The Validity of the Pharmanex BioPhotonic Scanner and The Rationale for Logical Nutritional Supplementation: *a Review of The Literature – 2017 update*

The Validity of the Pharmanex BioPhotonic Scanner and the Rationale for Logical Nutritional Supplementation:
A Review of The Literature – 2017 update

Louis B. Cady, M.D., Founder and CEO – The Cady Wellness Institute
Newburgh, IN

As CEO and Founder of Cady Wellness Institute, I find it imperative to me that any technology or laboratory assessment that I use for my patients meets the standards of current science, is thoroughly supported in the peer-reviewed medical literature by multiple citations that reinforce each other, and offers clear benefits that are unavailable by other technologies or assessments. It is also important to me that it be affordable for the patient, and that any measurement obtained offers me "actionable data," which I can use to directly improve either a patient's physical health, or mental health, or both.

As will be established in this paper, the determination of antioxidant capacity of a living organism is critical for an assessment of health, and in humans, particularly, the determination of the susceptibility to disease. But measurement and assessment of clinical risk is therapeutically impotent in the face of no available therapeutic interventions. Those interventions will also be reviewed.

Hence, in this paper, there are two over-arching themes:

- First, the relevance and scientific validity of the Pharmanex Biophotonic Scanner;
- Second, the rationale – based on a syntopical and comprehensive reading of the peer-reviewed medical literature – for a balanced, reasonable nutritional supplement regimen, which can produce measurable clinical results, and, indeed, *measurable results on the scanner.*

Skin Carotenoids & Antioxidant Levels: From the Patent to Real Consideration of Human Disease Risk

The Pharmanex Biophotonic Scanner is the only device that is available that makes a valid, reproducible antioxidant reading available in 30 seconds, painlessly, and on a beam of light. The technology is Raman Resonance Spectroscopy,[1] [2] and the use of Raman spectroscopy used with human tissue[3] is patented and held by the University of Utah with subsequent licensing to Pharmanex. The original patent was by Gellermann and colleagues[4] and described a "method and apparatus for noninvasive measurement of carotenoids and related chemical substances in biological tissue." This original patent staked out, among other things, that this was "a method of noninvasively determining the antioxidant status in skin tissue." This technology and its patents were further extended by a subsequent development of "process and compositions for synthetic calibration of bio-photonic scanners [US 7365839 B2]."[5]

---

[1] Long, DA. The Raman Effect: *A Unified Treatment of the Theory of Raman Scattering by Molecules.* © 2002 John Wiley & Sons, Ltd. ISBNs: 0-471-49028-8 (Hardback); 0-470-84576-7 (Electronic). Available entirely via web access here: http://www.kinetics.nsc.ru/chichinin/books/spectroscopy/Derek02.pdf

[2] Raman Effect. Encylopedia Britannica. Last updated 01-24-2014. https://www.britannica.com/science/Raman-effect [accessed Feb 12, 2017]

[3] Darvin ME et al. Optical methods for noninvasive determination of carotenoids in human and animal skin. J Biomed Opt. 2013 Jun;18(6):61230. doi: 10.1117/1.

[4] http://www.google.com/patents/US6205354. Accessed January 11, 2017. It should be noted that this research was independently funded, accomplished, the original device built and used clinically and the patent granted prior to the acquisition of all patent rights from the University of Utah, worldwide, by Pharmanex in 2001.

[5] http://www.google.com/patents/US7365839. Accessed January 11, 2017.

The relationship between carotenoid assessment and the implied amount of antioxidant protection was claimed as follows: "The present invention not only provides for a rapid, non-invasive assessment of carotenoids levels in a variety of human tissues and bodily fluids, but also has many additional beneficial uses. ***These include assessing the overall antioxidant status in human tissue….***"

Using this technology, as of January 31, 2017, there are 78 citations in the published medical literature looking at "Raman spectroscopy [and] skin carotenoid."[6] The very first paper that began this entire literature was published by Hata, Gellermann, et al. in the Journal of Investigative Dermatology in 2000.[7] It correlated the data produced by Raman spectroscopy of skin carotenoids with that compared to Raman spectroscopy of skin removed from patients undergoing abdominoplasty ("tummy tucks") and with a concomitant direct high performance liquid chromatography determination of carotenoid levels of the exact same skin. An excellent correlation was noted between carotenoid measurements done by Raman spectroscopy on both living skin and resected abdominal skin compared to the HPLC determination of carotenoids on the resected abdominal skin.

We will further examine the relationship of carotenoids as they pertain to their antioxidant capacity, specifically, and their relationship and reflecting of the total antioxidant system in the body, generally. Their use in testing to determine antioxidant insufficiency, the implication of oxidative stress, and their use as an inferential implication that other nutrients are being absorbed will also be examined in this paper.

Raman Spectroscopy and Its Application in the Pharmanex Biophotonic Scanner: A Brief Grounding

The mechanisms of action of the Raman spectroscopic analysis of dermal carotenoids involves, in terms of the specifications of the Biophotonic Scanner, a fine beam of photons, precisely calibrated at exactly 473 nm frequency, fired into the epidermis of the skin. The 473 nm wavelength photons strike carotenoid molecules in the skin, and, because of energy absorption of the alternating double bond carotenoid molecules, the photons are reflected back at 510 nm. 510nm is a slightly longer wavelength and lower frequency. This is the so-called "Raman shift." The change in blue photons shot out and green photons reflected back to the Raman spectrometer is what the Pharmanex Biophotonic Scanner measures. Indeed, all Raman spectrometers work this way. The only difference is the excitation frequencies used and the reflected frequencies detected, based on the substance or compound that is attempting to be identified or quantified.[8] [9] [10]

---

[6] https://www.ncbi.nlm.nih.gov/pubmed/?term=raman+spectroscopy+skin+carotenoid , accessed Jan 31, 2017.

[7] Hata, Gellermann, et al. Non-invasive Raman spectroscopic detection of carotenoids in human skin. Jrnl Inves Derm, September 2000, volume 115, issue 3, 4410448. Direct link: http://www.jidonline.org/article/S0022-202X(15)40992-3/abstract

[8] Raman shift calculator – Photon, Etc. website. http://photonetc.com/raman-shift-calculator accessed Feb 5, 2017.

[9] https://www.physics.rutgers.edu/grad/506/raman/raman.pdf accessed Feb 5, 2017.

[10] An example of Raman detection of the spectrum of polystyrene, and the effects of heavy atoms and weak bonds: http://www.renishaw.com/en/raman-bands-explained--25808. (This article reviews the use of Raman spectroscopy in industrial and physical chemistry applications. The same technique and theory apply, however. It is useful to know that Pharmanex has licensed the patent rights from the University of Utah for the *specific use* of Raman spectroscopy to determine *carotenoids levels* in *living tissue.* Other industrial and analytical uses are not covered by this patent. This is why every published citation in the peer-reviewed medical literature specifically noting the use of "Raman spectroscopy," "Carotenoids," and "skin" in the same article (dealing with people or animals who are *alive* and not referring to analytical techniques in a lab for biopsy or tissue specimens) can only refer to the Pharmanex Biophotonic Scanner. No one else is allowed to make or sell a Raman spectrometer for this specific purpose.

The Kaiser Optical Systems website has an excellent description:[11] "When light is scattered from a molecule most photons are elastically scattered. The scattered photons have the same energy (frequency) and, therefore, wavelength, as the incident photons. However, a small fraction of light (approximately 1 in 10^7photons) is scattered at optical frequencies different from, and usually lower than, the frequency of the incident photons. The process leading to this inelastic scatter is termed the Raman effect. Raman scattering can occur with a change in vibrational, rotational or electronic energy of a molecule. Chemists are concerned primarily with the vibrational Raman effect…."

The theoretical groundwork for the development of this technology was developed by Sir C.V. Raman and was first published as "a new type of secondary radiation" in 1928.[12] He was awarded the Nobel Prize in physics just two years later. Sir Raman's work has been known for the last 87 years and in actual use for 52 of those years as technology developed that made Dr. Raman's theoretical work practical and applicable.[13]

Finally, according to official documentation from Pharmanex, the conversion of Raman units on the scanner – or the "Biophotonic Scan Score" – into something meaningful for a clinician's purposes, uses the algebraic expression: Y = 12703 * X + 5891.7 (Where Y is the "SCS" [or "skin carotenoid score"], and X is the carotenoid concentration in MICROgrams/ml). It follows that a useful and quick rule of thumb is that for every 1,000 units on the SCS, there are .06 MICROgrams carotenoid/ml blood plasma. For example: take the scan score of 50,000, drop the three zeros at the end, and multiply by .06 for a total carotenoid level of 3 MICROgrams carotenoid/ml blood plasma. This would be representative of someone in the top quintile of normal distribution of carotenoid levels. When I am using this for clinical purposes, I will personally do this conversion and put it in the patient's chart so that other clinicians who will see the chart can see what the "scan score" means in typical laboratory units.

It should also be noted that, essentially, the Pharmanex Biophotonic Scanner is "agnostic" in terms of source of your carotenoid levels. One of my friends, who takes absolutely no supplements, came in and scored 81,000 on the Scanner. She is also a vegetarian, and eats at least 9 – 10 servings of *organic* fresh fruit and vegetables per day. A sales representative of another premium nutritional supplement line (a line noted for its excellent quality and science and sold predominantly in functional medicine practitioners' offices), good-naturedly took my challenge and scored 51,000 on the scanner, taking only supplements from his line. I have had some exceptionally fit and nutritionally sophisticated people who have come in to see where their nutrient intake placed them, and they have scanned in the 40,000 to 70,000 range.

Alternatives to the Biophotonic Scanner

Placing the scanner in context, and considering other potential clinically routine and accessible bio-markers available for the general clinician, one should note that there are several laboratory measures theoretically available for the measurement of oxidative stress and antioxidant status.

Laboratory measurements for oxidative stress are available in research facilities and "send-out labs," but are not commonly used in clinical practice.

---

[11] http://www.kosi.com/na_en/products/raman-spectroscopy/raman-technical-resources/raman-tutorial.php accessed Feb 5, 2017

[12] Raman CV, Krishnan KS. A new type of secondary radiation. Nature 121,501, March 31, 1928. Reference: http://www.soest.hawaii.edu/HIGP/Faculty/sksharma/GG711/GG711Spectroscopy04Raman.pdf accessed Feb 5, 2017.

[13] Zheltikov AM, Radi, P. Non-linear Raman spectroscopy 75 years after the Nobel Prize for the discovery of Raman scattering and 40 years after the first CARS experiments. Journal of Raman Spectroscopy Feb 2005, 36(2):92-94.

- The determination that malondialdehyde and thibobarbituric acid-reactives are markers for lipid peroxidation and "peroxidative tissue injury" is well established; these markers have been in the literature since at least 1990.[14] The problem is that specific tests are not available in commercial laboratories, and seem reserved for research purposes.
- Serum and plasma malondialdehyde[15] [16] [17] [18] as well as F2 isoprostanes [19] [20] [21] [22] - either in blood or urine specimens are frequently used in academic medical center settings and in research. F2 isoprostane levels have also been obtained from cerebrospinal fluid for better characterization of dementing processes thought to be related to oxidative stress.[23] These tests are certainly *not* available for the practicing clinician.
- An F2-isoprostane/creatinine ratio can, however, be obtained by a practicing clinician through the Cleveland Heart Lab (CPT Code: 82542/82570)[24] but this is an overly fussy procedure: the clinician needs to be set up with Cleveland Heart Lab for testing and have an account, and the testing is typically covered by insurance only in the context of cardiac disease workups.
    - Similarly, Myeloperoxidase - another marker of oxidative stress[25] [26](CPT Code: 83876) is also available from the same lab.[27] The same reservations apply.
- My own hospital lab at Deaconess Hospital in Evansville, Indiana – part of a major, regionally-based referral medical center – has none of these tests available for immediate clinical use. Malondialdehyde testing is not available from *any* reference lab.

Setting aside the more conventional "send the patient to a lab and have the blood drawn" paradigm, alternative testing pathways do exist:

- Doctor's Data has a straightforward "red blood cell glutathione" test.[28]
- Genova Diagnostics offers two different oxidative stress tests: one is from urine[29]and the other is from blood.[30]
- Finally, Spectracell Laboratories in Houston, Texas, offers an in-depth analysis of individual micronutrients, including a specific marker for antioxidant capacity called "Spectrox."[31]

---

[14] Janero, DR. Malondialdehyde and thiobarbituric acid-reactivity as diagnostic indices of lipid peroxidation and peroxidative tissue injury. Free Radic Biol Med. 1990;9(6):515-40.
[15] Templar J et al.,Increased plasma malondialdehyde levels in glomerular disease as determined by a fully validated HPLC method. Nephrol Dial Transplant (1999) 14 (4): 946-951.
[16] Demirdag K et al. Levels of plasma malondialdehyde and erythrocyte antioxidant enzyme activities in patients with chronic hepatitis B. Hepato-gastroenterology [2003, 50(51):766-770]
[17] Ozdemir E et al. Serum selenium and plasma malondialdehyde levels and antioxidant enzyme activities in patients with obsessive–compulsive disorder. Prog Neuropsychopharmacol Biol Psychiatry. 2009 Feb 1;33(1):62-5. doi: 10.1016/j
[18] Gönenç A. Plasma malondialdehyde (MDA) levels in breast and lung cancer patients**.** J Clin Pharm Ther. 2001 Apr;26(2):141-4.
[19] Roberts II LJ, Morrow JD. Measurement of F_2-isoprostanes as an index of oxidative stress in vivo. Free Radic Res. 2000 Aug;33(2):115-27.
[20] Masiá M et al. Oxidative Stress predictas all-cause moratlity in HIV-infected patients. PLoS One. 2016 Apr 25;11(4): e0153456
[21] Gopaul NK et al. Evaluation of the postprandial effects of a fast-food meal on human plasma F_2-isoprostane levels. Free Radic Biol Med. 2000 Mar 1;28(5):806-14.
[22] Ward WF et al. Effects of Age and Caloric Restriction on Lipid Peroxidation: Measurement of Oxidative Stress by F2-Isoprostane Levels. J Gerontol A Biol Sci Med Sci. 2005 Jul;60(7):847-51.
[23] Montine TJ et al. Increased CSF F_2-isoprostane concentration in probable AD. Neurology. 1999 Feb;52(3):562-5.
[24] http://www.clevelandheartlab.com/tests/f2-isoprostanecreatinine/ accessed Feb 4 2017.
[25] Leeuwenburgh C, Henecke JW. Oxidative Stress and Antioxidants in Exercise. Curr Med Chem. 2001 Jun;8(7):829-38.
[26] Rúbia C et al. Protective effect of topical formulations containing quercetin against UVB-induced oxidative stress in hairless mice. J Photochem Photobiol B. 2006 Jul 3;84(1):21-7.
[27] http://www.clevelandheartlab.com/tests/myeloperoxidase/ accessed Feb 4 2017.
[28] https://www.doctorsdata.com/rbc-glutathione/ [accessed June 5, 2016]
[29] https://www.gdx.net/product/oxidative-stress-2-test-urine [accessed June 5, 2016]
[30] https://www.gdx.net/product/oxidative-stress-analysis-2-test-blood [accessed June 5, 2016]
[31] http://www.spectracell.com/patients/patient-micronutrient-testing/ [accessed June 5, 2016]

The three functional medicine labs noted above are all expensive, they all involve a blood draw (or in one case, a painless urine specimen), and they all involve waiting for results. They are also *not* reimbursed by conventional medical insurance. Interestingly, when I have used these functional labs and also done a Biophotonic Scan on the same patient, the results are in remarkable agreement.

The Biophotonic Scanner's place in the testing universe, on the other hand, is unique. As will be established and referenced, it is accurate. It is fast, it is painless, and the results of the scan are available in only thirty seconds.

Evaluating the Literature of the Scanner, Oxidative Stress, Antioxidants, and Fruit/Vegetable Intake

Here are *just a few* of the representative findings from a review of the literature validating the scanner and the significance of carotenoids and their measurements:

- "RS accurately measures total carotenoids in human skin with less intra-individual variability than measurement of serum carotenoids by HPLC analysis. RS technology is a valid and reliable noninvasive method to rapidly assess carotenoid nutritional status in humans."[32]
- A single Raman resonance spectroscopy reading was found to be a valid indicator and representative of six months of separate readings. "There was good agreement between a single measure of skin carotenoids by RRS and multiple measures [6x in 6 months] (K=0.8). The same variables were significantly associated with carotenoid status based on single or multiple measures, including a positive association with intake of total carotenoids…." (Scamo et al. 2013)[33]
- In Archives of Biochemistry and Biophysics, 2013, Mayne and colleagues published another study confirming that "…skin carotenoids may effectively serve as an integrated biomarker of health, with higher status reflecting greater F/V [fruit and vegetable] intake, lack of smoking, and lack of adiposity. Thus, this biomarker holds promise as both a health biomarker and an objective indicator of F/V intake, …."[34]
- Another study (Holt, 2014) established that a low skin carotenoid concentration (<25,000 in Raman units calibrated on the Biophotonic scanner) was *clinically correlated with metabolic syndrome in adults.*[35]
- Even more interestingly, the ability of the Biophotonic Scanner to evaluate an increase in circulating carotenoids (as, for example, either in supplementation or improved eating of fruits and vegetables) was established in a unique study by Jahns and colleagues in 2014.[36] In their paper:
    - Skin and concomitantly obtained plasma carotenoids correlated at all time points. In other words, the scanner was just as good as blood draws.
    - Skin and plasma carotenoids ***both*** increased 200% in moving from a low carotenoid to high carotenoid diet.

[32] Zidichouski JA et al. Clinical validation of a noninvasive, Raman spectroscopy method to assess carotenoid nutritional status in humans. J Am Coll Nutr. 2009 Dec; 28(6):687-93.
[33] Scamo S et al. Single v. multiple measures of skin carotenoids by resonance Raman spectroscopy as a biomarker of usual carotenoid status. Br J Nutr. 2013 Sep 14;110(5):911-7.
[34] Mayne ST et al. Resonance Raman spectroscopic evaluation of skin carotenoids as a biomarker of carotenoid status for human studies. Arch. Biohem Biophys. 2013 June 30.
[35] Holt EW et al. Low skin carotenoid concentration measured by resonance Raman spectroscopy is associated with metabolic syndrome in adults. Nutr Res. 2014 Sept 6.
[36] Jahns L et al. Skin and plasma carotenoid response to a provided intervention diet high in vegetables and fruit: uptake and depletion kinetics. Am J Clin Nutr. 2014 Sep; 100(3):930-7. doi: 10.3945/ajcn.114.086900. Epub 2014 Jul 9.

- Their conclusion was that "Skin carotenoid status assessed by resonance Raman spectroscopy is a noninvasive, objective biomarker of changes in vegetable and fruit intake."

Surveying the current literature available on the National Library of Medicine[37] in early 2017, the following six citations are cited, in ascending order to the present time. They are not "cherry picked" but simply selected from the top six peer-reviewed studies that resulted in a search under the term "Raman spectroscopy skin carotenoid." [38] They are presented in ascending chronological order as displayed on the PubMed search.

- Moncada et al. (May 2016) published findings that Raman spectroscopy measurements of patients with melasma who did not respond to treatment showed "atypical Raman skin spectrum peaks associated with melanin not well defined, which is consistent with molecular degradation and protein breakdown."[39] (This is an example of use of laboratory Raman spectroscopy.)
- Aguilar et al. (Nov 2105) found that consumption of 20 to 120 ml of a carotenoid-rich juice (containing 2.75 – 11 mg of carotenoids) "significantly increased skin carotenoid status over an 8-week period among children aged 5 – 17 years." The p-value between high dose and low dose groups were <0.001.[40] (living tissue use of Biophotonic scanner)
- Massenti et al. (2015) took note of the fact that "dermal carotenoids are a good indicator of antioxidant status in the body," and performed a study to analyze whether regular consumption of orange juice would result in a hypothesized increase in dermal carotenoids. Their conclusions were that "skin carotenoids can be increased by regular consumption of fresh orange juice."[41] (living tissue use of Biophotonic scanner)
- Sharafi et al. (Oct 2015) examined the use of Raman resonance spectroscopy as a reliable tool to assess dietary quality among preschoolers. (living tissue use of Biophotonic scanner) They note that "HEPI "Healthy Eating Preference Index' scale] alone or with HEI ["Healthy Eating Index" score] explained variability in carotenoid status and adiposity in path models with adequate to good fits."[42] (This was another living tissue use of the Biophotonic scanner.)
- Possibly the most clinically impactful paper – which demands a re-evaluation of standard of care - is that of Perrone et al. (2016), looking at Raman spectroscopic measurements of dermal carotenoids in breast cancer operated patients. [43] Measurements were done for each

[37] https://www.ncbi.nlm.nih.gov/pubmed/

[38] It should also be noted that if in the published literature there is a reference to "Raman spectroscopy" in the same context as "skin carotenoid," then the experimental subject is being analyzed using a *living tissue* measurement(rather than tissue which is examined in a laboratory post-biopsy). These papers thus uniformly refer to the Pharmanex Biophotonic scanner. (The brand name is not cited in these studies). The world-wide patent rights for Raman spectroscopy of carotenoids in living tissue have been secured by the University of Utah, and no other company is permitted to develop, sell, market, or promote any device designed to measure carotenoid levels in *living tissue* other than the original Pharmanex licensed device, as well as subsequent generations.

[39] Moncada B et al. Raman spectroscopy analysis of the skin of patients with melasma before standard treatment with topical corticosteroids, retinoic acid, and hydroquinone mixture. Skin Res Technol. 2016 May;22(2):1703. doi: 10.1111/srt.12245. Epub 2015 Jul 14.

[40] AguilarSS, et al. Skin carotenoid response to a high-carotenoid juice in children: a randomized clinical trial J Acad Nutr Diet. 2015 Nov; 115(11):1771-8. 10.1016/j.jand.2015.06.011. Epub 2015 Aug 5.

[41] Massenti R et al. Regular consumption of fresh orange juice increases human skin carotenoid content. Int. J Food Sci Nutr. 2015;66(6):718-21 doi: 10.3109/09637486.2015.1077794. Epub 2015 Aug 17.

[42] Sharafi M et al. Preschool-Adapted Liking Survey (PALS): A Brief and Valid Method To Assess Dietary Quality of Preschoolers. Child Obes. 2015 Oct; 11(5):530-40.

[43] Perrone A, et al. Raman Spectroscopic Measurements of Dermal Carotenoids in Breast Cancer Operated Patients Provide Evidence for the Positive Impact of a Dietary Regimen Rich in Fruit and Vegetables on Body Oxidative Stress and BC Prognostic Anthropometric Parameters: A Five-Year Study. Oxid. Med Cell Longev. 2016;2016:2727403 doi:

of five years in 71 breast cancer patients *at high risk of recurrence*. The original skin carotenoid scores had been correlated with parameters relevant to breast cancer risk, which also included waist circumference and body mass index. There was a positive correlation between patients' skin carotenoids score and blood levels of lycopene. Interestingly, the level of skin carotenoids was inversely correlated with the patients' waist circumference and BMI. The conclusion of the paper was that "**noninvasive measurements of skin carotenoids can reveal an oxidative stress condition correlated with parameters of BC risk** and (ii) monitor dietary-related variations in BC patients." The clinical reality then follows: well, if the Raman spectroscopic measure "reveals an oxidative stress condition correlated with parameters of breast cancer risk" – then…. shouldn't we be doing something?

- The sixth and most recent paper again notes Raman Spectroscopy as one of the four techniques to measure nutritional interventions. Interestingly, only the Biophotonic Scanner was cited as being actually able to *directly measure* the results of the interventions. The other three were based on "interviews," smart phone bio-sensors, and eye-tracking technology.[44]

A historical appreciation of the relationship of carotenoids with total body antioxidant status (and, thus, resistance to oxidative stress) can be found in the following papers:

- Carotenoids can quench highly reactive singlet oxygen, and can also block free radical-mediated reactions.[45]
- Carotenoids by themselves are potent antioxidants, able to absorb 20 free radical hits before being destroyed.[46]
- Lutein and Zeaxanthin were found to support a protective role in delaying chronic disease.[47]
- Correlation between carotenoid levels and other classic antioxidants was established by Peng and colleagues in their Nutrition and Cancer article.[48] They evaluated the levels of seven carotenoids, two retinoids, and two tocopherols measured in plasma and buccal mucosal cells, as well as skin samples from 96 healthy subjects. The data clearly showed a correlation *between the levels of micronutrients in plasma as well as skin.* Their conclusion was that "*the status of these micronutrients in the …. skin may be estimated from their plasma concentrations."* (The reverse, obviously also applies.) Notably, the skin carotenoids were determined with a microplane harvesting of a skin specimen that was then submitted for HPLC analysis – a process far more painful than the painless Biophotonic scanner. The scanner was not available at the time of this study.
- In a different paper, Sies and colleagues (2004) *clearly identified carotenoids as one of the dietary antioxidants* [thus, part of the "antioxidant network"] along with vitamins E and C, polyphenols, and other micronutrients (specifically Selenium as an example).[49]
- Svilaas and colleagues found that levels of carotenoids are actually predictive of levels of other, more conventionally thought of, antioxidants such as Vitamins C and E.[50] In their study of 2,670 adults they found that the ability of carotenoids to predict serum levels of other

---

10.1155/2016/2727403. Epub 2016 Apr 26. Link to full Free PMC Article in its entirety here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4861805/

[44] Scherr RE et al. Innovative Techniques for Evaluating Behavioral Nutrition Interventions. Ad Nutr. 2017 Jan 17;8(1):113-125.

[45] Bendich A, Olson JA. Biological actions of carotenoids. FASEB J. 1989 Jun;3(8):1927-32.

[46] Tsuchiya M et al. Antioxidant radical-scavenging activity of carotenoids and retinoids compared to alpha-tocopherol. Methods Enzymol. 1992; 213:460-72.

[47] Mares-Perlman JA et a. The Body of Evidence to Support a Protective Role for Lutein and Zeaxanthin in Delaying Chronic Disease. Overview J Nutr. 2002 Mar;132(3):518S-524S.

[48] Peng YM et al. Concentrations and plasma-tissue-diet relationships of carotenoids, retinoids, and tocopherols in humans. Nutr Cancer. 1995;23(3):233-46.

[49] Sies H, et al. Nutritional, dietary and postprandial oxidative stress. J. Nutri. 2005 May;135(5):969-72

[50] Svilaas A, et al. Intakes of antioxidants in coffee, wine, and vegetables are correlated with plasma carotenoids in humans. J Nutr. 2004 Mar;134(3):562-7.

antioxidants was stronger than the predictive ability of alpha, beta, delta, and gamma-tocopherols as well as glutathione. In other words, the level of carotenoids is actually more important than the total level of Vitamin E – a much more conventionally cited antioxidant – *in inferring the total antioxidant protective level of the system.*

This is tantamount to a paradigm shift in the literature, where, suddenly, the measurement of a skin carotenoids score can legitimately be used to infer the total antioxidant capacity of the system.

- More recently, Perrone et al. (2014) used Raman spectroscopy in living skin to measure oxidative stress with iron burden in patients with thalassemia. Their conclusion was: "On this basis, the level of skin carotenoids can be considered a biomarker of the entire antioxidant status."[51]

It is important to be aware of exactly what the BioPhotonic Scanner actually measures: **"a detection of the total carotenoids content in human skin."**[52] Notably, the vibration of all of the double bonds of all carotenoids, as measured by Raman Spectroscopy, detects basically *all* of the skin carotenoids. Specifically listed in the patent[53] are the following: **all-trans-beta-carotene, lycopene, alpha-carotene, gamma-carotene, phytoene, phytofluene, sepapreno-beta-carotene, 7,7'dihydro-beta-carotene, astaxanthin, canthaxanthin, zeaxanthin, lutein, beta-apo8'carotenal, violaxanthins, and rhodoxanthin**." This is considerably more than "skin carotene." The patent notes, "These are chain-like molecules with different lengths and attachments, all having a carbon backbone with alternating carbon double and single bonds, respectively. The vibration of these bonds, *common to all carotenoids*, can be detected with Raman spectroscopy. It is known from separate measurements that the wavenumber shifts of these carotenoids are generally in the range from 8000 to 2000 cm.sup.-1 (wavenumbers)."

The question then arises: what is the relevance of measuring carotenoids in the skin (other than to see if children are eating healthy, drinking carrot or orange juice, or getting all of their "fruits and veggies"? The answer is three-fold:

- First, carotenoids in the skin are, in and of themselves, quite relevant in terms of the likelihood of malignant lesions such as basal cell carcinoma and melanoma [references follow].
- Secondarily, these *skin* readings are reflective of *total body* antioxidant status.
- Thirdly, and most subtly, if a nutritional intervention is conducted that simultaneously raises antioxidant capacity and simultaneously supplies the body with other critically required micronutrients, the Biophotonic Scanner will validate that the *antioxidant component* is being absorbed: that is, there is a "delta" – *a change* – in the patient's antioxidant capacity with the nutritional intervention as the direct and proximate cause. Given that long-chain carotenoid molecules are certainly not preferentially absorbed in the gut, and that smaller nutrients would be far more likely to be absorbed, lends the clinician some inferential satisfaction that not only are the antioxidants being absorbed, but also other nutrients, given along with the antioxidants, are presumptively being absorbed.

It is historically useful, going back to primary source documents, that the relevance of skin carotenoids was repetitively cited throughout the scanner's original patent. It was noted that "carotenoids are an

[51] Perrone A, et al. Raman spectroscopy technology to monitor the carotenoids in skin of thalassemia patients: a novel non-invasive tool relating oxidative stress with iron burden. Thalassemia Reports vol 4:2 (2014) **DOI:** http://dx.doi.org/10.4081/thal.2014.1967
[52] Loc. Cit. http://www.google.com/patents/US6205354
[53] Ibid.

important component of the skin's antioxidant defense systems, where they are thought to act as free radical and singlet oxygen scavengers." Also noted is the "correlation between the levels of carotenoids, retinoids, and similar chemical substances in the skin and the risk of skin cancer and other skin disorders. People with low levels of carotenoids in their skin are *at a significantly greater risk of getting skin cancer*."[54]

There are multiple interfacing and collectively synergistic papers and assertions found in the peer-reviewed medical literature to support this claim in the patent application, and many more have appeared since the patent was awarded.

1) As early as 1984, in an article published in the Proceedings of the National Academy of Sciences, a positive correlation was found between the levels of carotenoids and "maximal life-span potential of mammalian species."[55]

2) Carotenoids began to be clearly identified in 1992. Khachik and colleagues noted that five were abundant in the human diet, and that among these, five carotenoids – beta carotene, alpha carotene, lycopene, lutein, and zexanthin – are found in the blood and known to be important in human health.[56]

3) Carotenoids by themselves are potent antioxidants. Tsuchiya and colleagues, writing in 1994[57], noted that a typical carotenoids molecule is able to sustain more than 20 free radical hits by lipid radicals before it becomes completely destroyed. Also, obviously, if the carotenoids molecules are appearing in the skin, they have been absorbed by other cells of the body – along with their presumptive antioxidant effects. Tsuchiya and colleagues, with Lester Packer as a co-author, also published the first paper on this topic in 1992.[58]

4) There is an exciting eighteen-year rapid advance in the literature looking at the consumption of lycopenes and carotenoids in terms of the risk of prostate cancer.

    - As early as 1998, Giovannucci and Clinton published two studies beginning to examine the link between tomatoes, *lycopene*, and the development of prostate cancer.[59] [60]
    - Four years later, Miller joined Giovannucci in noting that "*lycopene is one of the compounds in raw and processed tomato products that may contribute to a lower risk of prostate cancer…. Other carotenoids and phytochemicals in tomato products may also contribute to the proposed benefits*."[61]
    - Two years later, Wu and colleagues analyzed 450 incident prostate cancer cases diagnosed from 1993-1998 and compared them to 450 controls by age, time, month, and year of blood donation.[62] "We found a *statistically significant inverse association*

[54] Loc cit. see patent.
[55] Cutler, RG. Carotenoids and retinol: their possible importance in determining longevity of primate species. Proceedings of the National Academy of Sciences, USA. 1984 Dec; (81)23: 7627-7631. Link to complete article: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC392201/
[56] Khachik F et al. Separation and quantification of carotenoids in human plasma. Methods Enzymol. 1992;213:205-19.
[57] Tsuchiya, M et al. Antioxidant activity of alpha-tocopherol, beta carotene, and ubiquinol in membranes:cis-parniaric acid-incorporated liposomes. Method Enzymol. 1994; 234:371-83.
[58] Tsuchiya M et al. Antioxidant radical-scavenging activity of carotenoids and retinoids compared to alpha-tocopherol. Methods Enzymol. 1992; 213:460-72.
[59] Giovannucci E, Clinton SK. Tomatoes, lycopene, and prostate cancer. Proc Soc Exp Biol Med. 1998 Jun;218(2):129-39.
[60] Clinton SK, Giovannucci E. Diet, nutrition, and prostate cancer. Annu Rev Nutr. 1998;18:413-40.
[61] Miller EC et al. Tomato products, lycopene, and prostate cancer risk. Urol Clin North Am. 2002 Feb;29(1):83-93.
[62] Wu K, et al. Plasma and dietary carotenoids, and the risk of prostate cancer: a nested case-control study. Cancer Epidemiol Biomarkers Prev. 2004 Feb;13(2):260-9.

between higher plasma lycopene concentrations and lower risk of prostate cancer, which was restricted to older participants and those without a family history of prostate cancer." They continued: "This observation suggests that tomato products may exhibit more potent protection against sporadic prostate cancer rather than those with a stronger familial or hereditary component. In addition, our findings also suggest that among younger men**, diets rich in beta-carotene may also play a protective role in a prostate carcinogenesis**."

Thus, it is clear that carotenoids themselves possess potent biologically active and chemoprotective effects.[63] Protection against prostate cancer is just one of the benefits cited in the literature. There are multiple others including skin cancer prophylaxis[64] [65] and atherosclerotic disease prophylaxis.[66] (Other references and citations will follow in this paper later.)

Specifically in terms of protection from skin cancer, the authors note that "Optical, non-invasive methods, *like resonance Raman spectroscopy*, allow a qualitative and quantitative online detection of the kinetics **of antioxidants such as carotenoids in the skin.**"[67]

In terms of prevention of lipid peroxidation and the conversion of LDL under oxidative stress to cause the promotion of arterial plaques, three groups of antioxidants are specifically mentioned: Vitamin E, the carotenoids, and the polyphenolic flavonoids.[68]

- Setting their own potently beneficial effects aside, and focusing on implied levels of other antioxidants, it's important to note that as early as 1995, correlation between levels of carotenoids as well as other antioxidants, ***specifically the tocopherols***, was noted. Peng and colleagues, writing in Nutrition and Cancer,[69] took note of the fact that micronutrients such as beta-carotene, Vitamin A and Vitamin E are *potential chemopreventive agents.* However, in 1995, their concentrations in human target tissues were largely unknown. In this study, the levels of seven carotenoids, two retinoids, and two tocopherols were measured in both plasma and buccal mucosal cells as well as skin samples from 96 healthy subjects. The data clearly showed a correlation **between the levels of micronutrients in plasma as well as skin**. Their conclusion was that "**the status of these micronutrients in the …. skin may be estimated from their plasma concentrations."**[70] The reverse, of course, also holds true: the status of these micronutrients in the plasma may be estimated from the status of these micronutrients in the skin (accessed via Raman spectroscopy). And it bears

[63] The preponderance of the evidence for chemoprevention of cancer by carotenoids in multiple other conditions will be reviewed later in this paper.
[64] Wright, TI et al. Chemoprevention of nonmelanoma skin cancer. J Am Acad Dermatol. 2006 Jun;54(6):933-46
[65] Darwin M et al. Functional food and bioavailability in the target organ skin. Hautarzt. 2006 Apr;57(4):286-90.
[66] Aviram M. Dietary antioxidants and paraoxonases against LDL oxidation and atherosclerosis development. Hanb Exp Pharmacol. 2005;(170):263-300.
[67] Wright, TI et al. Chemoprevention of nonmelanoma skin cancer. J Am Acad Dermatol. 2006 Jun;54(6):933-46
[68] Aviram M et al, 2005. Loc cit.
[69] Peng YM et al. Concentrations and plasma-tissue-diet relationships of carotenoids, retinoids, and tocopherols in humans. Nutr Cancer. 1995;23(3):233-46.
[70] Other corroboration on this point appears. El-Sohemy and colleagues at the Harvard School of Public Health, using actual adipose tissue biopsies in addition to plasma levels, reported in 2002 that "the usefulness of adipose tissue and plasma carotenoids as biomarkers of intake is similar, although correlations for individual carotenoids vary substantially." El-Sohemy A, et al. Individual carotenoid concentrations in adipose tissue and plasma as biomarkers of dietary intake. Am J Clin Nutr. 2002 Jul;76(1):172-9.

emphasizing that there was a correlation between the levels of the carotenoids and the tocopherols – Vitamin E, a known and potent antioxidant.

Other considerations in this study were also remarkable, including the fact that "the plasma and tissue concentrations of most micronutrients were lower in smokers than in nonsmokers and *higher in vitamin supplement users than in nonsupplement users."* Further*, "The differences remained significant [even] after adjustment for age, gender, and diet intake estimates."*[71]

Remarkably, an incidental finding was that lycopene was unique among the seven carotenoids studied because its concentration was not affected by either smoking or supplement users, but went down steadily with age. This correlates with other studies that show an age-related decline in retinol, total tocopherols, total xanthopylls, and total carotenoids in the frontal lobes of aging human brains.[72]

- In 1992, in the Annals of the New York Academy of Science, Sies and colleagues,[73] in an earlier paper, examined the role of carotenoids and their mechanism of action. "Carotenoids," they noted, "notably beta-carotene and lycopene as well as oxycarotenoids (e.g. zeaxanthin and lutein), exert antioxidant functions in lipid phases by free-radical or 1O2 quenching."
- It is also important to be fully aware that carotenoids are part and parcel of the total antioxidant network. Lester Packer, Ph.D., known as the "father of antioxidants" and the author of hundreds of scholarly papers in peer-reviewed journals, published **The Antioxidant Miracle** in 1999.[74] In it, Packer took note of Vitamins C & E, as well as Coenzyme Co-Q10 (ubiquinone), Alpha Lipoic Acid, and Selenium as all functioning as part of the antioxidant network. He specifically noted carotenoids as a first line of defense and their protective effect on Vitamins C and E. Later, Stahl and Sies, writing in May 2005,[75] noted that "there is convincing evidence that carotenoids are important components of the antioxidant network. …Lutein and zeaxanthin are the predominant carotenoids of the retina and are considered to act as photoprotectants preventing retinal degeneration." In terms of disease prevention, Stahl and Sies also reviewed that the *consumption of a diet rich in carotenoids [which would show up in the skin and be measurable] has been "epidemiologically correlated with a lower risk for several diseases."*
- In a different paper, Sies and colleagues (May 2005) **clearly identified carotenoids as one of the dietary antioxidants** [thus, part of the "antioxidant network"] along with vitamins E and C, polyphenols, and other micronutrients (specifically Selenium as an example).[76]
- The need to look outside the conventional water-soluble anti-oxidants, such as Vitamin C, was noted in a paper by Yeum and colleagues in 2004.[77] Specifically, they noted

[71] Peng YM et al. Loc cit.
[72] Craft NE, et al. Carotenoid, tocopherol, and retinol concentrations in elderly human brain. J Nutr Health Aging. 2004;8(3):156-62.
[73] Sies H et al. Antioxidant functions of vitamins. Vitamins E and C, beta-carotene, and other carotenoids. Ann N Y Acad Sci. 1992 Sep 30;669:7-20.
[74] Packer, Lester. The Antioxidant Miracle. John Wiley & Sons, Inc. © 1999.
[75] Stahl W, Sies H. Bioactivity and protective effects of natural carotenoids. Biochim Biophs Acta. 2005 May 30;1740 (2):101-7. Epub 2004 Dec 28.
[76] Sies H, et al. Nutritional, dietary and postprandial oxidative stress. J. Nutri. 2005 May;135(5):969-72/
[77] Yeum et al. Biomarkers of antioxidant capacity in the hydrophilic and lipophilic compartments of human plasma. Arch Biochem Biophys. 2004 Oct 1; 430(1):97-103.

"Conventional assays to determine antioxidant capacity primarily measure the antioxidant capacity in the aqueous compartment of plasma. Consequently, *water soluble antioxidants such as ascorbic acid, uric acid, and protein thiols mainly influence these assays, whereas fat-soluble antioxidants such as tocopherols and carotenoids play only a minor role.* However, there **are active interactions among antioxidants located in the hydrophilic and lipophilic compartments of plasma**. Therefore, **new approaches to define the 'true' total antioxidant capacity of plasma should *reflect the antioxidant network between water- and fat-soluble antioxidants*** in plasma." In other words, measuring Vitamins C and E were no longer enough.

- The actual anti-cancer effects of the antioxidant carotenoids were specifically noted, as well as their function as "potent antioxidants" in Sharoni et al., 2003.[78] Specifically they asserted the following: "It is widely accepted that diet changes are a powerful means to prevent cancer. The possible involvement of transcriptional activity in the **anticancer activity of carotenoids** will be the focus of this review. *Carotenoids function as potent antioxidants, and this is clearly a major mechanism of their action.* In addition, ***carotenoids action involves interference in several pathways related to cancer cell proliferation*** and includes changes in the expression of many proteins participating in these processes."

The Biophotonic Scanner – A Technological, Historical and Chronological Perspective up to the Present Time

Historically, it is fascinating to trace the history of Raman spectroscopy before it was used in its current form and patented at the University of Utah. It was used at the very foundation of its recent patent development to study carotenoids in the eye.

1) Looking outside the eye and the skin as far back as 1998, and at the University of Texas, Raman spectroscopy was used for the clinical diagnosis of cervical precancers via a fiber optic probe.[79]
2) Going back even further to 1992, in a much earlier form before the BioPhotonic scanner and its immediate precursors were designed, Raman spectroscopy was used as a diagnostic technique in separating diseased and normal biomedical media.[80] The authors concluded that: "A comparison of the intensity differences between various Raman modes, as well as the number of Raman lines, enables one to distinguish normal GYN [gynecological] tissues from diseased tissues."

The convenience of carotenoids as a measure of antioxidant status and their accessibility to Raman analysis [use of the BioPhotonic Scanner instead of blood testing or urine testing for inflammatory metabolites consistent with low anti-oxidant status] was asserted and first published in the peer-reviewed medical literature *as early as 1998* by Bernstein and colleagues at the University of Utah

[78] Sharon Y et al. Modulation of transcriptional activity by antioxidant carotenoids. Mol Aspects Med . 2003 Dec;24(6):371-84.
[79] Madadevan-Jansen, A. Development of a fiber optic probe to measure NIR Raman spectra of cervical tissue in vivo.. Photochem photobiol. 1998 Sep;68(3):427-31.
[80] Liu CH, et al. Raman, fluorescence, and time-resolved light scattering as optical diagnostic techniques to separate diseased and normal biomedical media. J Photochem Photobiol B. 1992 Oct 30;16(2):187-209.

where the scanner was originally under development.[81] This paper investigated the correlation of Raman measurements on human flat-mounted retinas and eyecups and in experimental animal eyes, and correlated this with macular carotenoids levels determined by high performance liquid chromatography [a conventional way to do it, but one that requires tissue or blood samples]. The results described were as follows: "Carotenoid resonance Raman scattering proved to be a highly sensitive and specific method for the noninvasive measurement of macular pigments in the human retina. Signal strength scaled linearly with actual macular carotenoids content as measured by HPLC." Their conclusions were as follows: "This new noninvasive optical method will facilitate studies of ocular carotenoids distributions and their role in degenerative diseases of the eye and may allow for the rapid screening of carotenoids levels in large populations at risk for vision loss from age-related macular degeneration, the leading cause of blindness in the elderly in the United States." The authors took note that "a prototype clinical instrument is under development."

- Four years later, following the awarding of the patent and further refinement of the scanner, Bernstein published again. Bernstein and Gellerman, sometimes writing with others, published three papers in quick succession in 2002.
    - In the first, they noted that Raman signals correlated perfectly with carotenoids content. They asserted, "The Raman technique is objective and quantitative and may lead to a new method for rapid screening of carotenoids pigment levels in large populations at risk for vision loss…"[82]
    - A second paper confirming the measurement of carotenoids in the living primate eye was published in Methods of Molecular Biology.[83]
    - Their third paper[84] looked at Raman measurement of macular carotenoids in normal subjects and compared them to levels in age-related macular degeneration patients. It was published in the leading journal of its field, *Ophthalmology*. Their conclusions agreed with the hypothesis, which they asserted again, that "low levels of lutein and zeaxanthin [two major carotenoids in the human macula] may represent a pathogenic risk factor for the development of AMD [age related macular degeneration]." They further asserted that "Resonance Raman measurement of macular carotenoids pigments could play an important role in facilitating large-scale prospective clinical studies of lutein and zeaxanthin protection against AMD, and this technology may someday prove useful in the early detection of individuals at risk for visual loss from AMD."

- The move from the use of the scanner to detect carotenoids noninvasively in the eye, all the way to using the scanner to detect total body carotenoids levels by scanning the hand, was complete in 2000. In the first article of its kind (previously referenced), Hata et al, writing in Journal of Investigative Dermatology, correlated the carotenoids score determined by Raman spectroscopy (the BioPhotonic Scanner) to levels of carotenoids obtained from tissue specimens of human skin removed from people in abdominoplasty procedures.[85] The experimental subjects were having abdominoplasty and had levels of carotenoids measured

[81] Bernstein P et al. Raman detection of macular carotenoids pigments in intact human retina. Invest Opthalmol Vis Sc. 1998 Oct;39(11):2003-11.
[82] Gellermann, Bernstein et al. In vivo resonant Raman measurement of macular carotenoids pigments in the young and the aging human retina. J. Opt Soc Am A Opt Image Sci Vis. 2002 Jun;19(6):1172-86.
[83] Bernstein, Gellerman. Measurement of carotenoids in the living primate eye using resonance Raman spectroscopy. Method Mol Bio. 2002;196:321-9.
[84] Bernstein, et al. Resonance Raman measurement of macular carotenoids in normal subjects and in age-related macular degeneration patients. Ophthalmology. 2002 Oct; 109(10):1780-7.
[85] Hata et al. Non-invasive Raman spectroscopic detection of carotenoids in human skin. J Invest Dermatol. 2000 Sep; 115(3):441-8.

on skin removed from their abdomen using standard high-performance liquid chromatography. This was cross-referenced with carotenoids levels obtained from other areas of their skin using the BioPhotonic Scanner.

The "set up" of this paper and the research is remarkable. First, in their abstract, the authors note that "carotenoids are thought to play a significant part in the skin's anti-oxidant defense system, and *may help prevent malignancy*."

They then note: "inability to measure skin carotenoids content readily has, however, made it difficult to establish the relationship between carotenoids concentration and the occurrence of cutaneous malignancy." In other words, it's been impossible to measure skin carotenoids unless you want to sacrifice a large piece of your skin for it to be prepared for examination with HPLC. Most people are unwilling to do that, no matter how interested they would be in learning their "skin carotenoid scores." It is also unreasonable to expect people to part with a piece of their flesh for a casual screening for health status. Since the abdominoplasty patients were going to be parting with large hunks of their flesh anyway – under total anesthesia - it was not a disincentive to participate in the experiment.

The authors look back to what has been done when they assert: "we have measured in vivo [in living tissue – eyes, specifically] carotenoids concentration using a noninvasive optical method, Raman spectroscopy."

They then state the purpose of their paper: "***To validate our instrumentation***, abdominoplasty skin was evaluated by both Raman spectroscopy and high-performance liquid chromatography determination for carotenoids content." In other words, this is going to be a paper about whether or not skin carotenoids scores are valid – obtained with Raman laser spectroscopy (the BioPhotonic scanner), when they are compared with skin carotenoids scores obtained by actually taking hunks of tissue from people's bodies, macerating it, liquefying it, and then analyzing it with HPLC.

This is how they did it: "Evaluation of the Raman signal in specific carotenoids solutions was also performed [from the abdominoplasty patients]. Precision of Raman measurements within skin sites, within subjects, and between subjects was measured. Sensitivity of the method was evaluated as a function of anatomical region and the distribution of carotenoids within the stratum corneum."

During their investigation, they *also* compared total levels of carotenoids at the exact site of actinic keratoses (pre-cancerous lesions) and basal cell carcinoma lesions with the levels of skin surrounding the lesions ***as well as the exact same sites on the bodies of age matched controls.***

Their results were astonishingly crisp:

- "Our results indicate that the Raman scattering method reflects the presence of carotenoids in human skin and is **highly reproducible."** [In other words, it correlated extremely well with carotenoids levels obtained from the "pieces of tissue" method.]
- "Evaluation of five anatomical regions demonstrated significant differences in carotenoids concentration by body region ***with the highest carotenoids concentration noted in the palm."*** [This established the palm as the body site from which measurements would be taken.]
- In looking at risk factors for skin cancer and the presence of precancerous lesions, they note: "Comparison of carotenoids concentrations in basal cell carcinomas, actinic

keratosis, and their perilesional skin demonstrate **a significantly lower carotenoids concentration than in region-matched skin of healthy subjects**. ***These results represent the first evidence that carotenoids concentration in the skin correlate with the presence or absence of skin cancer and precancerous lesions."***

- One year later, Ermakov et al, writing with Gellerman, published "Resonance Raman detection of carotenoid antioxidants in living human tissues" in the journal Optics Letters.[86] In their abstract, they assert: "We have used Resonance Raman scattering as a novel noninvasive optical technology to measure carotenoids antioxidants in living human tissues of healthy volunteers. By use of blue-green laser excitation, clearly distinguishable carotenoids Raman spectra superimposed on a fluorescence background are obtained. The Raman spectra are obtained within less than a minute, and the required laser light exposure levels are well within safety standards. Our technique can be used for rapid screening of carotenoids levels in large populations and may have applications ***for assessing antioxidant status and the risk for diseases related to oxidative stress***." [Note – they are asserting broadly that this is not just about "carotenoids in the skin", but, rather, is relevant for all disease states which are related to decreased antioxidant capacity.]

  In this paper, they cite the work of Boileau and colleagues,[87] who had previously reviewed an inverse correlation between high dietary intake of carotenoids and the risk of various cancers, cardiovascular disease, and degenerative diseases – and not just simply skin cancer. In other words, the higher your diet in carotenoids, the less likely your chances are for these diseases.

  They took note of the fact that they had already used their scanner to measure carotenoids levels in the skin, retina, oral cavity, and other tissues of the body.

  These investigators specifically noted that in human skin, the five most concentrated carotenoids antioxidants are lycopene, alpha-carotene, beta carotene, phytoene, and phytofluene, with lycopene and the carotenes accounting for 60 – 70% of total carotenoids content.

  They again took note of the difficulty – not to mention pain and suffering – of obtaining skin carotenoids scores with previous methods: "The standard technique for measuring carotenoids is high-pressure liquid chromatography. This chemical method works well for the measurement of carotenoids in serum (blood) but is difficult to perform in tissue, ***since it requires biopsies and processing of relatively large tissue volumes."***

  The authors scrupulously describe their methods and the science behind Raman spectroscopy in this paper. Among other things, there is a careful review of why the palm has been chosen as the best site for scanning:

  - Carotenoid levels in the palm are among the highest found in skin (because carotenoids are lipophilic and palm skin has a high lipid/protein ratio);
  - Differences in pigmentation among various skin types are minimal in the palm;
  - The stratum corneum thickness of the palm (approximately 400 micrometers) is high compared with other skin sites. Thus, the laser penetration depth in this skin layer,

[86] Ermakov, et al. Resonance Raman detection of carotenoid antioxidants in living human tissues. Optics Letters. 2001 Aug 26(15):1179-1181.
[87] Boieleau T et al. in Antioxidant Status, Diet, Nutrition, and health. A.M. Paps, ed. (CRC Press, Boca Raton, FL, 1999), p. 144

which is highly scattering, confines the measurement to this layer – the stratum corneum. As such, it decreases variability of the scoring.

Their conclusions: "…resonance Raman scattering appears to be a *feasible optical technique for the* ***measurement of carotenoids antioxidants*** *in living human tissue*. **It is precise, accurate, specific, and sensitive. Most importantly, it is noninvasive and suitable for clinical studies.** Pending a careful calibration of our measurement with that determined by high-pressure liquid chromatography, it should be possible to replace the highly invasive chemical method with a completely noninvasive and quantitative optical alternative. The laser excitation power used on our experiments is well below safety standards and can be easily increased to permit nearly real-time data collection. Our Raman technique may become a useful method to evaluate the correlation between tissue carotenoids levels and risk for malignancies or other diseases associated with oxidative stress." [88]

- Ermakov and Gellerman have continued to research the ramifications of their invention in multiple published papers, all peer reviewed. In the Nov-Dec 2005 issue of Journal of Biomedical Optics,[89] Ermakov and colleagues reviewed the main results achieved with Raman spectroscopy thus far. They took note of the fact that "initially we applied the method to the detection of macular carotenoids pigments, and more recently to the detection of carotenoids in human skin and mucosal tissues." They review the selection of the human palm as the ideal site for scanning. Summarizing the literature and the clinical findings using the BioPhotonic scanner to date, they assert: "These experiments reveal that carotenoids are a good indicator of antioxidant status. **They show that people with high oxidative stress, like smokers, and subjects with high sunlight exposure, in general, have reduced skin carotenoid levels, independent of their dietary carotenoid consumption.** We find the Raman technique to be precise, specific, sensitive, and well suitable for clinical as well as field studies. The noninvasive laser technique may become a useful method for the correlation between tissue carotenoid levels and risk for malignancies or other degenerative diseases associated with oxidative stress."

  This is a remarkable assertion, because **it crisply relates low skin carotenoids scores with the presence of oxidative stress**, and not just the consumption of dietary carotenoids. Their forward looking conclusion also addressed the correlation between tissue carotenoids levels and the actual risk for malignancies **in general** – and not just in terms of skin cancers. It also specifically addresses "degenerative diseases" – which include atherosclerosis, dementias, etc., all of which have literature to support the role of oxidative stress.

- Subsequent to that paper, Erkakov and Gellerman published a "Validation model for Raman based skin carotenoid detection) in 2010.[90] They also collaborated with other co-authors in 2010 to review Raman spectroscopic evaluation of fruit and vegetable consumption in adults,[91]

[88] Ermakov et al, 2001, loc cit.
[89] Ermakov IV, et al. Resonance Raman detection of carotenoids antioxidants in living human tissue. J Biomed Opt. 2005 Nov-Dec;10(6):064028
[90] Ermakov IV, Gellermann W. Validation model for Raman based skin carotenoid detection. Arc Biochm Biophys. 2010 Dec 1;504(1):40 – 9.
[91] Mayne ST et al (incl Ermakov and Gellerman). Noninvasive assessment of dermal carotenoids as a biomarker of fruit and vegetable intake. Am J Clin Nutr. 2010 Oct;92(4):794-800. Free PMC article available here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3133234/

and, in a later paper, in children.[92]

- Finally, if one searches the database of the National Library of Medicine on the topic of "Raman spectroscopy with carotenoids with antioxidant" there is an explosion of literature. In August, 2006 (the time of publication of this original paper), there were 169 citations found. Today, in early 2017, there are 339 papers.[93] The more general search on "Raman spectroscopy with antioxidants" yielded 224 in 2006 papers, but an astonishing increase to 966 today.[94] Obviously, not all are specifically relevant to humans and total antioxidant status, but a number of them are well worth reviewing.

Placing the Biophotonic Scanner in Context

Following the granting of the patent in 2001, further research on the clinical relevance of the scanner was performed by Pharmanex. In a paper published in-house by one of their chief scientists, significant data points were obtained correlating scan scores with fruit and vegetable consumption, smoking, and LifePak[95] usage.[96]

- **1,375** subjects entered into the population study. The mean score of these subjects was 19,072 Raman units, with a standard deviation of 8,828 units. The lowest measurement obtained was 1,556 units; the highest level was 73,416. The majority of the subjects (68%) fell between 10,244 and 27,900 Raman units for the "Skin Carotenoid Score."
- There was, as expected, a pronounced, positive relationship between fruit and vegetable consumption which was reported and the BioPhotonic measurements:
  - 1 or less serving/day netted a score of 16,827 +/-6,725
  - 2-3 servings/day : 19,669 +/-8,557
  - 4 -5 servings: 23,997 +/- 12,648
  - 6 or more servings: 25,377 +/- 12,953 units
- 562 subjects – a little less than half – also provided urine specimens for an MDA test.[97] There was a linear, stair step progression upward toward optimum (low) levels of MDA as the scan scores increased. In other words, the higher the BioPhotonic scanner score, the less evidence of oxidative damage and stress on the system.
- Smoking had the opposite effect: non-smokers had the highest scan scores on average: approximately 20,000. The more one smoked, the lower the scan score… all the way down to a mean of 11,593 for five or more cigarettes per day. Smoking and its antioxidant burden is well known[98]; it is only logical to suspect that the scan scores would have gone down, but the dramatic almost two-fold difference is startling.

---

[92] Scarmo S et al (incl Ermakov and Gellermann). Skin carotenoid status measured by resonance Raman spectroscopy as a biomarker of fruit and vegetable intake in preschool children. Eur J Clin Nutr. 2012 May;66(5):555-60. Free PMC article here: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3380427/

[93] https://www.ncbi.nlm.nih.gov/pubmed/?term=Raman+spectroscopy+with+carotenoids+with+antioxidant accessed Feb 3, 2017

[94] https://www.ncbi.nlm.nih.gov/pubmed/?term=Raman+spectroscopy+with+antioxidants accessed Feb 3, 2017

[95] "Lifepak"is a branded high potency, multi-vitamin, multimineral nutritional supplement developed and marketed by Pharmanex.

[96] Smidt, C. Clinical screening study: use of the Pharmanex ® BioPhotonic scanner to assess skin carotenoids as a marker of antioxidant status. Pharmanex, LCC, 75 West Center Street, Provo, UT. 2002

[97] a relatively well known but non-specific test of urine to determine levels of malondialdehyde – a known marker for oxidative stress and presumptively indicative of either low levels of antioxidants, high levels of oxidative stress, or both.

[98] Lesgards JF et al. Assessment of lifestyle effects on the overall antioxidant capacity of healthy subjects. Environ Health Perspect. 2002 May;110(5):479-86. Notably, Lesgards and colleagues also found *nonsmoking, vitamin and/or mineral supplementation, and regular physical activity were closely associated with* ***increased*** *overall antioxidant status*; *tobacco smoking, psychologic stress, alcohol consumption, moderate vegetable, low fruit, and low fish consumption were all associated with* ***decreased*** *antioxidant capacity*. High natural ultraviolent light was associated with decreased antioxidant capacity to a lesser degree.

- Finally, there was a strong and obvious correlation between the use of LifePak® supplementation and skin carotenoid measurements. Subjects who routinely consumed two packs of LifePak® supplements[99] at the recommended dosage of one packet twice daily measured 61% higher than those not using LifePak ($p<0.001$). In general, these routine LifePak® users had about the same BioPhotonic skin measurements as people who reported eating more than five servings of fruits and vegetables daily. Statistical analysis showed no confounding variables related to any significant changes in fruits or vegetables consumed by the study subjects.

Several obvious conclusions arise from this clinical study. First, the usual things that one associates with changes in total body antioxidant status correlated with the scan scores. If you smoked, you scanned less. If you ate more fruits and veggies, you scanned higher. And if you took two packets of LifePak per day, you scanned 61% higher. Thus, two positions were established:

1) The BioPhotonic scanner obtained scores which were logically what one would predict based on known models of oxidative stress and the dietary use of higher consumption of fruits and vegetables; indeed, the "skin carotenoid score" appeared to be an ***excellent*** biomarker of antioxidant status.
2) Taking Pharmanex LifePak® supplements improved the scores 61%. If one admits to the validity of the BioPhotonic scanner as a measurement of levels of oxidative stress, then the fact that the scan scores went up on LifePak® supplementation shows that the supplements don't just "raise skin carotenoid scores" but contribute to the total antioxidant status of the body.

A follow-up study by Smidt, this time looking exclusively at scan score increases as a function of LifePak® supplementation, produced similar results.[100] 25 healthy volunteers were recruited and supplemented their diet with LifePak for 12 weeks. BioPhotonic skin carotenoid readings increased significantly from a baseline value of 18,828 units to 32,175 units at the end of the study. This increase was not related to any changes in fruits or vegetables consumed throughout the study period.

Indeed, a previous study by Smidt and colleagues in 1999[101] examined functional effects of LifePak ® supplementation rather than scanner scores for a very simple reason: there was no scanner in existence at the time! Other ways had to be found to determine if the supplements were performing. Looking back at this study and then correlating it with new studies produces remarkable clarity at the interface between the BioPhotonic Scanner as a piece of measuring technology and the use of LifePak supplementation as something that is worth measuring. It is also pleasing to note that one of the three centers for this study was at GFI Pharmaceutical in Evansville, IN. The other two were the University of California at Davis Medical Center and the Pharmanex Research Institute in Provo, Utah.

In this 1999 study, Smidt and colleagues evaluated lipid peroxidation as a function of LifePak supplementation, and they concomitantly measured changes in plasma levels of ascorbic acid, beta-carotene, alpha-carotene, and alpha-tocopherol along with a ***functional measurement*** of antioxidant status: decreased LDL-oxidation. In a cross-over study involving 50 healthy non-smokers, 25 patients were placed on LifePak and 25 received placebo for six weeks. An intervening wash-out period of six

[99] This formulation was the best of its time, but inferior to the current LifePak Nano.
[100] Smidt, C. Effect of LifePak supplementation on antioxidant status using BioPhotonic Raman spectroscopy. Pharmanex, LLC, 75 West Center Street, Provo, UT 84601, 2003.
[101] Smidt, CR et al. The effects of a nutritionally complete dietary supplement (LifePak®) on antioxidant status and LDL-oxidation in healthy non-smokers. Federation of American Society for Experimental Biology. 1999;13(4). Pharmanex Clinical Study Report published February 23, 2000.

weeks was interposed between the first six weeks and the final six weeks, where the groups were crossed over or "flipped."

Their findings included the following:

- LifePak supplementation (1999 formulation) prolonged the time to LDL oxidation from 43 minutes to 51 minutes – an increase in 18%
- Ascorbic acid levels were increased 38%
- Alpha-carotene levels were increased 678%
- Beta-carotene levels were increased 114%
- Alpha-tocopherol levels were increased 84%.

Their conclusions, not surprisingly, were that LifePak "significantly increased antioxidant status, and decreased LDL oxidizability in healthy non-smokers."

More recently, these results were replicated in a large scale, multi-center, double-blind, placebo controlled study.[102] The paper is unfortunately not published, but the abstract is. This study included 150 non-smokers, ages 18 – 65 recruited in the Houston, Texas area. At baseline, the subjects were not taking any multi-vitamins or nutritional products and they were consuming less than five servings of fruits and vegetables per day. Seventy-five subjects received supplementation with LifePak in a double-blinded fashion, and 75 subjects received placebo "dummy" packets made up to look exactly the same. Blood and urine samples were taken at the start and end of the supplementation period and analyzed for vitamin C, vitamin E, carotenoids, and vitamin A, as well as serum oxygen radical absorption capacity, as well as markers of free radical damage: serum total alkenals hydroperoxides, urinary alkenals, 8-hydroxyguanosine, and 8-epiPGF. Plasma samples were prepared for LDL oxidizability assays.

An exact 18% prolongation of lag time of LDL oxidizability resistance was again obtained ($p<0.001$), with other results including increased total serum oxygen radical absorption capacity by 5%. The conclusions were: "LifePak ® supplementation for 6 weeks significantly increased antioxidant status, reduced serum alkenals, and improved LDL resistance to oxidation in healthy non-smokers consuming typical U.S. diets

2017 Updates on Antioxidants and Carotenoids – The Research of the Last 10 Years

Akbaraly and colleagues focused on total plasma carotenoids as they related to mortality in the elderly in 2009.[103] They followed 1,389 men and women, ages 59-71 years of age. In a nine-year longitudinal with six phases of followup. After correcting for any potential confounding factors, they found that *men in the lowest quintile of plasma carotenoids* (compared with men in the highest quintile) had **nearly three times the risk of dying from any cause,**[104] and nearly two times the risk of contracting cancer.[105]

[102] Smidt CR, et al. Double-blind, placebo-controlled study of the effects of LifePak ® supplementation on antioxidant status, free radical activity, and resistant to LDL-oxidation. [unpublished – abstract provided reference from Pharmanex, Provo Utah] http://whybioscan.com/wp-content/uploads/2013/09/likepaknano_clinicals.pdf

[103] Akbaraly TN et al. Total plasma carotenoids and mortality in the elderly: results of the Epidemiology of vascular Ageing (EVA) study. Br J Nutr. 2009 Jan; 101 (1):86-92.

[104] Exact numbers for Akbaraly – all cause mortality: relative risk of 2.94 (95% CI 1.21, 7.17))

[105] Exact numbers for Akbaraly – all cause mortality: relative risk of 1.72 (95% CI 1.02, 2.86 P=0.01))

In 2011, Michael Donaldson reviewed 62 studies of plasma carotenoids and health outcomes,[106] noting that the data had previously never been reviewed and assembled into a useful form. He looked at all the studies, synthesized the various ranges, and divided them between the 10th and 90th percentiles, ultimately coming up with five ranges. There were improvements in all cause mortality noted above every range except the bottom quintile. However, in terms of metabolic syndrome and cancer risks, there were significant positive health outcomes only above the higher cutoff points, perhaps, as Donaldson notes, quoting Ames (2006), due to a triage effect.

From Donaldson:

Summary of Data for the Carotenoid Health Index.

Averages across Percentiles, µM	Cutoff 1 10-18%	Cutoff 2 20-40%	Cutoff 3 50-62.5%	Cutoff 4 66-80%	Cutoff 5 84-90%
All Studies, $N = 62$	1.114	1.468	1.893	2.522	3.069
SEM ‡	0.078	0.079	0.085	0.129	0.204
Men Only, $N = 21$	1.091	1.359	1.735	2.263	2.923
Women Only, $N = 28$	1.237	1.800	2.336	3.025	3.411
No Benefit studies, $N = 10$	1.251	1.747	2.357	2.873	3.641
Benefit Studies, $N = 52$	1.123	1.463	1.874	3.012	3.679
Carotenoid Health Index, µM	<1	1 to <1.5	1.5 to <2.5	2.5 to <4	≥4
	Very High Risk	High Risk	Moderate Risk	Low Risk	Very Low Risk

‡ SEM = Standard Error of the Mean. Number of data points for the cutoff points are 32, 56, 72, 52, and 32 for cutoffs 1 to 5, respectively.

Of all of the 62 studies that were reviewed, 52 reported a benefit to higher carotenoid levels. The specific anti-cancer properties of carotenoids were noted as well.[107]

In 2012, in the Third National Health and Nutrition Examination Survey (NHANES III), Shardell and colleagues (2012) sought to examine whether serum carotenoid concentrations predict mortality among U.S. adults. There 13,293 adults >/= 20 years of age, enrolled in the study. Outcomes measured were all-cause [death from any cause], cardiovascular disease, and cancer mortality. They found that the subjects in the lowest quartile of carotenoids "had significantly higher all-cause mortality" with a mortality rate ratio of 1.38 (or a 38% increase rate of death) than the subjects in the highest quartile of carotenoids. For alpha-carotene, specifically, the highest quartile had the lowest all-cause mortality rates. "Analyses with continuous carotenoids confirmed associations of serum total carotenoids, alpha-carotene, and lycopene with all cause mortality." Significantly, using a "random survival forest analysis" [a technique used to study survival in populations], ***very low lycopene was the carotenoid most strongly predictive of all cause mortality, followed by very low total carotenoids***." [108]

[106] Donaldson, MS A carotenoid health index based on plasma carotenoids and health outcomes Nutrient. 2011 Dec; 3(12): 1003 – 1022.
[107] Ibidem
[108] Shardell MD et al. Low serum carotenoid concentrations and carotenoid interactions predict mortality in US adults: The Third National Health and Nutrition Examination Survey (NHANES III) Nutritional Research 2011 Mar;31(3):178-189.

Eliassen et al., published this theme of lower mortality being associated with higher levels of carotenoids, this time in terms of risk of contracting breast cancer, in the Journal of the National Cancer Institute in 2012. Looking at 80% of the world's published prospective data on plasma carotenoids and the potential association with the risk of breast cancer, they found a 20% reduction in risk of breast cancer for the women in the highest quintile of total plasma carotenoids.[109]

More recently, Narasimham L Parinandi, et al. (2015) wrote an overview[110] of all of the articles in the *Antioxidants in Longevity and Medicine 2014* compendium. They noted:

- "The balance between the ROS/RNS [reactive oxygen or nitrogen species, aka "free radicals"] and antioxidants is highly critical to maintain the cellular health and any alteration in that balance caused by either the elevation of production of ROS/RNS or decrease of antioxidant status in the cells will lead to diverse pathophysiological states."
- "…the *oxidative stress theory of aging* underscores the ROS-induced damage as being instrumental in *the progressive and unalterable alterations* at the molecular, cellular, and organ levels during aging and **shortening of life span.**

"Attenuating or inhibiting the overwhelming production and deleterious actions of ROS and RNS *by treatments with several antioxidants* is increasingly becoming sought-after therapeutic strategies to treat age-related diseases and ***extend the life span*** wherein the ROS-induced oxidative stress and RNS stress play crucial roles."

PIVOT POINT: Antioxidants, Micronutrient Supplementation, Cancer, Other Diseases and the Relationship with Dietary and Nutritional Supplementation

Thus far, I have reviewed interesting studies and epidemiologic risks. However, we are about to embark on a discussion of cancers and the potential use of antioxidants, carotenoids, and supplementation to decrease their risk of occurrence.

The following points are worth bearing in mind:

- In 1994, the Dietary Supplement Health and Education Act of 1991[111] – the "DSHEA act" – was passed by the United States Congress and signed into law. Final recommendations were codified and released on November 24, 1997. This act defines **dietary supplements** as food and not drugs.[112]
    - "Drugs," on the other hand, are "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" and "articles (other than food) intended to affect the structure or function of the body."
    - *Therefore* any "drug claim" for a dietary supplement (defined as "a food"), which hold out ***the incorrect and misleading promise*** that that dietary supplement will "diagnoses, cure, mitigate, treat, or **prevent** disease" changes the classification of the "supplement" to that of a "drug."
    - "Drugs" undergo – and rightfully so – exhaustive and multi-billion dollar assessments and proof to the FDA that they are safe and effective.
    - If a "drug claim" is made for a supplement, the FDA can immediately step in and regulate that supplement as a drug. This means, for all intents and purposes, it would be off the market.

[109] Eliassen, AH et al. Circulating Carotenoids and Risk of Breast Cancer: Pooled Analysis of Eight Prospective Studies. J Natl Cancer Inst. 2012 Dec 19; 104(24):1905-1916.
[110] Parinandi NL et al. Antioxidants in Longevity and Medicine 2014. Oxid Med Cell Longev. 2015; 2015:739417
[111] https://www.congress.gov/bill/102nd-congress/house-bill/2597/text
[112] http://www.anh-usa.org/dshea/

- Indeed, Quackwatch, the alleged and self-appointed internet watch dog for maintaining strict unthinking, allopathic, by-the- book, never question it and forget all the biochemistry you ever learned in medical school-style practice, has a lengthy discussion[113] about how the DSHEA Act allegedly allows the nutritional supplement industry to "game" the system. Nothing, in fact, could be further from the truth. This act cleaves the world of intervention into disease processes clearly into two camps: drugs and foods. The "food claims" of nutritional supplements – that they *support the structure and function of the human body* – is indeed an accurate assessment of what they do and how they work. And it is sufficient.
- Therefore, and I want to make this perfectly clear: nothing that I will cover in a moment would suggest, or should suggest, or should be taken as suggesting, that the use of *any* particular supplements, from anybody, at any time, should "reduce your risk" or "prevent" cancer, Alzheimer's disease, and so forth. Or, for that matter *cure anything.*
- What I am pointing out in this paper, both up to this point and in the discussion on specific health conditions that will follow this paper in a full book form, published in 2017, are the following:
    - There is abundant evidence that lack of dietary carotenoids and antioxidants are clearly related to cancer and other disease risk.
    - It is obvious to anyone that these levels can be increased by diet as well as supplementation.
    - In general, methods of dietary increase are preferable. They are also impractical.
    - In most cases, except for people with significant financial resources who buy totally organic, prepare their own food, and spend a great deal of their time sourcing and preparing what they eat, it doesn't happen.
    - Both Bruce Ames, in the Proceedings of the National Academy of Sciences[114] and Fairfield and Fletcher – the two American physicians publishing in the Journal of the American Association[115] – noted that the typical American diet is adequate to prevent gross deficiency disease but not to be able to optimize health and prevent chronic disease. Fletcher and Fairfield advised that "pending strong evidence …from randomized trials, it appears prudent for all adults to take vitamin supplements."
    - The Biophotonic Scanner measures antioxidant levels through skin carotenoids. It is accurate. It is reproducible. The skin carotenoid score correlates to dietary supplementation and it correlates to nutritional supplementation.
    - The higher the level, the higher your circulating carotenoids, and, presumptively, the less your risk of disease.
    - The final question is: "Where do you want your levels to be?" It is the answer to this specific question which will ultimately determine if you change your diet, elect to supplement, or both, and at what point you will conclude that you have maximized your health benefits (although the literature would suggest not stopping until you hit the fifth quintile).

- *Any reading of the following section, or indeed of the discussion of any disease state in this paper should never, under any circumstances, be distorted or conflated into the message that "talking vitamin supplements will prevent or cure cancer or disease."* This is not only illegal under the DSHEA Act, but it is bad science. One must evaluate the full weight of the peer-reviewed literature, do one's own personal (or clinical) risk/benefit analysis, and decide what to do, what dietary changes to make, and/or what supplements to use (if desired).

[113] http://www.quackwatch.org/02ConsumerProtection/dshea.html accessed Feb 7 2017.
[114] Ames B. loc cit.
[115] Fletcher and Fairfield. JAMA. Loc cit.

WHAT COMES ALONG WITH CAROTENOIDS IN SUPPLEMENTATION?

The utility of the Biophotonic scanner to measure carotenoids, and, by extension, representative levels of oxidative stress, is without dispute. However, two perhaps even more interesting questions arise. First, is it possible to absorb carotenoid molecules from nutritional supplements (and diet) without absorbing any other trace micronutrients and vitamins? (Answer: no.) Secondly, if one's skin carotenoid score goes up as a result of supplementation, and given that carotenoids cannot be differentially absorbed from other ingredients in the supplements, then doesn't an increase in skin carotenoid score serve as an excellent proxy for all other nutrients going up as well? (Answer: yes.)

Finally, the question remains: Why not just eat more carrots and tomatoes to raise your skin carotenoids scores? Wouldn't that be sufficient?

Indeed, you could raise the Skin Carotenoid Score measured by the BioPhotonic Scanner by eating lots of carrots and lots of tomatoes. My advice would be to eat as many as you possibly can, as well as green vegetables and cruciferous vegetables. And, as Smidt and colleagues substantiated in 1999, eating lots of carrots and tomatoes will most likely not raise your Beta-carotene levels 114%, your alpha-carotene levels 678%, your vitamin C levels by 38%, nor your alpha-tocopherol levels by 84%.[116]

Setting aside antioxidants and carotenoids for a bit, a quick review of the other micronutrients to which Bruce Ames was alluding[117] seems in order. It is here that a quick review of the current literature about micronutrient deficiencies is instructive.

- According to the United Nations Earth Summit held on June 13, 1992, in Rio de Janeiro, Brazil, the North American soil has been depleted of 85% of its minerals in the last 100 years.[118] [119]
- Michael Lockyear noted the following in February of 2016[120]about the state of our soil. This is an *en bloc* quote from his multiply sourced report:
    - *"Our planet has lost between 75-85% of its arable topsoil. This loss is due to erosion, improper use of inorganic nitrogen fertilizers, and other farming practices that leave the soil depleted. Topsoil loss and the related health and environmental issues must be considered a National Security concern. There is a consensus in the scientific community that this issue is the chief threat to future human survival.*
    - *Over the last ten-thousand years, the depletion of soil fiber, soil nutrients and microorganisms have resulted in soil erosion and the loss of topsoil. The planet is losing arable topsoil annually at rates estimated to be 25 million acres per year. At present rates of soil loss, it is believed that all topsoil will be gone in less than 60 years. (Maria-Helena Semedo, United Nations Food and Agricultural Organization (FAO)). The Nutritional Security Institute reports that complete topsoil loss will occur in just 40 years.*

---

[116] Smidt et al. FASEB 1999. Loc. cit.
[117] Ames BN. Loc. Cit.
[118] https://www.osti.gov/scitech/biblio/6289330 accessed Feb 5 2017 126
[119] https://sustainabledevelopment.un.org/content/documents/Agenda21.pdf [accessed Feb 13 2917].
[120] Lockyear, M S. A New Paradigm: Soil-Centered, High-Yield Intensive, Nutrient-Dense Farming, version 2.0 . http://fairfarmsnow.org/wp-content/uploads/2016/09/Nutrient-Dense-Farming-by-Michael-S.-Locklear-1.pdf [accessed Feb 13 2017]. This is an incredible source with multiple citation, statistics, and graphs.

- *The rate of soil erosion in the United States is ten times faster than the rate of replenishment. Erosion rates are 30 to 40 times faster than the rate of replenishment in China, India and Africa. Studies reveal that the nutritional values in food have declined significantly over the past 70 years due to depletion of minerals, microorganisms and fungi in the soil. [my emphasis – Cady]*
- *Without adequate nutrition in our food, we become susceptible to disease. Simply stated, nutrient deficiencies lead to malnutrition and malnutrition leads to disease. Health and well-being depends on the consumption of nutrient-rich food."*

- The need to enhance the nutritional quality of staple foods in this county has been known since 2001.[121]
- Severe depletion of trace minerals and micronutrients in the U.S. diet has been observed, in one study period, from 1940 to 2002.[122]
- According to the US Department of Health and Human Services (2015)[123], in their examination of the 2015 – 2020 Dietary Guidelines for Americans ("DGA's"), the nutrients potassium, dietary fiber, choline, magnesium, calcium, and vitamins A, D, E, and C were "consumed by many individuals in amounts below the EAR ["Estimated Average Requirement"] levels. Specifically cited as "nutrients of public health concern" were Vitamin D, calcium, dietary fiber, potassium, and iron.
- In recent paper from the US CDC (Center for Disease Control)[124], it was estimated that 10.5% of American (30 million of us) have a Vitamin B6 deficiency. Additionally 8.1% of Americans have a vitamin D deficiency.
- Micronutrient and macronutrient deficiencies are common in the general population "and may be even more common in patients with hypertension and cardiovascular disease due to genetic, environmental causes and prescription drug use."[125]
- Even for people trying to eat healthy vegetarian diets, iron and zinc deficiencies are common.[126]
- In another multiply sourced paper published as a supplement to the Journal of Family Practice by Blumberg et al (2016)[127], they reviewed the need for multivitamin/multimineral supplementation in order to meet dietary recommended amounts. Several excellent references were cited. [128] [129] [130] [131] [132]

---

[121] Graham RD et al. Addressing micronutrient malnutrition through enhancing the nutritional quality of staple foods: Principles, perspectives and knowledge gaps. Advances in Agronomy 2001. Volume 70:77-142.

[122] Thomas D. The mineral depletion of foods available to us as a nation (1940-2002)--a review of the 6th Edition of McCance and Widdowson. Nutr Health. 2007;19(1-2):21-55.

[123] U.S. Department of Health and Human Services and U.S. Department of Agriculture. 2015 – 2020 Dietary Guidelines for Americans. 8th Edition. December 2015. Available at http://health.gov/dietaryguidelines/2015/guidelines/. [accessed Feb 13, 2017].

[124] Centers for Disease Control and Prevention, National Center for Health Statistics. About the National Health and Nutrition Examination survey. Available at: http://www.cdc.gov/nchs/nhanes/nhanes2011-2012/overview_g.htm. [Accessed Feb 13, 2017].

[125] Houston MC. The role of cellular micronutrient analysis, nutraceuticals, vitamins, antioxidants and minerals in the prevention and treatment of hypertension and cardiovascular disease. Ther Adv Cardiovasc Dis. 2010 Jun;4(3):165-83. doi: 10.1177/1753944710368205. Epub 2010 Apr 16.

[126] Hunt JR. Bioavailability of iron, zinc, and other trace minerals from vegetarian diets. Am J Clin Nutr. 2003 Sep;78(3 Suppl):633S-639S.

[127] Blumber JB et al. Vitamin and Mineral Intake Is Inadequate for Most Americans: What Should We Advise Patients About Supplements? J Fam Pract. 2016 Sep;65(9 Suppl):S1-S8.

[128] Wallace TC, McBurney M, Fulgoni VL 3rd. Multivitamin/min- eral supplement contribution to micronutrient intakes in the United States, 2007-2010. *J Am Coll Nutr.* 2014;33(2):94-102.

[129] Bailey RL, Fulgoni VL 3rd, Keast DR, Dwyer JT. Examination of vitamin intakes among US adults by dietary supplement use. *J Acad Nutr Diet.* 2012;112(5):657-63.

- If you are poor, things get worse. Social class tended to predict American dietary quality. Essentially, the less money you had, then the more poorly you ate, nutritionally speaking.[133] In another study (Lewsi et al., 2003)[134] the dietary intakes of non-affluent women of the southern U.S. were examined for amounts of trace minerals (zinc, selenium, copper, manganese, iron, and molybdenum), antioxidants (Vitamins A, E, C, carotene, and alpha-tocopherol) and the B-vitamin riboflavin, "*Numerous dietary deficiencies in important antioxidant nutrients associated with metabolic antioxidant systems were identified.* Few race-related differences were detected. Intake of vitamin A was generally within recommended levels while vitamin E intake was below the EAR. The vitamin precursors, -carotene and a-tocopherol, were significantly (P<0.05) below customary intakes at all ages. *More than 60% of this population reported dietary copper, zinc, and selenium intakes below recommended levels*."

SOURCING OF NUTRITIONAL SUPPLEMENTATION

Compared to other nutritional companies, Pharmanex has the largest amount of scientists on its payroll of any other nutraceutical company in existence. There are over 75 or more scientists on staff (exact numbers vary by year, but never less than 75), of which 15 are at the PhD/MD level. The Pharmanex scientists are divided into Clinical Pharmacology, Chemistry Group, QA/QC, and R&D Group – Provo, as well as at Zhejiang Cinogen Pharmaceutical Company (Huzhou, China), the Information Group in China, the Raw Material Sourcing scientists, the Business Development scientists (scanner), and the Global Product Support scientists in Taiwan, the United States, Hong Kong, Japan, Philippines, Thailand, Korea, Malaysia, Australia, Belgium/Central Europe, Norway/Scandinavia, and Singapore. It is a multinational company with two research centers in China and one in the United States. The company is fanatical about quality and purity of both ingredients and finished products. The listed disciplines of this scientific team are as follows: pharmacology, immunology, biochemistry, pharmacognosy, dietetics, chemistry, nutrition, medicine, food science, molecular biology, pharmaceutical chemistry, biomedical engineering, and exercise physiology.

Points of Resistance, The Tyranny of the Status Quo and the Hypocrisy of the Nutri-gentsia[135]

Several years ago, the esteemed physician Dr. Imre Zs-Nagy, MD, the internationally renowned originator of the Membrane Hypothesis of Aging and founder and editor in chief of the Archives of Gerontology and Geriatrics, published this alarming statement: "[The] gerontological elite has instead sought to obfuscate the facts ... the reason for this is nothing less than an **abject fear** ... to *avert their loss of control, power, prestige, and position in the multi-billion dollar industry of gerontological medicine*."[136]

---

[130] Ganji V, Zhang X, Tangpricha V. Serum 25-hydroxyvitamin D concentrations and prevalence estimates of hypovitaminosis D in the U.S. population based on assay-adjusted data. *J Nutr.* 2012;142(3):498-507.
[131] Bailey RL, Fulgoni VL 3rd, Keast DR, Dwyer JT. Dietary supple- ment use is associated with higher intakes of minerals from food sources. *Am J Clin Nutr.* 2011;94(5):1376-81.
[132] Huang KE, Milliron BJ, Davis SA, Feldman SR. Surge in US outpatient vitamin D deficiency diagnoses: National Ambulatory Medical Care Survey analysis. *South Med J.* 2014;107(4): 214-7.
[133] Darmon N, Drewnowski A , Does social class predict diet quality. Am J Clin Nutr. 2008 May;87(5):1107-17.
[134] Lewis SM et al. Assessment of antioxidant nutrient intake of a population of southern US African-American and Caucasian women of various ages when compared to dietary reference intakes. J Nutr Health Aging. 2003;7(2):121-8.
[135] A new word, conceived by me, combining "nutrition establishment" and "intelligentsia."
[136] Zs-Nagy, Imre. Is consensus in anti-aging medical intervention an elusive expectation or a realistic goal? Arch Gerontol Geriatr. 2009 May-Jun;48(3):271-5.

It is, indeed, a given that the medical establishment and the academic "intelligentsia" are hostile to the notions of vitamins, supplements, and antioxidants.

The Academy of Nutrition and Dietetics cautions against supplements.[137] They quote the 2015 Dietary Guidelines for Americans, "Nutritional needs should be met primarily from foods. Individuals should aim to meet their nutrient needs through healthy eating patterns that include nutrient-dense foods ... [which] contain essential vitamins and minerals and also dietary fiber and other naturally occurring substances that may have positive health effects."

Bolzetta and colleague proclaimed in this organization's journal (2015)[138] that "the current RDAs are adequate for older women's intake of riboflavin, vitamin B-6, and folic acid." To their credit, they did advocate for raising the recommended daily allowance of vitamin B12 and vitamin C for older adults."

As recently as December, 2013, Bahar Gholipour published a dubious and deliberately hostile piece in Scientific American with the following title: "Multivitamins Are a Waste of Money, Doctors Say." His screed begins with the following topical sentence: "People should stop wasting their money on dietary supplements, some physicians said today, in response to three large new studies that showed most multivitamin supplements are ineffective at reducing the risk of disease, and may even cause harm."[139]

The problem with these two assertions is that they are wrong, and not based on a balanced reading of the peer-reviewed literature. They are also based on bald-faced hypocrisy:

- In a survey of dieticians in Oregon, published in the Journal of the American Dietetic Association in 2000[140], more than 80% of the dieticians surveyed were confident about "the effectiveness of functional foods and nutrient supplements for prevention of illness and treatment of chronic illness, and at least 89% were confident of their safety for these uses."
- **In a more recent survey in 2012, 74% of all dieticians were regular users of nutritional supplements**.[141] The "regular users" of dietary supplements stated that they were using them for the following reasons:
    - bone health – 70%
    - "fill nutrient gaps" – 67%
    - "overall health and wellness" – 49%
    - Fully 87% of the dieticians agreed with the following statement: "There are gaps in clients' diets that could effectively be address with dietary supplements."
    - Nor did these clinicians just recommend supplements. Personally, in addition to their own regular supplement use, they tried to eat a balanced diet, managed their stress, had regular checkups, exercised regularly, worked on maintaining a healthy weight, and got a good night's sleep. It is critical that the reader of this paper get the idea that this isn't just about busting the chops of the nutritionists for the hypocrisy of their trade journal, but, more subtly, recognizing that *the people that should know and be able to*

[137] http://www.eatright.org/resource/food/vitamins-and-supplements/dietary-supplements/vitamins-minerals-and-supplements accessed Feb 3 2017.
[138] Bolzetta F et al. Are the Recommended Dietary Allowances for Vitamins Appropriate for Elderly People? J Acad Nutr Diet. 2015 Nov;115(11):1789-97. doi: 10.1016/j.jand.2015.04.013. Epub 2015 Jun 2.
[139] https://www.scientificamerican.com/article/multivitamins-are-a-waste-of-money-doctors-say/ accessed Feb 3 2017
[140] Lee YK et al. The Knowledge, Attitudes, and Practices of Dietitians Licensed in Oregon Regarding Functional Foods, Nutrient Supplements, and Herbs as Complementary Medicine. J Am Diet Assoc. 2000 May;100(5):543-8.
[141] Dickinson, A., Bonci, L., Boyon, N., & Franco, J. C. (2012). Dietitians use and recommend dietary supplements: report of a survey. *Nutr J. 2012 Mar 14;11:14. doi: 10.1186/1475-2891-11-14.*

get all of their nutrients from their diet if they could have to supplement.

When we get to physicians, there is a bit more data on exactly what they do:

- HALF of 4,501 randomly sampled women physicians between the ages of 30 and 70 were taking vitamin-mineral supplements in the United States in 2000.[142] 35.5% of these female physicians did so regularly.
- In another survey of health professionals nine years later, 51% of all MD's and 59% of nurses were using dietary supplements.[143] (The survey was of 900 physicians and 277 nurses.) When asked if they ever recommended dietary supplements to their patients, 79% of the physicians and 82% of the nurses said that they did.
- One year later, Dickinson et al presented more findings to the Experimental Biology conference in Anaheim, CA.[144] They found that 37% of cardiologists, 50% of orthopedists, and 59% of all dermatologists were supplement users.

Moving from the hypocritical to the data-driven literature, a review of the significant inadequacy of our typical diets (even organic ones) to maximize health is in order.

In 2011, Victor Fulgoni and colleagues published *Foods, Fortificants, and Supplements: Where Do Americans Get Their Nutrients?*[145] The study population included all participants in the NHANES 2003-2004 and 2005—2006 studies with a combined total of 18,063 participants who had completed a 24 hour dietary intake data. He and his colleagues used the National Cancer Institute method to assess usual intakes of 19 micronutrients by source. Among his findings were that 8% of the population was deficient in vitamin B6 intake, 8% were folate deficient, and 8% were zinc deficient. However, 34% were below the recommended levels of Vitamin A, 25% were lower than ideal on C, 70% were low in Vitamin D, and 60% were low in vitamin E. 38% were also low in calcium, and 45% were low in magnesium.

It appears reasonable that supplementation with a good, solid multivitamin would be recommended.

Indeed, the bastion of conservative and essentially anti-holistic medical practice, the *Journal of the American Medical Association*, had already featured the previously cited paper in 2002, where the authors, Drs. Fletcher and Fairfield, noted that "suboptimal intake of some vitamins, *above levels causing classic vitamin deficiency*, is a risk factor for chronic diseases and **common in the general population**, especially the elderly.[146] They specifically note that "suboptimal levels of vitamins B6 and B12 are a risk factor of cardiovascular disease, neural tube defect, and colon and breast cancer, and that low levels of vitamin D contribute to osteopenia and fractures, and that low levels of the antioxidant vitamins (Vitamins A, E, and C) may increase risk for several chronic diseases." Their recommendation: **"Pending strong evidence of effectiveness from randomized trials, it appears prudent for all adults to take vitamin supplements."** The presence of this statement in the Journal of the American Medical Association represents nothing less than a tectonic shift in its previous stance that "people should be able to get all of the vitamins and nutrients they needed from diet alone"

---

[142] Frank E et al. Use of vitamin-mineral supplements by female physicians in the United States. Am J Clin Nutr. 2000 Oct;72(4):969-75.

[143] Dickinson A et al. Physicians and nurses use and recommend dietary supplements: report of a survey. Nutr J. 2009 Jul 1;8:29. doi: 10.1186/1475-2891-8-29.

[144] Dickinson, A., Shao, A., & Boyon, N. (2010). *Use of dietary supplements by cardiologists, dermatologists and orthopedists: report of a survey.* Paper presented at the Experimental Biology, Anaheim, CA.

[145] Fulgoni VL et al. Foods, fortificants, and supplements: where do Americans get their nutrients? J Nutr. 2011 Oct;141(10):1847-54.

[146] Fletcher RH, Fairfield KM. Vitamins for chronic disease prevention in adults: clinical applications. JAMA. 2002 June 19;287(23)3127-9.

– even though that position flew in the face of all scientific evidence to the contrary, including the USDA CSFII reports previously cited.

Four years later, the renowned researcher Bruce Ames published his paper that has subsequently been referred to as the "micronutrient triage theory of disease" [147] in the Proceedings of the National Academy of Sciences, USA. Dr. Ames' conjecture at the time – and the literature has born him out on this – is that "DNA damage and late onset disease are consequences of a triage allocation response to micronutrient scarcity." In other words, *in a diet that is not replete with adequate micronutrients* (including carotenoids and minerals), there is enough nutrition to keep people living, *but there is not enough to keep them living optimally or to help them repair their DNA, fight off cancer, or even keep their brains healthy. As a result, they age and die prematurely.*

In fact, the weight of the literature is against you in terms of being able to get all of your nutrients up to the U.S. recommended "RDA's" from diet alone, even with lots of veggies on your plate. Additionally, simply driving up your antioxidant score with determination, and avoiding the trace minerals and elements, plus B-vitamins and all the other antioxidant vitamins (C, and E), as well as neglecting the vitamins and minerals required for bone health would simply be stupid.

The "gerontological elite" are not giving up without a fight, however. To be fair, one can find multiple papers in the peer-reviewed literature, apparently well done, that "show" that multivitamin supplementation not only doesn't work but may be harmful. One favorite study quoted by the "anti-supplement crowd" is the Iowa Women's Health Study.[148] If one only read the "conclusions" sections of the abstract, one reads the following, fairly dire, statement: "In older women, several commonly used dietary vitamin and mineral supplements may be associated with increased total mortality risk; this association is strongest with supplemental iron. In contrast to the findings of many studies, calcium is associated with decreased risk."

The interesting thing, however, is that *if you actually read the study*, the following real results were noted:

- early results showed women who used C, D, E, and Calcium had significantly lower rates of death.
- And there was the little issue of mortality. The women who started the study average 61 years of age. The average age for the women at the end of the study was 82 years of. The average mortality for all women at the time in 2003 (during the study) was 80.
    - In other words, the women finishing the study were living, at that time, *two years longer* than the average. ***The conclusion was actually that "over 50% of the women in the Iowa study lived longer than the average life expectancy."***

Strange, isn't it, that this key point didn't make it into the abstract!

A more recent news item was the research done by Dr. Jaakko Mursu and colleagues which involved the National Cancer Institute, the Academy of Finland, the Finnish Cultural Foundation, and the Fulbright program.[149] In this study of 38,772 older women, there was a hazard ratio of 1.06 for multivitamin use, as well as hazard ratios in the range of 1.08 – 1.15 for supplementation with copper, zinc, magnesium, iron, folic acid, and B6. The results were reported as "consistent with their original

[147] Ames BN. Loc cit.
[148] Mursu J et al. Dietary supplements and mortality rate in older women: the Iowa Women's Health Study. Arch Intern Med. 2011 Oct 10;171(18):1625-33. doi: 10.1001/archinternmed.2011.445.
[149] Brookes L, Mursu, J. "Vitamins and Mortality: An Interview with Jaakko Mursu." Medscape Cardiology. January 24, 2012. http://www.medscape.com/viewarticle/757150_2 [accessed Feb 14, 2017].

hypothesis, the use of most dietary supplements was not associated with a reduced rate of total mortality. In contrast, in this multivariable-adjusted analysis, many supplements were associated with increased risk for total mortality compared with corresponding nonuse."

Interestingly, not discussed in this report was any disclosure or discussion about "user bias." In other words, *why* were the older women in this study using vitamins? Was it to "protect their health?" Or were some of them, in fact, tired and run down (iron, B6), having migraines and muscle pains, or even constipation (magnesium), etc. There is also no discussion about *when* these older women began using them. Had they begun using the multivitamins in their 20's and 30's for health maintenance, stopped any supplement containing iron at menopause to avoid iron overload, and, used these supplements for disease prevention (per the work of Bruce Ames and others), then certainly the *slightly* higher hazard ratios as an older adult would be worrisome. If, on the other hand, these women were healthy up until later in life, felt their health fading, and their aches and pains increasing, and then they motored on over to the vitamin store to pick up supplements - that puts an entirely different bias on the users of supplements vs. non-users in this "study."

More recently, Vega and Kulchalywat (2012) published their article "Trash the Vitamins: Convince Your Patients" – a "best evidence review" on Medscape.[150] The title essentially sums up their thesis. "Convince your patients not to take vitamins" was the gist.

These are the types of games that are played with "studies" as well as hortatory exhortations by the anti-supplement crowd. One final thought about this. Who benefits from all of the anti-vitamin hype (In Scientific American, Reader's Digest, multiple studies in peer-reviewed journals, and the like)? Answer: the entire medical-industrial complex that exists to treat (and profit from) disease, rather than a profession dedicated to the prevention and optimization of health. For a more cynical analysis, I recall a brilliant and blunt history teacher I had in college, whose explanation for all the military conflicts in recorded human history was this: "Follow the money trail."

The nutrigentsia that publish papers like these recently cited ones, in obvious hypocritical contrast to what physicians and nutritionists actually *do* is, in my opinion, representative of an attempt to curry favor with the current medical and pharmaceutical industry funding establishment. This establishment - except for bright spots in the literature like Bruce Ames, Fletcher and Fairfield, and some of the numerous other published authors I have quoted and cited in this document (and others that are available for your discovery on "Pub Med") – has been in bed with the pharmaceutical and insurance industry as well as organized medicine. The current medical establishment has historically been vehemently anti-holistic and not focused on prevention. They are anti-hormone optimization (even though the literature supports it). They are anti-vitamin (even though the literature supports it). They are pro-statins, pro-anti-hypertensives, pro-cardiac drugs, pro-vaccines, pro-antibiotics (and anti-virals), pro-surgical procedures, pro-medical devices. You get the idea. Truly, if you "follow the money trial," then certainly prevention of disease and an emphasis on health and wellness would have a devastating financial impact on all of the economic interests that will benefit from keeping us sicker, longer.

[150] Vega CP, Kulchalyawat DO. Trash the vitamins: convince your patients. Medscape. http://www.medscape.com/viewarticle/756190?trendmd-shared=1&src=trendmd_pilot [accessed Feb 14 2017].

How much of a good thing is safe (Pharmanex and others)?
The concept of HORMESIS

Mae West, immortalized in many ways, is also noted for her quote that "Too much…. Of a *good* thing…. Is *wonderful.*" Of course, scientists and practicing clinicians know that too much of *anything*, including water, can be harmful and even fatal.

According to a document released by NuSkin Enterprises,[151] the parent company of Pharmanex: "The levels of all nutrients found in Pharmanex products are based on well documented epidemiological, clinical, pre-clinical and safety studies. LifePak® is formulated to provide optimal nutrition with substantiated levels of nutrients that will not induce a pro-oxidative state. Included in the comprehensive blend of antioxidants is a balanced carotenoid combination in amounts similar to those provided by diets high in fruits and vegetables: 7.5 mg ß-carotene, 5 mg lycopene, 2 mg a-carotene and 2 mg lutein. Each ingredient in LifePak® is present in amounts that are documented to be safe for long-term supplementation. Further, LifePak® is safe when taken in conjunction with a diet high in fruits and vegetables. The daily amounts of all vitamins and minerals are well below the No-Observed Adverse Effect Levels (NOAEL) established by the Council for Responsible Nutrition (CRN) in 1997 and the Upper Limits (UL) established by the Food and Nutrition Board of the National Research Council."

The subsequent development of LifePak Nano ® increased the absorbability of ingredients, but the formula – with the exception of the addition of high potency omega 3 fish oil – was largely unchanged.

In terms of fair balance, the use of any type of multivitamin, or multimineral, or carotenoid/ phytochemical supplement should be carefully considered. "Hormesis" is a principle which basically contradicts Mae West. Too much of a good thing is, in fact, harmful.[152] From one of the original papers on hormesis by Mattson(2008):[153] "Recent findings suggest that several heavily studied phytochemicals exhibit biphasic dose responses on cells with low doses activating signaling pathways that result in increased expression of genes encoding cytoprotective proteins including antioxidant enzymes, protein chaperones, growth factors and mitochondrial proteins. Examples include: activation of the Nrf-2—ARE pathway by sulforaphane and curcumin; activation of TRP ion channels by allicin and capsaicin; and activation of sirtuin-1 by resveratrol."

It is this *biphasic dose response* with "low doses" activating signaling pathways that is relevant. In other words, a low dose of something healthful might be good for you, but you still need to leave some room for stress in the system. And, conversely, too much of a good thing could be bad for you. This is the principle of DER – or dietary energy restriction – covered in Mattson's excellent paper.

The hormetic concept of "enough but not too much" of the "good things" continues to be described in the peer-reviewed literature:

---

[151] "Response to criticisms regarding the Pharmanex® BioPhotonic Scanner." NuSkin Enterprises.

[152] The principle of *hormesis* is also referenced, but not named, in the NuSkin "response" paper, just cited, where they specifically (but inferentially) note that they have considered the safe levels of antioxidants and that their products are formulated to *not* induce a "pro-oxidative state."

[153] Mattson MP., Dietary factors, hormesis and health. Ageing Res Rev. 2008 Jan;7(1):43-8. Epub 2007 Sep 1. Access to full text article: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2253665/

- "…the hormetic dose-response concept and present possible mechanisms and applications to neuroprotection" is noted in Peeisi et al's remarkable paper in Journal of Neuroscience Research (2016)[154]
- The confounding divergent outcomes of antioxidant intervention trials – where some people get better and have benefit, but others don't – was reviewed by Conti et al (2016).[155] The authors specifically note; "The interplay of both endogenous and exogenous antioxidants with the systemic redox system is very complex and represents an issue that is still under debate.
- Principles of hermetic caution in the use of antioxidant interventions in autism have also been published. [156]
- The Nietzschean concept of "that which does not kill me makes me strong" is seen in the paper in Oncotarget (2016)[157] where actual "low-dose radiation "induces hormesis and adaptive response in normal cells but not in cancer cells." In other words, a little stress could be good for you.

What is a fair-minded, thoughtful, clinician to do with this new-found "hormetic knowledge"? Several principles, it seems to me, obtain:

- A balanced reading of the literature clearly shows a relationship between higher levels of carotenoids and decreased risk of prostate cancer, breast cancer, macular degeneration, and specifically oxidation of LDL. Indeed, it is almost axiomatic that "oxidative stress" and low antioxidant levels (implied by and correlated with low carotenoids) raise one's risk for disease and all-cause mortality, and higher levels reduce it.
- As early as 1991, there were papers published, such as that of Dorgan and Schatzkin, noting that, "Diet studies suggest protective effects of fruits and vegetables on risk of cancer at several sites. Inverse associations between dietary carotenoids and serum beta-carotene and lung cancer have been observed repeatedly. Vitamin C has also been consistently inversely associated with risk of oral and esophageal cancer in diet studies and with stomach cancer in both diet and plasma studies."[158]
- Michael Donaldson's massive paper of 2011[159] clearly found that for every quintile increase of carotenoid antioxidants (other than the first quintile), there were steadily increasing health benefits. Clearly, this lower end of the hormetic dosing curve (up through the fifth quintile) seems to have increasing benefits at rational levels of carotenoids. At two, three, or four standard deviations above the mean, the results might be different. Translation: avoid mega-dosing in any supplements.
- A balanced approach would therefore seem to be avoiding the use of "mega-dose" supplements, including antioxidants. Determine thoughtfully where a useful level of antioxidant (and trace mineral) protection would be. A scan score on the Biophotonic Scanner of 50,000 and up (3 MICROgrams carotenoids/ml plasma) would put one in the top quintile of carotenoids – a nutritionally virtuous place considering *any* of the studies in this paper correlating antioxidant levels with disease and disease risk. Given that I have seen

[154] Pennisi M et al. Inflammasomes, hormesis, and antioxidants in neuroinflammation: Role of NRLP3 in Alzheimer disease. J Neurosci Res. 2016 Nov 8. doi: 10.1002/jnr.23986.
[155] Conti V et al. Antioxidant Supplementation in the Treatment of Aging-Associated Diseases. Front Pharmacol. 2016 Feb 12;7:24. doi: 10.3389/fphar.2016.00024.
[156] Calabrese V et al. Hormesis, cellular stress response, and redox homeostasis in autism spectrum disorders. J Neurosci Res. 2016 Dec;94(12):1488-1498. doi: 10.1002/jnr.23893. Epub 2016 Sep 19.
[157] Yang G et al. Distinct biological effects of low-dose radiation on normal and cancerous human lung cells are mediated by ATM signaling. Oncotarget. 2016 Nov 1;7(44):71856-71872. doi: 10.18632/oncotarget.12379.
[158] Dorgan JF Schatzkin A. Antioxidant micronutrients in cancer prevention. Hematology Clinics of North America [1991, 5(1):43-68]
[159] Donaldson, MS A carotenoid health index based on plasma carotenoids and health outcomes Nutrient. 2011 Dec; 3(12): 1003 – 1022. (already cited)

vegetarians with scores of 81,000 on the scanner – a score accomplished by eating physiologically reasonable amounts of organic vegetables – then it follows that a level of 50,000 to 80,000 or so on the scanner seems intuitively correlated with optimal dietary and antioxidant protection.

- It appears clear from the work of Fulgoni,[160] Ames,[161] and Fletcher and Fairfield[162] that Americans do not get enough micronutrients or minerals.
- With a mineral depletion of 85% of the North American continent's soil in the last 100 years[163] it seems delusionally unreasonable to assume that a normal consumer is going to get an adequate supply of nutrients without consuming truly stupendous and physiologically improbable amounts of food in a frantic attempt to eat one's way into nutritional adequacy.

CONCLUDING COMMENTS:
A Personal and Professional Reflection

The clinicians at Cady Wellness Institute (CWI), as well as I, personally, have used and frequently recommend supplements from other companies in addition to those from Pharmanex. Foundationally, however, I buy Pharmanex supplements for my front office staff to take because I want them healthy, and I don't want them sick. I do this for purposes of both altruism and selfishness. Altruistically, it's the right thing to do if you're running a wellness institute and you care about your people. Selfishly, business flows a lot more smoothly if "all hands are on deck."

However, to presume that there is a one source, simplistic answer for every nutritional, neuroendocrinologic, or detoxification problem that walks through our doors is naive. Simplistic solutions rarely work. And, at CWI, we frequently treat patients who have failed to get better every place else.

In considering the "price: performance" proposition of other multivitamin offerings compared to Pharmanex, there are several pitfalls: there is no other product that has a specific "performance guarantee" that it will do anything measurably in improving your antioxidant levels. As well, every other nutritional supplement company is shut out of rapid measurement and assessment of the performance of their products by Raman spectroscopy because only Pharmanex holds the license on the patent rights to do so.

In terms of validating treatments, and in looking at the preponderance of the evidence in the medical literature, it is important to note that the BioPhotonic scanner comes from an honorable and multi-decade long progression from bench science to patented invention. Raman spectroscopy has been used in everything from ascertaining pathological gynecological tissue and precancerous lesions, to assessing risk factors in the retina for macular degeneration as a function of carotenoid levels, and finally to its current design where a quick thirty second scan of the palm of the hand will reveal a person's current antioxidant status to a remarkably accurate degree.

There is also abundant evidence that Pharmanex LifePak supplements, based on their formulation, significantly and potently increase antioxidant levels as evidenced not only by skin carotenoid scores, but also as evidenced by direct comparisons with blood levels of Vitamins C and E, as well as alpha and beta-carotene. Perhaps most significantly, the supplements actually ***perform*** in terms of functionally reducing LDL-oxidizability. Evidence abounds, reading the literature syntopically and as

[160] Fulgoni, loc cit.
[161] Ames B. loc cit.
[162] Fletcher and Fairfield. JAMA. Loc cit.
[163] UN Earth Summit Report 1992, loc cit.

an integrated whole, that the Raman index, or the "Skin Carotenoid Score," is a legitimate and extremely valuable approximation of total body antioxidant status.

The original "LifePak" supplementation multivitamin antioxidant system was developed before the BioPhotonic Scanner came into existence, and it was conceived and formulated based on what should be in a multivitamin supplement that would reproduce what nutrient levels would be in the system of people eating a diet high in fruits and vegetables. The formulation has subsequently been enhanced with new "Nano" technology to increase the absorption of antioxidants and carotenoids, including such critical nutrients as Coenzyme Q10.

The Pharmanex line of supplements, however, is designed for optimal, foundational nutrition, and not the "treatment" of particular conditions. These supplements are insufficient for rebuilding a patient's adrenal axis, targeted supplementation of the thyroid, high-intensity liver detoxification, and specific micronutrient insufficiency repletion. They are inadequate for rebuilding a healthy microbiome after major gastrointestinal illnesses and infectious trauma. Even Joe Chang, Ph.D., the NuSkin chief scientific officer, cheerfully noted to me that many people need extra Vitamin D supplementation – indeed, more than is in any of the Pharmanex products.[164]

What this line of supplements ***is*** useful for, however, is *a starting point. A foundation.* And it appears to be a good one. What I have seen in the last decade of using these products – both personally and professionally – is that both my patients and I have stopped getting sick all the time. I have not had the flu in over a decade and a half. I have heard anecdotal reports – both from friends and patients – that their fibromyalgia just "went away," that they were sleeping better, had more energy, and actually felt mentally and emotionally improved. Two of my friends are ladies in their 80's that look like they're in their 60's. They are independent, feisty, drive themselves everywhere, have excellent night vision, unlimited mobility and they are also fashion-plates. Conversely, I have seen patients that pooh-pooh nutritional supplementation, feel that it's "too expensive," and are beginning to look like broken down wrecks in their 40's and 50's.

The obsessive, data-driven clinician and scientist reading the above will snort and say, "Yeah – but that's just anecdotal." To which I would reply – "you are absolutely right, but I've surely seen a bunch of those anecdotes walking around" – both good and bad ones – and it makes sense based on a balanced reading of the entire peer-reviewed literature the needs for absolutely adequate levels of micronutrients, carotenoids, and antioxidants in our diet.

It is objectively unknown to me if the high-dollar supplements from the premium nutraceutical companies would perform as well as those from Pharmanex. I doubt it. Their formulations do not include the significant amount of specifically targeted antioxidants that the Pharmanex preparations include, and there is simply no objective, countervailing evidence that they would perform in this area. I have seen some people who scan well on the scanner, but they have to take multiple products from the same company to achieve it – at both a higher monetary cost than they would be paying for a balanced multi-vitamin, multi-mineral, fish oil, bone health, metabolic health, cardiac health, and brain health designed supplement. My personal experience from scanning numerous people taking supplements from the other "MLM" companies is quite direct: their products do not significantly increase antioxidant levels as measured by the Skin Carotenoid Score. Which means that they do not increase antioxidant levels adequately. Period.

The situation becomes even more interesting when one considers the chemical and formulating "ancestry" of the current LifePak® line of supplements. The first human who was not a clinical patient

[164] Chang, Joseph. Personal communication.

or a research subject, Nathan Ricks, took one packet of the forerunner of LifePak® every day for eight years before he sat with his hand in front of the scanner prototype at the Cancer Research Institute of the University of Utah. He also ate healthfully. His scan socre was 48,000 – the highest scan ever recorded at that time.[165] It is clear that the scientists formulating the original LifePak® products were on the right track with their focus on antioxidant supplementation, in addition to adequate supplementation of all other necessary vitamins and minerals. Further research, development, and acquisition of new technologies and delivery systems have only served to solidify their position as the market leader.

Since the time that Pharmanex acquired the scanner rights and deployed it for the first time in the United States in 2003, a novel "feedback loop" has been set up between people taking Pharmanex supplements, a questionnaire about which and how many of the supplements the person takes *that is completed while the person is being scanned*, and the integration of that information with ongoing scan scores by *frequent uploading of data to the company*. This data base correlates what the person is being "fed" in terms of supplements, (as well as dietary intake of fruits and vegetables), body mass index, consumption of other supplements, and change in scan scores. In that sense, people on the LifePak® supplement line (as well as other specific Pharmanex products) continue to serve as valid sources of data to allow the Pharmanex scientists to see if their current vitamin formulations are raising BioPhotonic Scanner scores as they intended. It is also worth noting that these scan scores are extremely important to the company, and not just from a point of academic interest: if the antioxidant levels do not rise as measured by the skin carotenoid score in two months, Pharmanex refunds every penny paid for supplements over the preceding two months. Based on my survey of steadily increasing scan scores of patients that I place on these supplements, and how my patients have been doing on them for the last decade, the day is rare indeed when anyone qualifies for a refund – or would want one.

Since the integration of the ***formulate-feed-scan-reformulate*** scenario with the arrival of the BioPhotonic Scanner, Pharmanex subsequently acquired the patent rights to formulate their latest supplement line, LifePak Nano®,[166] with "nano-ized" versions of the carotenoids as well as Coenzyme Co-Q10, rendering them even more capable of raising skin carotenoid (and antioxidant) levels.[167] This appears to be validated in reports of scan score "jumps" when people switched from the standard LifePak® line to the "Nano-ized" version. Thus far, as of 2017, no other nutritional supplement maker has a line of "nano-ized" multivitamins, and it is unlikely that they will have them in the near future since Pharmanex has secured the patent rights to that technology, as well.

The scanner, itself, has been updated. The original scanner used a laser to elicit the Raman shift effect, took nearly an hour to calibrate using three types of color specific putty over the laser lens, would only stay in calibration for four hours, and was very sensitive to temperature fluctuation. This version took three minutes to perform a scan. The second version, or "S2" came out in 2006, and featured the replacement of the laser with an easier to calibrate high intensity monofrequency LED light source, was easier to calibrate, and would stay in calibration for five days. The third version (S3), or "Everest" version because it was developed by Pharmanex for a research project to measure antioxidant levels of Sherpas on a climb up Mt. Everest, became available in 2007. With this one, the time per scan was reduced to two minutes. The most recent upgrade[168] shrank the size of the Raman device to a battery operated, Bluetooth enabled scanner which couples to an iPad and provides scan

[165] Ricks, Nathan. Personal communication with Louis B. Cady, M.D., August, 2006.
[166] http://www.nuskin.com/content/dam/global/library/pdf/products/lifepak_nano_pip.pdf [accessed Feb 12 20178].
[167] This nanotechnology, using the ring-shaped glucose molecule of cylcodextrin for increased nutrient absorption, is well described in this article from 2007: http://www.newhope.com/dietary-supplements/nanotechnology-little-things-are-making-big-waves-dietary-supplement-industry [accessed Feb 12, 2017].
[168] https://www.nuskin.com/content/nuskin/en_US/products/pharmanex/scanner/s3_whatis.html [accessed Feb 12 2017].

results in only 30 seconds. The software continues to be continually updated.

In the final analysis, and specifically in considering the needs of the patient, only a few questions legitimately remain in terms of obtaining live-tissue measurements of antioxidant status and then deploying a performance guaranteed complete and balanced multi-vitamin, multi-mineral, multi-trace element, and multi-antioxidant syste

- "What is in the best interest of the patient/client?"
- "What is the relevant science published in the peer-reviewed medical literature?"
- "What can I personally do in my practice that is in the patient's/client's best interest?"

Perhaps the most uplifting way to conclude this discussion is to review the concept of "doing right by your patient," summed up by William J. Mayo, M.D., in 1935:[169] "Perhaps the ability not only to acquire the confidence of the patient, but to deserve it, to see what the patient desires and needs, comes through the sixth sense we call intuition, which in turn comes from wide experience and deep sympathy for and devotion to the patient, giving to the possessor remarkable ability to achieve results."

I believe that as long as we as clinicians balance the competing claims of various companies (who also wish us to use their products and services) on the fulcrum of science and with a veneration for the integrated and balanced opinion of the peer-reviewed medical literature, we will be able to make the correct, honorable, and ethical choices to promote the health and welfare of our patients.

And, in the final analysis, that's all that really matters.

[169] Mayo, Charles Horace. Aphorisms of Dr. Charles Horace Mayo, 1865-1939, and Dr. William James Mayo, 1861-1939. Mayo Foundation for Medical Education and Research, Rochester, MN, 1988.