

The Anti-Aging Movement

A clinician explores various philosophies pertaining to the anti-aging movement, as well as the pharmacopoeia between precaution and proactivism.

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For over 30 years, a considerable number of individuals (“life extensionists”) in developed countries are using myriad nutraceutical ingredients, such as vitamins, minerals, trace elements, bioactives and botanicals on a daily basis in higher concentrations, as needed to avoid mere deficiencies, or to meet the respective minimal physiological requirements. The goal is to extend disease-free- and possibly absolute life spans.

A majority of these life extensionists follow a healthy lifestyle and usually possess high levels of health literacy. They also frequently use bioidentical hormone replacement therapy (HRT), if appropriate according to their age and to the results of blood tests, respectively. Parenthetically, this adds selection bias to any future effort to retrospectively compare the outcomes of such strategy

in terms of a healthy life span between those who use supplements and those who do not.

Compounds supposedly containing anti-aging properties target biochemical pathways known to positively modulate lifespan in experimental organisms. These compounds have been shown to improve biomarkers of human physiology. Very promising animal and human data exist for several compounds (e.g., trans-resveratrol, selenium, lycopene, L-carnitine, coenzyme Q10, cacao-catechins, vitamin D, Pycnogenol, constituents of pomegranate, green tea and curcumin).

Today there is certainly a shift from the supplements of the 1980s, which were mostly made of “naked” isolated vitamins (mostly B vitamins and antioxidant vitamins) and some trace elements, toward very complex nutra-

ceutical regimens. These modern schedules consist of high-quality botanicals (berry fruit and vegetable extracts, etc.), the so-called bioactives or mitochondrials, such as coenzyme Q10 (CoQ10), carnitine-derivatives, creatine, R-alpha-lipoic acid, carnosine and amino acids. And we cannot forget the “good lipids,” such as omega 3 fatty acids (eicosanoids) and conjugated linoleic acid (CLA). Up to 50 and more different substances are usually com-

This article in a nutshell:

- Rising star resveratrol
- The problem with traditional science
- The real life perspective
- Help from contemporary philosophy?
- How risky is this biological bet?
- Analysis & conclusions

prising a typical supplement program of extreme life extensionists.

Rising Star Resveratrol

The current superstar molecule of anti-aging research is trans-resveratrol (3,5,4-trihydroxystilbene), a phyto-

chemical found in grape skin, peanuts and giant knotweed, which has already been shown to prolong lifespan in brewers yeast, *Caenorhabditis elegans*, zebra fish and under certain conditions, mice.

Mice were quite remarkably protected by trans-resveratrol against the negative consequences of an experimental high-calorie diet. The authors of one study

New Study on Anti-Aging Products Released

While the potential benefits are many, researchers claim clinical studies are few.

Findings from a study released in mid-August revealed that a limited amount of clinical research exists to prove the effectiveness of many over-the-counter (OTC) anti-aging products. The study was published in the July/August 2007 issue of the *Aesthetic Surgery Journal* (ASJ), the official peer-reviewed journal of the American Society for Aesthetic Plastic Surgery (ASAPS).

OTC anti-aging products represent a billion-dollar industry: wrinkle creams have been marketed to the American public since the early 19th century, and Americans spent more than \$2 billion on these products in 2000 alone. While a limited body of evidence exists to prove the efficacy of many of these products, their popularity continues to increase.

"This study underscores the need for much greater study of, and public education on, the effectiveness of OTC anti-aging products," said Timothy Miller, MD, chief of plastic surgery at UCLA, and lead author of the study. "Although there are a number of beneficial OTC remedies in existence, for many patients, prescription-strength or surgical procedures may be necessary to achieve desired results."

The study consisted of a review of existing research on ingredients commonly found in OTC anti-aging creams. Key compounds under review included vitamins, antioxidants, alpha-hydroxyl acids, moisturizers, pentapeptides and botanicals. Of these, vitamin C, alpha-hydroxyl acids and pentapeptides were shown to be the most extensively researched with proven anti-aging benefits.

Vitamin A, or retinols have also shown great promise, however their effects have only been proven in prescription-strength formulations; OTC benefits have not been determined. Minimal studies have been performed on vitamin B, though what evidence does exist is promising. Moisturizers have not been extensively researched, but have been shown to improve the hydration and appearance of skin.

Botanicals such as grape seed extract, soy compounds, green tea and ginkgo biloba are relatively new in the market and have gained great popularity in recent years, but researchers believe their healing qualities have yet to be proven through randomized, placebo-controlled human trials. Many cell culture and animal experiments have been conducted to investigate the efficacy of these botanical compounds, however, indicating the potential for many beneficial effects such as increased collagen expression, improved antioxidant activity, accelerated healing and enhanced hydration.

"Consumers need to be realistic about the outcomes they can expect from OTC anti-aging creams, at least until solid clinical evidence of their efficacy exists," said Foad Nahai, MD, Atlanta plastic surgeon, president of ASAPS and associate editor of ASJ. "No matter what the treatment—OTC, prescription or surgical procedure—it is always important for patients to educate themselves and discuss options with their doctor."

stated, "Parametric analysis of gene set enrichment revealed that resveratrol opposed the effects of the high-calorie diet in 144 out of 153 significantly altered pathways." It is also known that four established key predictors of longevity—low levels of blood glucose and insulin, little weight gain during middle age, and low body temperature—are all positively affected by trans-resveratrol.

So far, these findings appear promising to the informed reader. So would it be too presumptuous then for life extensionists to start taking, let's say, about 5 mg/kg per body weight in order to benefit from the speculative positive anti-diabetic, anti-obesity, and pro-mitochondrial effects before all studies about pharmacokinetics and dosimetry of resveratrol in humans have been done? For a scientist, it might be painful to witness such a shotgun approach, as an inner voice yells: "Hold on, we need a study protocol, a control group, predefined endpoints, an ethics committee permit, etc."

Well, traditional science has already started to test trans-resveratrol under controlled conditions (e.g., in obese individuals with metabolic syndrome and for cancer prevention purposes.) The former study group makes sense, because the mechanisms through which trans-resveratrol exerts its beneficial effect operate by positively interfering with human metabolism at the intersection of energy metabolism and aging of cells. And mechanisms that are considered to be protective against cancers are also fostered by resveratrol.

The Problem with Traditional Science

Resveratrol is just one example, as there is certainly a large, bona fide anti-aging pharmacopoeia out there already in use for a considerable period of time by seemingly healthy individuals—the life extensionists.

Sooner or later, traditional scientists who contemplate the pros and cons of consuming nutraceuticals will eventual-

ly reach the stage that "it-is-impossible-to-study-everything-properly-according-to-the-evidence-based-medicine-1a-level-border" of traditional acquisition of knowledge.

Logic says that possible interactions between two micronutrients can turn out to be neutral, synergistic or counter-productive. But the same can also be true when changing the dose, duration of exposure, or presence of other factors, such as different lifestyles, ages or gender. All of these may change the outcome of one compound being tested for its beneficial effect on health and lifespan. Unfortunately using randomized-controlled trials (RCTs) will not reveal all of the answers we need in time. The combinations and permutations of possibilities may also lead to astronomically high numbers, a classical dilemma. A future option might be to develop computer simulations capable of creating the homo sapiens siliconensis. The key word here is systems biology.

It is very common for scientific and news articles about micronutrient supplementation to start off describing the history of nutritional sciences and the discovery of one-nutrient-one-deficiency disease relationships (scurvy/vitamin C, xerophthalmia/vitamin A, etc.). But eventually those articles come to a point where authors claim the status of knowledge regarding the myriad possible interactions between micronutrients, environments, age-stages, gender, races, etc., is still preliminary. And those articles usually conclude by saying it would be premature and even dangerous to uncritically consume those mid- and high-dose nutraceutical pills.

There are determined anti-supplement campaigns in science and mainstream media. This includes recent meta-analyses about seemingly negative results of some compounds (beta-carotene, vitamin A, vitamin E), caged by the authors into the over simplistic frame of being an antioxidant, that have, for reasons to be discussed elsewhere, brought some confusion among the public. These meta-analyses do not display the "real life" situation about the advanced nutraceutical regimens, which

are typically used by life extensionists. The methods applied in some of the anti-supplement meta-analyses in question resemble an archer who shoots the arrow first, and places the target where the arrow hits afterward. There has been and always will be an anti-supplement camp within the sciences and mass media.

The Real Life Perspective

So let's look at micronutrient supplementation from a different angle (i.e., the "real life perspective" of the modern world). There is a considerably large raw material nutraceutical industry worldwide, albeit on a much smaller scale when you compare it to the pharmaceutical industry. But consider the following:

- A broad range of micronutrient retailers, web-based and/or flagship stores and major pharmaceutical companies offer nutraceutical supplements of various quality and combinations to customers worldwide. Some also provide high quality open-source knowledge about micronutrients and health on their websites.
- A large number of health conscious individuals worldwide consume high-, mid- and low-dose nutraceuticals on a daily basis, without the support of the upper echelons of evidence-based-medicine (EBM).
- The inherent speed of scientific knowledge by performing randomized-controlled trials (RCTs) will not yield ultimate results, which allow decision-making according to the top EBM criteria in the near future.
- Nutraceuticals are not as strictly regulated as prescription drugs, although there are strong efforts to increase regulation. Regulatory authorities, such as the European Food Safety Authority (EFSA), the World Health Organization's CODEX Alimentarius Commission and the U.S. Food and Drug Administration (FDA) are sometimes overzealous in their commendable goal to protect consumer health. The pharmaceutical industry is the genuine com-

petitor of the nutraceutical industry and for profit reasons seek to put pressure on the nutraceuticals industry through subtle lobbying at the aforementioned regulatory authorities and the press.

So what are the practical consequences of understanding these facts? And what practical options are left after realizing that current science will not achieve crucial answers to important questions within the lifetime of today's living individuals, as to whether a 20-compound multi-supplement strategy plus healthy lifestyle will extend healthy and absolute lifespans in humans?

Help from Contemporary Philosophy?

Perhaps the answers and inspiration can be found within the contemporary philosophical school of transhumanism.

In an article in the December 17, 2006, edition of *The San Francisco Chronicle*, renowned and respected scientist Bruce Ames was quoted as saying: "Let 100 flowers grow and we'll see which one blooms." Dr. Ames was suggesting a multi-(micronutrient supplement) approach to counter the effects of the growing obesity epidemic in the U.S. According to his rationale, a "hidden hunger" occurs when people eat a low-cost diet that's filling, but provides few micronutrients. Therefore, he said they would benefit from multivitamins in terms of satiety. In other words, Dr. Ames was saying: "Let's give it (the multi-micronutrient approach) a try and see what happens." This is in stark contrast to the EBM viewpoint, which would likely be: "Show me data from randomized controlled trials first."

A very similar remark, with the only difference being "1000 flowers" instead of 100, and which might have served as inspiration for Dr. Ames, can be found on the Extropy Institute's website. The Extropy Institute was a transhuman project whose mission it was to act "...as a networking and information center for those seeking to improve the human future by using technology to extend

healthy life, augment intelligence, optimize psychology, and improve social systems." Transhumanism itself is an outgrowth of secular humanism and the enlightenment, and, according to *Wikipedia*, "...an international intellectual and cultural movement supporting the use of new sciences and technologies to enhance human cognitive and physical abilities and ameliorate what it regards as undesirable and unnecessary aspects of the human condition, such as disease, aging and death."

The opponents of transhumanism, regarding the goal to enhance human nature by means of technology, which includes nutraceutical supplements, have gathered in the camp called bio-conservatives. The article "In Defence of Posthuman Dignity," published in 2005 by N. Bostrom in *Bioethics*, offers a very good overview about the debate between these two poles.

So how does one connect transhumanistic viewpoints, the habit of consuming micronutrients and implementing other life extension strategies? And how can transhumanism help us navigate in the face of unavoidable uncertainty (due to the lack of ultimate study results) about the net result of living healthy lives

and popping nutraceutical pills?

The evidence cascade of medical science not only compromises the concrete-solid 1a-level, derived from systematic review of several RCTs, it goes down to level-5, which is defined as expert opinion without explicit critical appraisal, based on physiology, bench research or "first principles." Bruce Ames' plea for multi-vitamin/mineral supplementation for the obese is a classical example for this EBM level-5.

To recapitulate, the doctrine to request level-1a evidence obtained from "systematic reviews of RCTs with low homogeneity" as a prerequisite for population-wide recommendations for supplementation is based on the prevailing precautionary principle of traditional medical science, which is rooted in one of medicine's leading record, "do not harm."

A different and more straightforward approach besides the aforementioned precautionary principle is represented by the proactionary principle. The proactionary principle, defined by contemporary philosopher Max More and cultural strategist Natasha Vita-More, is "an ethical principle intended as a pro-innovation counterbalance to the more famous precautionary principle".

The proactionary principle means to "assess risks and opportunities according to available science, not popular perception, and allow for common reasoning biases. To account for both, the costs of the restrictions themselves, and those of opportunities foregone. To favor measures that are proportionate to the probability and magnitude of impacts, and that have a high expectation value. To protect people's freedom to experiment, innovate, and progress.

The transhumanistic viewpoint considers "restrictive measures (strict regulation of access to high-dose nutraceuticals for the public) only if the potential impact of an activity (harmful effect of a given supplement) has both significant probability and severity. Most important, the explanation of the proactionary principle by Max More and Natasha Vita-More continues by stating: "In such cases, if the activity also generates benefits, discount the impacts according to the feasibility of adapting to the adverse effects."

"Discount restrictive measures by adapting to new insights..."(i.e., the beta-carotene examples.

One example for what is meant by discounting "restrictive measures by adapting to the adverse effects" if an

“activity also generates benefits” might be illustrated by taking a second look at the well known alpha tocopherol-beta-carotene (ATBC) trial, which revealed untoward effects of high doses of isolated synthetic beta-carotene on long-time smokers.

Contrary to the epidemiological data at the time (1994)—i.e. that beta-carotene concentrations in serum of smokers and lung cancer patients were found to be reduced—the prescribed supplementation of 30 mg of isolated beta-carotene/day for long-term male smokers taken over several years sur-

prisingly turned out to be associated with a significant increase in lung cancer cases. This finding and the results of another 1996 trial (CARET) investigating beta-carotene and vitamin A supplementation lead authorities to impose very strict regulations on beta-carotene as a food supplement and as part of nutraceutical supplements.

It is of note, and usually not mentioned by critics, that in the beta-carotene/vitamin E (50 mg) combination arm of the ATBC trial, lung cancer numbers were no more elevated compared to placebo. Moreover, vitamin E supple-

mentation was significantly associated with lower prostate cancer cases. In addition, reanalysis of the ATBC data by creating a dietary antioxidant index that summarized the combined intake of individual carotenoids, flavonoids, tocopherols, tocotrienols, selenium and vitamin C, revealed that higher antioxidant index values were predictive for lower lung cancer risk among male smokers participating in the trial.

Today we know what mistakes researchers in the ATBC trial made: they assumed that synthetic beta-carotene or an incomplete vitamin E formulation

Future Product Opportunities in Cosmeceuticals

(Excerpted from a Business Insights report published in July 2007.)

According to a new report from Business Insights, London, U.K., the overlap between supplements, food, drink and cos-

metic companies will become more important as the population ages and spending power increases. And because cosmeceuticals represents such an emergent market, the report suggests there are plenty of opportunities for food and drink manufacturers. But there are barriers to contend with too, as consumers come to grips with this evolving sector. *Table 1*

Table 1

<u>NPD Opportunity</u>	<u>Potential Barriers</u>	<u>Solutions</u>
Transfer brand reputation from food/drink arena into cosmeceuticals	Consumers may get confused by the cross-category offering	Educating consumers about brand values relevant to both categories through carefully targeted marketing
Lower and lighter versions in beauty and diet products are interrelated for most consumers	Concerns over taste profile of “diet” variants of standard products	Conduct taste trials throughout the NPD process and make it clear that it tastes “as good” as the standard variant
Single serve portions	Portion size may be too small for the individual; consumer may be looking for a product to share with colleagues or consume over a longer period	Offer a range of pack sizes to suit single and sharing occasions
Upscale and premium	The whole brand image should be “premium,” including packaging, recipe and ingredients to tap into treating and self-reward occasions	Ensure the entire brand proposition and communications are in line with the premium positioning
Natural and organic external health benefits	Skepticism regarding effectiveness of food/drink for beauty	Use natural ingredients that are well known for external health benefits; communicate benefits on packaging
Scientific support for specialist ingredients	Difficult to get the balance right between natural and scientific benefits and communications	Provide access to more in-depth scientific support through website and accompanying literature
Innovative and exciting new area for retailers to exploit	Misunderstanding by retailers and buyers regarding location of products in-store vs. personal care fixtures	Provide ongoing support to retailers as well as point of sale merchandising

alone will do the trick, instead of using other carotenoids and dietary antioxidants derived from fruit, berries and vegetables that do have cancer suppressing effects. And of course, the dosage of 30 mg of isolated synthetic beta-carotene was too high. Finally, experiments with ferrets exposed to cigarette smoke revealed that beta-carotene in high doses must be regarded as a co-carcinogen in association with smoking. Lastly, it was found that high alcohol consumption increased lung cancer cases among the study group that received beta-carotene.

Regardless of the many critical points, which are often raised when another anti-supplement study or meta-analysis is pumped through the mass media, the anti-supplement camp is always quick to say: "I told you so. Stay away those vitamin pills!"

But the transhumanist's advice of "adapting to new insights" for a proactionary thinker would, in the case of the ATBC and CARET trials, translate into: "Okay, according to the data and being a smoker, I should abstain from isolated high-dose beta-carotene supplementation. Although, I might already be pro-

tected against the harmful effects of beta-carotene with respect to lung cancer by ingesting 50 mg of synthetic vitamin E. Comfortingly, I am reducing my risk for prostate cancer at the same time.

A proactionary scientist would go on by stating that a mix of carotenoids with a much lower proportion of beta-carotene, plus full spectrum vitamin E (comprising tocopherols and tocotrienols), selenium and flavonoids vs. placebo be tested in a similar fashion as synthetic beta-carotene and racemic vitamin E in the ATBC trial. Nobody would dispute this as the next logical

lays out some of the opportunities and challenges manufacturers face in product positioning and communication.

Currently in the cosmeceutical food and drink sector there remains a strong focus on the science behind the functionality of products rather than a simple, unfussy communication that can appeal directly to the consumer. It is expected that over the next six to 12 months food and drink manufacturers will start to consider promoting their products as "real" and "realistic" for the average consumer in line with the marketing trends witnessed in the personal care industry. While scientific support is important in the functional food and drink market, there is only a certain level of detail that most consumers are interested in, and more detailed information should be available to those who want it (i.e., on a website or through direct mail), rather than "the science bit" being the leading marketing message.

The food and drink industry should also take some inspiration from the popularity of associating brands with "real" people rather than targeting health conscious consumers. In reality, consumers often swing between healthy and indulgent eating habits, with "healthy indulgent" products growing in popularity. Brands that demonstrate realistic brand values and communicate realistic marketing messages are more likely to engender trust and customer loyalty.

Over the next five years, particularly in North America, more manufacturers within both the personal care and the nutraceuticals sectors will choose to invest in research and development focusing on the concept of "beauty from within" through the launch of new food and drink products. Currently, North America lags behind Asia-Pacific and Western Europe in terms of cosmeceutical market development, which is marked by the fact that it is the third largest market in terms of NPD

share, growing 3% to a 20% share of global cosmeceutical launches in 2007. However, the huge success of the nutraceuticals market, valued at more than \$21 billion in 2006, and the fact that the U.S. has the highest spend per capita for both cosmeceutical personal care products and nutraceuticals, means the signs are very positive for cosmeceuticals. The U.S. also has the most advanced personal care market in the world, which is likely to drive NPD as brands expand into the food and drink arena in search of further growth opportunities.

Business Insights selected the following 10 flavors as "ones to watch" over the next two years. It is predicted that these flavors will become more regularly used in cosmeceuticals NPD, as manufacturers strive to offer something unique, natural, healthy and with added "luxury." Some of the top flavors that will likely be associated with these types of products include:

Top 10 Flavors for Cosmeceutical Products

Aloe
Honey
Hibiscus
Bitter Chocolate
Rooibos
Schisandra
St. John's Wort
Flax
Dragonfruit
Lychee

step. This requires another long-term study, but it is unlikely this hypothetical trial will be carried out in the near future. Again, as outlined before, it is impossible to study all the myriad permutations of supplement combinations according to EBM level-1 criteria.

How Risky is this Biological Bet?

It is important to differentiate which disease or human condition the target of an intervention or strategy might be when EBM level 1a-evidence is absent. If a serious and life-threatening disease is the target, and death or fast deterioration are the only alternatives, it is routine in medicine to “give it a try” after carefully weighing the risks and benefits, and of course including the informed consent of the patient. If a life-enhancement strategy—i.e., anti-aging medicine—involves healthy people ingesting multi-nutraceutical supplements and practicing healthy lifestyles, the situation becomes more complex.

Informed individuals (e. g., physicians, biochemists, biologists) have an advantage over the average person when it comes to the “biological bet” of popping nutraceutical pills.

But the average consumer, who is neither among the group of self-educated laypersons, nor a trained scientist, is constantly being bombarded by nutraceutical advertising from numerous sources. To deliver complete information to all consumers is not always feasible for the mass market and it is very easy to unscrupulously exploit the hope of living longer or healthier. Therefore, a certain degree of consumer protection through regulation is certainly a good thing. On the other hand, mankind would have never

evolved this far if every decision in technique and architecture would have been made according to today’s EBM level-1a criteria only.

Analysis & Conclusions

In the end, both approaches (the precautionary and the proactionary) are needed and both have their place in real life—traditional science at a snail’s pace and the freedom of choice-based biological bet for curious individuals (i.e., the life extensionists.) Considerable pieces of evidence for



the latter already exist, so it would be wise for traditional scientists to study (at least in cohort trials) and document the effects of ongoing uncontrolled “mega-trials” that life extensionists are undertaking. Twenty years from now it might turn out that groups of remarkably healthy and vibrant individuals in their 70s will emerge, displaying objective and subjective biological features, which today living persons without supplements usually exhibit in their 50s. And by looking at what these super healthy life extensionists have in common, it might be found that they were the ones, who embarked on life exten-

sion programs in the 1980s and 1990s when there was a relative absence of EBM level-1a support for the nutraceuticals they were taking.

In the end, from the point of view of an anti-aging clinician who treats patients with both prescription drugs and nutraceuticals, it is upsetting to see the predominant reluctance of the nutraceuticals industry to support those MDs who use nutraceuticals with scientific data by means of rigorously funding reasonable, appropriately clinical trials. There are, however, some positive exceptions, but the

industry must unite so scientists can undertake high-quality clinical trials in humans. Yet I can hear nutraceutical executives now: “But how can I protect my IP after participating in expensive studies?” My answer is: sorry I cannot guarantee 100% IP protection, although there may be solutions for some companies. Regardless, the nutraceuticals industry must do something about building a database of research supporting these beneficial ingredients. Otherwise, more of those tricky meta-analyses and science-by-design studies we all know and dislike might emerge and

do more harm to the industry and consumers in the future. **NW**

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References furnished upon request.