Vitamine C bij kanker

Nieuwe mogelijkheden voor orale inname

Het ideale antikanker middel

- Niet of nauwelijks toxisch
- Geen schade aan het lichaam
- Afremming van de groei van kankercellen of geleidelijk aan doden van kankercellen
- Verlengde levensverwachting van de patiënt met weinig bijwerkingen van de behandeling
- Goedkoop
- Liefst orale inname

Vitamine C als ideaal antikanker middel?

1969:

Onderzoekers van het National Institute of Cancer:

Vitamine C in hoge doseringen (evt. samen met een catalase remmer) kan kankercellen doden.

Benade L, Howard T, Burk D. Synergistic killing of Ehrlich ascites carcinoma cells by ascorbate and 3-amino-1, 2, 4, -triazole, Oncology, 1969, 23, 33-43.

Theorie: Het antikanker effect van vitamine C berust op de pro-oxidatieve werking: vorming van vrije radicalen in de kankercel.

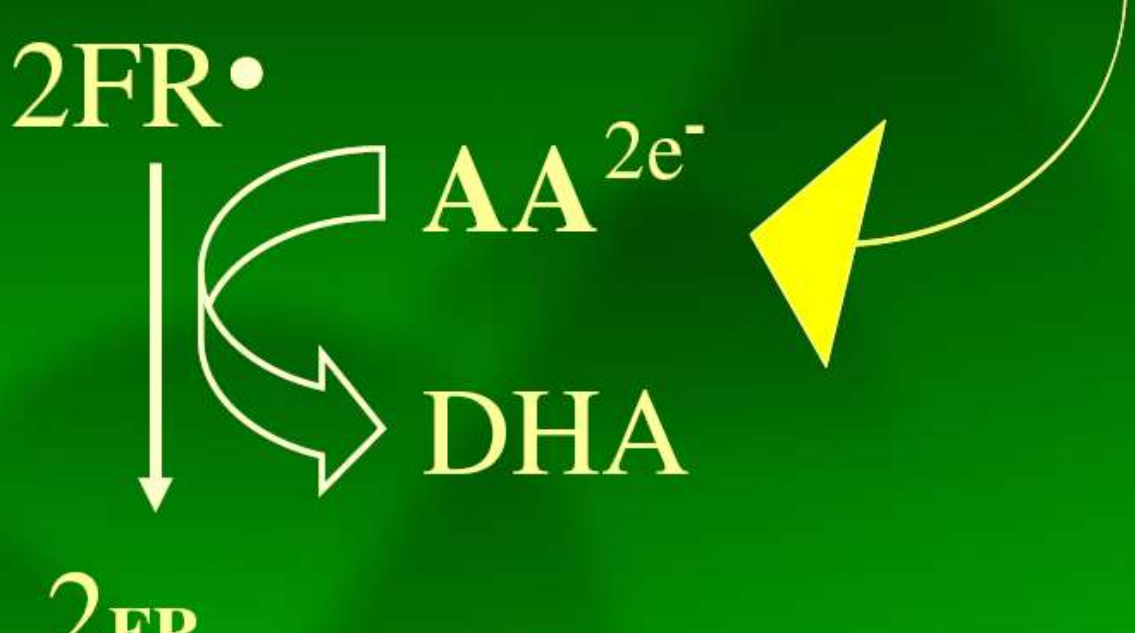
J Transl Med. 2008 Sep 12;6(1):50. [Epub ahead of print] Anti-angiogenic effect of high doses of ascorbic acid. Mikirova NA, Ichim TE, Riordan NH.

Redox Synergy

Ron Hunninghake, M.D.
Chief Medical Officer
The Brightspot for Health
Wichita, Kansas

Ascorbic Acid

Vitamin C Acting as an Anti-oxidant



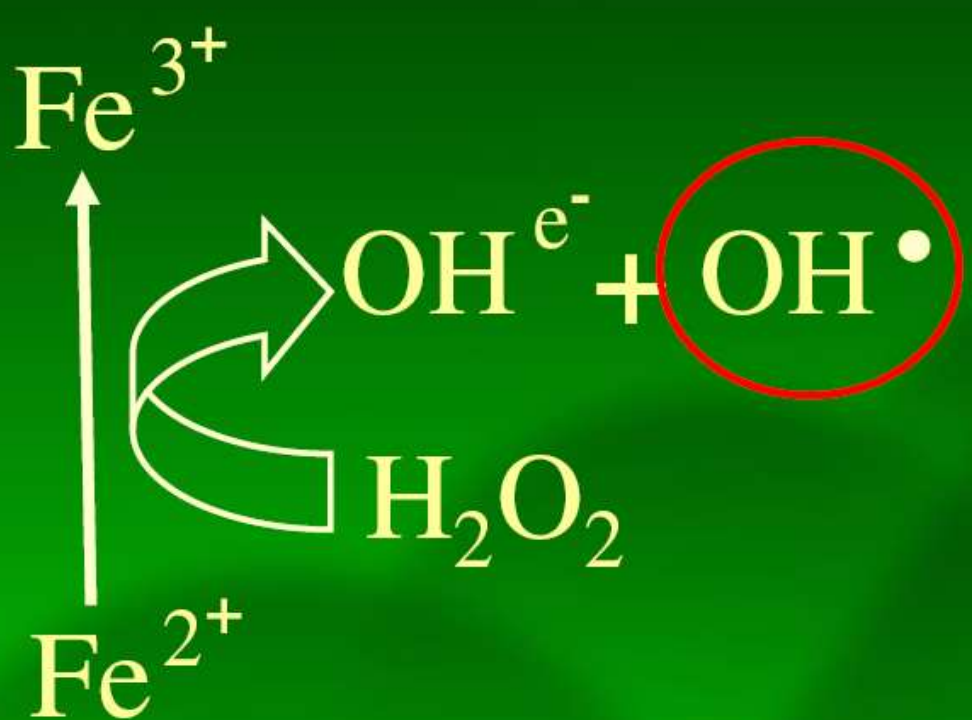
Dehydroascorbic Acid

Oxidized Vitamin C (DHA) Is Not Reabsorbed

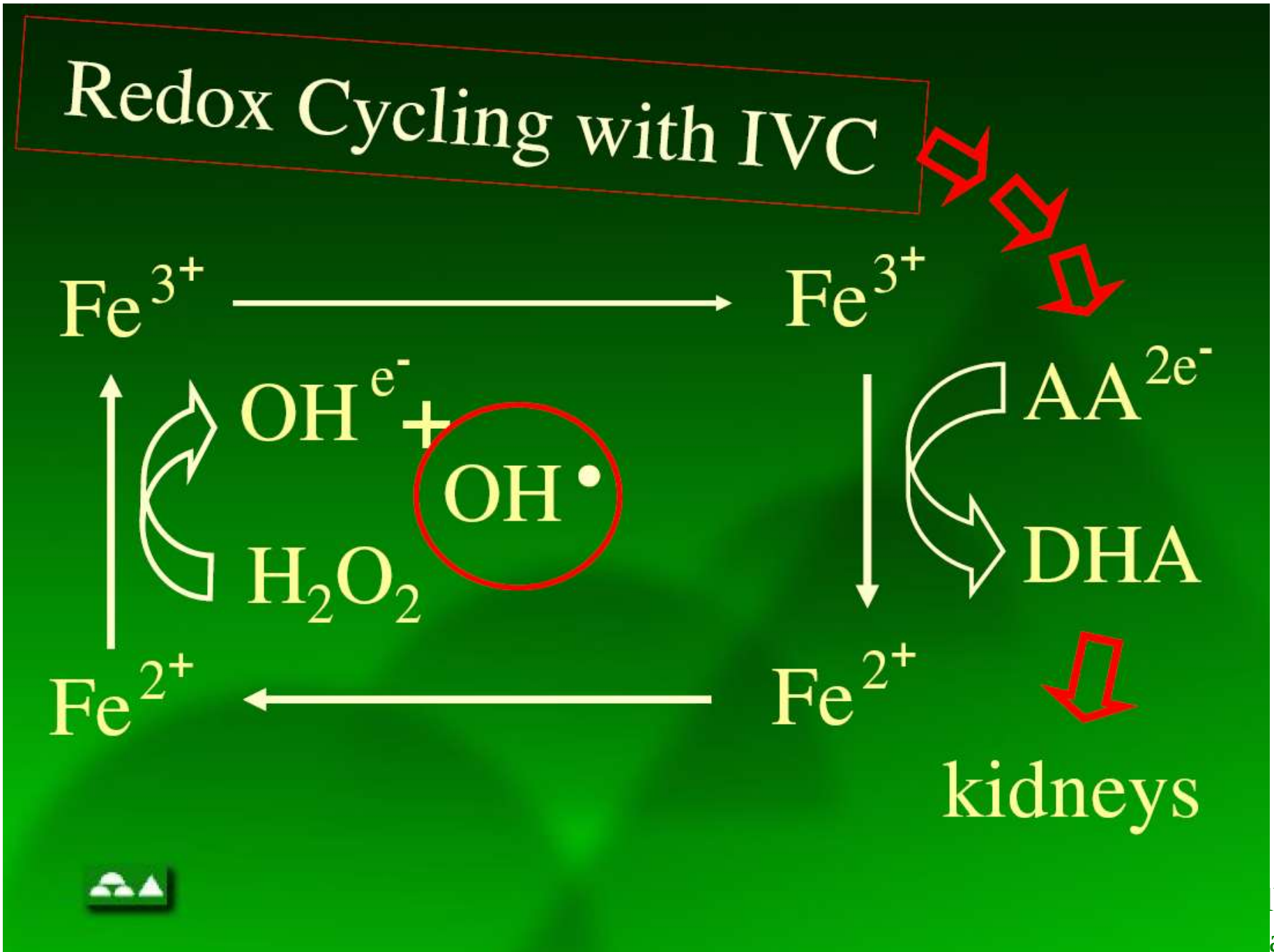
Two ferric ions are reduced to the ferrous state

Fenton's Reaction

Ferrous Iron is Oxidized Back to Ferric State

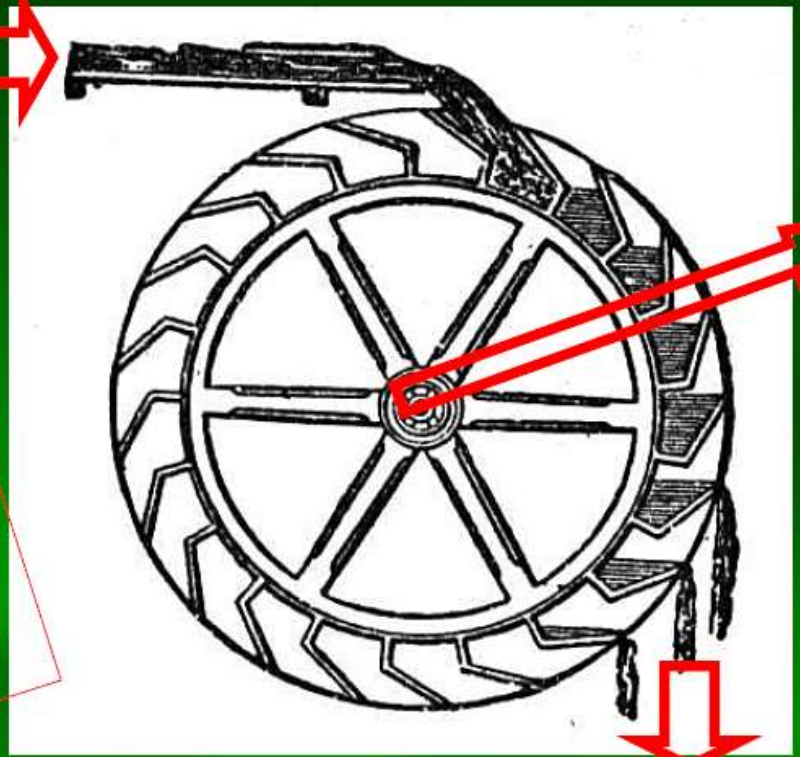


Hydroxyl Radical


Redox Cycling with IVC
Fe 3+
Fe 3+
OH e-
+
OH •
AA 2e-
H2O2
DHA
Fe 2+
Fe 2+
kidneys

Water Wheel Analogy –
Vitamin C Generating a Pro-oxidant

AA



$OH^{\bullet}$

Redox Cycling

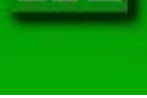
DHA

The Cellular Redox Environment

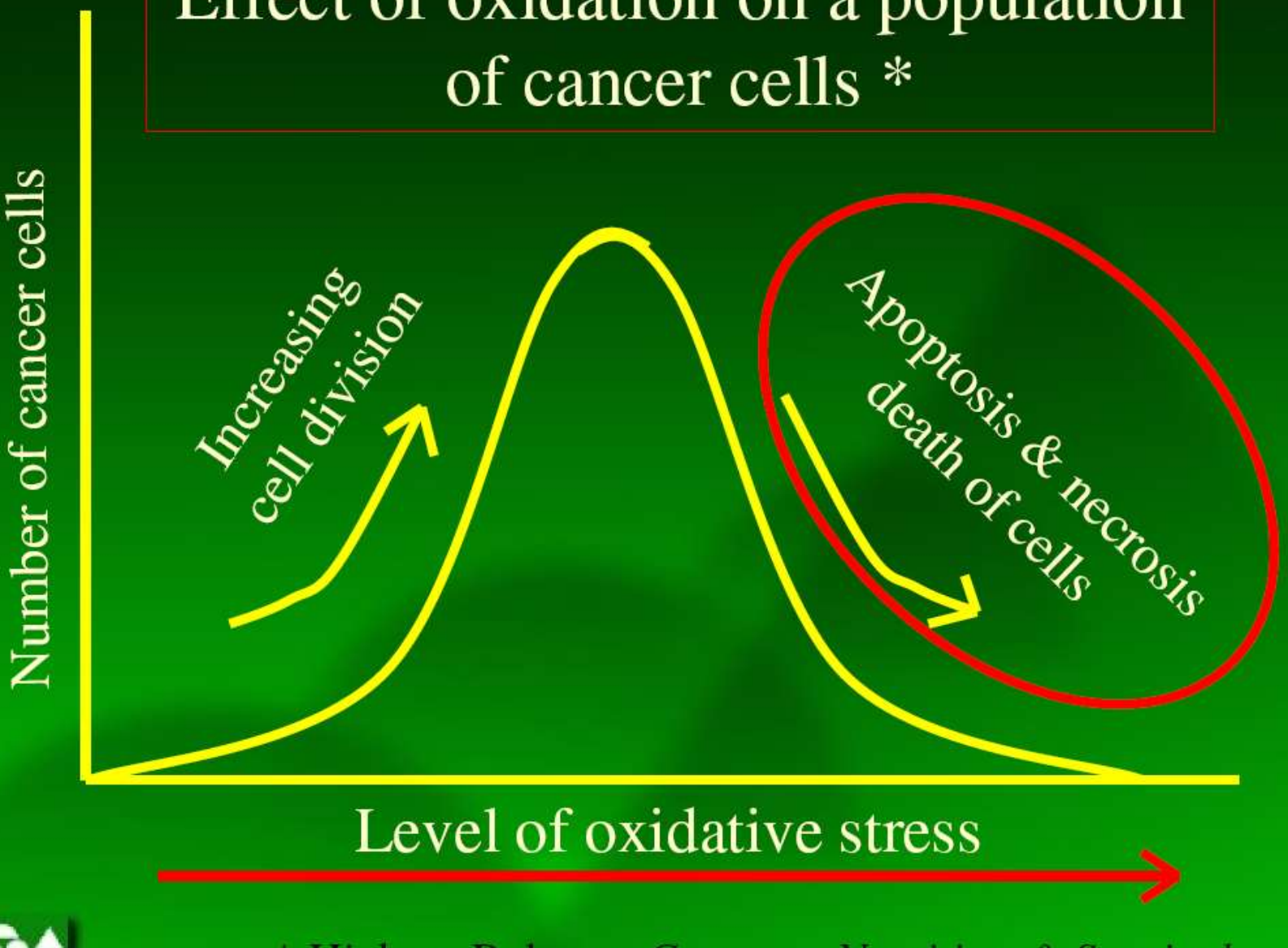
"A simple rule of thumb is that the environment of healthy cells is reducing, rather than oxidizing. Although we depend on oxidation for metabolism, immune defense, and cell signaling purposes, we must also avoid the damage it can cause."

Dr. Steve Hickey

Cancer – Nutrition and Survival



Effect of oxidation on a population of cancer cells *



* Hickey, Roberts; *Cancer – Nutrition & Survival*

Pro-Oxidant Properties of Vitamin C: Direct Tumor Cytotoxicity

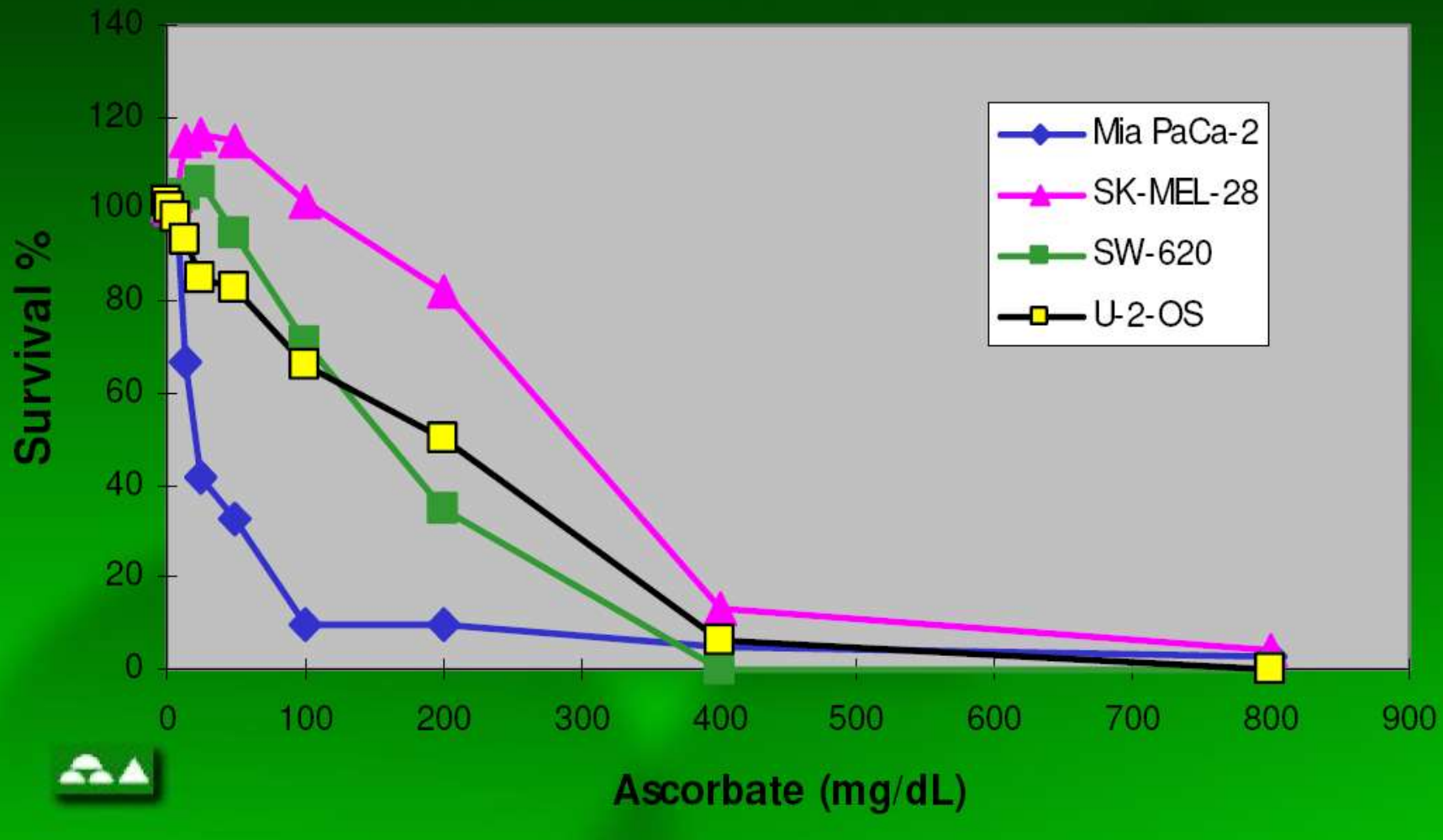
- High dose intravenous Vitamin C generates hydroxyl radicals which can damage cells.
- Healthy cells neutralize peroxide with catalase.
- Tumor cells are low in catalase.

  → more sensitive to the damaging effects of hydroxyl radicals

Information derived from:

- *Benade et al, Oncology 23:33, 1969*
- *Koch et al, J Cell Phys 94:299, 1978*
- *Riordan et al, Med Hypoth 44: 207, 1995*

The responses, to increasing doses of ascorbate, of four human tumor cell lines grown in dense monolayers in a medium of human serum.



Validation of RECNAC's Pioneering Work

- Sept. 20, 2005 – National Institutes of Health
- "Pharmacologic ascorbic acid concentrations selectively kill cancer cells: action as a pro-drug to deliver hydrogen peroxide to tissues"
  - *Proceedings of National Academy of Science*
  - Chen, Espey, Krishna, Mitchell, Corpe, Buettner, Shacter, **Levine**
    - *Sept 20; 102: 13604, 2005*

IVC Redox Chemotherapy

- IV Ascorbate reaches cytotoxic plasma levels for only a short duration (several hours)
- IVC is typically prescribed twice a week
- The potential exists for the emergence of IVC Redox chemotherapy-resistant tumor cells
- **Can IVC Redox be augmented with Oral C Redox and Redox Synergy?**

Redox *Re-cycling* & Synergy

- Redox Re-cycling:
  - An oxidized vitamin C molecule (DHA) can be reduced back to ascorbic acid
- Redox Synergy:
  - Using several antioxidants in a synergistic manner can increase the efficiency of redox re-cycling

Re-cycling Dehydroascorbate (DHA) Back to Reduced Ascorbic Acid

DHA

$2e^-$

Ao

Ao

$2e^-$

AA

Ao =

Anti-

oxidant

Vitamin C Pharmacokinetics: Implications for Oral & IV Use

- Padayatty, Riordan, Levine, et al
  - *Ann Intern Med.* 2004;140:533-537
- Measured plasma C after oral & IV administration of 0.015 to 1.25 gr of C
- ***Calculated*** plasma concentrations for 1-100 gr of oral and IVC
- Peak plasma C after 1.25 gr oral ~ 135 µmole/L
- Peak plasma C after 1.25 gr IV ~ 885 µmole/L

Effects of Sodium Ascorbate (Vitamin C) and 2-Methyl-1,4-Naphthoquinone (Vitamin K_3) Treatment on Human Tumor Cell Growth In Vitro

I. Synergism of Combined Vitamin C and K_3 Action

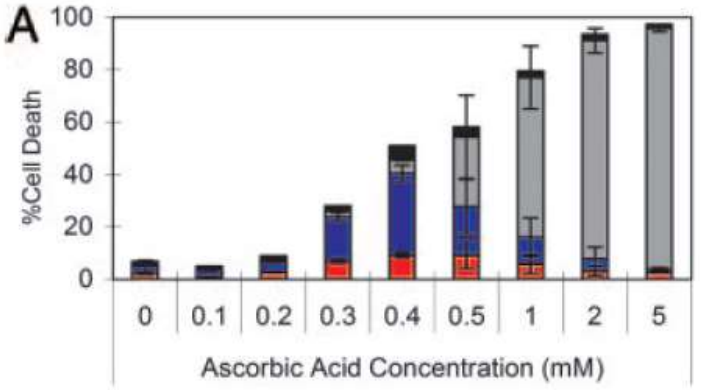
VINCENZO NOTO, MD,* HENRYK S. TAPER, MD,† JIANG YI-HUA, MD,*‡ JAAK JANSSENS, MD,§ JAN BONTE, MD,§ AND WILLIAM DE LOECKER, MD*

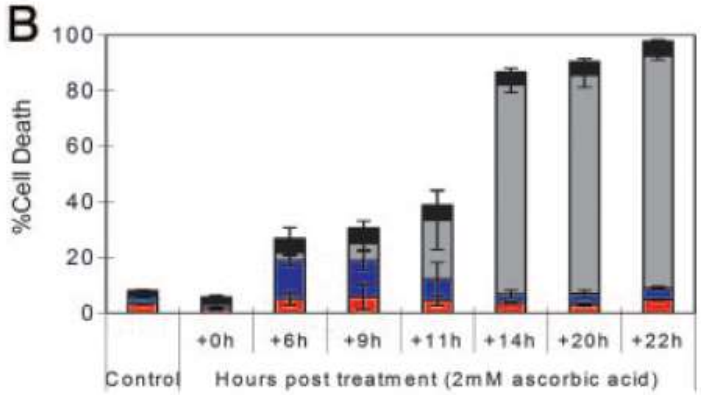
The effects of sodium ascorbate (vitamin C) and 2-methyl-1,4-naphthoquinone (vitamin K_3) administered separately or in combination on the *in vitro* cultured human neoplastic cell lines MCF-7 (breast carcinoma), KB (oral epidermoid carcinoma), and AN_3-CA (endometrial adenocarcinoma) have been examined. When given separately, vitamin C or K_3 had a growth inhibiting action only at high concentrations (5.10^3 μmol/l and 10^5 nmol/l, respectively). Combined administration of both vitamins demonstrated a synergistic inhibition of cell growth at 10 to 50 times lower concentrations. At this level separately given vitamins are not toxic. The sensitivity to this treatment was somewhat different in the three cell lines, being slightly higher for KB line. This tumor cell growth inhibitory effect was completely suppressed by the addition of catalase to the culture medium containing vitamins C and K_3, suggesting an excessive production of hydrogen peroxide as being implied in mechanisms responsible for the above-mentioned effects.

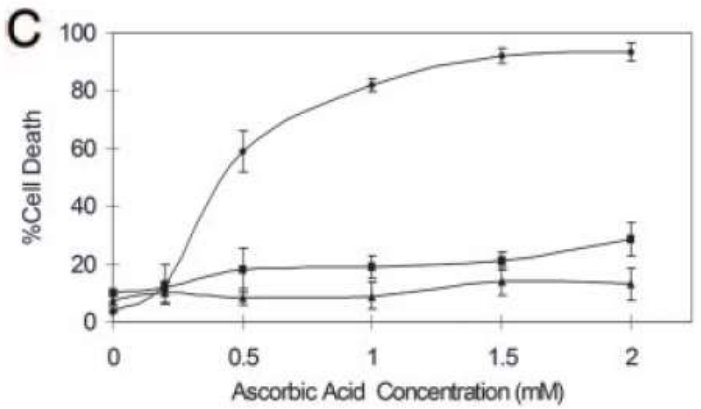
***Cancer* 63:901–906, 1989.**

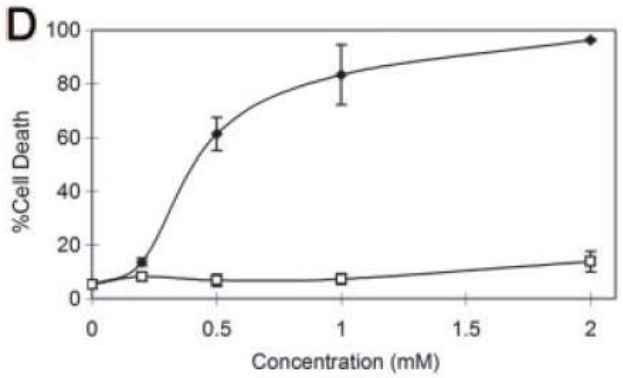
AMONG CHEMICAL compounds attracting great interest in cancer prevention and treatment, several vitamins have been examined. Thus, ascorbic acid (Vit C) has been shown to inhibit the formation of carcinogenic and mutagenic compounds in foods and has been suggested to be useful in the prevention of gastric cancer.[1] At nontoxic concentrations, Vit C potentiates the growth inhibitory effect of certain agents such as 5-fluorouracil, bleomycin sulfate, sodium butyrate, cyclic AMP-stimulating agents, and x-irradiation on neuroblastoma cells.[2] Ascorbate also is known to potentiate the cytotoxicity of misonidazole[3] and of 6-hydroxydopamine on mouse neuroblastoma cells,[4] on human neuroblastoma cells *in vitro*,[5] and of 3-amino-1,2,4,-triazole (ATA) on Ehrlich ascites carcinoma cells.[6] Vitamin C may accumulate in the tumors thus decreasing its level in peripheral blood of some cancer bearing subjects.[7,8] *In vitro* Vit C may even reverse malignant cell transformation as demonstrated on C3H/10T½ mouse embryo cells transformed by 3-methylcholanthrene,[9] or may demonstrate a cytotoxic action towards different tumor cells.[5,6,10,11]

Similarly it has been described that vitamin K_3 inhibits the growth of different types of mammalian tumor cells in culture.[12] It increases the thermosensitivity of Ehrlich ascites carcinoma cells and enhances *in vitro* the antineoplastic activity of 5-fluorouracil in Friend murine erythroleukemia cells, and of methotrexate in tumor-bearing animals.[13,14] *In vivo* administration of vitamins C and K_3 combined to hepatoma bearing mice, results in a potentiating effect of chemotherapy at cytotoxic dose levels proportionally lower than used in human cancer treatment.[15]









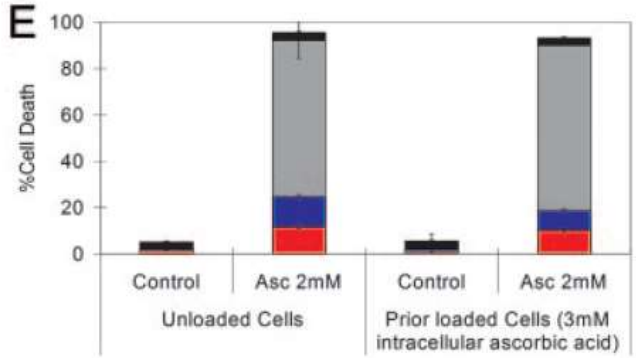


Fig. 2. Effects of ascorbic acid on human Burkitt's lymphoma cells. Cells were treated for 1 h, washed, and recultured without ascorbate. Amounts and types of cell death were determined 18–22 h later by nuclear staining with Hoechst/PI. Types of cell death: necrosis (black), pyknosis/necrosis (gray), early apoptosis (blue), and late apoptosis (red). (*A*) Amount and type of cell death as a function of external ascorbate concentration. (*B*) Time course and type of cell death after 1 h external ascorbate (2 mM). (*C*) Cell death as a function of external ascorbate concentration in human Burkitt's lymphoma cells (◆), normal lymphocytes (■), and normal monocytes (▲). (*D*) Cell death as a function of external ascorbate (◆) or dehydroascorbic acid (□) concentrations (1-h incubation). (*E*) Type and amount of cell death with 2 mM ascorbate treatment, in cells previously loaded to contain 3 mM ascorbate (right), compared with unloaded cells (left).

Epidemiologische studies over vitamine C bij kanker

Block G.
Am J Clin Nutr. 1991 Jan;53(1 Suppl):270S-282S.
Vitamin C and cancer prevention: the epidemiologic evidence.

Epidemiologic evidence of a protective effect of vitamin C for non-hormone-dependent cancers is strong. Of the 46 such studies in which a dietary vitamin C index was calculated, 33 found statistically significant protection, with high intake conferring approximately a twofold protective effect compared with low intake. Of 29 additional studies that assessed fruit intake, 21 found significant protection. For cancers of the esophagus, larynx, oral cavity, and pancreas, evidence for a protective effect of vitamin C or some component in fruit is strong and consistent. For cancers of the stomach, rectum, breast, and cervix there is also strong evidence. Several recent lung cancer studies found significant protective effects of vitamin C or of foods that are better sources of vitamin C than of beta-carotene. It is likely that ascorbic acid, carotenoids, and other factors in fruits and vegetables act jointly. Increased consumption of fruits and vegetables in general should be encouraged.

Epidemiologische studies over vitamine C bij kanker

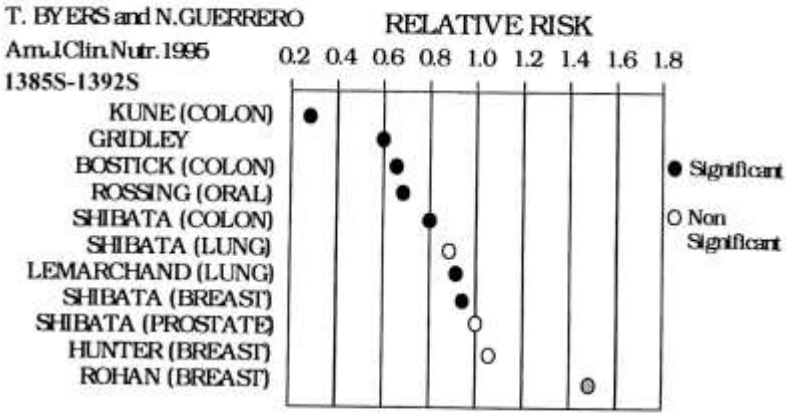


Figure 6.1 Analysis of 11 studies on vitamin C intake and the incidence of cancer. Seven showed a statistically significant effect of vitamin C. Curiously, one study on breast cancer showed an apparent deleterious effect of vitamin C that was almost significant. (From Ref. 367.)

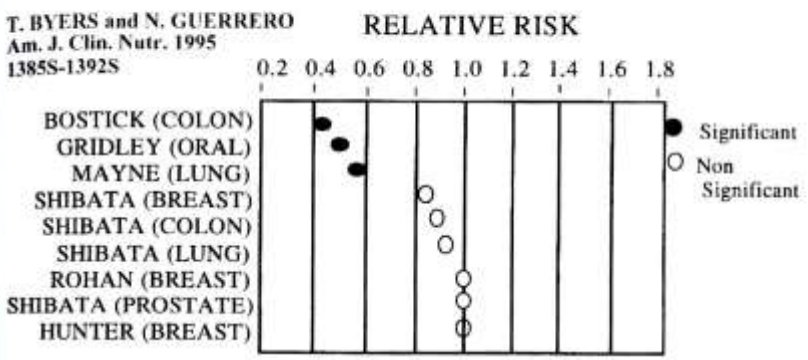


Figure 6.2 Analysis of 9 studies on vitamin E intake and the incidence of cancer. Three studies showed a statistically significant, strongly protective effect of vitamin E: Bostick et al. (Iowa Women's Health Study), on colon cancer in 35,215 women between 55 and 69 years of age; Gridley et al., on oral cancers in 2500 persons (multivitamins showed no effect); and Mayne et al., on lung cancer in 1000 nonsmokers. (From Ref. 367.)

Diets high in fruit and vegetables, and hence high in vitamin C, have been found to be associated with lower risk for cancers of the oral cavity, esophagus, stomach, colon, and lung.

Am J Clin Nutr. 1995 Dec;62(6 Suppl):1385S-1392S. Epidemiologic evidence for vitamin C and vitamin E in cancer prevention. Byers T, Guerrero N.
PMID: 7495236

Cameron and Pauling

- 10 grams of IVC daily for 10 days followed by 10 grams orally in terminal cancer patients
- Review of their 1976 paper in *Proc. Natl. Acad. Sci.* –
  - Unclear if 10 gram oral C dose was single or divided
  - 4-fold increase in life expectancy
  - They speculated that "larger amounts than 10 gr/d might have a greater effect."

The Hoffer Cancer Regimen

- Dr. Abram Hoffer in 1978 started a 15-year test of his own orthomolecular vitamin redox regimen on 134 advanced cancer patients:
  - Beta carotene – 30,000 IU
  - B complex – B50 to B100
  - Vitamin C – 12,000 mg (as high as 40,000)
  - Vitamin E – 300 IU
  - Selenium – 600 mcg
  - Zinc – 60 mg

Mean Survival (mos.) of Cancer Pts. with Hoffer's Regimen*

Cancer Type	With Vitamins	Without Vitamins
Breast	70	3.7
Uterus	99	4.0
Ovary	16	3.6
Lung	17	2.0
Pancreas	40	2.4
All types	45	2.6

* J of Orthomolecular Med 1990 and 1993

Moertel CG, Fleming TR, Creagan ET, Rubin J, O'Connell MJ, Ames MM.
N Engl J Med. 1985 Jan 17;312(3):137-41.

High-dose vitamin C versus placebo in the treatment of patients with advanced cancer who have had no prior chemotherapy. A randomized double-blind comparison.

It has been claimed that high-dose vitamin C is beneficial in the treatment of patients with advanced cancer, especially patients who have had no prior chemotherapy. In a double-blind study 100 patients with advanced colorectal cancer were randomly assigned to treatment with either high-dose vitamin C (10 g daily) or placebo. Overall, these patients were in very good general condition, with minimal symptoms. None had received any previous treatment with cytotoxic drugs. Vitamin C therapy showed no advantage over placebo therapy with regard to either the interval between the beginning of treatment and disease progression or patient survival. Among patients with measurable disease, none had objective improvement. On the basis of this and our previous randomized study, it can be concluded that high-dose vitamin C therapy is not effective against advanced malignant disease regardless of whether the patient has had any prior chemotherapy. PMID: 3880867

Hoffer LJ, Levine M, Assouline S, Melnychuk D, Padayatty SJ, Rosadiuk K, Rousseau C, Robitaille L, Miller WH Jr.

Ann Oncol. 2008 Jul 25.

Phase I clinical trial of i.v. ascorbic acid in advanced malignancy.

BACKGROUND: Ascorbic acid is a widely used and controversial alternative cancer treatment. In millimolar concentrations, it is selectively cytotoxic to many cancer cell lines and has in vivo anticancer activity when administered alone or together with other agents. We carried out a dose-finding phase I and pharmacokinetic study of i.v. ascorbic acid in patients with advanced malignancies.

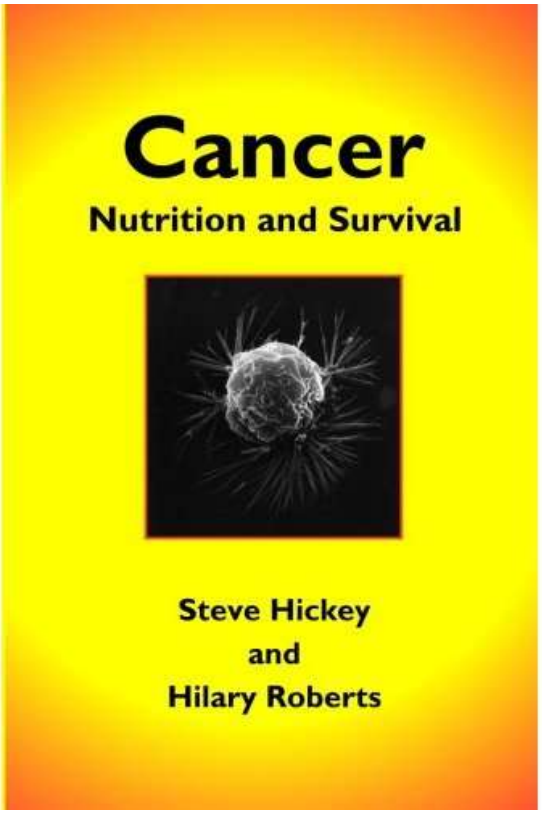
PATIENTS AND METHODS: Patients with advanced cancer or hematologic malignancy were assigned to sequential cohorts infused with 0.4, 0.6, 0.9 and 1.5 g ascorbic acid/kg body weight three times weekly.

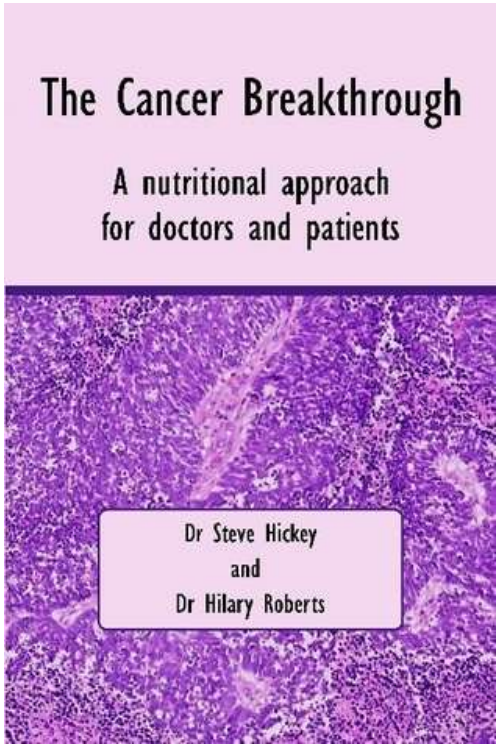
RESULTS: Adverse events and toxicity were minimal at all dose levels. No patient had an objective anticancer response.

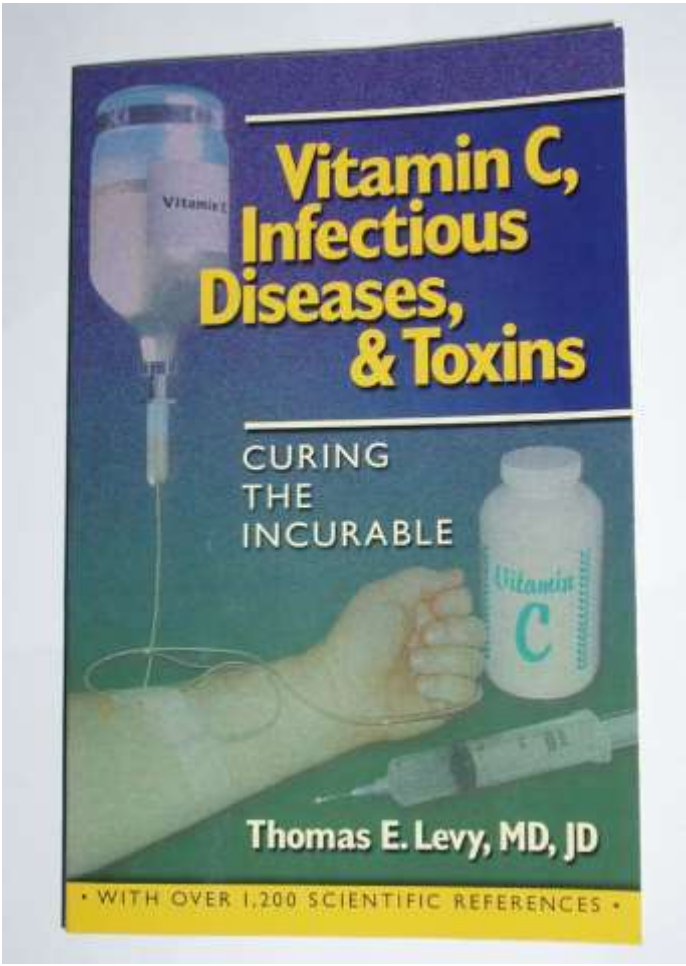
CONCLUSIONS: High-dose i.v. ascorbic acid was well tolerated but failed to demonstrate anticancer activity when administered to patients with previously treated advanced malignancies. The promise of this approach may lie in combination with cytotoxic or other redox-active molecules. PMID: 18544557

In een reply op dit artikel schreef Dr. S. Hickey:

……. cytotoxic levels of plasma ascorbate can be sustained with oral doses.[4] Ascorbate levels in excess of 400 microM/l can be sustained with liposomal formulations.[4][5] …….







Zie op www.lulu.com

	Vit. C in Serum in microM/l
12 g C+ Bioflav.	193
6g Lipospheric C (LC)	204

Dear Johan,

Thank you for your email.

The difference in plasma levels with liposomal vitamin C appears at the higher doses. Repeated standard doses can increase sustained blood levels effectively up to perhaps 250 microM/L (depending on the person and their state of health). Even the NIH (who incorrectly suggest that the body is saturated at 70 microM/L) have published data for 3g every 4 hours showing sustained plasma levels at 220 microM/L in a simulation.

The absorbance of ascorbic acid from the gut is adequate to achieve these levels. Because of the higher cost of liposomal formulations it does not make sense to use liposomes with lower doses. Our results suggest that the dose needs to exceed 5g before an appreciable liposomal effect is demonstrated.

However, we have tried single liposomal doses of 20g and 36g and obtained plasma levels above 400 microM/L. The paper is about to be published in JNEM

Pharmacokinetics of oral vitamin C

Journal of Nutritional & Environmental Medicine, 31 July 2008

STEPHEN HICKEY[1,2], HILARY J. ROBERTS[3], & NICHOLAS J. MILLER[4]

[1]*Faculty of Computing, Engineering and Technology, Staffordshire University, Staffordshire, UK,* [2]*School of Biology, Chemistry and Health Science, Manchester Metropolitan University, Manchester, UK,* [3]*Freelance scientific writer, and* [4]*Biolab Medical Unit, London, UK*

Abstract

Purpose. To test whether plasma vitamin C levels, following oral doses in supplemented volunteers, are tightly controlled and subject to a maximum in the region of 220 $\mu M\,L^{-1}$, as suggested by previous researchers for depleted subjects. To determine plasma levels following single, variable-sized doses of standard and liposomal formulations of vitamin C and compare the effects of the different formulations. To determine whether plasma levels above ~280 $\mu M\,L^{-1}$, which have selectively killed cancer, bacteria or viruses (in laboratory experiments), can be achieved using oral doses of vitamin C.

Design. This was a single blind study, measuring plasma levels in two subjects, in samples taken half-hourly or hourly for 6 hours, following ingestion of vitamin C. Data were compared with published results and with data from 10 years of laboratory plasma determinations.

Materials and methods. Standard 1 gram tablets of vitamin C; liposomal vitamin C. Plasma levels were analysed using the method of Butts and Mulvihill.

Results. Preliminary investigations of the effects of liposomal and standard formulation ascorbate showed that blood plasma levels in excess of the previously assumed maximum of 220 $\mu M\,L^{-1}$ are possible. Large oral doses of liposomal ascorbate resulted in plasma levels above 400 $\mu M\,L^{-1}$.

Conclusions. Since a single oral dose can produce plasma levels in excess of 400 $\mu M\,L^{-1}$, pharmacokinetic theory suggests that repeated doses could sustain levels well above the formerly assumed maximum. These results have implications for the use of ascorbate, as a nutrient and as a drug. For example, a short *in vitro* treatment of human Burkitt's lymphoma cells with ascorbate, at 400 $\mu M\,L^{-1}$, has been shown to result in ~50% cancer cell death. Using frequent oral doses, an equivalent plasma level could be sustained indefinitely. Thus, oral vitamin C has potential for use as a non-toxic, sustainable, therapeutic agent. Further research into the experimental and therapeutic aspects of high, frequent, oral doses of ascorbic acid either alone or (for cancer therapy) in combination with synergistic substances, such as alpha-lipoic acid, copper or vitamin K3, is needed urgently.

Table I. Protocol for doses.

	Day 1	Day 2	Day 3
Subject 1 (M)	5 g (stn)	20 g (lip)	36 g (lip)
Subject 2 (F)	5 g (lip)	5 g (stn)	36 g (lip)

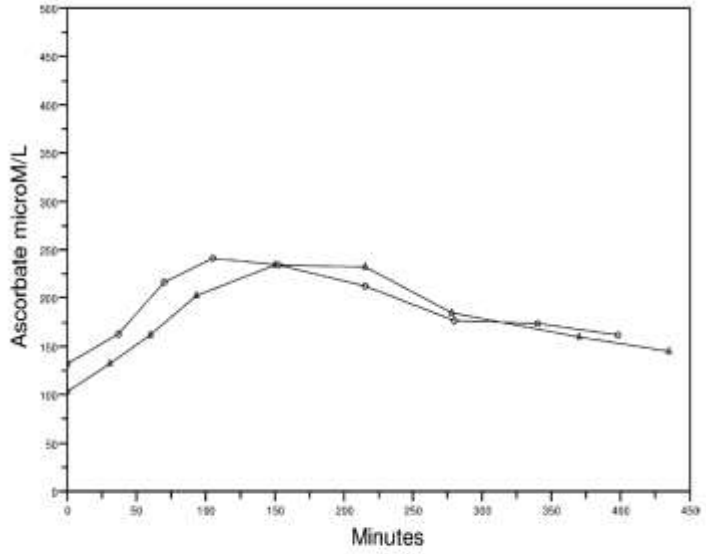


Figure 1. Plasma response curve following 5 g oral doses of standard vitamin C tablets (o) and liposomal ascorbate (Δ) *in the same subject.*

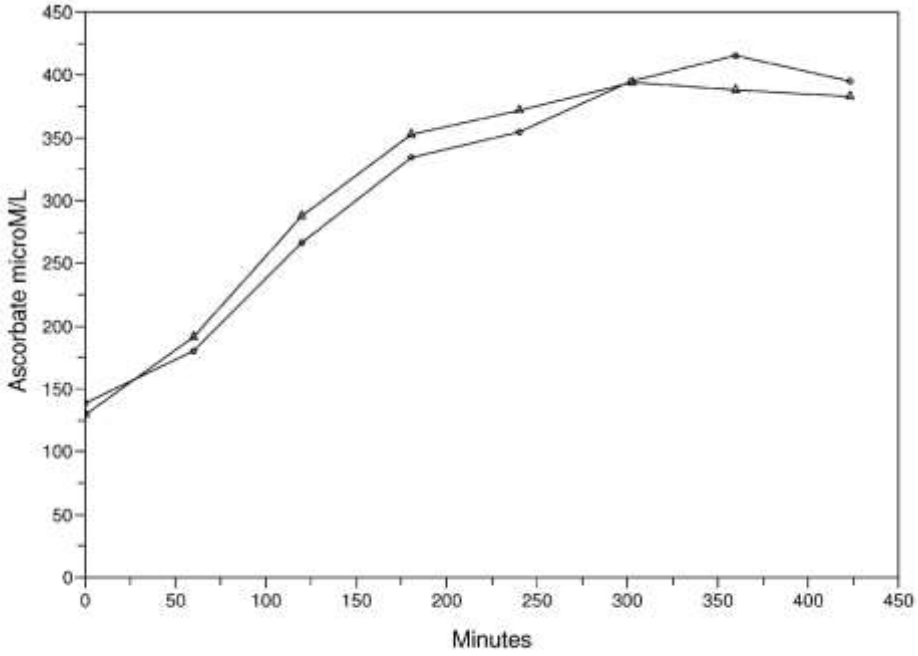


Figure 3. Plasma response to a single 36 g dose of liposomal ascorbate in two subjects.

Bronnen van vitamine C

Enhancement of human natural killer cytotoxic activity by vitamin C in pure and augmented formulations

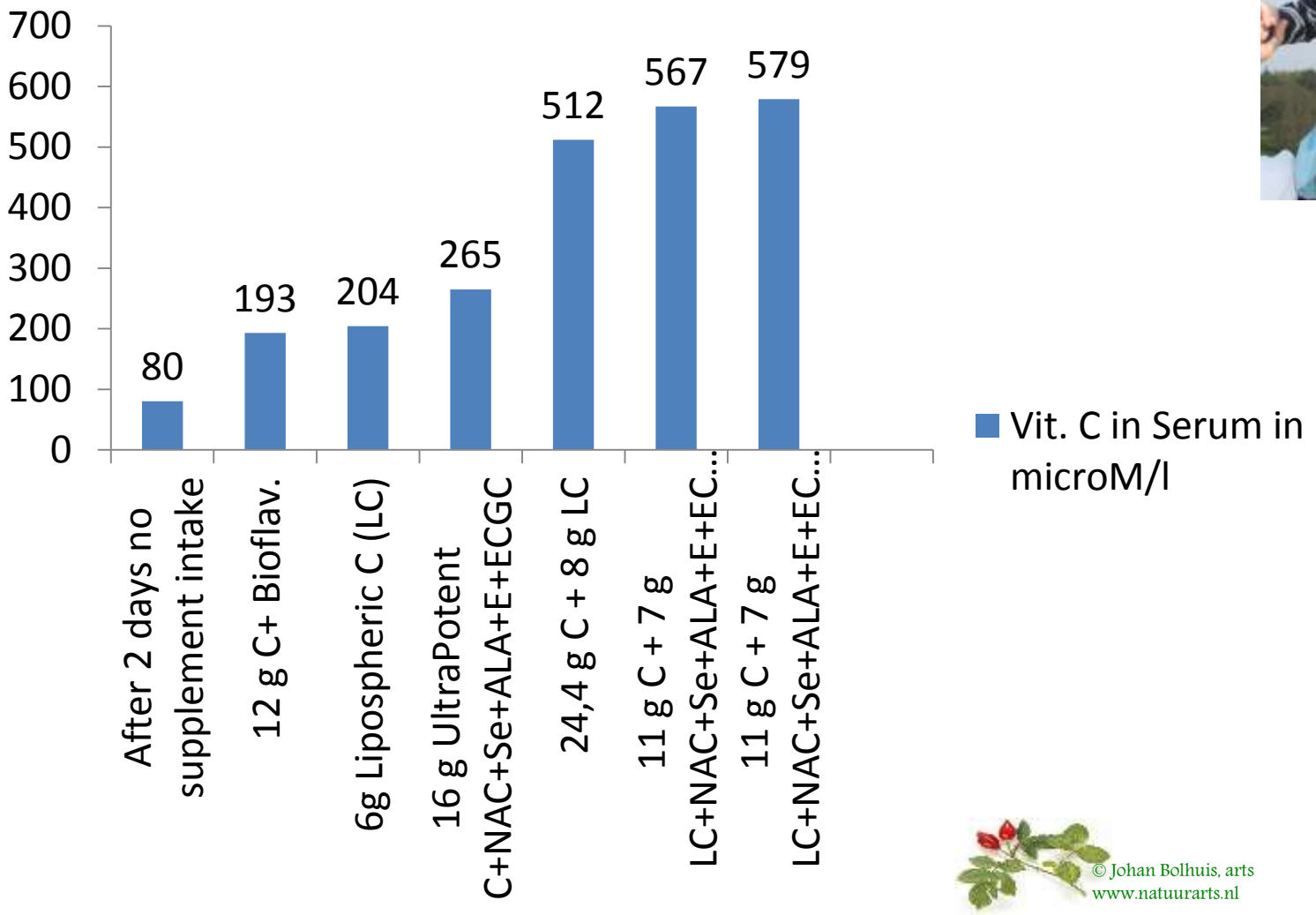
VOJDANI A. & NAMATALLA G.

Journal of nutritional & environmental medicine; 1997, vol. 7, nº3, pp. 187-195

Abstract

The antitumor activity of ascorbic acid has been reported by different investigators. In this study, we determined the in vivo effects of ascorbic acid and its modified formulation (Ultra Potent-C) on human natural killer (NK) cell activity. Twenty-two healthy subjects were given either ascorbic acid or Ultra Potent-C orally at a concentration of 60 mg kg^{-1}. Vitamin C uptake was measured in the plasma and by peripheral blood lymphocytes (PBLs). The uptake of vitamin C by PBLs was maximized at 2-4 h and was maintained at a high level up to 24 h. At the maximal point the uptake of Ultra Potent-C was higher by 18-25% than plain ascorbic acid. In addition, PBL-NK activity was measured by a 4-h ^{51}Cr release assay using K562 as targets. The results demonstrated that ascorbic acid has a biphasic pattern of NK function; an early transient depression in NK activity (29%) at 1-4 h that is subsequently followed by a significant enhancement (200-400%) between 8 and 24 hours. However, the pattern of NK activity in the Ultra Potent-C group was different from the ascorbic acid group and the early transient depression in NK activity was not observed. We conclude that ascorbic acid or its modified form is a potent immunomodulator.

Vit. C in Serum after intake of different vitamin C supplements in one person: Johan Bolhuis, M.D.



All tests performed by the
European Laboratory for Nutrients, Bunnik

	Vit. C in Serum in microM/l
After 2 days no supplement intake	80
12 g C+ Bioflav.	193
6g Lipospheric C (LC)	204
16 g UltraPotent C+NAC+Se+ALA+E+ECGC+Multi	265
24,4 g C + 8 g LC+NAC+Se+ALA+E+ECGC+Multi	512
8 g C + 7 g LC+NAC+Se+ALA+E+ECGC+ 11.00 a.m.	567
11 g C + 7 g LC+NAC+Se+ALA+E+ECGC+ 1.15 p.m.	579

How did I got this high levels?

- Before breakfast (7.00 a.m.) :

1 caps. Seleniummethionine 200 mcg (Now foods)

5 tabs. Vitamin C 1000 mg pure ascorbic acid (Plantina)

3 tabs. Multi junior (Plantina)

2 tabs. Active alpha-lipoic acid 300 mg (Country life)

2 caps. Gamma E tocopherol (Life Extension)

1 caps. Tea Care: Epigallo catechine galate 150 mg

7 grams Lypo-Spheric Vitamine C (Livonlabs)

2 caps. Magnesium/potassium 100 / 90 mg (Douglas Labs)

How did I got this high levels?

All supplements taken with only purified water, no juices, no sugars and two cups of green tea

Breakfast high in protein, low in sugars (yoghurt, Omega-3 oil, cocosfibre, muesli)

At 10.15 : **3 tabs. Natural C 1000 mg** (Douglas labs)

1 tab Active Alpha lipoic Acid 300 mg (Country life)

At 12.15 : **3 tabs. Natural C 1000 mg**

1 tab Active Alpha lipoic Acid 300 mg

1 tab N-Acetyl Cysteine (NAC) 600 mg (Now foods)

1 caps. Tea Care (ECGC 150 mg)

How did I got this high levels?

In between only green tea as beverage, no sugars, no coffee.

At 11.00 the first sample was taken: 567 microM/l

At 13.15 the second sample was taken: 579 microM/l

!!! At 400 microM/l cytotoxic effects on cancercells are found

Side effects: flatulence and frequent loose bowel movements

Questions:

- At what level the best cytotoxic effect on cancercells?
- Is it wise to supplement with extra Copper and vitamin K3 ?
- Has the lypo-spheric vitamin C the same anti-cancer effects?
- Do sugars and flavonoids inhibit vitamin C absorption? (I had more flatulence with a higher intake of bioflavonoids).
- If I took bloodsample 1-2 hours later, would the vitamin C level raise or drop?
- Are there long term side-effects and is it safe?

Johan Bolhuis, M.D. 22 sept. 2008.

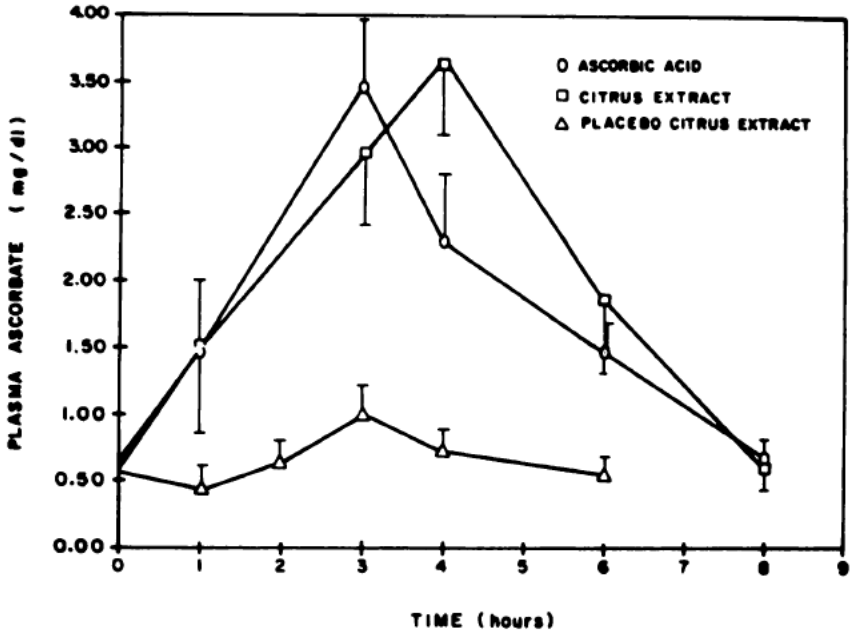


FIG 1. Plasma time-concentration curves for eight fasting subjects ingesting 500 mg of ascorbate as synthetic ascorbic acid (AA) alone or in 2 g of a citrus extract, or 2 g placebo citrus extract, or 2 g placebo citrus extract ($\bar{x} \pm$ SD). (To convert mg/dL to μmol/L, multiply by 56.78.)

TABLE 3
Net 24-h urinary excretion of ascorbate after oral administration of a placebo citrus extract or 500 mg synthetic ascorbic acid (AA) alone or in a citrus extract (mg)*

	Urinary ascorbate			
Subjects	AA	Placebo citrus extract	Citrus extract	p†
Males (n = 6)	181 ± 89	−2.3 ± 11.4	72 ± 35	<0.05
Females (n = 6)	93 ± 32	−26.9 ± 38.7	71 ± 29	NS
All subjects	135 ± 79	−10.5 ± 23.2	72 ± 31	<0.05

* $\bar{x} \pm$ SD.
† Significance of difference between AA and citrus extract by a paired t test.

after ingestion of CE and the difference between the two forms was significant ($p < 0.05$).

Discussion