THE MYTH OF ANTIOXIDANT SUPPLEMENTATION

(IMPLICATIONS REGARDING INFLAM-AGING)

SUMMARY: We have 2 aging pathways --- Exogenous INFLAM-AGING beginning prenatally, and Endogenous INFLAM-AGING beginning at age 23. The 2 are related in that the mitochondrial aspect of Endogenous Aging feeds into Exogenous Aging. But, attempting intense antioxidant defense against the inflammation of Exogenous Aging can exacerbate Endogenous Aging, thus decreasing Lifespan.

Due to their apparent antioxidant and anti-inflammatory properties, antioxidant supplements are widely popular among "natural" health cure enthusiasts. The nature cure industry (including the health food industry, nutritionists, and Alternative Medicine practitioners) has eagerly fed the public's hunger for antioxidants. However, research fails to justify antioxidant supplementation in anything but minimal quantities.

The truth? ----- Excessive supplementation with antioxidants actually accelerates aging-associated diseases (such as CVD) and shortens Lifespan --- first, by causing Reductive Stress, and then, by promoting the development of Senescent Cells.

Surprised? So, taken aback you just cannot believe antioxidants will make our lives shorter and weaker? --- the antithesis of your NUTRI-SPEC goal … **LIVE STRONGER LONGER?** ------- Read on …

How did the notion that aging is caused by oxidative damage --- and by inference, that antioxidants could protect against aging --- originate? It all started way back in the 1950's with a theory proposed by the extraordinary and thoroughly published researcher Denham Harman --- with his Free Radical Theory of Aging.

Harman's tentative conclusions regarding oxidative damage have become one of the most tested and well-known theories in aging research. Its core statement is that aging results from the accumulation of oxidative damage --- which is closely linked with the release of Reactive Oxygen Species (ROS) from mitochondria --- and the subsequent buildup of other oxidative end-products such as protein carbonyls, superoxide, hydroxyl radicals, nitric oxide, malondialdehyde, lipofuscin --- and the list goes on.

Although the Free Radical Theory of Aging has been well-acknowledged for many decades, conflicting evidence is piling up in research throughout the 21st century. This more recent evidence not only seems to disprove the entire theory of Oxidative Stress (OxS) as the primary cause of aging, but goes on to

show that attempting to control OxS with antioxidants is not only futile --- but actually damaging in many cases.

----- The uncomfortable truth? --- Injudicious supplementing with antioxidants can make us die young. ----- Ouch.

As paradoxical as it may seem --- ROS --- as long as they are not produced excessively, and as long as they are controlled --- serve a critical function as signaling molecules that induce protective defense in response to age-dependent damage.

----- The truth --- is enough to make everyone connected to the health food industry squirm a bit, since it invalidates the premise of half the Nature Cure Remedies they peddle. Yes, the truth is that not only do ROS not cause life-shortening damage, but actually protect us against aging.

The only argument for antioxidant supplementation derives from Harman's Free Radical Theory of Aging. Harman was the first to postulate that aging results from accumulation of ROS-mediated damage. The problem with that theory is that the amount of ROS-mediated damage required to shorten Lifespan is almost never achieved without major (and uncommon) traumatic or chronic exposure to exogenous toxins or to radiation. ------- Even Harman, the father of the ROS Theory, acknowledged in a 2003 interview that the notion of ROS being THE cause of aging was based on a "wild guess".

Thousands upon thousands of research studies have confirmed that oxidative damage can indeed be detrimental --- creating …

- pathophysiological inflammatory reactions in the immune system,
- catabolic tissue destruction, and
- organ dysfunction.

--- But, the whole truth? ----- The damage from Oxidative Stress (OxS) significantly decreases Health Span, but NOT Lifespan.

Health Span is shortened by all 10 environmental stresses that elicit OxS =

- unhealthy microbiota
- mold exposure
- radiation exposure
- excess UV light exposure
- excess blue-green light exposure + deficient red-yellow (sun)light
- emotional stress
- sleep disturbance
- nutrient deficiency
- high sugar diet
- high vegetable oil diet

These environmental sources of OxS cause exogenously-derived pathophysiology (= from the outside-in), and so we can say Health Span is shortened by Exogenous Aging.

Lifespan is shortened by entirely different, endogenously-derived, pathophysiology (= from the inside-out). ----- In other words, we live and die with OxS, but not of it. ----- The length of life depends upon Endogenous Aging.

After many decades of the Free Radical Theory of Aging being without a doubt the most studied and the most recognized as THE cause of aging --- it began, in the early 21st century, to fall apart. The hypothesis was that ROS will arise inevitably from normal mitochondrial energy metabolism and damage cells --- and that the accumulation of this damage over time is THE cause of aging.

Claiming ROS damage to be THE cause requires additional implicit claims --- such as that ROS are the only source of damage that is unavoidable or that can never be completely repaired. This core statement simply does not stand up to scientific scrutiny.

There are three testable components of this core statement --- and the theory fails all three. If the theory were valid …

1. Decreasing ROS levels --- by either supplementing antioxidants, or by testing animals with genetic over-expression of antioxidant activities --- would increase Lifespan. But studies show just the opposite --- that even though ROS can be decreased with antioxidants, and are much less prevalent in animals bred to produce high levels of antioxidants endogenously, decreasing ROS does not increase Lifespan in the least --- and antioxidant supplementation actually causes many detrimental effects.

2. The corollary is that increasing ROS levels by genetic inactivation of antioxidant activities should shorten Lifespan. On the contrary, genetically depriving test animals of antioxidant capacity yields at worst normal Lifespan, and in many instances actually increases Lifespan over normal control animals. And that improved Lifespan is seen even though decreasing antioxidant capacity does cause detrimental effects (adversely affecting the animals' Health Span). This lessoning of antioxidant protection does absolutely nothing to decrease Lifespan.

3. Determining oxidative status in long-lived species and in species genetically altered to yield a longer Lifespan should, if the theory is valid, show decreased ROS production in these animals, and less oxidative damage. On the contrary, long-lived animals show normal, or in many cases increased, ROS production, and normal or even greater oxidative damage than short-lived species.

Failing all three of these criteria, the Free Radical Theory of Aging is unequivocally falsified.

On the other hand, while the core statement of the theory is false, there is an associated hypothesis that is very true. That hypothesis relates to Endogenous Aging, and has five components …

a) mitochondrial oxidative damage accumulates with chronological age

b) mitochondrial function declines with chronological age

c) mitochondrial ROS production increases with chronological age

d) global oxidative damage to proteins, DNA and lipids increases with chronological age

e) oxidative damage participates in the functional deterioration of aging.

These five components were put to the test …

Analyzing mitochondrial function and oxidative markers throughout life, and analyzing their link to health --- if this associated hypothesis is valid --- should show decreased mitochondrial function and increased oxidative damage as part of aging. And --- there should be less oxidative damage with age in long-lived compared to shorter-lived animals. Countless research studies have verified this associated hypothesis.

What does this all mean? ----- We see confirmation here that oxidative damage --- OxS --- very definitely contributes to the failing health that progresses as we age. But, these states of disease relate to our Health Span --- yet do not correlate with Lifespan.

Does this mean there is no connection between OxS and aging? No, it does not. The intracellular portion of the damage from OxS directly feeds into the largely pre-programmed processes of Endogenous Aging (= INFLAM-AGING "from the inside-out"). Via Exogenous OxS ("from the outside-in"), that Endogenous process of INFLAM-AGING is magnified --- with the production of additional inflammation --- that then feeds right back into the Exogenous process of INFLAM-AGING ---in a vicious cycle.

Picture it this way … Exogenous Aging (which is a major determinant of Health Span) is driven by external forces --- from the outside-in --- the 10 environmental stresses that elicit OxS listed on Page 2. But there is an 11th factor that exacerbates Exogenous Aging --- one that derives from the inside-out --- from one aspect of Endogenous Aging. The mitochondrial-associated functional and structural damage is at the core of both Endogenous Aging and Exogenous Aging.

ILLUSTRATION: A man smokes, drinks, consumes grotesque quantities of sugar and HOHUM PUFAs, and lives in a moldy environment. Yet, he lives to the ripe old age of 94 --- even though he looked and felt as badly if he were 90 when in his 60's.

If that man had not lived such a high OxS lifestyle with all its associated Exogenous INFLAM-AGING, he would have been in robust good health all through his last few decades of life --- but would still have given in to the cumulative effects of INFLAM-AGING associated with Endogenous Aging at the same age of 90.

It is the mitochondrial aspect of Endogenous INFLAM-AGING that, while limiting Lifespan, also exacerbates Exogenous INFLAM-AGING that devastates Health Span.

An uninterrupted supply of energy is necessary to sustain cellular function and organ health, and maintain life. Mitochondrial action in coordination with nutrient sensors in the oxidative generation of cellular energy --- along with mitochondrial regulation --- are linked to longevity.

Mitochondrial energy generation also generates Reactive Oxygen Species, and if in excess, ROS result in harmful and destructive OxS, which damages the mitochondria. As explained above, this mitochondrial ROS is the one aspect of Endogenous Aging that exacerbates Exogenous Aging.

Under physiological conditions, cells must perform a delicate balancing act of preventing excess accumulation of ROS, while simultaneously preventing depletion of ROS.

Mitochondrial dysfunction (deficiency of cellular energy) and mitochondrial OxS are two sides of the same coin, with one leading to the other. Maintaining a harmonious Metabolic Balance between preventing cellular OxS and promoting optimal cellular mitochondrial productive oxidative energy generation is the primary role of cellular Glutathione.

Intracellularly, Glutathione is "The Master Antioxidant". ----- Glutathione deficiency results in mitochondrial dysfunction.

Supplementing with Glycine + NAC, along with Lipoic Acid and Carnosine (as in REJUVENATOR) to boost intracellular production of Glutathione, corrects all three deficits --- Glutathione deficiency, OxS, and mitochondrial dysfunction.

The intracellular Glutathione defense mechanism secondarily defends against Exogenous Aging --- but more fundamentally, against Endogenous Aging --- thus increasing Lifespan.

However, Endogenous Aging does not begin until age 23, and become a factor in reasonably healthy individuals until age 33. It then becomes a major factor at about age 43; and becomes an overwhelming consideration at age 53. It is based on this Stage of Life timetable that we recommend beginning REJUVENATOR supplementation at age 33 --- an increased amount at about age 43 --- and then considerable supplementation at age 53.

In essence, we have 2 aging pathways --- Exogenous INFLAM-AGING beginning prenatally, and Endogenous INFLAM-AGING beginning at age 23. The 2 are related in that the mitochondrial aspect of Endogenous Aging feeds into Exogenous Aging. But, attempting intense antioxidant defense against the inflammation of Exogenous Aging can exacerbate Endogenous Aging, thus decreasing Lifespan.

It is advantageous for longevity purposes to avoid excessive supplemental antioxidants, and instead rely on intrinsic Glutathione biosynthesis (from Stage of Life-appropriate supplementation with REJUVENATOR), which is fine-tuned to match cellular redox status and promote homeostatic ROS signaling.

The Lifespan-protecting REJUVENATOR will complement the Health Span-protecting low-dose antioxidant supplementation that, in a reasonably healthy individual, should begin before age 23 and gradually increase through age 43 to prevent Exogenous INFLAM-AGING.

A major consideration here, however, is that “reasonably healthy” individuals are the exception rather than the rule in contemporary America. With the grotesque consumption of fructose and HOHUM PUFAs (Hydrogenated, Oxidized, Heated, and otherwise Unmetabolizable Polyunsaturated Fatty Acids) Exogenous Aging begins in childhood --- resulting in pathophysiology that progresses (in parallel with Endogenous Aging --- which becomes a concern sometime between age 23 and 33) throughout life.

In our zeal to inhibit the damage from OxS, we must remain ever cognizant that cells require a small amount of ROS for normal function, as the ROS participate in cell signaling. Excess depletion of ROS results in Reductive Stress, a harmful condition that causes cell and organ damage just as severely as does OxS. Consider these studies …

Zhang, et al. Glutathione-dependent Reductive Stress triggers mitochondrial oxidation and cytotoxicity. FASEB J. 2012.

Ma, et al. Reductive Stress-induced Mitochondrial Dysfunction and cardiomyopathy. OXID MED CELL LONGEV. 2020.

These studies show that an excess of intracellular (endogenous) Glutathione can be "too much of a good thing" --- almost as harmful as popular antioxidants such as Vitamin E, Vitamin C, NAC and Resveratrol.

This potential excess is why we recommend only a little Stage of Life REJUVENATOR supplementation in young adulthood --- delaying more intense supplementation until later decades. At the same time, the defense against Exogenous Aging with popular antioxidants such as Vitamin E, Vitamin C, CoQ10, (and even the amazing ADAPTOGEN (and Glutathione production inducer) Lipoic Acid), is essential, but must be limited in quantity.

Therein lies the problem with NAC supplementation when not given concomitantly with Glycine. NAC has a greater capacity to create Reductive Stress than do most of the other antioxidants. NAC must be supplemented only to the extent it can be combined with Glycine intracellularly to produce "The Master Antioxidant" Glutathione. [See our article on NAC.]

Animal studies suggest that a major mechanism by which antioxidants accelerate aging and decrease Lifespan is via inhibition of SKN-1-mediated transcription. As paradoxical as it may seem, a reasonably high level of ROS in mitochondria, combined with a low level of thiol antioxidants (Glutathione), triggers UPR (Unfolded Protein Response). UPR is the means to elevate cellular stress resistance that increases Lifespan. In other words, healthy ROS signaling is essential to protect against aging.

Another consideration against antioxidant supplementation is that antioxidants such as alpha-tocopherol allow cells to survive beyond what is called their "Hayflick limit" … when they should have succumbed to healthy apoptosis (programmed death). The resulting Senescent Cells become "aging factories" --- producing uncontrollable Endogenous INFLAM-AGING.

So, antioxidants cause the Reductive Stress, formation of Senescent Cells, and over-activation of other Endogenous Aging factors that inhibit the autophagy and mitophagy and apoptosis essential to maximize Lifespan. [See our article on Endogenous Aging.]

Aging research (Gerontology) advanced far enough by about 2014 that numerous studies can be found in the peer-reviewed journals stating unequivocally that the Free Radical Theory of Aging is no longer considered to

be true. ----- All these years later, Alternative Medicine practitioners are still peddling antioxidants with the insinuation that they will assure a longer life.

Efforts to inhibit Endogenous Aging (such as Glycine + NAC supplementation to increase intracellular Glutathione, as well as supplementation with Carnosine, Lipoic Acid, Quercetin and NADH) promote autophagy and mitophagy and apoptosis. These supplements thereby eliminate defective mitochondria and serve as a scavenger and an apoptosis defender of cells in response to Oxidative Stress during aging. These functions mediate the restoration of cells, or the adaptation of cells, in response to aging for survival/longevity.

In other words, defending against Endogenous Aging (with REJUVENATOR + ACTIVATOR) simultaneously and automatically defends against the ramifications of mitochondrial damage that result from Exogenous Aging.

How much of each antioxidant (Exogenous INFLAM-AGING defense) is enough, and yet not too much? That answer is provided by NUTRI-SPEC clinical analysis procedures and NUTRI-SPEC supplements.

How much REJUVENATOR supplementation to produce intracellular Glutathione is enough, and not too much? That is difficult to determine. It is important to recognize that every organ generates its own individual amount of ROS, and maintains a different amount of Glutathione than any other organ --- in a dynamic and rapidly changing cellular redox milieu --- which changes from year to year, month to month, week to week, and even day to day.

The best we can do in estimating need for Endogenous INFLAM-AGING defense is to go by the Stage of Life plan described above. The rationale behind that is that Endogenous Aging proceeds under its own clock --- independent of Exogenous Aging --- even though Endogenous Aging can be “speeded up” by a high level of Exogenous Aging, and by excessive use of antioxidants.

It is essential you focus on your NUTRI-SPEC SOLID DNP (Stage of Life INFLAM-AGING Defense Diphasic Nutrition Plan). ----- It is what you must do, and is all you can do --- for yourself, your family, and your patients --- if you want to **LIVE STRONGER LONGER**.