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Science is the ignorance of the expert (Richard Feynman)

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Scienza è credere
nell'ignoranza degli esperti
(Richard Feynman)

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Summary

I'll argue that Iannis Ioannidis (1) is not only right, but that -for instance- antioxidant supplements seem to *increase* overall mortality due to gastrointestinal cancers (2); antioxidants *prevent health-promoting* effects of physical exercise in humans (3); multivitamin use has *little or no* influence on the risk of common cancers, CVD, or total mortality in postmenopausal women (3); vitamins and minerals are supplied in abundant amounts in the foods we eat... Except for persons with special medical needs, there is no scientific basis for recommending routine use of dietary supplements (4); long-term or high-dosage consumption of vitamin C may play a role in calcium oxalate kidney stone formation (5). Clinicians need to be alerted to the potential dangers of large dose ingestion of vitamin C in some individuals (5); a physiological increase of oxidative stress has been observed in pregnancy. A routine iron supplement, especially a combined iron and vitamin C supplementation, without biological justifications could therefore aggravate this oxidative risk. These data show that pharmacological doses of iron, associated with high vitamin C intakes, can result in uncontrolled lipid peroxidation (6); overall, the evidence now appears clear. Taking some multivitamins, in particular those containing the antioxidants vitamin E and A (and its precursor beta-carotene), is dangerous and should be avoided by people eating a healthy diet. We therefore caution against taking regular, long term supplementation with the antioxidant vitamins E and A, or any mixture containing them (7), etc.

Riassunto

In questo lavoro sosterrò la tesi che non solo Iannis Ioannidis (1) è nel giusto, ma che -per esempio- gli integratori antiossidanti sembrano aumentare la mortalità generale a causa di tumori gastrointestinali (2); gli antiossidanti ostacolano gli effetti salutari dell'esercizio fisico negli esseri umani (3); l'uso di multivitaminici ha poca o nessuna influenza sul rischio di tumori comuni, CVD, o sulla mortalità totale nelle donne in postmenopausa (3); le vitamine e i sali minerali sono forniti in quantità abbondante nei cibi che mangiamo ... Tranne che per persone con particolari esigenze mediche, non vi è alcuna base scientifica per raccomandare l'uso di routine di supplementi dietetici (4); a lungo termine o ad alte dosi il consumo di vita-

mina C può giocare un ruolo nella formazione di calcoli di ossalato di calcio nel rene (5). I medici devono essere informati sui potenziali pericoli dell'ingestione di massicce dosi di vitamina C in alcuni individui (5); un aumento fisiologico di stress ossidativo è stata osservato durante la gravidanza. Una supplementazione di routine di ferro, soprattutto quella combinata di ferro e vitamina C, senza giustificazioni biologiche potrebbe quindi aggravare questo rischio ossidativo. Questi dati mostrano che dosi farmacologiche di ferro, associate con assunzione di alte dosi di vitamina C, possono provocare una perossidazione lipidica incontrollata (6); nel complesso, le prove sembrano ormai chiare. Assumere alcuni multivitaminici, in particolare quelli contenenti le vitamine antiossidanti E e A (e il suo precursore il beta-carotene), è pericoloso e dovrebbe essere evitato da persone che consumano una dieta sana. Dobbiamo quindi stare in guardia contro l'assunzione regolare e l'integrazione a lungo termine delle vitamine antiossidanti E e A o di una qualsiasi miscela che le contengano (7).

A Quote from Iannis Ioannidis (1)

“Consider... the endless stream of results from nutritional studies in which researchers follow thousands of people for some number of years, tracking what they eat and what supplements they take, and how their health changes over the course of the study... the odds are that in any large database of many nutritional and health factors, there will be a few apparent connections that are in fact merely flukes, not real health effects. But even if a study managed to highlight a genuine health connection to some nutrient, you're unlikely to benefit much from taking more of it, because we consume thousands of nutrients that act together as a sort of network, and chang-

ing intake of just one of them is bound to cause ripples throughout the network that are far too complex for these studies to detect, and that may be as likely to harm you as help you. Even if changing that one factor does bring on the claimed improvement, there's still a good chance that it won't do you much good in the long run, because these studies rarely go on long enough to track the decades-long course of disease and ultimately death. Instead, they track easily measurable health “markers” such as cholesterol levels, blood pressure, and blood-sugar levels, and meta-experts have shown that changes in these markers often don't correlate as well with long-term health as we have been led to believe. On the relatively rare oc-

casions when a study does go on long enough to track mortality, the findings frequently upend those of the shorter studies. (For example, though the vast majority of studies of overweight individuals link excess weight to ill health, the longest of them haven't convincingly shown that overweight people are likely to die sooner, and a few of them have seemingly demonstrated that moderately overweight people are likely to live *longer*.) And these problems are aside from ubiquitous measurement errors (for example, people habitually misreport their diets in studies), routine misanalysis (researchers rely on complex software capable of juggling results in ways they don't always understand), and the less common, but serious,

problem of outright fraud (which has been revealed, in confidential surveys, to be much more widespread than scientists like to acknowledge).

If a study somehow avoids every one of these problems and finds a real connection to long-term changes in health, you're still not guaranteed to benefit, because studies report average results that typically represent a vast range of individual outcomes. Should you be among the lucky minority that stands to benefit, don't expect a noticeable improvement in your health, because studies usually detect only modest effects that merely tend to whittle your chances of succumbing to a particular disease from small to somewhat smaller. The odds that anything useful will survive from any of these studies

are poor - dismissing in a breath a good chunk of the research into which we sink about \$100 billion a year in the United States alone. And so it goes for all medical studies. Indeed, nutritional studies aren't the worst!" (1).

**The Scientist is a Doubter
(Claude Bernard)**

"There are known knowns. These are things we know that we know. There are known unknowns. That is to say, there are things that we know we don't know. But there are also unknown unknowns. There are things we don't know we don't know." (Donald Rumsfeld, after the sack of the National Museum of Baghdad, 2003). Despite the author of this infamous and wide-

ly circulated quote, there is some truth in it. Humans claim that they are rational, but they are too often irrational and take refuge in faith, religion, obsolete textbooks, the Internet, or worse. Most of us practice wishful thinking and take for granted positive results of questionable hypotheses, or simply rehash "ancient wisdom". The fragile veneer of science serves quacks, preachers, and snake oil merchants. But there are a few major hurdles that are carefully ignored or discarded, the first and major one being the **placebo effect**.

The placebo effect is the "elephant in the room". Placebos have proven effective, most of the time as much as the prescription drug or healing techniques (sham), in the following medical conditions:

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| <ul style="list-style-type: none"> • ADHD: adult, child • Amalgam fillings: attributed symptoms (inert "chelation" therapy) • Anxiety disorders • Asthma (water aerosol inhalant) • Asthma • Autism: language and behavior problems • Benign prostatic enlargement • Binge eating disorder • Bipolar mania • Cough, Crohn's disease • Depression (light treatment; low red light placebo) • Depression • Dyspepsia and gastric motility | <ul style="list-style-type: none"> • Epilepsy • Erectile dysfunction • Food allergy: ability to eat ill-making foods • Gastric and duodenal ulcers • Headache • Heart failure, congestive • Herpes simplex. Hypertension: mild and moderate • Irritable bowel syndrome • Migraine prophylaxis • Multiple sclerosis • Nausea: gastric activity • Nausea: chemotherapy • Nausea and vomiting: postoperative (sham acupuncture) | <ul style="list-style-type: none"> • Pain • Panic disorders • Parkinson's disease • Pathological gambling • Premenstrual dysphoria disorder • Psoriatic arthritis • Reflux esophagitis • Restless leg syndrome • Rheumatic diseases • Sexual dysfunction: women • Social phobia • Third molar extraction swelling (sham ultra-sound) • Ulcerative colitis • Vulvar vestibulitis |
|--|---|---|

And these are/were proven, real, medically diagnosed conditions, i.e. “patients”, sick people!

If we now consider supplements, health foods, nutraceuticals they are freely promoted, available, purchased and widely consumed by *healthy* individuals, who - by definition - do **not** need any of them. Then why? Because of the fear-mongering orchestrated by the manufacturers and their associations, by the lobbyists who buy out politicians, by scientists who need to beef up their list of publications, by the media that all depend on advertising, by the humongous budgets allocated to all forms of mental degradation and social abasement, by the carelessness of the governmental agencies supposedly in charge of regulation and protection of their peoples -and the list goes on. Very few voices have been heard (11); and even then evidence is swept away by a constant tsunami of seductive, diabolic ads.

Science is a Process

“Religious systems are inherently conservative, science inherently progressive” (12). One can believe in miracles, but when science is correctly applied even publications in *Nature* crumble under ridicule. Science mimics Cronus (Kronos) and devours its children; not much

“scientific evidence” remains after a decade or two, and if it does complexity has changed its appearance. Our genes can be influenced by external or internal [i.e. the ones we make] factors: food components, nutraceuticals, health foods, intestinal flora (normal and/or changing), emotions (pleasure, disgust, stress), disease, etc.

In fact, besides our DNA, a very large number of actors and factors influence our health, e.g. the subject(s): genes, epigenetics, digestion, environment, medical conditions, etc.; the food; the intestinal flora; the industry: food, nutraceuticals, health foods; the epidemiologists; the policy makers; etc. However most scientists are forced to live - and publish - with a tunnel vision. It is not appropriate to claim “*I do not know*” when you are supposed to be omniscient. But because our knowledge, individual or global, is and will remain the emerging tip of the iceberg (i.e. 10% -at best), and because this ratio will not change, Richard Feynman said “*Science is the ignorance of the expert*”.

Each individual is unique. He/she has nothing in common with pure strain mice or rats. Every culture, environment, taboo, and many more influence who we are, and who we will become. Think that over 100,000 papers have looked at the immune system of lab mice, but less than 5 at wild mice! (16)

Humans from Goldman Sachs (or members of the HK Jockey Club) are very different from survivors of the Haiti (or Sichuan) earthquake, or sub-Saharan populations. We are also in large part what we (like to) eat. We are also changing every second and the difference between the newborn and his self as a centennial is galactic. Our genes influence how we digest, what we absorb, how we metabolize, etc. Our genes and our intestinal flora regulate what we **need**, and if we try to overcome them we **may/will get sick**. Which is the case with nutraceuticals/health foods: buyers are pushed to take very large doses of pure chemicals (even natural ones) outside the aliment environment.

A Cautionary Tale about Nutraceuticals/Health Foods

Antioxidants increasingly have been praised for their benefits against disease and aging, but recent studies at Kansas State University show that they also can cause harm.

Researchers in K-State’s Cardiorespiratory Exercise Laboratory have been studying how to improve oxygen delivery to the skeletal muscle during physical activity by using antioxidants, which are nutrients in foods that can prevent or slow the oxidative damage to

the body. Their findings show that sometimes antioxidants can impair muscle function.

“Antioxidant is one of those buzz words right now. Walking around grocery stores you see things advertised that are loaded with antioxidants. A lot of people don’t realize is that the antioxidant and pro-oxidant balance is really delicate. You can’t just give a larger dose of antioxidants and presume that there will be some sort of beneficial effect. In fact, you can actually make a problem worse.” (11).

David C. Poole and Timothy I. Musch, K-State professors from both the departments of kinesiology and anatomy and physiology, direct the Cardiorespiratory Exercise Laboratory, located in the College of Veterinary Medicine complex. Researchers in the lab study the physiology of physical activity in health and disease through animal models. Copp and Daniel Hirai, an anatomy and physiology doctoral student from Manhattan working in the lab, have conducted various studies associated with how muscles control blood flow and the effects of different doses and types of antioxidants.

Abnormalities in the circulatory system, such as those that result from aging or a disease like chronic heart failure, can impair oxygen delivery to the skeletal muscle and increase fatigability during physi-

cal activity. The researchers are studying the effects antioxidants could have in the process.

“If you have a person trying to recover from a heart attack and you put them in cardiac rehab, when they walk on a treadmill they might say it’s difficult,” Poole said. “Their muscles get sore and stiff. We try to understand why the blood cells aren’t flowing properly and why they can’t get oxygen to the muscles, as happens in healthy individuals.”

There is a potential for antioxidants to reverse or partially reverse some of those changes that result from aging or disease. However, K-State’s studies have shown that some of the oxidants in our body, such as hydrogen peroxide, are helpful to increase blood flow.

“We’re now learning that if antioxidant therapy takes away hydrogen peroxide - or other naturally occurring vasodilators, which are compounds that help open blood vessels - you impair the body’s ability to deliver oxygen to the muscle so that it doesn’t work properly,” (17).

Poole said antioxidants are largely thought to produce better health, but these studies have shown that antioxidants can actually suppress key signaling mechanisms that are necessary for muscle to function effectively.

“It’s really a cautionary note that before we start recommending

people get more antioxidants, we need to understand more about how they function in physiological systems and circumstances like exercise,” (17).

Women who took beta carotene or vitamin C or E or a combination of the supplements had a similar risk of cancer as women who did not take the supplements, according to data from a randomized controlled trial.

Epidemiological studies have suggested that people whose diets are high in fruits and vegetables, and thus antioxidants, may have a lower risk of cancer. Results from randomized trials that address the issue, however, have been inconsistent and have rarely supported that observation.

In one recent study (18), Jennifer Lin, Ph.D., of the Brigham and Women’s Hospital and Harvard Medical School in Boston, and colleagues tested the impact of antioxidant supplements on cancer incidence in a randomized controlled trial. A total of 7,627 women who were at high risk of cardiovascular disease were randomly assigned to take vitamin C, vitamin E, or beta-carotene. With an average of 9.4 years of follow-up time, there was no statistically significant benefit from antioxidant use compared with placebo in terms of disease risk or mortality due to cancer. Overall, 624 women developed cancer and 176 died

from cancer during the follow-up time. Compared with placebo, the relative risk of a new cancer diagnosis was 1.11 for women who took vitamin C, 0.93 for women who took vitamin E, and 1.00 for women who took beta carotene. None of these relative risks was statistically significantly different from 1.

“Supplementation with vitamin C, vitamin E, or beta carotene offers no overall benefits in the primary prevention of total cancer incidence or cancer mortality,” the authors conclude. “In our trial, neither duration of treatment nor combination of the three antioxidant supplements had effects on overall fatal or nonfatal cancer events. Thus, our results are in agreement with a recent review of randomized trials indicating that total mortality was not affected by duration of supplementation and single or combined antioxidant regimens.”

Most Americans and Canadians up to age 70 need no more than 600 international units (IUs) of vitamin D per day to maintain health, and those 71 and older may need as much as 800 IUs, says a new report (19) from the Institute of Medicine. The amount of calcium needed ranges, based on age, from 700 to 1,300 milligrams per day, according to the report, which updates the nutritional reference values known as Dietary

Reference Intakes (DRIs) for these interrelated nutrients.

The report’s recommendations take into account nearly 1,000 published studies as well as testimony from scientists and stakeholders. A large amount of evidence, which formed the basis of the new intake values, confirms the roles of calcium and vitamin D in promoting skeletal growth and maintenance and the amounts needed to avoid poor bone health. The committee that wrote the report also reviewed hundreds of studies and reports on other possible health effects of vitamin D, such as protection against cancer, heart disease, autoimmune diseases, and diabetes. While these studies point to possibilities that warrant further investigation, they have yielded conflicting and mixed results and do not offer the evidence needed to confirm that vitamin D has these effects. Rigorous trials that yield consistent results are vital for reaching conclusions, as past experiences have shown. Vitamin E, for example, was believed to protect against heart disease before further studies disproved it.

At the Heart Institute of the Cedar-Sinai Medical Center in Los Angeles, California, Toasheng Li and Eduardo Marbán have reported (20) that intracellular ROS levels were moderately decreased in physiological oxygen, but dra-

matically decreased by the addition of high-dose antioxidants. Quantification of DNA damage in cardiac stem cells and in human embryonic stem cells revealed a biphasic dose-dependence: antioxidants suppressed DNA damage at low concentrations, but potentiated such damage at higher concentrations. High-dose antioxidants decreased cellular levels of ATM (ataxia-telangiectasia mutated) and other DNA repair enzymes, providing a potential mechanistic basis for the observed effects. These results indicate that physiological levels of intracellular ROS are required to activate the DNA repair pathway for maintaining genomic stability in stem cells. The concept of an “oxidative optimum” for genomic stability has broad implications for stem cell biology and carcinogenesis.

Provisional Conclusion

Too much of a good thing is not necessarily better. In fact too much of a given nutrient will create imbalance with deleterious, and poorly predictable effects. The wishful thinking attitude, the faith in unproven hypotheses, the deliberate selection of favorable (?) lab results in pure strain rodents, the disgusting hype of unleashed marketing messages are unfortunate daily occurrences in nutrition. The

fearmongering reigns supreme: “You are eating all the wrong foods/nutrients/dishes, and you *must* take this supplement/health food to live better and/or longer”. Unfortunately several factors will not vanish by a strike of a magic wand: our genes have reigned supreme for millions of years –even before humans started wandering the globe- and regulate our digestion, absorption, metabolic pathways, health and aging; the food we like –and digest better- is >80% the one we liked before the age of six; our culture, including, how, when, with whom, where we eat conditions much more than the nutritional content of what we absorb our well-being; our mood is possibly the major factor that influences our health and survival. The recent promotion of supplements/nutraceuticals/health foods is biased: some are useful for specific *patients* and can eventually avoid or delay the use of prescription drugs. But these categories of products are drilled into the mind and forced down the gullet of *normal, healthy* subjects, including children and the elderly, with essentially no evidence of benefits, or regulatory controls. As M. Siahpush concluded: “Everything else being equal, if you are happy

and satisfied with your life now, you are more likely to be healthy in the future. Importantly, our results are independent of several factors that impact on health, such as smoking, physical activity, alcohol consumption and age (21)”. Cheers - more than ever!

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