HMO's might investigate the possible savings by vitamin augmentation. The vitamins are exceedingly safe compared to standard cancer therapies. The probability of a more comfortable and longer life is high. Side effects and costs with vitamins are low. Vitamins C in the form of oxidized sodium ascorbate is economical and useful but less effective than the Hoffer regimen."

To conclude Houston stated: "Current cancer patients can consider using sodium ascorbate solution or Hoffer's regimen under medical supervision."

Neutral Study (Table 3)
Study 1, 2002

Lesperance ML, Olivotto IA, Forde N, Zhao Y, Speers C, Foster H, Tsao M, MacPherson N, Hoffer A: Mega-Dose Vitamins and Minerals in the Treatment of Non-Metastatic Breast Cancer: An Historical Cohort Study. *Breast Cancer Research and Treatment*, 2002; 2372-02: 1-7.

Summary

This study by Lesperance et al. is described as "an observational study" and it admits that "other unknown factors" may have influenced its results. These showed that high dose vitamin/mineral treatment in combination with chemotherapy did not provide a greater rate of survival or a lower rate of recurrence for a treated group over a controlled group. The authors therefore suggested "caution" when using high dose vitamin-mineral therapy for breast cancer.

Lesperance et al. described the background to the test as follows: "Subjects were women with unilateral, non-metastatic breast cancer diagnosed between 1989 and 1998 inclusive and referred to the British Columbia Cancer Agency-Vancouver Island Centre (BCCA-VIC).... The BCAA maintains a medical database containing information for all women diagnosed with breast cancer in B.C; complete diagnostic and treatment data are recorded from 1989 onwards."

The authors continued: "The vitamin/mineral prescribed patients (cases) were seen by a single physician, not affiliated with the BCAA, who has treated over 900 cancer patients with mega-doses of vitamins and minerals in Victoria, British Columbia. Office records identified 271 patients with breast cancer.... Using the identity number, name, and date of birth, each case was linked to the BCCA medical database, and their record retrieved." The 90 most recent of the 271 patients, all of whom were on the vitamin-mineral treatment, were matched with the BCCA patients.

"The controls were drawn from 2360 women ... referred to the BCCA-VIC over the same time period. The cases were matched to the controls (2:1)" using various criteria.

The determinants for the selection of the 90 patients in the treated group and the 180 patients in the controlled group were:

"BCSS, the number of days from diagnosis to death from breast cancer;" and "DFS, the number of days from diagnosis to systemic relapse (regional or distant) or death from breast cancer."

The results showed that both the survival and the recurrence rates of the treated group "were worse" than those of the controls. Lesperance et al. stated:

"Overall survival at 5 years was 72% (s.e. 5%) and 81% (s.e. 3%) for the cases and controls, respectively. Ten-year survival was 65% (s.e. 7%) and 76% (s.e. 4%), respectively, for the vitamin/mineral treated cases and the controls."

The authors explained that the shorter survival time of the treated group was determined after adjustment of certain criteria. They recognised that their "observation [contrasted] with an anticipation of survival enhancements due to mega-doses of vitamins and minerals" in the Hoffer and

Table 3. Neutral study, negative study, negative reviews.

Neutral Study		
Lesperance ML, Olivotto IA, Forde N, et al:	Breast Canc Res Treatment	2002; 2372-02: 1-7.
Negative Study		
Agus DB, Vera JC, Golde DW:	Cancer Research	1999; 59: 4555-4558.
Negative Reviews		
Labriola D, Livingston R:	Oncology	1999; July: 1003-1008.
Labriola D:	Townsend Lett Doctors Patients	1999; Nov: 120-121.

Pauling 1993 study, seen elsewhere in this presentation. However, they suggested "caution" when using high dose vitamin/mineral treatment as an adjunct to chemotherapy in the treatment of breast cancer.

Their general concern acknowledged: "Some oncologists believe that antioxidants could interfere with the actions of some chemotherapy agents, however, the scientific debate on this subject is still ongoing."

Lesperance et al. stated: "A limitation of the study, however, was that the ultimate sample size was not large enough to provide adequate power to discern small differences in survival between the two groups." They continued: "Our initial working hypothesis was that the vitamin/mineral prescribed patients would display a 25-30% increase [as reported by Hoffer and Pauling as above] in BCSS and DFS over the controls." In addition, the authors noted that "unknown factors" could have accounted for the shorter survival time and unimproved recurrence of the treated group over the controlled group.

In conclusion, Lesperance et al. stated: "The magnitude of the effects on survival observed in this study may be useful information, especially to groups planning to undertake controlled clinical trials of mega-dose vitamin/mineral regimes for the treatment of breast cancer. The results suggest that the vitamin/mineral regime prescribed is not a cure for breast cancer."

Negative Study (Table 3)
Study 1, 1999

Agus DB, Vera JC, Golde DW: Stromal Cell Oxidation: A Mechanism by which Tumors obtain Vitamin C. *Cancer Research,* 1999; 59: 4555-4558.

Summary

Agus et al. noted as reported by several investigators: "Whereas much is known about vitamin C and vitamin C deficiency states, there is little information regarding the physiology of the vitamin in cancer. Given the well-documented role of vitamin C in the maintenance of normal immune processes and host defense, it is popularly believed that supplemental vitamin C 'strengthens' the immune system. Patients with cancer who take vitamin C generally believe that it can enhance immune defense against the cancer. These notions give little attention to the nutritional needs of the cancer itself. Cancer cells readily take up vitamin C *in vitro*, and studies have demonstrated high vitamin C concentrations in neoplasms compared with the adjacent normal tissue. The mechanism by which cancers accumulate vitamin C *in vivo*, however, is unknown."

The authors continued: "Certain specialized cells can transport ascorbic acid directly through a sodium ascorbate cotransporter, but in most cells, vitamin C

enters through the facilitative glucose transporters (GLUTs) in the form of dehydroascorbic acid, which is then reduced intracellularly and retained as ascorbic acid."

A test observed: "Mice with xenograft tumors were injected into the tail vein with [^{14}C]ascorbic acid, [^{14}C]dehydroascorbic acid, or [^{3}H]sucrose and sacrificed 1 [minute] after injection. Approximately 4% of the injected dehydroascorbic acid radioactivity (...) was found in the brain of the xenograft groups after 1 [minute], a result consistent with our previous work [1997]." These last square brackets are the writer's - the earlier ones are those of the authors who continued:

"Injected ascorbic acid and sucrose yielded only trace radioactivity in the brain homogenate at 1 min, confirming that ascorbic did not readily pass the blood-brain barrier. Sucrose is not metabolized or transported, and therefore it is used as a marker of plasma volume [according to other investigators]. The xenograft tumors accumulated injected dehydroascorbic acid at [various concentrations with different cancers]." Agus et al. continued: "The results [showed] that the vitamin C accumulated in the tumors was >86% ascorbic acid in animals injected with dehydroascorbic acid as well as those injected with ascorbic acid."

From these results the authors concluded: "The involvement of the GLUTs in vitamin C uptake by the xenografted tumors was demonstrated by competitive initiation with D-glucose but not L-glucose. Because the malignant cells were not capable of directly transporting ascorbic acid, we reasoned that the ascorbic acid was oxidized to dehydroascorbic acid in the tumor microenvironment."

The authors "hypothesized that ascorbic acid was oxidized in the tumor microenvironment by superoxide anion. To test this concept, we coinjected animals bearing xenografts with ascorbic acid and SOD, catalase, or saline. The animals receiving SOD and radiolabeled ascorbic acid had an ~50% reduction in tumor vitamin C accumulation, whereas there was no change in the tumor accumulation of vitamin C in animals coinjected with dehydroascorbic acid and SOD. There was no effect of coadministration of ascorbic acid and catalase, indicating that peroxide likely did not play a role in oxidizing ascorbic acid to dehydroascorbic acid."

The authors also "tested the ability of the tumor cells themselves to generate superoxide anion." They argued that: "Because minced xenograft tumors, distinct from the cell lines, had a prominent ability to generate superoxide anion, we concluded that nonneoplastic cells in the tumor stroma were responsible for the superoxide generation."

Agus and coworkers, as reported by other investigators, confirmed that: "A sodium ascorbate cotransporter is present in many organs", but they did not find any "sodium-dependent ascorbic acid uptake in" the test materials of the present study. They continued: "Thus, the uptake of vitamin C in the form of dehydroascorbic acid through the GLUTs appears to be a general mechanism for vitamin C uptake." They added that "the sodium ascorbate cotransporter may have a role in vitamin C uptake of certain tumors."

Agus and coauthors concluded by referring to studies that dealt with positive use of vitamin C in anti-tumor therapy: "The increased intracellular concentration of vitamin C may have effects on tumor growth and the tumor's ability to respond to oxidative stress associated with chemotherapy and radiation therapy." However, they added:

"Although studies evaluating the role of vitamin C supplementation in cancer patients have generally shown no benefit with respect to survival or tumor regression [as reported by investigators], it is not known whether high concentrations of vitamin C in human tumors afford the malignant cells with a metabolic advantage." As seen in this bibliography, subsequently published re-

search have documented the effectiveness of vitamin C treatment with chemotherapy.

In conclusion, Agus and coworkers pointed out: "Our studies show the transport of dehydroascorbic acid by GLUTs is a means by which tumors acquire vitamin C and indicate the oxidation of ascorbic acid by superoxide anion produced by cells in the tumor stroma as a mechanism for generating the transportable form of the vitamin."

Negative Reviews (Table 3)
Review 1, 1999

Labriola D, Livingston R: Possible Interactions between Dietary Antioxidants and Chemotherapy. *Oncology,* 1999; July: 1003-1008.

Summary

Labriola and Livingston noted: "The popularity of nonconventional therapies, for a myriad of diseases, has increased dramatically. Most patients use some form of alternative therapy, often concurrently with conventional treatment and frequently without advising their conventional health care provider. Relying on media reports, Internet advertising, and industry marketing, many patients believe that nonconventional therapies offer cures for literally every disease, including cancer; that they do not interfere with other treatments; and that they are uniformly free of toxicity at any dosage level" as reported by other investigators.

They continued: "Since many patients treat themselves with oral antioxidants during chemotherapy, clinicians need to formulate a credible position on this subject if they are to provide their patients with timely advice about the potential risks."

Labriola and Livingston continued: "To date, no definitive human studies have demonstrated the long-term effects of combining chemotherapeutic agents and oral antioxidants. Fortunately, the mechanisms of action of both are understood well enough to predict the obvious interactions and to suggest where caution should be exercised with respect to both clinical decisions and study interpretation" as reported by other investigators.

The objective of Labriola and Livingston's review was to "describe [the above] potential interactions and areas of concern, based on the available data. It ... also [suggested] several potential courses of action clinicians may take when patients demonstrate an interest in alternative therapies."

Labriola and Livingston discussed available information under the following headings and sub-headings:

- -Cytotoxic Actions of Chemotherapeutic Agents
- -Actions of Antioxidant Compounds
- -Predictable Mechanisms of Interaction
- -Factors that may predict Interactions
- -Fraction of Drug Effectiveness that depends on Reactive Oxygen Species
- -Nature of the Reactive Oxygen Species generated by the Chemotherapeutic Agent
- -Dosage and Concentration of Reactive Oxygen Species
- -Nature of the Antioxidant
- -Concentration of the Antioxidant
- -Temporal Relationship between the Antioxidant and Reactive Oxygen Species
- -Implications for Future Research
- -Implications for Clinical Practice
- -Options for the Patient interested in Nonconventional Therapies
- -Suggested Plan for Adjunctive Nonconventional Treatment
- -Warning Signs of Possible Interactions

Conclusions

Labriola and Livingston's review made no specific reference to vitamin C, except to note that "[m]ost of the nonconventional treatments recommended for use with oncology patients have antioxidant activity. The most common of these include: vitamins A (including beta-carotene), B6, C, and E...." They stressed that: "One [of] the objectives of this article is to increase oncologists' attention to potential interactions by articulating these mechanisms."

Review 2, 1999

Labriola D: Guest Editorial-Antioxidants and Chemotherapy: What You Need to Know Before Combining Them. *Townsend Letter for Doctors & Patients,* 1999; Nov: 120-121.

Summary

This guest editorial responded to the "considerable attention" which ensued from the 1999 Labriola and Livingston negative review of the use of antioxidants during chemotherapy.

In this editorial Labriola stated: "It is important to note that this paper [as above] does not address efficacy, even though it references a number of studies showing the positive effects of nutritional supplementation during chemotherapy. It does, however, discuss those circumstances when the use of antioxidants may interfere with the tumor killing actions of some chemotherapeutic agents. It also describes strategies for safely using both."

The author then detailed a case which involved the use of alternative treatments, including antioxidants, with chemotherapy to support his theory, and he referred the reader to a published account of this patient's case history.

Lastly, Labriola engaged "providers and patients" through questions and answers on four of what he called: "The most common questions" asked.

This publication makes no specific mention of vitamin C.

Positive Responses (Table 4)

Response 1, 2000

Reilly P: Dr. Labriola's Editorial on Antioxidants and Chemotherapy, *Townsend Letter for Doctors & Patients,* 2000; Feb/Mar: 90-91.

Summary

This letter to the editor was a response to the 1999 Labriola and Livingston article and Guest Editorial of Labriola (1999) as above. Reilly wrote that these publications have "left many readers confused and scared."

He continued: "It is important to clarify that Dr. Labriola's concern is based upon a *theory* which has been shown to be unfounded when actually tested in clinical trials. Contrary to their statement, there have been numerous studies including in-vitro experiments, animal trials and small human trials which have consistently shown an *enhancement* of tumor kill and patient survival when antioxidants are combined with conventional oncology care."

The author then referred the reader to three reviews that support the use of antioxidants with chemotherapy (Cole et al. 1997, Prasad et al. 1999 and Lamson and Brignall 1999). Two of these references appear in this bibliography.

Reilly noted: "Many of the references cited in [Labriola and Livingston 1999] are not even relevant to the discussion of combining chemotherapy and antioxidants, but are review articles on the favorable use of antioxidants in the prevention of cancer, or general articles on the topic of complementary therapy and its popularity (or totally irrelevant such as a discussion of antioxidants in myotonic dystrophy). The one reference which did specifically examine the topic showed an enhancement of in-vitro and in-vivo antitumor action of [fluorouracil] and doxorubicin when combined with antioxidants. The conclusion of the referenced article was 'chemotherapeutic agents administered in the presence of antioxidants may provide a novel therapy for colorectal cancer.' "

The author described this article under discussion as "basically a pharmacology essay", and he stated: "Its conclusion is therefore basically a biochemical theory based upon other biochemical theories." He continued: "Frankly I am surprised that the authors seem to believe their own conclusions in the face of a large body of actual clinical research which contradicts them."

After noting non-negative examples on side effects in Labriola and Livingston 1999, Reilly reported on six positive examples "published in peer reviewed literature that

Table 4. Positive responses.

1. Reilly P:	Townsend Lett Doctors Patients	2000; Feb/Mar: 90-91.
2. Gignac MA:	Townsend Lett Doctors Patients	2000; Feb/Mar: 88-89.
3. Hoffer A:	Facts and Factoids: An Information Sheet for Patients	2003; May: 1-9 http://www.doctor yourself. com/hoffer_factoids.html.
4. Prasad KN, Cole WC, Kumar B, et al:	J Am Coll Nutr	2001; 20/5: 450S-463S.

support the contention that antioxidants not only reduce the side effects of cancer treatments but also enhance tumor kill."

With reference to vitamin C, the author referred to Prasad et al. 1994, Skimpo et al. 1991 and Kurbacher et al. 1996 which are reviewed elsewhere in this annotated bibliography.

The author also noted an article - Hunter et al. 1994 - which described the use of antioxidants with chemotherapy as perhaps being "beneficial".

Lastly, Reilly stated: "Meta-analysis of chemotherapy shows it to be curative in a few tumor types, but to have much smaller benefit in the most common cancers. If nutrition can reduce the side effects and perhaps even improve tumor kill, as most studies suggest, then the cost benefit equation for use of chemotherapy and radiation begins to favor rational application of these modalities in situations where little else is available. Nutritional support clearly reduces side effects of treatment. This benefit alone allows many patients to complete treatment who would otherwise discontinue due to side effects."

In conclusion, he stated: "Theory is a starting point for research, but when the evidence contradicts the theory, then we must recognize the primacy of evidence. The evidence at this point strongly favors the use of antioxidants to improve efficacy of treatment, reduce short term side effects and hopefully reduce the incidence of secondary cancers caused by the treatment. The primary rule of medicine is *first do no harm.* [Medical practitioners] must look at the harm we cause by ignoring data that does not fit our expectations and denying patients access to protective factors."

Reilly ended by stating: "The current research does need to be expanded upon with larger studies, both *in vitro* and *in vivo.* However to ignore the results of over 200 studies showing benefit based upon the same criteria used to judge other medications is irrational. Using the same logic, taxol could not be approved for use until 20 years had passed in order to prove that the initial benefit was longstanding. The problem with this logic is that cancer patients don't have 20 years to wait. If 180 articles agree a treatment can be beneficial, then we owe it to our patients to begin utilizing it while continuing to support research to further clarify any potential contraindications."

Response 2, 2000

Gignac MA: Antioxidants and Chemotherapy: What You need to know before following Dr. Labriola's Advice. *Townsend Letter for Doctors & Patients,* 2000; Feb/Mar: 88-89.

Summary

This letter to the editor is a second response to the 1999 Labriola and Livingston article and Guest Editorial of Labriola (1999) as above. Gignac wrote that the former resulted in his "consulting with

numerous confused and frightened cancer patients".

He continued: "The original article references 31 papers with no substantive data to support their contention that antioxidants interfere with chemotherapy. What is worse, this 'scientific' paper virtually ignores the fact that there are literally hundreds of articles (in vitro, in vivo, and human studies) which support the positive benefits of combination treatments. In light of the obvious bias of this article, one can hardly justify its inclusion in a 'scientific' journal."

Gignac stated that Labriola's "central premise is that dietary antioxidants most likely undermine the effectiveness of chemotherapy and that when in doubt, do not use *any* supplements while on chemotherapy!"

He continued: "I am growing more and more perplexed as to why a naturopathic physician who purports to be a specialist in the treatment of cancer would ever write an article that is so clearly biased and one-sided. This article, and its aftermath, had done more to harm the patient perception of 'integrated' oncology care than anything else that I can think of. How am I to understand Dr. Labriola's presumed objectivity when he fails to even mention that well over 100 scientific articles refute his contention that antioxidants interfere with chemotherapeutic effectiveness?"

The author then referred the reader to the three reviews mentioned in Reilly above that support the use of antioxidants with chemotherapy (Prasad et al. 1999, Lamson and Brignall 1999 and Cole et al. 1997).

Gignac then turned his attention to the Guest Editorial of Labriola (1999), stating that the editorial was "so full of weak assumptions and faulty conclusions" that he wanted "to address them individually." The discussion was in five parts including the example of the case involving alternative treatments, among them antioxidants, with chemotherapy.

In conclusion, Gignac stated: "The future of cancer treatment lies in the proper integration of conventional and complementary treatments. Oncologists should not be complacent about the fact that an estimated 40% of cancer patients die of malnutrition. According to Kern [1988] and Ollenschlager [1991], between 40 and 80% of *all* cancer patients have clinical signs of malnutrition. Many responsible physicians believe that much of the toxicity symptoms from chemotherapy are directly exacerbated by systemic nutrient depletion, secondary to treatment. Some German physicians are now openly recommending 'high-dose supplementation of essential antioxidants for patients undergoing bone marrow transplantation' [Clemens 1989]. Until more research is completed, the preponderance of existing data supports the concurrent use of antioxidants with chemotherapy."

Response 3, 2000

Hoffer A: Facts and Factoids: An Information Sheet for Patients, *http://www.doctoryourself.com/hoffer_factoids.html,* May 2003; 1-9

Summary

In this article Hoffer described the difference between a fact and a factoid, and he also responded to the 1999 Labriola and Livingston review.

With regard to the discussion on facts and factoids the author wrote: "*Fact*: Something that has really occurred or is the case: hence a datum of experience, as distinct from conclusions. Loosely defined, something that is alleged to be, or might be a 'fact.' "

"*Factoid:* A factoid is a fact that never existed before it appeared in print, but has been reprinted ever since. It is truly launched if it first appears in a reputable medical journal like the *Journal of the American Medical Association* and republished in the *New York Times* which gives it international stature. A factoid, using

simple Anglo Saxon terminology, is a lie, and like many lies and misconceptions, once it has been published develops a life of its own and is reprinted over and over, from textbook to textbook. The best example is the lie (factoid) that vitamin C causes kidney stones."

Hoffer then elaborated on facts and factoids in general and then under the headings:

Evidence required to establish Facts in Clinical Medicine

Evidence required to establish Factoids in Clinical Medicine

In reference to Labriola and Livingston (1999), Hoffer noted the "rebuttals" by "Reilly, Gignac, and Lamson and Brignall", but he did not report on the "arguments". He stated however, that "it was evident that Dr. Labriola was not convinced by the points put forward by Reilly and Gignac" and said: "I think the factoid repeated by Dr. Labriola would have a much better chance of becoming a fact if he had considered [certain] points." These points were outlined in five parts thus:

What is the therapeutic value of chemotherapy without any antioxidants?

The difference between possibility and probability.

If he had not tried to bolster his argument by referring so frequently to the peer reviewed journal in which his paper appeared.

Moss points out that oncologists have no objection to using xenobiotic antioxidants during chemotherapy.

Dr. Labriola emphasizes that long term studies must be used.

Hoffer stated: "In conclusion, as the proponents of the old paradigm [vitamins-as-prevention] see it, facts are facts only after double blind controlled experiments conducted by the right investigators from the correct school and published in the correct medical journals. Factoids can be thought up by anyone and immediately become facts in the profession if the factoid attacks the evidence against the new paradigm [vitamins-as-treatment]."

He continued: "These factoids are based upon hypotheses. There is no clinical data to support any of them and almost all studies show that they are not true or real. They are not supported by any studies." He then listed a number of current factoids about megadose vitamin C which included that the vitamin "inhibits chemotherapy" and "prevented Linus Pauling from living longer".

Finally, Hoffer stated: "The opposite of a factoid is a fact. The good news is that as none of [the] factoids [in the list mentioned above] are true, the opposite is true. This summary statement is based upon literally thousands of published papers in medical literature and hundreds of books that have been published in the past twenty years." The author said that he could "not provide references to these numerous clinical studies, but readers of the *Journal of Orthomolecular Medicine* have ready access to the facts and also to the book reviews of over one hundred of these books. The internet contains a large number of excellent discussions of vitamins and, of course, the facts and factoids which are current."

The author then listed some maladies, conditions and treatments for which vitamin C was used. Under the headings "Alleged Toxicity", "Factoid (lies)" and "Fact", he noted what the factoid claims and what the fact is. These included, for the purpose of this bibliography, the use of vitamin C with chemotherapy and the factoid that the combination "Decreases efficacy," and the fact that it "Increases efficacy." This list also included Linus Pauling's use of vitamin C as having "Shortened his life", to which Hoffer remarked: "A ridiculous claim. He died age 94, fully mentally alert."

As an overall conclusion, Hoffer stated: "The factoids about vitamins, used in optimum doses when needed, are not true, are not based upon clinical evidence, do not have any studies including

double blind controlled clinical data to support them, and are used primarily to attack the new paradigm, the vitamins-as-treatment paradigm. Be wary of factoids whether they are in print, on the internet, in the news media, on radio or on television...." The author ended by stating:

"The unfortunate result of these lies is that patients are made fearful, some will stop taking their vitamins, medical costs will increase since patients want to see their doctor again to discuss these matters, and more patients will relapse. The harm done by these factoids is immeasurable, but fortunately is slowly decreasing as the population becomes more knowledgeable and sophisticated about nutrition and nutrients. In the same way that drug companies are not allowed to make false therapeutic claims about their products, we need a system which will neutralize the factoids as they are proposed. And above all we need the public media to become much more intelligent and less subservient to major papers like the *New York Times*."

Response 4, 2001

Prasad KN, Cole WC, Kumar B, Prasad KC: Scientific Rationale for Using High-Dose Multiple Micronutrients as an Adjunct to Standard and Experimental Cancer Therapies. *Journal of the American College of Nutrition,* 2001; 20/5: 450S-463S.

Summary

This review by Prasad et al. responded to the negative review of Labriola and Livingston (1999).

Prasad et al. wrote: "Two opposing hypotheses regarding the use of antioxidants as an adjunct to standard cancer therapy have recently been proposed. We have suggested that high-dose multiple antioxidant supplements before and during standard or experimental cancer therapy may improve treatment efficacy by increasing tumor response and decreasing toxicity [1999]. An alternative hypothesis is that antioxidant supplements should not be used while treating cancer patients with standard therapy because they would protect both normal and cancer cells against free radicals that are produced by most of the anticancer agents [Labriola and Livingston 1999]."

The authors continued: "These two conflicting hypotheses can be resolved if the following scientific principles are followed: (a) the results of the effects of low-dose (physiological range) antioxidants on cells are not extrapolated to those obtained with high-dose (pharmacologic, but non-toxic dose range) antioxidants; (b) data on the effects of a single antioxidant on cells are not extrapolated to those obtained with multiple antioxidants; (c) results of the effects of antioxidants on cancer cells are not extrapolated to those on normal cells; (d) data obtained on the effects of short treatment duration with antioxidants are not extrapolated to those obtained after long treatment duration; (e) all biological observations on the effects of antioxidants on cells are not related to their action of scavenging free radicals; and (f) all antioxidants do not produce similar effects on cells."

Prasad et al. stated: "The purpose of this review [was] to analyze each of the above scientific principles to demonstrate that current opinions opposing the use of antioxidants as an adjunct to standard cancer therapy have no scientific basis, and that micronutrient supplementation, including antioxidants, under appropriate conditions may improve the efficacy of the current management of human tumors."

In reference to vitamin C or vitamin C with other vitamins and chemotherapy, a few examples were cited and explanations given for the principles (Cameron et al. 1979, Patiak et al. unpublished information and Prasad et al. 1979, 1994, 1999) - the last two references also appear in this bibliography.

Lastly, the authors stated: "Another part of [their] proposed hypothesis is that antioxidant vitamins in combination with standard therapeutic agents may reduce the toxicity of

these agents on normal cells. Several studies using animal models (...) also support this part of the hypothesis [Prasad et al. 1999]." The authors cited two examples of vitamin C which showed that (1) the vitamin "reduces the adverse effects of some chemotherapeutic agents on normal cells, such as those from adriamycin [Fujita et al. 1982]", and (2) vitamins C+E+A "reduce bleomycin-induced chromosomal breakage [Trinza et al. 1993]."

In conclusion, Prasad et al. stated: "Substantial laboratory data and limited human studies indicate that supplementation with high-dose multiple micronutrients, including appropriate antioxidants (vitamin C, ...), as an adjunct to standard or experimental therapy (...), may improve their efficacy by increasing tumor response and decreasing toxicity. Clinical trials on this issue are in progress. The responses of tumor cells to antioxidants differ from those of normal cells. Antioxidants, in part, have different mechanisms of action on tumor cells. In addition, some antioxidants, depending upon doses, can produce a bi-phasic effect on certain tumor cells. Additional mechanistic studies on antioxidants alone and in combination with standard tumor therapeutic agents are needed."

Discussion

This annotated bibliography presents research findings that assess the effectiveness of vitamin C alone, or with other vitamins, when used during chemotherapy.

The summaries presented lead to the general conclusion that vitamin C can play a safe and positive role in cancer treatment as an adjunct to chemotherapy. This literature review suggests that the use of vitamin C alone with chemotherapy results in:

-an increase in survival time (Hoffer 1996, Meadows et al. 1991, Sarna et al. 1993, Skimpo et al. 1991)
-enhancement of chemotherapy (Meadows et al. 1991, Prasad et al. 1994, Sarna et al. 1993)
-inhibition of tumor growth (Chiang et al. 1994, Meadows et al. 1991)
-a decrease in toxicity (Skimpo et al. 1991)
-decreased elevated lipid peroxide (Skimpo et al. 1991)
-modulation of genotoxicity of chemotherapy (Blasiak et al. 2002)
-an increase in cell death (Reddy et al. 2001)
-When vitamins C and K3 were used with chemotherapy, results showed that the vitamin "did not increase the general and organ toxicity that accompanies cancer chemotherapy" (Taper et al. 1987)
-the vitamin treatment "produced a distinct chemotherapy-potentiating effect" for certain drugs (Taper et al. 1987) and "selectively potentiated tumor chemotherapy [and] produced sensitization of tumors resistant to some drugs" (Calderon et al. 2002)
-the application resulted "in a synergistic effect on growth inhibition" (Kurbacher et al. 1996)
-the combination was more effective than the chemotherapy alone (De Loecker et al. 1993)
-When vitamin C was given together with other vitamins or during chemotherapy, results showed that the mixture "markedly enhanced the growth inhibitory effect" of the chemotherapy (Prasad et al. 1994)
-"reduced growth of melanoma cells by about 85%" (Prasad et al. 1994)
-decreased side effects (Drisko et al. 2003)
-increased survival time (Hoffer 1990)
-enhanced quality of life (Hoffer 1990)
-was "added adjunctively to chemotherapy without adversely affecting outcome of survival" (Drisko et al. 2003)
-that combined treatment with chemotherapy and vitamins was more effective than drug alone (Abdel Rehim et al. 2003)

All but one of the studies and reviews presented in this bibliography support the use of vitamin C with chemotherapy. One neutral study, however, suggests "caution" when using high dose vitamin-mineral therapy for breast cancer. The only negative review warned of "Possible Interactions between Dietary Antioxidants and Chemotherapy." This stimulated four responses supporting the use.

In conclusion, this annotated bibliography of literature on the effectiveness of vitamin C alone, or with other vitamins, during chemotherapy confirms the conclusions of Prasad and coworkers (1999):

"... antioxidants [including vitamin C] do not protect cancer cells against free radical and growth-inhibitory effects of standard therapy. On the contrary, they enhance its growth-inhibitory effects on tumor cells, but protect normal cells against its adverse effects."

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