Citrulline Treats Erectile Dysfunction, Fights Aging and Obesity

Citrulline treats erectile dysfunction and increases virility. It also functions as a potent ergogenic aid during exercise.

Citrulline is a cheap, safe, over-the-counter, amino acid.

Citrulline treats erectile dysfunction

Oral L-citrulline supplementation improves erection hardness in men with mild erectile dysfunction.

In this study, 24 men, average age 56, with mild erectile dysfunction, took either 1.5 grams of citrulline, an amino acid, or placebo, for one month. As it was a cross-over study, all the men took part in both placebo and citrulline segments. In the treatment arm, 50% of the men reported an improvement in erectile function, compared to 8% of the men in the placebo arm. Frequency of intercourse rose from 1.3 per month at baseline to 2.3 at the end of the treatment phase. The authors conclude:

Although less effective than phosphodiesterase type-5 enzyme inhibitors [such as Viagra], at least in the short term, L-citrulline supplementation has been proved to be safe and psychologically well accepted by patients. Its role as an alternative treatment for mild to moderate ED, particularly in patients with a psychologically fear of phosphodiesterase type-5 enzyme inhibitors, deserves further research.

Citrulline appears safe. It works by increasing levels of arginine, which it
does more efficiently than does arginine supplementation itself, and this in turn increases levels of nitric oxide, which is the principal factor increasing penile blood circulation. Arginine is a potential exercise ergogenic, with some research suggesting that it increases levels of growth hormone, so it seems that citrulline may do the same.

Citrulline increases exercise capacity

A study done on mice found that citrulline increased exercise time to exhaustion.

Much more impressively, in humans, the ingestion of citrulline resulted in greatly decreased sensations of fatigue, and a 34% increase in the production of aerobic energy through ATP.

Also, in a study in which 41 men were the subjects, citrulline dramatically increased the number of reps the men could do on the last set, and also substantially decreased post-exercise muscle soreness.

L-citrulline decreases mortality and fat mass, increases muscle mass, in rats

A recent study found that Citrulline Supplementation Induces Changes in Body Composition and Limits Age-Related Metabolic Changes in Healthy Male Rats. Aged male rats were supplemented with citrulline at 0.1% of their diet (1 gram per kg food). Over a 12-week period, the supplemented rats had zero mortality, compared to a death rate of 20% of the controls. They also had 9% greater lean mass, 13% lower fat mass, and oxidative stress was much lower.

There appears to be no reason that this writer can see why these results wouldn’t apply equally well to humans. At 0.1% of the diet as citrulline, one 750 mg capsule a day might just do it, which isn’t much to change body comp for the better. Note that these were already healthy animals, so the citrulline was not correcting some defect; therefore it could increase lean mass even if you’re already doing everything right.

The question I have from this study is whether citrulline’s effects on erectile function work acutely, that is, after one dose, or does it need to be taken continually. My guess here is that it would indeed work acutely. Indeed, in exercise studies such as the above cited one, citrulline worked immediately after ingestion, which suggests that for both purposes (erectile dysfunction and ergogenic enhancement), daily doses are unnecessary, the supplement needing only to be taken immediately before the desired effect, whether exercise or sex.

L-citrulline is available at Amazon.
Carbohydrate restriction may increase lifespan

Staff of life? Not really.

Carbohydrates are essentially just long chains of glucose molecules strung together. Glucose is a sugar, which requires insulin in order to be taken up by cells. When carbohydrates are metabolized (digested), the effect on the body is virtually the same as if one had eaten the same amount of sugar. The type of carbohydrate can make somewhat of a difference; fast-digesting carbohydrates, like those in white bread, pasta, or white potatoes, can cause a large enough glucose spike that is almost indistinguishable from eating the same amount of sugar; slower digesting carbs, such as in vegetables, not so much.

Glucose restriction extends lifespan in *C. elegans*

It’s been found that in the model organism *C. elegans* (a tiny worm frequently used in aging studies), restricting glucose from their diet results in longer life: [Glucose Restriction Extends *Caenorhabditis elegans* Life Span by](#)
Inducing Mitochondrial Respiration and Increasing Oxidative Stress.

The fact that glucose restriction induces oxidative stress appears to be key here, since that makes glucose restriction a form of hormesis, which the authors dub “mitohormesis”, since it acts upon the mitochondria. As a form of hormesis, glucose restriction induces antioxidant enzymes such as catalase, and causes an upregulation of cellular stress defense mechanisms.

Antioxidants abolish lifespan extension

Importantly, treatment of these worms with antioxidants abolished life extension, which shows that the increased oxidative stress is necessary to for increased longevity. Glucose restriction also caused an increase in fat burning. Also importantly, disruption of the worm equivalent of AMPK abolished lifespan extension by glucose restriction, showing that activation of AMPK is necessary. As we recently saw, activation of AMPK alone, by whatever means, be they chemical compounds, drugs, exercise, or fasting, increases lifespan, since AMPK controls the aging process.

Addition of glucose shortens lifespan

Next, we see that the addition of glucose to the food of C. elegans does just what we would expect: it shortens lifespan. The authors refer to glucose in this regard as “a potent lifespan-shortening agent”.

Low-carb diets, antioxidants, and longer life

A co-author of this second study was Cynthia Kenyon, one of the most renowned aging researchers, who now works for Google in their start-up anti-aging company, Calico. When Kenyon made this discovery about glucose and lifespan, she gave up refined carbohydrates, and eats a diet that looks very much like paleo. I think the rest of us can take a lesson from this.

The fact that antioxidants abolished the effect of glucose restriction on lifespan means, in my opinion, that one should be careful about supplementing with them. On an intermittent fast, for instance, one shouldn’t take them, and if extra vitamin C is desired (which I take myself), it should be in rather small amounts, say 500 mg, and taken in the fed state and away from workouts.

Probably the biggest caveat here is that these studies were done in nematodes (worms), and to my knowledge it has not been repeated in mammals. However, glucose does increase insulin/IGF-1 signaling, and it is known that decreased insulin/IGF-1 signaling increases lifespan, so to me that’s a fairly compelling reason to think that these results are applicable to mammals.
Activating AMPK for lifespan extension

AMPK senses the energy status of cells

AMPK is a highly evolutionarily conserved energy sensor. By evolutionarily conserved is meant that essentially all living organisms, including of course humans, have it. Increased AMPK activation is associated with longer lifespan and better health; AMPK causes a signaling cascade that promotes fat oxidation, increases cellular stress defenses and autophagy, and decreases inflammation.

Some scientists go so far as to say that AMPK controls aging: AMP-activated protein kinase (AMPK) controls the aging process via an integrated signaling network.

Efficient control of energy metabolic homeostasis, enhanced stress resistance, and qualified cellular housekeeping are the hallmarks of improved healthspan and extended lifespan. AMPK signaling is involved in the regulation of all these characteristics via an integrated signaling network. Many studies with lower organisms have revealed that increased AMPK activity can extend the lifespan. Experiments in mammals have demonstrated that AMPK controls autophagy through mTOR and ULK1 signaling which augment the quality of cellular housekeeping. Moreover, AMPK-induced stimulation of FoxO/DAF-16, Nrf2/SKN-1, and SIRT1 signaling pathways improves cellular stress resistance. Furthermore, inhibition of NF-κB signaling by AMPK suppresses inflammatory responses. Emerging studies indicate that the responsiveness of AMPK signaling clearly declines with aging. The loss of sensitivity of AMPK activation to cellular stress impairs metabolic regulation, increases oxidative stress and reduces autophagic clearance. These age-related changes activate innate immunity defence, triggering a low-grade
inflammation and metabolic disorders. We will review in detail the signaling pathways of this integrated network through which AMPK controls energy metabolism, autophagic degradation and stress resistance and ultimately the aging process.

The image below shows what can activate AMPK and in turn the effects of activation and inactivation of AMPK.

Activation of AMPK is crucial for health and long life. The question is, how do you activate it? Following are a number of ways.

**Activating AMPK for lifespan extension – how to do it**

1. **Curcumin**: In a head-to-head comparison with metformin, the most widely prescribed anti-diabetes drug and an AMPK activator, “curcuminoids increased the phosphorylation of AMP-activated protein kinase (AMPK) and its downstream target acetyl-CoA carboxylase (ACC) in H4IIE and Hep3B cells with 400 times (curcumin) to 100,000 times (THC) the potency of metformin.”

2. **Aspirin**: Aspirin is a known life-extender, and it is no coincidence that it activates AMPK. “At concentrations corresponding to plasma concentrations in humans treated with high doses of aspirin or salsalate, salicylate
activated wild-type AMPK... There have been numerous observational studies suggesting that metabolic parameters improved in diabetic patients who were taking salicylate-based drugs.”

3. **Fasting and exercise**: “...AMPK acts as the primordial trigger for fasting- and exercise-induced adaptations in skeletal muscle and that activation of SIRT1 and its downstream signaling pathways are improperly triggered in AMPK-deficient states.”

4. **Resveratrol**: “Resveratrol induces mitochondrial biogenesis and protects against metabolic decline... Mice treated with a moderate dose of resveratrol showed increased mitochondrial biogenesis and function, AMPK activation, and increased NAD+ levels in skeletal muscle, whereas SIRT1 knockouts displayed none of these benefits.”

5. **Tea and chocolate polyphenols**: “... we found that mice administered Mitochondria Activation Factor (MAF) combined with exercise training could run longer distances and for a longer time compared with the exercise only group; MAF is a high-molecular-weight polyphenol purified from black tea. Furthermore, MAF intake combined with exercise training increased phosphorylation of AMPK and mRNA level of glucose transporter 4 (GLUT4).”

The common mechanism that ties together a number of processes (fasting and exercise) and chemical compounds (the rest) is the activation of the energy sensor AMPK.

**PS: Check out my books, Dumping Iron, Muscle Up, and Stop the Clock.**

**PPS: You can support this site by purchasing through my Supplements Buying Guide for Men.**

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**Light exposure, obesity, and health**
Humans exhibit a strong circadian rhythm in many physiological processes, with certain of these processes more strongly at work during daytime hours rather than night, and for others, vice versa. Most obviously, we sleep at night, and at that time melatonin production increases and the metabolic rate decreases, reversing polarities during the day. If this rhythm becomes dysfunctional, health can suffer, as can lean body weight. Working graveyard shifts is associated with a substantially increased rate of cancer and heart disease.

I wrote about using light as one step of many in overcoming chronic fatigue.

The topic of circadian rhythms and health is sufficiently huge that we’ll just focus on a couple of aspects here: obesity and mental health.

Obesity

A number of studies have looked at the relation between obesity and light exposure. In mice, disruption of the circadian rhythm through exposure to light leads to obesity. In humans, an association has been found between obesity and the amount of exposure to “light at night”. And a recent paper found that Timing and Intensity of Light Correlate with Body Weight in Adults.

In this study, the researchers used a measure of both intensity of light exposure and its time of day, which they called the MLiT500.

The results of this study demonstrate that the timing of even moderate intensity light exposure is independently associated with BMI. Specifically, having a majority of the average daily light exposure above 500 lux (MLiT500) earlier in the day was associated with a lower BMI. In practical terms, for every hour later of MLiT500 in the day, there was a 1.28 unit increase in BMI. The complete regression model (MLiT500, age, gender, season, activity level, sleep duration and sleep midpoint) accounted for 34.7% of the variance in BMI. Of the variables we explored, MLiT500 contributed the largest portion of the variance (20%).

According to this, the amount and degree of exposure to light explained more of the variance in obesity than did age or even activity level, that is, physical exercise.
Daily light exposure of greater than 500 lux, especially earlier in the day, was important to maintaining a lean body weight. The average indoor room light, the authors explain, is only 100 to 500 lux, so the intensity of exposure needed is that equivalent to outdoors. Outdoor light, even on a cloudy day, can be many times more intense than indoor lighting, a fact that goes unappreciated by many, since our eyes adjust to the amount of light available.

Is the association between light exposure and obesity causal in the direction indicated, or mere association? While that question can’t be definitively answered, it certainly appears causal, and the study references a number of other studies that show how sleep duration and light exposure disrupt glucose metabolism, appetite, and body fat. It’s also been shown how short sleep duration causes disruption in the levels of the hormones leptin and ghrelin, which are responsible for regulating hunger. And as mentioned above, animal studies show that light exposure at the wrong times can cause weight gain. So all this points in the direction of causality. It also seems possible that the amount of light exposure indicated is a mere marker for sleep, since if one sleeps late into the day, then exposure to bright light in the morning will be less. This idea makes sense in that it will also explain the known association between short, poor sleep and obesity.

If you are trying to lose weight, it would seem important to get exposure to bright light early in the day. Getting up early and walking or exercising outside could have real health benefits, especially if you work indoors and won’t get much other exposure during the day. A suggestion from Dr. Daniel Kripke, a psychiatrist who has extensively studied the health effects of sleep, is to eschew the use of sunglasses when driving to work in the morning, which may allow enough marginal bright light exposure to make a difference. (I highly recommend Dr. Kripke’s e-book, free at the link.) In winter, one can use a bright light box; the linked one is rated at 10,000 lux, and I used this version when I was trying to overcome chronic fatigue, at which I was successful. (How much light played a role I’ll never know, although I did shift work most of my adult life.)

Since late sleep and early light exposure are negatively related, and since poor sleep is also associated with obesity, optimizing sleep is important, and here light also plays a role. Exposure to light in the blue end of the spectrum seriously disrupts the production of melatonin, the sleep hormone. Blue light comes predominantly from video and computer monitors, so if you use a computer, including a tablet, at night, you should have the programs f.lux (for PC) or Twilight (for Android) installed; these automatically change the color temperature and intensity of the screen at the appropriate times for your latitude. I’ve had good success with them, my sleep being noticeably improved since I installed them. Blue-blocking glasses also work in this way, but you have to remember to wear them, which I consistently failed at doing, so I like the computer programs better.

Light exposure plays only one role in weight gain, though whether it’s a large or small role seems difficult to say at this point. However, as I emphasized in my book on obesity, we live in what has been characterized as an obesogenic environment, in other words, an environment in which many
factors figuratively conspire to make us overweight. Eliminating the various factors one by one is a good strategy for weight loss, and light exposure, in the appropriate amount and at the right times, and not at the wrong times, is one of those factors that should be fine-tuned.

**Depression**

Sleep and depression are closely related. On the one hand, insomnia is characteristic of depression, but on the other, one night of total or partial sleep deprivation causes instant relief of depression in most patients.

As for light, it’s been found that light therapy is not only effective against depression, but that the effect size is as large as that of antidepressant drugs. Here’s a treatment that the drug companies don’t want you to hear about. In their defense, though, most people would rather pop a pill than make any effort to help themselves, that is, if it takes real effort.

The type and length of light therapies have not been standardized, but typically light therapy is begun first thing in the morning, using a light box of 10,000 lux brightness, duration of one-half to one hour. Even one session has been shown to have effects on depression. Side effects are few; those with a tendency to mania may want to avoid light therapy, as that can be an effect in those so inclined. (We also see the same thing in sleep deprivation therapy.)

For those not clinically depressed, a simple walk in morning sunshine should help keep mood elevated. In sleep deprivation, mood becomes elevated even in those not clinically depressed, so we could hazard a guess that light therapy should do the same.
Organic food is a waste of money and a scam

So-called “organic” food is everywhere now, as the striking success of Whole Foods shows; even major chain supermarkets have organic sections. All the hip people eat organic, and even plenty of not-so-hip people.

But why? Do they know something I don’t know or is it just possible they are the victims of a giant scam? Somehow I’m thinking it’s the latter…

Let’s get one thing out of the way first: “organic”, as science uses the word, means something that is composed mainly of the element carbon, as are virtually all molecules in any living creature. (Exceptions would be minerals such as sodium and potassium.) “Organic”, as Whole Foods and others use it, means free of artificial chemicals such as pesticides or fertilizers.

Organic food and pesticides: does it matter?

The idea behind eating organic food seems to be that pesticide residues in food cause harm to health. The idea makes some sort of sense; after all, pesticides are used to kill pests, so they must be toxic. But there are a few problems with this logic.

One is that conventional food doesn’t have enough pesticide residue to be of concern:

Organic fruits and vegetables can be expected to contain fewer agrochemical residues than conventionally grown alternatives; yet, the significance of this difference is questionable, inasmuch as actual levels of contamination in both types of food are generally well below acceptable limits. Also, some leafy, root, and tuber organic vegetables appear to have lower nitrate content compared with conventional ones, but whether or not dietary nitrate indeed constitutes a threat to human health is a matter of debate. On the other hand, no differences can be identified for environmental contaminants (e.g. cadmium and other heavy metals), which are likely to be present in food from both origins.

The average consumer of organic food would, I suppose, say that they’re going to be extra cautious, just in case. If they want to spend their money paying double the price of regular food, and if Whole Foods is willing to take their money, fine by me.

What makes the case against paying more for organic food more damning is the fact that our natural, human diet is loaded with pesticides, natural ones. All those dietary phytochemicals in fruits and vegetables that are so good for us are composed largely of chemicals made by plants to defend themselves
from predators. It may be surprising for some to learn that plants do not want to be eaten.

Plants make their own pesticides

Animals defend themselves either by fight or by flight. Plants cannot flee, literally rooted to the ground as they are, so they fight using the only means possible: chemical warfare. Coffee plants don’t produce caffeine in order to satisfy human consumers; they do it to poison animals and insects that want to eat them. The sulforaphanes in cruciferous vegetables, the solanine in potatoes, the epicatechins in tea: none of those were put there for our benefit. The difference between an edible and an unedible plant lies merely in our ability to tolerate the toxins of an edible plant.

This was spelled out in a classic paper by Bruce Ames, Dietary pesticides (99.99% all natural) (PDF). The abstract:

The toxicological significance of exposures to synthetic chemicals is examined in the context of exposures to naturally occurring chemicals. We calculate that 99.99% (by weight) of the pesticides in the American diet are chemicals that plants produce to defend themselves. Only 52 natural pesticides have been tested [as of 1990] in high-dose animal cancer tests, and about half (27) are rodent carcinogens; these 27 are shown to be present in many common foods. We conclude that natural and synthetic chemicals are equally likely to be positive in animal cancer tests. We also conclude that at the low doses of most human exposures the comparative hazards of synthetic pesticide residues are insignificant.

Nearly all of the pesticide chemicals that humans are exposed to are natural, produced by the plants themselves, and the fact that there’s little if any difference between natural and synthetic pesticides can be seen in the fact that half of the natural pesticides tested caused cancer in rodents.

Furthermore, the quantity of natural pesticides that humans ingest daily is many orders of magnitude greater than the amount of synthetic pesticides:

Concentrations of natural pesticides in plants are usually measured in parts per thousand or million rather than parts per billion, the usual concentration of synthetic pesticide residues or of water pollutants. We estimate that humans ingest roughly 5000 to 10,000 different natural pesticides and their breakdown products.

The natural pesticides that are known to cause cancer are present in the most common foods ingested too.

...the 27 natural pesticides that are rodent carcinogens are present in the following foods: anise, apple, apricot, banana, basil,
broccoli, brussels sprouts, cabbage, cantaloupe, caraway, carrot, cauliflower, celery, cherries, cinnamon, cloves, cocoa, coffee, collard greens, comfrey herb tea, currants, dill, eggplant, endive, fennel, grapefruit juice, grapes, guava, honey, honeydew melon, horseradish, kale, lentils, lettuce, mango, mushrooms, mustard, nutmeg, orange juice, parsley, parsnip, peach, pear, peas, black pepper, pineapple, plum, potato, radish, raspberries, rosemary, sesame seeds, tarragon, tea, tomato, and turnip. Thus, it is probable that almost every fruit and vegetable in the supermarket contains natural plant pesticides that are rodent carcinogens. The levels of these 27 rodent carcinogens in the above plants are commonly thousands of times higher than the levels of synthetic pesticides.

Science, real actual science, shows that virtually every plant food we eat contains large amounts of natural pesticides, some of which are known to cause cancer in lab animals.

The conclusion must be that organic food is a waste of money, and to the extent that some people and corporations profit from the ignorance of the public, and even feed that ignorance, a scam.

PS: Check out my Supplements Buying Guide for Men.
My blood lipid panel on a low-carbohydrate, paleo diet

Recently I went to the doctor for a checkup, and he ordered a blood lipid panel, which indicates, or is supposed to indicate, heart disease risk.

The levels of various blood lipids are associated with heart disease, but lipids probably don’t cause it, even though mainstream medicine has tried for years to convince us that cholesterol, a required constituent of cells and a steroid hormone precursor abundantly manufactured by the body for its requirements, causes arteries to narrow by accumulating in arterial walls.

By now, most of us know that the absolute level of total cholesterol is not at all a good indicator of heart disease risk. Here’s Dr. Malcolm Kendrick demolishing the cholesterol hypothesis in about one minute. How anyone can believe in the cholesterol hypothesis after watching this is probably not even worth talking to:

A number of studies have overturned the conventional cholesterol wisdom.

For example, the Honolulu Heart Program found that not only was there no association between total cholesterol and heart disease, but that those with the lowest cholesterol levels, in the bottom tertile, had the highest risk of death. “Only the group with low cholesterol concentration at both examinations had a significant association with mortality (risk ratio 1·64, 95% CI 1·13–2·36).” Other studies have found the same. Another study found no association between cholesterol levels and either heart disease or all-cause mortality in persons over 70 years of age. In fact, above age 70, high cholesterol is associated with better health and longer life. And no one has ever found an association between cholesterol levels and heart disease in women. Weird that this evil molecule that binds to arterial walls has no effect in women and is protective after age 70.

Cholesterol also seems to be protective against cancer and infections. For instance, take a look at this chart, which shows World Health organization data, for men, all-cause mortality by cholesterol level. (Borrowed from Zoe Harcombe.) It can be seen that the higher the cholesterol level, the lower the risk of death.
Others have dealt with the cholesterol hypothesis and demolished it, so if you’re not familiar with the arguments, you can read Dr. Uffe Ravnskov or Dr. Malcolm Kendrick or the above-mentioned Zoe Harcombe.

**Triglyceride/HDL ratio, the most important lipid marker**

So, total cholesterol is no indicator at all of heart disease or mortality risk; however, a strong association between lipid levels and heart disease risk has been found in the ratio of triglycerides to HDL cholesterol. In *Fasting Triglycerides, High-Density Lipoprotein, and Risk of Myocardial Infarction*, researchers found that those with the highest triglyceride to HDL ratio, in the top quartile, had 16 times the heart disease risk of those in the lowest quartile. The ratio in the lowest quartile in this study was about 1.3. Other studies have found similar results. These lipids are likely not causal of heart disease either, but are related to insulin resistance and are markers for it; diabetics, who have 2 to 4 times the heart disease risk of non-diabetics, typically have elevated triglyceride levels and low HDL levels.

It’s generally accepted that a ratio of triglycerides to HDL below 2.0 is ideal, with a ratio of 6.0 or above as “much too high”.

Before I get to my numbers, a word about diet. We’ve been told for the last several decades to cut the fat, especially saturated fat, from our diets. But I’ve ignored that, as smart people everywhere are now doing, and I’ve been eating a low-carbohydrate, high fat, paleo-style diet for the past approximately 6 years, a diet that in olden times doctors would have said was going to give me a heart attack. We now know how wrong that is; not only that, but the doctors preferred alternative, the low-fat high-carbohydrate diet, can raise triglycerides, so it may actually increase risk of heart disease. Indeed, higher risk with more carbohydrates has recently been found. Of course, the low-fat diet also contributed to the obesity epidemic.

Here are the numbers from my lipid panel:

Total cholesterol: 241
Triglycerides: 41
LDL: 125
HDL: 92

My ratio of triglycerides to HDL is 0.45, which is an astonishingly low number, with less than 2.0 as ideal. My ratio of total cholesterol to HDL, an older measure of risk still used by many doctors, was 2.6, and according to the American heart Association, the ideal ratio is below 3.5. Allegedly this gives me well under half of the average risk of heart disease.

**Heart disease risk on a low-carb, high fat, paleo diet appears nil**

In light of everything outlined above, it appears that my low-carb high-fat diet has given me an extremely low risk of heart disease, at least judging by lipid numbers. My father developed heart disease at about age 50, and lived with it the rest of his life (although he died at a ripe old age), so knowing that my heart disease risk is low is important to me. You youngsters in the audience may not care as much, since heart disease rates and deaths have been on a steady decline for decades now. But when I was growing up, the risk of dying of a heart attack when we got older was something you thought about a lot if you were the least bit health conscious.

Now for the funny part. My doctor looked at my LDL levels, which, according to my lab work, were barely within optimal range, and told me to go on a low-fat diet. Needless to say, I’ve ignored him and have no intention of changing the way I eat, as that would be positively counterproductive. It’s obvious that my doctor knows little if anything about the studies I’ve outlined in this post, i.e. he’s ignorant, not to put too fine a point on it, and I imagine that one could expect the same knowledge and advice from the average doctor. Fortunately, I have enough knowledge and resources to be able to figure this out on my own, but many people do not, and they are at the mercy of their doctors. It’s possible that some doctors would want to prescribe me statins given my age, sex, cholesterol numbers, and family history of heart disease. That’s the reality of modern medicine.

Oh, another thing. When he examined me, my doctor told me I was in great shape and asked me whether I exercised and in what form. I told him I lifted weights a few times a week, at which he then told me I should do cardio. I don’t have any intention of changing that either.
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.
Muscle, fasting, and health: a rant

Approaches that don’t maximise/preserve your muscle tissue optimally: – Intermittent fasting – Bulletproof Coffee – Carb Backloading Fads.

– Nutrition & Training (@AlexFerentinos7) February 4, 2015
I wanna be stacked and leave a pretty corpse though @Mangan150...however rugby met my face a lot & I really like ice cream. @CaloriesProper

— Nutrition & Training (@AlexFerentinos7) February 4, 2015

Well, at least this fellow Mr. Ferentinos, a former rugby player and now a “nutritional consultant”, doesn’t deny that being in the fed state constantly may be bad for your health and shorten your life.

Furthermore, in what sense is intermittent fasting a “fad”? Paleo eating is an attempt to attain or recover health by eating in a style close to that of our paleolithic ancestors. But just as much attention should be given, in my opinion, to when you eat as to what. Ancestral peoples didn’t awake in the morning to a pot of coffee and a box of donuts, they had to hunt, gather, and then prepare their food. Sure, they may generally have had some leftovers around to munch on in the morning, but given lack of any means of preserving food, mostly they would have to go get it afresh daily. The pattern of eating of hunter-gatherer tribes usually seems to be that of a nearly all day fast, with a huge meal eaten at the end of the day when all was prepared and ready. In any case, long periods without food would likely have been the norm.

Our bodies and the cellular systems that constitute them are not adapted in evolutionary terms to being constantly fed. Our modern system of constant food availability, especially as that has come to be over the past few decades, bears a great deal of responsibility for the epidemic of diabetes and obesity. Our bodies are adapted to make use of stresses, among them the stress of going for periods of time without food, and this is the basis of hormesis.

Mark Mattson, one of the preeminent scientists in the study of aging, advocates a tripartite rule for good health and long life, and these include dietary phytochemicals, exercise, and intermittent fasting, all of which are hormetic.

So you can see that intermittent fasting is not only not a fad, but it conduces to health and life.

But what about Ferentinos’s charge that those items on his list won’t maximize or preserve muscle tissue optimally? What he is implying is that one must be in the fed state almost all the time, or else one loses muscle. But is that true? For one thing, fasting causes an increase in the secretion of growth hormone, likely with the purpose of preserving muscle mass. For another, numerous studies have found that protein timing is much less important than the amount of protein. Sure, you want to be in the fed state when working out – or very shortly thereafter – but this idea of constantly being in the fed state hearkens back to the discredited notion of some bodybuilders that you have to eat six meals a day to optimally gain muscle.

In short, if you fast intermittently, so long as you eat enough protein during the feeding window, muscle preservation and growth should be fine,
more so if you lift weights during that time.

There’s another issue as well, and that is that being in the fed state constantly, as Mr. Ferentinos appears to advocate, abolishes autophagy, which is one leg of the optimal anti-aging strategy. Longer-lived humans and animals have elevated autophagy; genetically modified animals that have been engineered to have elevated autophagy can live up to ten times longer than their non-modified versions. There’s every reason to think that increasing autophagy in humans, whether through fasting, resveratrol, curcumin, exercise, or even drinking water at night, will result in better health and longer life. Being in the fed state all the time could help you look like a rugby player, but will not help you live longer.

Mr. Ferentinos says that he wants to leave a “pretty corpse”, and if that’s his goal, fine by me. But I want my body to both look good and be healthy, and to be on this earth a good while.

You see this kind of argument everywhere. Oh, you have to eat a big, protein-filled breakfast if you don’t want to get fat, for example. You have to eat six meals a day to be a real bodybuilder. Etc. No, you don’t.

End of rant.

Update: Dimitry Klokov, Russian weightlifter, does fasted training.
More muscle, less fat with chocolate and green tea polyphenols

In my latest book, Top Ten Reasons We’re Fat – go ahead and click that link, you know you want it – I discussed the drinking of coffee and tea as possible fat-loss aids. For coffee, most of the link with leanness is association only, that is, leaner people tend to drink more coffee than the overweight. However, with green tea constituents and other polyphenols, an extensive amount of research has shown that they cause fat loss in lab animals, and in humans. Most of the research has focused on EGCG, the major polyphenol constituent of green tea, but it’s also been found that caffeine and theanine have anti-obesity effects as well.

A 2-gram bag of green tea contains about 500 mg of polyphenols, which seems a substantial amount, and if several cups are drunk daily, likely enough to see an effect on fat loss.

A nice review article sums up much of the research. In obesity, accumulation of fat is associated with increased inflammation. The causal arrow of the inflammation and increased fat is somewhat ambiguous. It’s thought that
increased inflammation can lead to insulin resistance and other metabolic problems. On the other hand, fat depots are not the inert storage organs that they were thought to be until recently; it’s now known that they actively secrete various inflammatory cytokines, and increase whole-body levels of inflammation. What seems sure is that obesity and inflammation go together, and that decreasing inflammation could be the key to both fat loss and maintaining a lean body weight.

In cell cultures, green tea polyphenols have the effect of “inhibiting preadipocyte differentiation, decreasing adipocyte proliferation, inducing adipocyte apoptosis, suppressing lipogenesis, and promoting lipolysis and fatty acid beta (β)-oxidation”. So fewer fat cells are made and their proliferation inhibited, fat-burning is promoted, and fat cells encouraged to kill themselves (apoptosis).

Both resveratrol and curcumin also have anti-obesity effects, again in cell culture, animals, and humans, although the results don’t appear to be quite as strong as for green tea polyphenols.

Green tea constituents appear to be quite safe: “We conclude that it is safe for healthy individuals to take green tea polyphenol products in amounts equivalent to the EGCG content in 8–16 cups of green tea once a day or in divided doses twice a day for 4 weeks.”

Green tea has the highest concentration of EGCG: “Compared to black tea and oolong tea, green tea contains the highest amount of green tea catechins [15], the major polyphenols in green tea that constitutes about 35% of its total dry weight [14].” However, as someone who drinks mainly black tea, I should point out that black tea contains theaflavins, which are the fermented products of tea polyphenols, and these are thought to be as equally effective as epicatechins.

Chocolate is another source of polyphenols, including epicatechin, of which it has more than green tea. A neat piece of research was just published showing that epicatechin, found in chocolate, can increase grip strength in humans after only 7 days: Effects of (−)-epicatechin on molecular modulators of skeletal muscle growth and differentiation. In mice (part of the same experiment), epicatechin decreased levels of myostatin significantly and substantially, up to 21%, and increased levels of follistatin, an antagonist to myostatin, by up to 56%. Since myostatin inhibits muscle growth and follistatin promotes it, you can see the potential here for muscle hypertrophy.

In the human part of the study, grip strength increased by about 7% in the subjects, average age 62, and the plasma ratio of follistatin/myostatin increased by ~50%.

The human subjects were given 25 mg pure epicatechin twice a day for 7 days. It looks like a healthy heaping teaspoon of cocoa powder may approach this dose. Chocolate also has far more flavonoids than tea or red wine, about two to four times more.
Basically, adding tea and chocolate to your regimen looks like it could very well promote both fat loss and muscle hypertrophy, the latter combined with a suitable weight-training program of course — although the subjects described above did no exercise at all.

Hat tip to Michael Lustgarten.

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.
Mindset

He who has always spared himself much will in the end become sickly of so much consideration. Praised be what hardens! – Nietzsche

Meet Sonny (Sam Bryant, Jr.), a 70-year old body builder who says he’s never going to stop weightlifting, never going to retire from the sport. Sonny started at age 44, didn’t know a thing about weights, and never looked back. This guy looks damned good, too.

That shows the power of mindset. Most older men could be following the same path as Sonny, feeling and looking fantastic, not to mention the tremendous feeling of accomplishment that you get from working out; but they don’t, preferring to wallow in their creature comforts, watching their bellies grow, their powers wane, feeling depressed, wondering all the while when cancer or a heart attack will catch up with them. That is no way to live.

All around you, you see men wandering through what I would consider a living death. Maybe they don’t consider it that, maybe they’re just comfortable and see nothing wrong with developing a swollen belly. Maybe they’ll get to the point that their blood sugar won’t stay down and then they gladly start shooting the insulin that their doctors eagerly prescribe them.

It doesn’t have to be this way. What I truly don’t understand is the emphasis on luxury, on soft living, which have been recognized from the dawn of time as leading to a downfall, whether social or personal. Putting pressure on yourself, making yourself work hard, and yes, sometimes denying yourself, leads to a much better life, in my humble opinion.

Barring a calamity, I’ll be going to the gym until I no longer can. I’ll be reading, learning, and writing until I no longer can. Those are my particular goals and avocations; for other men, the goals and avocations may be different. But what becomes of a man when he gives up, or gives in? When that
happens, it’s over.

Thanks to Mike Cernovich and Steve Parker for posting this video on Twitter.

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Anxiolytic, Nootropic, and Fat-Burning Theanine

A fairly large amount of research has studied green tea and its components, because they “may contribute to a reduction in the risk of cardiovascular disease and some forms of cancer, as well as to the promotion of oral health and other physiological functions such as anti-hypertensive effect, body weight control, antibacterial and antivirasic activity, solar ultraviolet protection, bone mineral density increase, anti-fibrotic properties, and neuroprotective power”. (Link.) Even if green tea only reduces risks of these diseases by a small amount, it would still be a potent weapon against them precisely because it has such a broad spectrum of action. Much of the health effect of green tea and its extracts comes from a component called EGCG, a polyphenol and one of those “noxious dietary phytochemicals” that induces hormesis and causes an increase in cellular stress defense mechanisms, such as up-regulated antioxidant defenses and phase 2 enzymes, both of which are
cancer-protective. While most of the research in this area has been done with green tea, there’s some evidence that black tea components may have equal power to effect favorable changes in health markers. Black and green tea are both made from the same plant, but the black version undergoes fermentation.

Another component of green tea has profound effects on cognition and memory, that component being the amino acid theanine. Theanine may protect against cognitive dysfunction and prevent oxidative stress related brain aging. Especially in combination with caffeine, theanine improves mood and cognitive function. Theanine extends lifespan in C. elegans.

Green tea components including theanine have a significant anti-obesity effect. Some researchers see green tea and its components as almost an obesity panacea:

Green tea, green tea catechins, and epigallocatechin gallate (EGCG) have been demonstrated in cell culture and animal models of obesity to reduce adipocyte differentiation and proliferation, lipogenesis, fat mass, body weight, fat absorption, plasma levels of triglycerides, free fatty acids, cholesterol, glucose, insulin and leptin, as well as to increase beta-oxidation and thermogenesis. Adipose tissue, liver, intestine, and skeletal muscle are target organs of green tea, mediating its anti-obesity effects. Studies conducted with human subjects report reduced body weight and body fat, as well as increased fat oxidation and thermogenesis and thereby confirm findings in cell culture systems and animal models of obesity.

Looks like if you’re overweight you should start drinking green tea immediately, or perhaps get some green tea extract for a more potent dose. (This particular one contains only 16 mg caffeine, but when taking GTE, one should be cognizant of caffeine content, since adding it on to regular caffeine consumption means its addition could pack a wallop.) Theanine alone significantly reduced body fat in mice, and reduces feeding behavior in rats as well as lowering insulin levels.

A number of studies show that theanine relieves anxiety, including in schizophrenics.

I’ve only cited a handful of studies out of what must be hundreds. But virtually every one that I’ve looked at has confirmed my own experience with it. A dose of 200 mg along with a cup of tea or coffee can put one into the zone of concentration, helping with tasks, such as writing, that require extended focus. Theanine also reduces stress levels noticeably. Since I spend a lot of time writing at a computer, theanine-induced increase in concentration is of real benefit.

See the Recommended Supplements page for a good brand of theanine at only about 22 cents a dose. Bulk theanine is even cheaper, and I’ll be adding that to the supplements page. Or buy theanine at Amazon.
See also Meditation in a Pill.

Fasting and Exercise Increase Brain-Derived Neurotrophic Factor

Brain-derived neurotrophic factor (BDNF) is a protein, one of a number of nerve growth factors. The longstanding dogma that the brain does not make new nerve and brain cells has been dropped; neurons require BDNF for their survival, and it promotes the growth of new ones. Expression of the BDNF gene is decreased in Alzheimer’s and other neurological disorders. Fasting and exercise increase brain-derived neurotrophic factor.

Lower BDNF levels are associated with depression, and antidepressant treatment raises levels, which suggests that changes in brain neuroplasticity are linked to depression and its treatment. It seems to be the case that brain plasticity must be kept at a normal or basal level, and when it is not,
depression could result.

BDNF also appears to be related to memory and cognitive function.

So, BDNF appears to be very important for brain and mental health. It could mean the difference between a healthy old age and dementia. Can we go about raising it, or ensuring that levels remain adequate, and thus prevent cognitive decline or mental illness?

It seems that we can. In rats, calorie restriction (CR) increases both BDNF and the level of neurogenesis. CR does the same in primates.

As we've discussed previously, CR is difficult to maintain and is a hard sell for most people. But intermittent fasting has many or even more of the benefits of CR. Maybe fasting can increase BDNF. From Mark Mattson and co-author:

> Emerging findings suggest that brain-derived neurotrophic factor (BDNF) serves widespread roles in regulating energy homeostasis by controlling patterns of feeding and physical activity, and by modulating glucose metabolism in peripheral tissues. BDNF mediates the beneficial effects of energetic challenges such as vigorous exercise and fasting on cognition, mood, cardiovascular function, and on peripheral metabolism. By stimulating glucose transport and mitochondrial biogenesis BDNF bolsters cellular bioenergetics and protects neurons against injury and disease. By acting in the brain and periphery, BDNF increases insulin sensitivity and parasympathetic tone. Genetic factors, a ‘couch potato’ lifestyle, and chronic stress impair BDNF signaling, and this may contribute to the pathogenesis of metabolic syndrome. Novel BDNF-focused interventions are being developed for obesity, diabetes, and neurological disorders.

Congruent with the above excerpt, BDNF levels are lower in type 2 diabetes, which is the premier example of the couch-potato lifestyle.

Exercise also increases levels of BDNF, in rats, and in humans, and exercise is known to increase the potential for brain plasticity. Exercise also increases brain volume.

Also well worth mentioning is that zinc supplementation decreases depression and increases BDNF at the same time.

So, the couch-potato lifestyle is associated with, or leads to, lower levels of BDNF, as well as metabolic disorders that are in turn associated with lower BDNF. Intermittent fasting and exercise raise levels of BDNF, increase brain volume, protect against stresses and chemical and physiological insults to the brain, and lead to better cognition, and protect against depression and dementia. The lesson here seems to be that being a couch potato diminishes brain function, and being active and not eating all the time protects and even enhances brain function.
And don’t be zinc deficient either.

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**Podcast with Jay Campbell, and a new edition of ‘Smash’**

A little blogging news: first of all, I recorded [another podcast with Jay Campbell of FabFitOver40.com](https://fabfitover40.com). Jay’s a great podcast host, and really keeps the ball rolling. We discussed hormesis, intermittent fasting, and even a bit about Bulletproof Coffee. I think the podcast went really well, thanks in great part to Jay.

The other bit of news is that I published a revised second edition of my book [Smash Chronic Fatigue](https://www.smashchronicfatigue.com). I believe that this book can greatly help anyone who suffers from chronic fatigue, and all modesty aside, probably better than most doctors can do.
Resolving the Resistance Training Paradox

The Resistance Training Paradox: Growth vs Longevity

A few weeks ago I wrote about what I called The Resistance Training Paradox, the paradox consisting of the fact that resistance training (weightlifting) promotes growth, and a necessary trade-off exists between growth and longevity. Exercise, however, is health- and longevity promoting. So how could resistance training both promote growth and aging and be a health-promoting exercise? One or the other must give. This post is about resolving the resistance training paradox.

I believe the answer is that resistance training does not in fact promote aging, and is health- and longevity-promoting. The explanation follows.
The hormone that is mainly responsible for growth, including growth of muscle tissue, is insulin-like growth factor 1, or IGF-1. Growth hormone itself (GH) appears to act by increasing the amount of IGF-1 in circulation.

**IGF-1 promotes aging**

IGF-1 definitely promotes aging. For example, humans who are genetically deficient in growth hormone receptors have “severe GHR and IGF-1 (insulin-like growth factor–1) deficiencies”, and the title of the article from which this quote comes is instructive: Growth Hormone Receptor Deficiency Is Associated with a Major Reduction in Pro-Aging Signaling, Cancer, and Diabetes in Humans. In mice, genetic deficiency of IGF-1 means longer life. A recent review by two stalwarts in anti-aging research, The key role of growth hormone–insulin–IGF-1 signaling in aging and cancer, states, “The life-prolonging effects of caloric restriction are likely related to decreasing IGF-1 levels.” And by the way, there are many, many studies linking IGF-1 to aging and its diseases; no cherry-picking of studies here, I’m not making this up.

So, calorie restriction, a known life-extender, appears to work by decreasing IGF-1 levels. IGF-1 in turn modulates autophagy, i.e. the more IGF-1, the less autophagic activity. We saw in a recent post here that autophagy is critical for the optimal anti-aging strategy.

IGF-1 promotes growth. So does resistance training. However, resistance training does not result in higher IGF-1 levels. In Hormonal Responses and Adaptations to Resistance Exercise and Training, the authors, again experts in this field, state that the IGF-1 response to resistance training is an acute one, and that resting concentrations remain normal. Another paper, Resistance training alters plasma myostatin but not IGF-1 in healthy men, reported on a study of volunteers who underwent 10 weeks of resistance training, and reported that “IGF-1 did not change from pre- to post-training”. Myostatin, however, did decrease substantially, which presumably accounts for muscle growth. Conclusion:

Myostatin may play a role in exercise-induced increases in muscle size, its circulating levels decreasing with resistance training in healthy men. Exercise of the whole body versus the elbow flexors alone did not provide a supplementary stimulus in altering resting plasma IGF-1 or myostatin, or in increasing muscle strength or size. Thus, by default, growth factor responses local to the muscle may be more important than circulating factors in contributing to muscle hypertrophy with resistance training.

Resistance training does not increase circulating levels of IGF-1, except perhaps acutely, within an hour or two after the workout. Therefore resistance training does not promote aging.

But, we’re still left with the growth-longevity trade-off, and there is something peripheral to resistance training that does appear to promote
aging, and that is high protein. I’ll have more to say about this in a future post.

Further reading

The insulin/IGF-1 signaling in mammals and its relevance to human longevity
‘Anti-Aging’ Hormone May Actually Shorten Life
The paradox of the insulin/IGF-1 signaling pathway in longevity.
Protein and amino acid restriction, aging and disease: from yeast to humans
Long-term effects of calorie or protein restriction on serum IGF-1 and IGFBP-3 concentration in humans
Chronic resistance training activates autophagy and reduces apoptosis of muscle cells by modulating IGF-1 and its receptors, Akt/mTOR and Akt/FOXO3a signaling in aged rats
GDF11/Myostatin and aging. This article actually may make a case against resistance training.
Prolonged Fasting Reduces IGF-1/PKA to Promote Hematopoietic-Stem-Cell-Based Regeneration and Reverse Immunosuppression

New Book: Top Ten Reasons We’re Fat
My new e-book has dropped: Top Ten Reasons We’re Fat is available on Amazon in Kindle format. If you don’t have a Kindle, don’t worry, as you can download a Kindle reading app for PC (Windows), Mac, and Android; it’s free and allows you to read Kindle books on any PC, tablet, or phone. The book is specially priced for three days only at $2.99.

Weight loss and diet books are legion, so you may wonder why I decided to write on this topic. For one thing, the crowded field indicates that lots of people are interested in weight loss, and the obesity epidemic indicates that they are justified in being interested.

More importantly, almost every weight-loss book or guru or fitness “expert” tells their readers and followers that they have the secret to weight loss, that if you only follow their (sometimes expensive) instructions, you will become lean with little effort. While some of those books and gurus are on the right track, many are not. What I hope to show in this book is the multifactorial nature of obesity and weight loss. For example, the book contains a chapter on how sleep might affect weight gain and loss, why that is, and a few things you can do to improve sleep and hence weight loss. The idea here is that, while sleep isn’t even close to the whole story on obesity, if you are trying to lose weight, improving your sleep in both quantity and quality is one of the many steps that you should take. It could be the case that many overweight people say to themselves that they’re hungry all the time and they don’t know why, and it might be because, or partly because, of poor quality of sleep or short sleep duration.

Throughout the book I also discuss why the obesity epidemic began when it did, and what needs to happen to stop it.
Is the response to calorie restriction purposeful?

Today's post is a bit different, since so far as I can see no actionable advice can come from it. So you may wish to stop reading here.

Several months back, I wrote a paper on some ideas of mine, hoping to get it published in a refereed scientific journal. For various reasons, that didn’t work out. However, a site that exists in order to publish scientific articles, “an open access online science publishing platform that employs open post-publication peer review”, The Winnower, has allowed me to publish it: Is the response to calorie restriction purposeful? A challenge to life history theory.

The crux of the article is this: calorie restriction (CR) reliably extends lifespan in virtually all animals tested. Yet how it does so is debated. One school of thought holds that, since growth and longevity are negatively related, the mere cessation of growth causes a decrease in aging. If this is the case, then the response to CR is not purposeful, being merely an artefact (we might say) of growth cessation.
However, another school of thought holds that organisms have been shaped by evolution to respond to periods of less food or even outright famine by allocating resources to anti-aging repair, delaying fertility, strengthening antioxidant defenses, and so on. If this is the case, an organism’s response to CR is purposeful.

Life history theory holds that organisms respond to their environments in such a way as to maximize implicit fitness, that is, to have the maximum number of viable offspring. Life history theory would imply that less food in the environment would produce a response leading to a change in life history strategy. And in fact, CR produces changes that look very much like a change in life history strategy, for instance fewer offspring, delayed fertility, greater anti-aging defenses.

Depending on whether the response to calorie restriction is purposeful or not, then either life history theory or the “quasi-program” theory of aging may need to be modified.

This may be a lot of hooey on my part. But the more I thought about it the more I thought that something had to give, so there it is.

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The Optimal Anti-Aging Strategy
Most of us who are into health and fitness also want to know how we can inhibit the aging process, so as to have a healthy old age free of illness, and hopefully live a long time. We’re aware of the usual healthy practices such as clean diet, exercise, a good night’s sleep, limiting the use of alcohol, ensuring we’re well nourished with vitamins, and so on. But we still age. What further measures can we take to slow aging? What’s the optimal anti-aging strategy?

The process I’m going to write about here is not merely an addendum to a healthy diet, exercise, and so on. It is likely as important or more so than those.

The Optimal Anti-Aging Strategy

This strategy is based on the critical knowledge that exceptionally long-lived lab animals, those that have lifespans that are double and more than those of the shorter-lived varieties, have mutations that increase the process of autophagy. Autophagy is the process of cellular “self-eating” that occurs in all animals regularly, and is increased by fasting. In aging, cellular “junk”, such as malfunctioning mitochondria, misfolded proteins, and damaged organelles accumulate, causing the maladies of aging. But this junk accumulates precisely because the organism is unable to initiate and maintain autophagy.

These mutant animals that live twice as long or more than normal animals do eventually die. But the fact that increased autophagy extends their lives shows that it is the most important, the limiting factor in lifespan.

In virtually all organisms tested so far, and there’s no reason to believe that humans are an exception, calorie restriction (CR) extends lifespan, often dramatically. But why does CR do this? In the worm *C. elegans*, autophagy is required for lifespan extension from CR.

Dietary restriction extends life span in diverse species including *Caenorhabditis elegans*. However, the downstream cellular targets regulated by dietary restriction are largely unknown. Autophagy, an evolutionary conserved lysosomal degradation pathway, is induced under starvation conditions and regulates life span in insulin signaling *C. elegans* mutants. We now report that two essential autophagy genes (bec-1 and Ce-atg7) are required for the longevity...
phenotype of the C. elegans dietary restriction mutant (eat-2ad1113) animals. Thus, we propose that autophagy mediates the effect, not only of insulin signaling, but also of dietary restriction on the regulation of C. elegans life span. Since autophagy and longevity control are highly conserved from C. elegans to mammals, a similar role for autophagy in dietary restriction-mediated life span extension may also exist in mammals.

In a review, Autophagy and Aging, the authors state:

Genetic inhibition of autophagy induces degenerative changes in mammalian tissues that resemble those associated with aging, and normal and pathological aging are often associated with a reduced autophagic potential. Pharmacological or genetic manipulations that increase life span in model organisms often stimulate autophagy, and its inhibition compromises the longevity-promoting effects of caloric restriction... Here, we discuss the probable cause and effect relationship between perturbed autophagy and aging, as well as possible molecular mechanisms that may mediate the anti-aging effects of autophagy.

I included excerpts from both of these articles to emphasize how central autophagy is to aging. Many other treatments besides CR that slow aging and extend life, such as lithium and resveratrol, appear to work by enhancing autophagy.

The mitochondrial theory of aging attempts to account for aging by the increased number of damaged, malfunctioning, and free-radical-producing mitochondria. However, under normal, healthy conditions, autophagy removes and recycles these mitochondria, so a more fundamental reason for aging is deranged, that is repressed, autophagy.

Normally, autophagy in humans rises and declines with a strong daily rhythm. Since autophagy is upregulated by fasting (or starvation), it strongly increases at night and in the early morning, since no food is taken during the night. During the day, during the fed state, autophagy proceeds at a low, basal level.

Humans and other organisms exhibit a strong diurnal rhythm of anabolism and catabolism. Both are equally necessary to life and health. With aging, however, that rhythm declines in amplitude. At night, when autophagy should be strongly activated, it is only weakly so or not at all. In the day, when anabolism should be at full speed, aging weakens the process. This is known as anabolic resistance.

Also due to the diurnal or circadian rhythm in autophagy, levels of glutathione, a tripeptide that is the body’s most important antioxidant, rises and falls. The liver, for example, may contain as much as 100% more glutathione during the day as in the early morning.
As a consequence of the age-related decline in autophagy, the amino acids that are necessary for the synthesis of glutathione fall, and not enough glutathione is produced. Since glutathione is an important antioxidant, if cells don’t make enough, free radicals become abundant and a state of oxidative stress ensues, which is a hallmark of aging. Not good. Oxidative stress in turn causes autophagy to decline, so we have a vicious cycle of less autophagy, more oxidative stress, even less autophagy, and so on.

Now, sarcopenia, or muscle wasting, is also characteristic of aging, and anabolic resistance causes it. Maintaining a healthy amount of muscle mass is crucial to healthy aging and longevity. This healthy amount of muscle mass also decreases oxidative stress, since muscle is the main source through which autophagy releases amino acids, and thus synthesizes glutathione.

The key: to avoid aging, one must go through periods of time of a strong breakdown in tissue (autophagy), followed by a rigorous building up again of the same tissue (anabolism). In this way, the body is rejuvenated, since the tissues that are broken down are old, damaged mitochondria, misfolded proteins, and other cellular debris.

By now you’re probably wondering how to do this, and the answer is very simple. Here’s the equation for living a long time: fasting for a time followed by weightlifting + protein = longer life.

**The Second Step: Anabolism**

I’m dead serious about this. If you fast, you increase autophagy, which rids your cells of junk. But you must follow this by anabolism, and the best way to accomplish this, even if you’re old, is by lifting weights and eating enough protein.

Ideally, one wants to take protein around workouts, and whey protein has been shown to give the best anabolism bang for the buck. It causes amino acid levels to rise rapidly in the blood, which ensures maximum anabolism. Whey also has the additional benefit of being rich in cysteine, which is the rate-limiting factor in glutathione synthesis. Thus whey can increase levels of glutathione, and this is especially beneficial in older people. And you thought it was only good for bodybuilders.

Whey can also be taken with benefit by older people in the morning. The cysteine and other amino acids in whey will help replenish glutathione, and so lower oxidative stress. Alternatively, n-acetylcysteine, a source of cysteine, may be beneficial for this, and should be taken with the first meal of the day to ensure that other amino acids are present.

As for fasting, well, we’ve discussed intermittent fasting a lot around here. Fasting is crucial to maintaining a high level of autophagy as we grow older. A 12-hour fast, between dinner and breakfast, will likely suffice for those not too old. An even healthier practice might be a daily feeding window of 8 to 10 hours, and during the rest of the time not eating at all. (Exercise should of course be done during the feeding phase.) Eating late at night – or in the middle of the night – is to be strongly discouraged, as this is when
you want autophagy going full blast.

There are other ways to increase autophagy, such as drinking water at night or in the early morning. And a number of methods exist to overcome anabolic resistance.