From My Forthcoming Book: Can You Get Too Many Plant Polyphenols?

In my forthcoming book on supplements, Best Supplements for Men, I give some consideration to the dosage of polyphenols, the beneficial plant chemicals that are associated with much lower death rates. Can you get too many plant polyphenols? Are all plant polyphenols created equal? Read on for my thoughts on that topic. The book is in progress.

Polyphenols: The Right Dose

Several of the supplements in this section [of the book], including resveratrol, green tea, curcumin, quercetin, and berberine, are polyphenols, a class of chemicals found in plants. In addition, coffee, black tea, chocolate, and red wine contain relatively large amounts of these phytochemicals. If you consume these foods/beverages and also supplement, is it possible to get too many polyphenols?

Consumption of polyphenols is robustly associated with better health and 37% lower death rates, as well as a 46% reduction in cardiovascular disease risk. However, these studies were based on the polyphenol content of foods, such as coffee, fruits and vegetables, etc., as well as a spot urine test for polyphenols, not supplement use. The highest intakes of polyphenols, that is, those associated with the lowest death rates, averaged about 1235 mg a day.

Polyphenols in food

To get a handle on this, it helps to know the polyphenol content of some common food items, notably those high in them as we’ve discussed. I’ve listed
the total polyphenol content, by serving, in the following, calculated from
the amount in 100 grams or in 100 ml from “Identification of the 100 richest
dietary sources of polyphenols: an application of the Phenol-Explorer
database”.

- Dark chocolate: ~500 mg
- Coffee: ~300 mg
- Black tea: ~150 mg
- Green tea: ~120 mg
- Red wine: ~150 mg

Someone who drinks two regular-size (6-ounce) cups of coffee daily, eats a
serving of dark chocolate, and drinks two glasses of red wine (for example),
will have a polyphenol intake of around 1400 mg. (Rough calculation.) That's
about the level seen in the highest category of polyphenol consumption and
the category with the lowest death rates. Using some different assumptions,
it would appear to be relatively easy to get total daily polyphenol uptake
into the several-thousand-milligram daily range. In fact, a 20-ounce coffee
of the kind sold in chain coffee shops may alone have 1200 mg of polyphenols.

For comparison, some of the doses of supplements we've discussed, such as
berberine and curcumin, are 500 mg. Resveratrol suggested doses are lower, at
100 mg or less.

Could you get too many plant polyphenols? Or is there even such a thing as
too many?

**Hormesis and polyphenols**

Unfortunately, the answer is not known. It may or may not follow that,
because those who consumed 1250 mg of polyphenols a day had the lowest death
rates, those who consumed 2500 mg a day have even lower death rates. Maybe
they do, maybe they don’t.

A point of diminishing returns likely exists somewhere. Furthermore, not all
polyphenols are the same and some have greater effects than others and/or use
different mechanisms of action, so adding them into all one basket for
purposes of calculating total intake may be of limited value.

**Stilbenes and lignans**

The study that found 37% lower death rates also reported, “Among the
polyphenol subclasses, stilbenes and lignans were significantly associated
with reduced all-cause mortality [HR 0.48 and 0.60, respectively], with no
significant associations apparent in the rest (flavonoids or phenolic
acids).”

If polyphenols cause lower death rates (not mere association), then only
certain classes of them count for much.
The two classes of polyphenols that mattered were stilbenes, which include resveratrol, pterostilbene, and other compounds in grapes, wine, and cocoa; and lignans, the richest source of which is flaxseed.

Since polyphenols most likely work through hormesis, the process by which low doses of toxins or stressors produce beneficial health effects, it follows that at some dosage, polyphenols may become overtly toxic, and damage health.

The point I wish to make is to be aware of what you’re taking and not to overdo it. Don’t indiscriminately take large amounts of different polyphenol supplements in the quest for ever better health, especially if you already drink coffee, tea, and wine, and eat chocolate. Not to mention berries (another source of large amounts of polyphenols) or if you cover your food with cloves (just kidding, but that’s the number one food for polyphenols).

Although we don’t know at what, if any, level that polyphenols become a problem, and overt toxicity in animals seems to occur only at very high doses, if you tally up your polyphenol intake and find it at, say, over a couple thousand milligrams daily, you might consider cutting back. These considerations may not apply to those with special health needs, such as someone taking berberine several times a day for blood sugar control, but such people should have cleared their use of supplements with their doctor first.

PS: Check out my Supplements Buying Guide for Men.

Notes


Hormesis for Health and Longevity: A Guide

It’s obvious that people we refer to as couch potatoes have worse health than others, although these days the couch potatoes outnumber the others. The reason for their worse health is that they are not placing enough stress on their bodies, which adapt to a low-stress state. Then when a real stress comes along, they’re not prepared for it. The phenomenon called hormesis is one in which small doses of toxins or other stressors cause the increase in the body’s (or cell’s) stress defense mechanisms. Hormesis is robustly associated with good health and long life. Anyone wanting to take charge of his health should know about it, so here’s a guide to hormesis for health and longevity.

What hormesis is

Hormesis has been known, albeit in a vague way, for a long time. Famously, King Mithridates VI of Pontus allegedly took small doses of various poisons in order to fortify himself against real doses. Whether that’s true or not, it shows that people knew enough about how that works to concoct a legend about it.

Hormesis is the beneficial effect caused by low levels of potentially toxic agents. (Ref.) In essence, what doesn’t kill you makes you stronger, although that expression should be tempered by the fact that doses of a stress much less than that needed to kill you have beneficial, hormetic effects.

Many types of stressors can cause hormesis, for example:

- exercise
- phytochemicals (from plants)
- radiation, both solar and other
Hormesis is characterized by a so-called J-shaped (sometimes U-shaped) curve, in which a small amount of a substance or stress results in better health than a zero amount. Increasing the dose increases the stress response up to a point, beyond which increasing doses worsen health.

Figure 1

This curve illustrates the concept. With increasing exposure, or dose, health risk decreases to a nadir of risk, after which it rises. At some point of increasing dose, the risk rises above that seen initially, at which point the dose can be truly said to be toxic and promoting ill health. Sometimes this curve is shown upside down, but the meaning is the same.

Hormesis activates biochemical stress defenses, most notably through the Nrf2 transcription factor that regulates the expression of antioxidant, protective mechanisms. Among these mechanisms are enzymes like catalase, superoxide dismutase, glutathione peroxidase, and the so-called phase 2 detoxifying enzymes.

A principle of hormesis is that of pre-conditioning. To use an example, if
you train to run 10 miles, you become pre-conditioned, and if you had to run 15, you could do it. If you only trained for 1 mile, and then had to run 10, you would not be able to, or only with great difficulty and harm to your health.

The opposite of hormesis is, for lack of a better term, one that I’ve called the couch potato lifestyle, one in which the organism is never challenged. Then, when an untoward event or stress or toxin comes its way, it’s unprepared.

Activating stress response pathways via hormesis is essential for health and anti-aging.

**Agents of hormesis**

**Exercise**

Probably the most familiar of hormetic agents is exercise. When you exercise, you consume more oxygen than usual to burn more energy, and *this results in increased levels of free radicals (also known as reactive oxygen species, ROS)*.

...exercise-induced ROS production plays a role in the induction of antioxidants, DNA repair and protein degrading enzymes, resulting in decreases in the incidence of oxidative stress-related diseases and retardation of the aging process.

**Phytochemicals**

Phytochemicals are plant-derived molecules with beneficial health effects. They include phenols, flavonoids, and others.

While animals can defend themselves by fighting or fleeing, plants are literally rooted to the ground and thus can’t do that. It may come as a surprise that plants do not want to be eaten.

To defend themselves, plants use chemical warfare.

Many or most of the various phytochemicals that benefit human health are toxins, low doses of which upgrade stress defense mechanisms and *prevent cancer and heart disease*. Dietary phytochemicals are likely responsible for the health benefits of fruits and vegetables.

*Coffee, tea, chocolate, and red wine also have known health benefits*; as these are all plant products, the polyphenols and other chemicals in them provide the benefits.

A short list of hormetic phytochemicals would include:

- curcumin – from the spice turmeric
- epigallocatechin gallate (EGCG) – from tea
- chlorogenic acid – from coffee
- resveratrol – from red wine
- sulforaphane – from cruciferous vegetables like broccoli
- chocolate flavonoids

Many of these compounds may also chelate iron, accounting for a great deal of their health benefits. Chocolate appears to be a huge source of polyphenols, larger than red wine and green or black tea.

**Radiation**

Solar radiation causes the production of vitamin D in the skin, but in addition, the radiation itself may be beneficial due to hormesis, and the same goes for other forms of radiation both cosmic and terrestrial. Low dose radiation

- upgrades cellular stress defense
- activates DNA damage repair
- prevents harm from high doses of radiation
- stimulates removal of precancerous cells
- suppresses inflammation and prevents inflammatory diseases
- stimulates immunity
- may slow aging

Nuclear shipyard workers appear to have lower cancer rates than others. Radiation increased the lifespans of British radiologists. In airline pilots and crew, who are exposed to cosmic radiation, a “significant negative risk trend for all-cause mortality was seen with increasing dose of radiation.” The health effects of many spas have been attributed to radiation.

Sunbathing is also associated with longer life, and sun avoidance has been compared to smoking a pack of cigarettes daily.
The map above (from SUNARC) shows colon cancer mortality in white men in the U.S., 1970-1994. Areas with lots of solar radiation had much lower death rates; the results for breast and ovarian cancer, as well as multiple sclerosis are similar.

How much radiation exposure is healthful, and how should you get it? I’m not sure anyone knows the answer. As it concerns solar radiation, sunburning should be avoided. I’ve seen reports of people wearing radioactive rocks around their necks; I wouldn’t be willing to do that though unless we had a much better understanding of doses needed as well as how much radiation the rocks emit.

**Heat and Cold**

Both heat and cold are stresses.

*Sauna bathing* is associated with greatly reduced cardiovascular and all-cause mortality. Note that in this study, they compared only frequency of sauna use, so that sauna bathers were compared only to other sauna bathers. It’s suggested that sauna bathing may be comparable to physical exercise in its effects.

*Winter swimmers have higher levels of stress defense molecules*, including glutathione, indicating that cold induces hormesis. *Cold showers* also have health benefits.
Alcohol

Alcohol functions as a low-dose toxin and initiates hormesis. Alcohol is robustly associated with lower death rates; however, much of the benefit comes from red wine, so in most cases, plant polyphenols play a greater role than alcohol itself in promoting health.

Calorie restriction and intermittent fasting

Calorie restriction and intermittent fasting are solid life-extension interventions, and they produce a stress. They both promote hormesis.

Toxic metals

Please don’t try this at home, but very low doses of methylmercury greatly increased the hatching rate of mallard duck eggs, and it promotes hormesis in C. elegans.

Conclusion

Activating hormesis is robustly associated with better health and longer life. Most anti-aging and life-extending interventions work via hormesis.

The body contains robust anti-aging mechanisms, but they must be activated before they work. The couch potato lifestyle, which features lack of exercise and round-the-clock eating of junk food, is anti-hormesis.

To slow aging and extend lifespan, use a broad program of hormesis using the factors above. That program would consist of exercise, consumption of phytochemicals, sun exposure, intermittent fasting, and heat and/or cold exposure.

PS: Check out my books, Dumping Iron, Muscle Up, and Stop the Clock. (Stop the Clock is most relevant for hormesis.)

PPS: You can support this site by purchasing through my Supplements Buying Guide for Men.
**Why Is Obesity Low in Colorado?**

Of all the states in the U.S., Colorado has the lowest rate of obesity, at about 20% as of 2015. Mississippi has the highest rate at about 35%. Why is obesity low in Colorado?
What could account for the huge differences in obesity from state to state? Here’s a list of some possible factors:

- education
- physical activity
- amount of processed food
- race
- altitude
- radiation, both solar and background
- vitamin D

Since this is a huge topic, I’m going to focus on the last three: altitude and three of its attributes: hypoxia, radiation, and vitamin D.

**Hypoxia**

A reader sent me a link to a very interesting presentation at the Ancestral Health Symposium on the possible link between hypoxia — low levels of oxygen — and lower obesity. (Everything there is copyrighted, so I won’t reproduce any of it here, but I encourage you to read it.)

The author makes the case that the high altitude of Colorado, which means less oxygen in the atmosphere, is responsible for the lower rate of obesity.
there. He points out that there’s also an “island” of less obesity in the Southeast, in the Appalachians, also at altitude, though lower.

A study done in 2013 found that “after adjusting for lifestyle (smoking, physical activity and diet) and demographics (age, sex, race/ethnicity, education, employment status and income)”, those living at <500 meters above sea level had about 5 times the odds of obesity as those living at >3,000 meters above sea level.[1. Voss, Jameson D., et al. “Association of elevation, urbanization and ambient temperature with obesity prevalence in the United States.” International journal of obesity 37.10 (2013): 1407-1412.]


Hypoxia activates numerous cellular stress-defense mechanisms; in other words, it’s a form of hormesis.

A number of other studies support the idea that hypoxia is beneficial in obesity, although it must be pointed out that taking people to high altitude and seeing that they lose weight – which they do – doesn’t rule out other effects of altitude, such as radiation and vitamin D.[3. Lippl, Florian J., et al. “Hypobaric hypoxia causes body weight reduction in obese subjects.” Obesity 18.4 (2010): 675-681.]

At high altitude, basal metabolic rate increases and food intake decreases, which sounds like a hormetic effect, regardless of the exact mechanism.

**Radiation**

The Rocky Mountain states, of which Colorado is one, have a higher level of background radiation. Colorado Springs, for example, has about 5 times the level of background radiation as Houston, Texas.[4. Jagger, John. “Natural background radiation and cancer death in Rocky Mountain states and Gulf Coast states.” Health Physics 75.4 (1998): 428-430.]

Idaho, Colorado, and New Mexico together have about 3.2 times the level of background radiation as Alabama, Mississippi, and Louisiana, and the death rate from cancer is lower in the Rocky Mountain states.

While cancer is not obesity, the same hormetic mechanisms could be expected to play a role in both.

In addition to high background radiation, higher altitude means more exposure to solar radiation, since less of the atmosphere is available to block it out.

Again, the same hormetic mechanisms would likely be at work in both overall longevity and obesity.

**Vitamin D**

It’s difficult to untangle the effects of vitamin D from those of solar radiation. But more solar exposure leads to greater longevity.

A survey of women who had breast cancer, compared with others that had no cancer, found that both dietary vitamin D intake and solar exposure led to large risk reductions in breast cancer, from 0.35 to 0.75.[6. John, Esther M., et al. “Vitamin D and breast cancer risk: the NHANES I epidemiologic follow-up study, 1971–1975 to 1992.” *Cancer Epidemiology Biomarkers & Prevention* 8.5 (1999): 399-406.]


**Conclusion**

It’s entirely possible, indeed likely in my view, that all three of these factors, hypoxia, radiation, and vitamin D play a role in the low obesity rate of Colorado.

Other factors are surely at work too, such as education and ethnic differences, but these can’t be changed.

Obesity has increased over the past few decades in Colorado, as in every other state, so whatever is causing the obesity epidemic (24/7 availability of junk food, in my view) has overridden Colorado’s advantages in that respect, to an extent.

What can this knowledge do for the obese, and for the obesity epidemic? What steps can be taken?

**Hypoxia training.** While training at altitude has shown solid results, the hypoxia masks recently in vogue are questionable. Therefore if you want to train in hypoxic conditions, access to high altitude would seem to be important.

This summer, I found myself doing a lot of underwater swimming. I don’t know if that would have the same effect, but I think it would.

**Vitamin D.** If you have little or no sun exposure, taking vitamin D supplements may be helpful. I take 5,000 IU daily myself, except in summer, when I get some sun exposure.

**Solar radiation.** Obvious solution here, get out in the sun more. Avoid sunburning though. If you work a graveyard shift, or in an office all day long, you may need a concerted effort to get more sun exposure.
Background radiation. Here’s an area that’s intrigued me for some time: how to get more background radiation exposure. Some people have gone so far as to wear radioactive minerals around their necks, but given that you wouldn’t know the dose you’re getting, I don’t think I’m willing to do that. Some of the historic spas in Europe that were renowned for their curative powers may have worker their cures through high background radiation.

You could always move to Colorado.

PS: For more on how to fight obesity and live long, see my books Muscle Up, Dumping Iron, and Stop the Clock.

PPS: Check out my Supplements Buying Guide for Men.

The Richest Sources of Dietary Polyphenols Are Not What You Think

Polyphenols are plant compounds that are associated with good health.(1)

“Polyphenols are secondary metabolites of plants and are generally involved in defense against ultraviolet radiation or aggression by pathogens. In the last decade, there has been much interest in the potential health benefits of dietary plant polyphenols as antioxidant. Epidemiological studies and associated meta-analyses strongly suggest that long term consumption of diets rich in plant polyphenols offer protection against development of cancers,
cardiovascular diseases, diabetes, osteoporosis and neurodegenerative diseases.”

Consumption of polyphenols is thought to be behind much of the health benefit of vegetable and fruit intake.

As part of my anti-aging program, I try to keep my intake of polyphenols high.

**Hormesis**

Polyphenols and other plant compounds such as terpenes and alkaloids are thought to work by hormesis. In other words, these compounds represent low-dose toxins, to which the body mounts a defense, strengthening cellular stress-defense mechanisms. The result is akin to lifting weights: the application of a stress causes the body to react by becoming stronger.

The idea that polyphenols are in reality toxic makes perfect sense, since many of them are produced by plants to fend off and poison predators. The bitterness of many of them serves as a warning to insects and other predators of plants that they’re toxic and not to be eaten.

Plants do not want to be eaten, and are incapable of running away, so polyphenols and other phytochemicals for part of their arsenal in chemical warfare against microorganisms, insects, and animals.

**The richest sources of dietary polyphenols are not what you think**

It turns out that many fruits and vegetables, especially the latter, are not terribly high in polyphenols. Instead, many of our favorite vice foods, like coffee, tea, red wine, and chocolate, rank quite high on the list, outranking many foods that we usually think of as being healthy – broccoli for instance.

A list of the top 100 foods in polyphenol content, published by the European Journal of Clinical Nutrition, and ranked by the amount in a typical serving, shows that many vegetables are relatively low in polyphenols.

Berries, such as blackberry, strawberry, and blueberry, are high in
polyphenols.

A closer look at the list reveals something odd: coffee is number 6 on the list, and going down the list, we find dark chocolate, cocoa powder, black tea, green tea, and red wine.

All of these are much higher on the list than broccoli, onions, tomatoes, pears, peaches, lettuce, and green peppers.

It looks like my daily habit of coffee, tea, chocolate, and red wine gives me more polyphenols than eating even double the recommended five servings a day of fruits and vegetables.

Throw in some blueberries and/or dark chocolate for dessert after dinner and you’re good to go.

The logic behind these food and drink items having high polyphenol contents is that they are in reality highly concentrated plant products.

*A glass of red wine, for instance, requires around 100 grapes to make.* A cup of coffee is made from *about 70 coffee beans.*

If you ate 100 grapes, assuming you could, you’d get an awful lot of sugar with it. Red wine in moderation is healthier than eating grapes for that reason.

**Do you really need fruits and vegetables?**

The question arises: do you even need to eat fruits and vegetables to get their health benefit? Maybe if you consume the food and drink discussed above, you get all the polyphenols you need.

That then leads to the question whether all the benefits of fruits and vegetables arise from their polyphenol content. Perhaps they provide something else that coffee, etc, do not provide.

That other thing could be fiber, which is largely eliminated from these other products. (Cocoa powder retains the fiber.)

Fiber is fermented in the gut by bacteria, leading to the production of butyrate, which is healthy for the intestinal lining and may be one of the main benefits of fiber.

But polyphenols alone modulate gut bacteria and lead to the production of butyrate.(4)

Furthermore, *fiber in and of itself may not be terribly healthy for you.* Many of the alleged health benefits of fiber turn out to be poorly supported by science.

As for the vitamin and mineral content of fruits and vegetables, it appears that meat is a whole lot better:
You’ve probably heard the phrase, “Include superfoods in your daily diet”. If a “superfood” exists, red meat is one. pic.twitter.com/UcbFA0yxJt

– Michael Joseph (@Nutradvance) May 19, 2016

My stance on the benefits of fiber, and thus of fruits and vegetables: agnostic. I do eat vegetables, but pretty much avoid fruit other than berries because of the sugar content. But I don’t worry about whether I get “enough”, because my intake of polyphenols from my “vices” is so high.

I typically drink a cup of coffee when I get up in the morning, one or two cups of tea and a cup of chocolate during the day, and two glasses of red wine before/with dinner. That amounts to an intake of approximately 1150 mg of polyphenols daily.

I also directly ingest polyphenols from supplements. Curcumin, for instance, is a polyphenol.

PS: Check out my Supplements Buying Guide for Men.

Bonus: Rogue Hot Chocolate Recipe

Put 1 heaping teaspoon of cocoa powder in a cup, add 6 ounces of water, microwave for 1 minute. Then stir well. Add a good dollop of cream. No sugar. Contains caffeine and theobromine for stimulation, and over 100 mg polyphenols.
Can excessive running kill you?

The concept of hormesis says that small doses of toxins can actually promote health. Chemical compounds such as resveratrol or sulforaphane cause an increase in cellular stress defense mechanisms. Too much of anything can be toxic; as Paracelsus said, the dose makes the poison, i.e. anything can be poisonous in the right dose, even normally innocuous substances like water.

The concept of hormesis applies to exercise as well. Contrary to what might be expected, exercise reduces levels of oxidative stress. The way it does so is by inducing oxidative stress in the first place; the body reacts by increasing levels of antioxidant enzymes and glutathione, overcomes exercise-induced oxidative stress, and becomes healthier than before.
But too much exercise has the potential to be damaging, since the dose makes the poison. How much is too much? Researchers looked at data from the Copenhagen City Heart Study, in which 1,098 healthy joggers and 3,950 healthy nonjoggers have been prospectively followed up since 2001.

They found that the optimal jogging frequency in terms of mortality was 2 to 3 times a week, or even only 1 or fewer times a week. Joggers in the former category had a hazard ratio of .32, meaning that they were only about 1/3 as likely to die during the study period as sedentary people. The best pace for mortality was slow to moderate.

However, joggers, which in this case we would term runners, who were in the category that the researchers deemed “strenuous”, had a hazard ratio of 1.97, meaning that they were nearly twice as likely to die during the study period as sedentary people.

This must come as a shock to many, since the notion that fitness equals health is a popular one. In reality, the “strenuous” joggers were probably quite fit, yet they died at a much higher rate.

The researchers concluded:

> The findings suggest a U-shaped association between all-cause mortality and dose of jogging as calibrated by pace, quantity, and frequency of jogging.

The U-shaped curve is exactly what would be expected from exercise as hormesis. As exercise increases from the sedentary point, mortality drops to a low; then increases as more exercise is added.

It must be said that a degree of statistical uncertainty exists here, as can be seen in the lowest bar on the graph, but the likeliest hazard ratio was approximately 2.0.

I used to be one of those strenuous runners. I did what I was told, that is, exercise more and more so I could be “healthy”, yet I ended up with a case of chronic fatigue that lasted many years, until I figured out how to overcome it.

Although to my knowledge no study like this has been done with weight trainers, it seems entirely possible that one could overdo it. Training 5 or more days a week might be one of those ways of overdoing it. In a recent video lecture, Doug McGuff, author of Body by Science, recounted how he trained in the gym hard for three days a week for many years, and constantly felt like, in his words, “dog crap”. McGuff advocates one day a week in the gym, although I believe that that is a bit too cautious and you can exercise more than that while still retaining good health.
The military school of health and long life

Aging means a progressive deterioration in physiological function and increasing susceptibility to disease and injury. In a nutshell, age means that the body weakens. Therefore, to deter aging, you have to be strong and remain that way.

The most obvious way to stay strong involves exercise, and especially the form of exercise we like to follow here on this blog, weightlifting. Lifting weights causes the body to adapt to the stress of being forced to lift weights, all the more so when done to failure.

The body possesses plasticity, that is, body tissues and organs can change their size and structure according to the environmental pressures placed on them. In endurance athletes, the heart gets bigger in order to pump more blood and allow the athlete to perform at a high level for a long time. Capillaries grow to bring that blood into the tissues where oxygen is needed. For weightlifters, muscles and even bone grow bigger and stronger — even tennis players develop heavier bones in their dominant playing arm. In people who have lost one of their kidneys, the other kidney becomes larger to take on the task of shedding waste products.
Exercise like this exerts stress, which is a response of the body to any demand for change, in the words of the psychologist Hans Selye. Hit a tennis ball hard enough and long enough, and sufficient stress has been placed on the bones of the arm to cause a response: they grow larger and stronger.

We can use the concept of exercise as stress as to look at the effect of other health-promoting processes on the body, for the fact is that many things that promote health do so by increasing stress. Hormesis, for example, just is, that is nothing but, the placing of a stress on cellular or organ systems. Calorie restriction and intermittent fasting, for instance, are stresses placed on the body, and the body up-regulates stress defense mechanisms. When CR or IF are practiced, there is an increase in free radicals (reactive oxygen species, ROS), and these act as signals for the cell to increase its defenses.

...several longevity-promoting interventions may converge by causing an activation of mitochondrial oxygen consumption to promote increased formation of reactive oxygen species (ROS). These serve as molecular signals to exert downstream effects to ultimately induce endogenous defense mechanisms culminating in increased stress resistance and longevity, an adaptive response more specifically named mitochondrial hormesis or mitohormesis.

The older free radical theory of aging posited that ROS caused aging by causing damage. A newer way of looking at it is that damage is necessary, causing increased adaptation to stress, and thus promoting health and longevity. More mitochondria are produced, and levels of the antioxidant enzymes superoxide dismutase and catalase are increased, as well as enzymes that produce the endogenous antioxidant glutathione.

Other longevity-enhancing agents work much the same way. The phytochemicals in fruits and vegetables, and in substances like resveratrol and curcumin, are perceived by the body as toxins, i.e. they place a stress from which the body acts to defend itself. This is even the case with frankly poisonous substances, like arsenite. In effect, what doesn’t kill the body makes it stronger. As Nietzsche called this aphorism, it’s the military school of life.

Antioxidants can abolish the health-promoting effects of exercise. The reason that they do this – or possibly could do this, research is ongoing – is because they abolish the cellular signals, ROS, that indicate that a stress is being placed on the body. No stress, no adaptation.

Radiation can also promote health in the same way, by placing stresses on cells, which then essentially fight back.

Psychological stresses can be healthy as well, such as missing half a night’s sleep. And for the brain, all of stresses mentioned above work on it also, increasing levels of brain-derived neurotrophic factor, and causing the
growth of new neurons.

What happens when not enough stress is placed on the body? Diabetes, for one. Or by constantly feeding your body everything it wants, and never depriving it, obesity. It’s the couch-potato lifestyle, the body always in a non-stressed mode. Plenty of health-promoting agents are non-stressful, like food, sleep, and sex, for instance. (Maybe there’s something to the denial of sex in asceticism that really does promote health. The use of pornography definitely does not.)

But, if you deprive yourself of stresses like those discussed above, you will not be healthy, nor are you likely to live long. Hardening and denying yourself, not always giving in to the demands of your psyche for comfort, a certain degree of asceticism, are essential.

Hormesis for health

Plant containing noxious dietary phytochemicals.

In the last post I wrote about the process of hormesis for health and how it relates to exercise. As noted in that post, hormesis describes a process that has wide application, namely the placing of a stress on a biological system that results in that system becoming stronger, as it increases processes for
coping with stress.

In a new review paper, Mark Mattson, who has done a large amount of work on the cell biology associated with calorie restriction and intermittent fasting, discusses how hormesis can radically improve health: Challenging Oneself Intermittently to Improve Health. Mattson also practices what he preaches; see here.

Mattson concentrates on three forms of hormesis: intermittent fasting, exercise, and “noxious dietary phytochemicals”.

Our ancestors and hormesis for health

Our human ancestors lived and survived in ages when food may have often been hard to come by, when exercise in the form of walking, hunting, building, gathering, and so on were daily required activities, and in which they ate plants that contained toxins. It stands to reason that we’re adapted to these conditions, and any deviation from them is potentially injurious to health.

We now live in an age of, we might call it, anti-hormesis. Exercise is no longer a requirement, food is available whenever we want it, and a junk food diet excluding dietary phytochemicals is the norm for many. As a result, we have the obesity epidemic, rampant diabetes and heart disease, and all the rest.

In his paper, Mattson describes the biological mechanisms that strengthen the organism upon being exposed to these hormetic stresses. Intermittent fasting protects against obesity, diabetes, cancers, neurodegenerative diseases, and can extend life in experimental animals by 30%. Exercise does much the same, and also improves neural connections and number; those who exercise regularly can literally expand their brains, and presumably their cognitive capacity, i.e. intelligence.

The third category is dietary phytochemicals, which Mattson specifically labels “noxious”. This fact appears to be little appreciated even among scientists, who continue to mislabel these chemicals as antioxidants. The fact is, plants do not want to be eaten, and they have developed an array of chemical weaponry that discourages animals from eating them. Specifically mentioned as potent hormetic phytochemicals are sulforaphane (from broccoli and other cruciferous vegetables), curcumin (from turmeric), resveratrol (red wine), and epicatechin (tea and chocolate). All of these elicit potent responses from the cells of the animal that ingests them, including upregulating antioxidant defenses, phase 2 enzymes, and other processes that increase health and extend life.

In the last part of the paper, Mattson decries the routine use of drugs to treat metabolic diseases, when diet, fasting, and exercise are far more appropriate, safe, and cheap. Unfortunately, in my opinion, the use of these natural treatment modalities will always be the choice of a minority, for the simple reasons that they require, willpower, effort, and may be uncomfortable, all things that go directly against the spirit of the age.
Fitness does not equal health

Dose-response curve of hormesis.

Damaging your body through excessive exercise

I was inspired to write this on seeing a recent video (which I can’t find at the moment) of a couple of female runners crossing the finish line of the Bay to Breakers race, a 7.5 mile course. The runners literally couldn’t hold themselves upright, and crawled across the finish line, cheered on by the spectators. They were clearly damaging themselves by their excessive, for them, running.

Exercise is a form of hormesis

Exercise is a form of hormesis, which is a form of stress placed on a biological system – the body as a whole, or cells, or an organ – that results in the upregulation of stress response systems. This can include better mitochondrial function and increased numbers of mitochondria, increased antioxidant defenses, and higher levels of so-called phase 2 enzymes, which defend against toxic insults. The idea is that a small stress results in
health as the organism grows stronger in order to be able to withstand these stresses.

Hormesis is the basis on which any number of inputs causes better health. It might not be going too far to say that hormesis is the very basis of health, in that any input that causes better health, inputs such as exercise, fruits and vegetables, cold showers, intermittent fasting and calorie restriction, ionizing radiation from the sun, all of these work by producing a stress, hence they work by hormesis. (It might interest you to know that fruits and vegetables are health-giving precisely because they contain small amounts of toxic phytochemicals, from which the body must defend itself, broccoli being a prime example.) The opposite of producing hormetic stress can be seen in the couch potato lifestyle that leads to obesity, diabetes, heart disease; failure to subject the body to the right amount of stress produces ill health.

**Stresses can be too high**

However, hormesis exists on a continuum, as illustrated in the figure above. Points 1 and 2 we might call the couch potato zone, in which there is little or no exercise, fruits and vegetables in the diet, or other stressors. Points 4 through 7 are in the hormetic zone, with the area between 5 and 6 producing the optimal hormetic effect. Points 9 and 10 are in the unhealthy area again: too much stress applied, and the organism becomes broken down due to inability to handle so much stress. Finding the optimal point of hormesis for any given stress can be difficult, but in such areas as exercise or diet, paying attention to how these make one feel can go a long way toward determining that point.

Can we pinpoint any inputs that clearly cross over into the unhealthy zone? Take a well-known toxic compound like methylmercury. It doesn’t take much for this compound to poison living things, but even here, small doses can be hormetic: see Enhanced reproduction in mallards fed a low level of methylmercury: An apparent case of hormesis. What about exercise? To my mind, a clear case of going beyond what is healthy, of applying more stress than the body can handle, and that results in damage, sometimes permanent, is marathon running. This takes a good thing, exercise, and by overdoing it, it becomes toxic.

**Distance running is associated with heart damage**

In young men, a high frequency of vigorous exercise, specifically running, was associated with an increased risk of atrial fibrillation. Clearly they were overdoing it. Another study found that the rate of atrial fibrillation in practitioners of long-term endurance sports was about four times the rate of sedentary controls. A long-distance run of 21 km produces biomarkers of cardiac damage in young men. And “ostensibly healthy marathon runners” have a much higher rate of myocardial damage than controls.

This is not even to mention the joint injuries caused by distance running. Runners also often overtax themselves so as to run down their immune systems, with more colds and flu as a result. This could even increase the risk of
cancer. World champion marathon runner Grete Waitz died of it at age 57. Of course this is an anecdote, but it does seem possible to say that marathon running did not make her healthier, and in my opinion it may have hastened her demise. Overtraining, which almost by definition is what an elite marathoner does, is associated with increased incidence of upper respiratory tract infections and overall lower immune function. Hence cancer could be a result of prolonged overtraining.

**Hormetic stress must remain in the zone of health**

Many people apparently think that fitness equals health, that the more you exercise, the healthier you are. But clearly it’s possible to overdo it, and many people are. The body needs rest and recovery as well as stress, and the stress applied must not be too great, or it tips the body into a state of ill health. If you exercise a lot, and constantly feel tired, or develop colds more often than seems normal, that could be a sign that you need less exercise and more rest. (It could be a sign of other things too, such as poor nutrition.) It’s difficult to say how much is too much, but daily strenuous exercise, especially running, may cross that line. What doesn’t kill you may not always make you stronger, but weaker.

(Illustration taken from Inflammatory modulation of exercise salience: using hormesis to return to a healthy lifestyle.)

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**Activate the stress response for health and long life**

**A pesticide extends lifespan in C. elegans**

In a recent study, researchers screened for a number of chemicals that might extend lifespan in C. elegans, the tiny worm that is often used in aging research. They found one, a pesticide: Extension of Lifespan in C. elegans by Naphthoquinones That Act through Stress Hormesis Mechanisms

Hormesis occurs when a low level stress elicits adaptive beneficial responses that protect against subsequent exposure to severe stress. Recent findings suggest that mild oxidative and thermal stress can extend lifespan by hormetic mechanisms. Here we show that the botanical pesticide plumbagin, while toxic to C. elegans nematodes at high doses, extends lifespan at low doses. Because plumbagin is a naphthoquinone that can generate free radicals in vivo, we investigated whether it extends lifespan by activating an adaptive cellular stress response pathway. ... Our findings reveal the potential for low doses of naturally occurring naphthoquinones to extend lifespan by engaging a specific adaptive cellular stress
response pathway.

It’s important to note that low doses were used; at higher doses, the pesticide was still toxic. More isn’t better in this case.

**Stress response mechanisms are the key to health and long life**

The stress response mechanism in this case, and many others, is known as hormesis, which is characterized by a U-shaped curve: beneficial effects starting at low doses, but the effects becoming harmful at higher doses. In other words, low doses of some substance that we normally think of as toxic can be actually beneficial. This has even been shown with such classic poisons as mercury (*Hormesis associated with a low dose of methylmercury injected into mallard eggs*).

Hormetic effects have been found in a wide range of substances and practices, but the key point is that they all activate cellular stress response mechanisms. One of the main mechanisms at work is Nrf2, which activates over 200 genes. These genes in turn are anti-inflammatory, antioxidant, and stimulate of mitochondrial biogenesis.

It’s thought that the level of activation of Nrf2 plays perhaps the key role in differences in longevity between species.

**Longevity promoting effects are due to activation of stress response**

Many substances and actions have been found to activate the stress response. Calorie restriction and intermittent fasting, exercise, broccoli and curcumin, other fruits and vegetables, chocolate, and many other phytochemicals. Restricting glucose extends lifespan (in C. elegans) as well.

Furthermore, type 2 diabetes may come about due to a lack of hormesis. Since diabetes is a kind of archetype of aging and the ill health associated with obesity and modern life, it’s not too far-fetched to say that the stress response due to hormesis is necessary for health and long life.

**Daily doses of good stress for health**

One must stress the body to remain in good health. Being a couch potato and eating to excess will send one’s health on a downward spiral. In contrast, exercise, intermittent fasting, eating a variety of fruits and vegetables, an occasional glass of red wine, some supplements such as resveratrol and curcumin, restricting sugar and refined carbs in the diet, will all cause an increase in the cellular stress response and lead to better health and, hopefully, longer life.
Resistance to type 2 diabetes mellitus: a matter of hormesis?

Type 2 diabetes mellitus is characterized by subclinical systemic inflammation and impaired regulation of blood glucose levels. Interestingly, impairment of glycemic control occurs despite substantial insulin secretion early in the course of this disease. Dysfunction of several organs (including pancreatic islets, liver, skeletal muscle, adipose tissue, gut, hypothalamus and the immune system) has been implicated in the pathogenesis of type 2 diabetes mellitus. However, diabetes-promoting lifestyle factors do not inevitably cause disease in all persons exposed. Hence, defense mechanisms must exist that can keep the detrimental influence of these risk factors at bay. Hormesis describes the phenomenon that exposure to a mild stressor confers resistance to subsequent, otherwise harmful, conditions of increased stress. This Review discusses the emerging concept that the effectiveness of an adaptive (hormetic) response to detrimental lifestyle factors determines the extent of protection from progression to type 2 diabetes mellitus. Further analysis of these protective hormetic responses at the molecular level should help to identify novel targets for preventive or therapeutic intervention in patients at risk of developing type 2 diabetes mellitus or those with overt disease.

Glucose restriction and life extension

Glucose restriction extends Caenorhabditis elegans life span by inducing mitochondrial respiration and increasing oxidative stress.


Abstract Increasing cellular glucose uptake is a fundamental concept in treatment of type 2 diabetes, whereas nutritive calorie restriction increases life expectancy. We show here that increased glucose
availability decreases Caenorhabditis elegans life span, while impaired glucose metabolism extends life expectancy by inducing mitochondrial respiration. The histone deacetylase Sir2.1 is found here to be dispensable for this phenotype, whereas disruption of aak-2, a homolog of AMP-dependent kinase (AMPK), abolishes extension of life span due to impaired glycolysis. Reduced glucose availability promotes formation of reactive oxygen species (ROS), induces catalase activity, and increases oxidative stress resistance and survival rates, altogether providing direct evidence for a hitherto hypothetical concept named mitochondrial hormesis or “mitohormesis.” Accordingly, treatment of nematodes with different antioxidants and vitamins prevents extension of life span. In summary, these data indicate that glucose restriction promotes mitochondrial metabolism, causing increased ROS formation and cumulating in hormetic extension of life span, questioning current treatments of type 2 diabetes as well as the widespread use of antioxidant supplements.

New paper by Ristow group on mitochondrial hormesis

Mitochondrial hormesis links low-dose arsenite exposure to lifespan extension.


Abstract
Arsenite is one of the most toxic chemical substances known and is assumed to exert detrimental effects on viability even at lowest concentrations. By contrast and unlike higher concentrations, we here find that exposure to low-dose arsenite promotes growth of cultured mammalian cells. In the nematode C. elegans, low-dose arsenite promotes resistance against thermal and chemical stressors and extends lifespan of this metazoan, whereas higher concentrations reduce longevity. While arsenite causes a transient increase in reactive oxygen species (ROS) levels in C. elegans, co-exposure to ROS scavengers prevents the lifespan-extending capabilities of arsenite, indicating that transiently increased ROS
levels act as transducers of arsenite effects on lifespan, a process known as mitohormesis. This requires two transcription factors, namely DAF-16 and SKN-1, which employ the metallothionein MTL-2 as well as the mitochondrial transporter TIN-9.1 to extend lifespan. **Taken together, low-dose arsenite extends lifespan, providing evidence for nonlinear dose-response characteristics of toxin-mediated stress resistance and longevity in a multicellular organism.**

Mithridates was on to something.

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**Cancer mortality and elevation**
Cancer mortality, state mean elevations, and other selected predictors.

This ecological inquiry compares cancer mortality rates in the U.S. to the predictor of natural background radiation (via land elevation means) along with eight other predictors thought to be associated with cancer mortality. Age-adjusted cancer mortality in 2006 was compared to the predictors of mean land elevation, percent of smokers, educational attainment, percent of population without health insurance, income, obesity, health perception, physical activity, and diet. Among the six predictors considered appropriate for multiple linear regression, three were found to be statistically significant; from strongest to weakest, these three were: smoking, land elevation, and educational attainment. The predictors of smoking and educational attainment have long been considered associated with cancer mortality. The finding that the predictor of land elevation / natural background radiation is inversely related to cancer mortality is another piece of evidence supporting the theory of radiation hormesis. In this study, land elevation / natural background radiation ranked second in predictive strength regarding cancer mortality, behind smoking and ahead of educational attainment. Since this is an ecological inquiry, no causal inferences can be made.
Small γ-Ray Doses Prevent Rather than Increase Lung Tumors in Mice.

We show evidence for low doses of γ rays preventing spontaneous hyperplastic foci and adenomas in the lungs of mice, presumably via activating natural anticancer defenses. The evidence partly relates to a new study we conducted whereby a small number of female A/J mice received 6 biweekly dose fractions (100 mGy per fraction) of γ rays to the total body which prevented the occurrence of spontaneous hyperplastic foci in the lung. We also analyzed data from a much earlier Oak Ridge National Laboratory study involving more than 10,000 female RFMf/Un mice whereby single γ-ray doses from 100 to 1,000 mGy prevented spontaneous lung adenomas. We point out the possibility that the decrease in lung cancer mortality observed in The National Lung Screening Trial Research Team study involving lung tumor screening using low-dose computed tomography (CT) may relate at least in part to low-dose X-rays activating the body’s natural anticancer defenses (i.e., radiation hormesis). This possibility was apparently not recognized by the indicated research team.

Evidence supporting radiation hormesis in atomic bomb survivor cancer mortality data

A recent update on the atomic bomb survivor cancer mortality data has concluded that excess relative risk (ERR) for solid cancers increases linearly with dose and that zero dose is the best estimate for the threshold, apparently validating the present use of the linear no threshold (LNT) model for estimating the cancer risk from low dose radiation. A major flaw in the standard ERR formalism for estimating cancer risk from radiation (and other carcinogens) is that it ignores the potential for a large systematic bias in the measured baseline cancer mortality rate,
which can have a major effect on the ERR values. Cancer rates are highly variable from year to year and between adjacent regions and so the likelihood of such a bias is high. Calculations show that a correction for such a bias can lower the ERRs in the atomic bomb survivor data to negative values for intermediate doses. This is consistent with the phenomenon of radiation hormesis, providing a rational explanation for the decreased risk of cancer observed at intermediate doses for which there is no explanation based on the LNT model. The recent atomic bomb survivor data provides additional evidence for radiation hormesis in humans.

Superoxide and Longevity

A Mitochondrial Superoxide Signal Triggers Increased Longevity in Caenorhabditis elegans

Author Summary Top

An unequivocal demonstration that mitochondria are important for lifespan comes from studies with the nematode Caenorhabditis elegans. Mutations in mitochondrial proteins such as ISP-1 and NUO-6, which function directly in mitochondrial electron transport, lead to a dramatic increase in the lifespan of this organism. One theory proposes that toxicity of mitochondrial reactive oxygen species (ROS) is the cause of aging and predicts that the generation of the ROS superoxide should be low in these mutants. Here we have measured superoxide generation in these mutants and found that it is in fact elevated, rather than reduced. Furthermore, we found that this elevation is necessary and sufficient for longevity, as it is abolished by antioxidants and induced by mild treatment with oxidants. This suggests that superoxide can act as a signal triggering cellular changes that attenuate the effects of aging. This idea suggests a new model for the well-documented correlation between ROS and the aged phenotype. We propose that a gradual increase of molecular damage during aging triggers a concurrent, gradually intensifying, protective superoxide response.

This strikes me as pretty earth-shaking in the world of aging research, since the former putative cause of aging, namely oxygen radicals, are seen in this experiment as inducing longevity rather than aging. The free radical theory of aging looks defeated.

This also makes sense of some phenomena such as hormesis as well as the fact
that antioxidant supplements seem to promote aging. Exercise also fits into this scenario, since it increases generation of reactive oxygen species yet promotes longevity (or retards aging, however you want to look at it).

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**Resistance to type 2 diabetes mellitus: a matter of hormesis?**

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Abstract  
Type 2 diabetes mellitus is characterized by subclinical systemic inflammation and impaired regulation of blood glucose levels. Interestingly, impairment of glycemic control occurs despite substantial insulin secretion early in the course of this disease. Dysfunction of several organs (including pancreatic islets, liver, skeletal muscle, adipose tissue, gut, hypothalamus and the immune system) has been implicated in the pathogenesis of type 2 diabetes mellitus. However, diabetes-promoting lifestyle factors do not inevitably cause disease in all persons exposed. Hence, defense mechanisms must exist that can keep the detrimental influence of these risk factors at bay. Hormesis describes the phenomenon that exposure to a mild stressor confers resistance to subsequent, otherwise harmful, conditions of increased stress. This Review discusses the emerging concept that the effectiveness of an adaptive (hormetic) response to detrimental lifestyle factors determines the extent of protection from progression to type 2 diabetes mellitus. Further analysis of these protective hormetic responses at the molecular level should help to identify novel targets for preventive or therapeutic intervention in patients at risk of developing type 2 diabetes mellitus or those with overt disease.
Stress tolerance and lifespan are correlated

*Caenorhabditis elegans*

Certain manipulations of organisms will reliably extend their lifespans, manipulations such as calorie restriction or the genetic reduction of insulin and IGF-1 (insulin-like growth factor) signalling. But what is the physiological mechanism behind the extension of longevity? In the following study, the researchers wanted to know whether the upregulation of cytoprotective pathways, which occurs in calorie restriction and impaired insulin/IGF-1 signaling, merely accompanied the extension of longevity or was necessary to it. They devised an ingenious way to test this.

**Induction of Cytoprotective Pathways Is Central to the Extension of Lifespan Conferred by Multiple Longevity Pathways**

Many mutations that increase animal lifespan also confer stress tolerance, suggesting that cytoprotective mechanisms underpin the regulation of longevity. It has not been established, however, whether the induction of individual cytoprotective pathways is essential for lifespan extension, or merely correlated. To establish whether the regulatory pathways for the induction of cytoprotective responses are key in the extension of lifespan, we performed an RNAi screen for gene inactivations that decouple the activation of cytoprotective pathways from xenobiotic stimuli that normally induce them. The screen identified 29 genes that constitute the regulatory cascades of the unfolded protein response, oxidative stress response, and detoxification. These upstream regulatory genes are critical to stress tolerance and the extension of lifespan conferred by decreased insulin/IGF-1 signaling, disruption of mitochondrial function, or caloric restriction, but have little effect on normal longevity.
So the answer is that when these cell defense responses were disrupted, the extension of longevity normally seen in calorie restriction and the rest did not occur, meaning that these responses are essential to increased lifespan.

From the discussion section:

Stress tolerance and lifespan extension are remarkably correlated. The contradictory extension of lifespan by ostensibly deleterious conditions, and the concomitant induction of stress tolerance, suggests that lifespan extension may occur through the hormetic induction of damage-buffering cytoprotective mechanisms. [...] 

Lifespan poses an evolutionary conundrum, as the genetic determination of lifespan ostensibly suggests post-reproductive selection. Our data suggests that lifespan-determining genes do not specify lifespan per se, but rather the activity of damage-buffering cytoprotective pathways normally engaged only in response to stress stimuli, such as toxins.

Once again, it’s hormesis for the win. These stress responses are activated in the face of potentially damaging stimuli, such as exercise, toxins, fasting, and solar radiation. If one wants the chance to live a longer life, activation of these responses on a regular basis is the way to go.