The by-now famous experiments that have tied the circulations of young and old animals together, showing the rejuvenating effects of “young blood”, have also shown that the harmful effects of old blood may be greater than the rejuvenating effects of young blood. There’s something about old blood – likely many things – that cause a young animal to show signs of aging; I’ve speculated that two of the more important factors might be iron and bacterial lipopolysaccharides – or possibly the bacteria themselves. Here we’ll discuss the links among young blood, aging, and iron.

Of course, other elements in old blood differ in quantity from those in young blood, and scientists are studying a number of candidates that take the form of proteins, as Josh Mitteldorf discusses in his latest article. (See my review of Josh’s book, Cracking the Aging Code.) One of the proteins under investigation is VCAM-1, for vascular cell adhesion molecule, the level of which increases in old blood.

Exposure of young animals to old blood increases the expression of VCAM-1.

Studies from our lab and others have recently shown that brain function – specifically neurogenesis, synaptic plasticity and cognitive function in the hippocampus, a key center for learning and memory – is inhibited in young mice connected to aged mice through heterochronic parabiosis or aged plasma intravenous injections…. BECs [brain endothelial cells] upregulate expression of vascular adhesion molecules as a result of increased systemic inflammatory signaling resulting from multiple diseases that afflict the CNS. We discovered that BEC-specific VCAM1 increases in the hippocampus during normal aging. Exposure of young BECs to an aged systemic environment induces BEC activation and upregulation of VCAM1 both in vitro and in vivo. Specifically, systemic
injections of aged human blood into young immunodeficient (NSG) mice—acutely over 4 days or spread over 3 weeks—increased BEC-specific VCAM1 expression, increased brain inflammation as assessed by microglial activation, and inhibited hippocampal neurogenesis. Blocking VCAM1 signaling systemically with a neutralizing monoclonal antibody rescued neurogenesis and prevented aged plasma induced microglial activation. This study suggests preventing BEC-immune cell crosstalk through VCAM1 may be a therapeutic target for ameliorating aged blood induced decline in brain function.

To decipher: old blood injected into young mice → brain inflammation and ↑VCAM-1 production. Blocking VCAM-1 with an antibody abolished this effect, showing that VCAM-1 is the culprit, or one of them, in brain inflammation.

But, what is it about old blood that causes an increase in VCAM-1 expression? It may very well be iron. The addition of iron chelators to endothelial cell cultures reduces, in a dose- and time-dependent manner, the production of VCAM-1.

These data suggest that iron plays a critical role in TNFα mediated VCAM-1 induction in HDMEC [human dermal microvascular endothelial cells], and the target for iron effects may be IRF-1, NF-kB, and potentially chromatin remodeling.

Iron could be one of the main factors in old blood that causes inflammation and damage.

NF-kappa B is another molecule that’s been suggested as a pro-aging factor in old blood; it’s a master regulator of factors that increase inflammation, which is a key characteristic of aging.

Iron chelators block the increase in NF-kappa B.

These results demonstrate that the iron chelator effectively blocks NF-kappa B activation and coordinate TNF-alpha and IL-6 gene upregulation by HM [hepatic macrophages] in cholestatic liver injury or under in vitro lipopolysaccharide stimulation. These findings support a pivotal role for iron in activation of NF-kappa B and cytokine gene expression by HM in vitro and in vivo.

Iron satisfies a few other requirements for evidence of being involved in aging:

1. Iron increases in aging.
2. Iron promotes oxidative stress, a key characteristic of aging.
3. Iron is implicated in diseases of aging, including heart disease,
cancer, and Alzheimer’s.
4. Iron promotes infections, which increase in aging.
5. Iron promotes mTOR activation, thought to be critical in aging.

Here we have an element, iron, which looks to me like a prime candidate in aging promotion. Why aging researchers generally don’t see this, I don’t know, but possibly iron just isn’t a sexy topic. Or, I could be wrong, but obviously I doubt it.

I’ll just leave you with one other item of interest.

Restored Vulnerability of Cultured Endothelial Cells to High Glucose by Iron Replenishment. When endothelial cells are serially cultured, they lose their sensitivity to damage by high glucose, which is normally toxic. It turns out that serial culturing causes them to lose their iron, to a level only 10% that of normal. When the cells were incubated with iron, they took it up, their iron levels were restored to normal, and high glucose once again became toxic to them.

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.
Low-carbohydrate, high-fat diets (LCHF) have many health benefits. They can cause weight loss in overweight people without hunger, and improve insulin resistance and dramatically improve diabetes. Even more, LCHF diets greatly improve lipid markers of cardiovascular disease risk. Besides the beneficial effect on cardiovascular markers and weight loss, I’ll show here how a low-carbohydrate diet slows aging.

Glucose shortens lifespan in *C. elegans*

Carbohydrates are long chains of sugar molecules; in the case of common foods like wheat, rice, and potatoes, the carbohydrates are long chains of glucose, the same type of sugar as in the blood. The influence of glucose as a food source has been studied in aging research.

In the worm *C. elegans*, dietary glucose shortens lifespan. One of the most important ways it seems to do this is through the production of advanced glycation end products, or AGEs. These molecules result from the attachment of glucose to proteins (hence glycation), and they are implicated in diabetic complications. AGE’s may also be important in the buildup of irremovable cellular junk (lipofuscin), resulting in the garbage crisis of aging.

On the other hand, glucose restriction increases lifespan in *C. elegans*. Restricting glucose activates the equivalent of AMPK, the cellular energy sensor, which in turn inhibits mTOR and increases stress defense mechanisms, notably Nrf2. Essentially, it acts as a form of hormesis.

Important to note that the biochemical pathways involved in *C. elegans* lifespan extension are evolutionarily conserved mechanisms, so these results are of relevance to humans, though how much is a different question.

Glucosamine extends lifespan by reducing glucose metabolism

Glucosamine is an over-the-counter supplement, and it extends lifespan not only in *C. elegans*, but in mice too. (Important because that gets us closer to human physiology.) Mice who got glucosamine show an induction of mitochondrial biogenesis, lowered blood glucose levels, enhanced expression of several murine amino-acid transporters, as well as increased amino-acid catabolism. Taken together, we provide evidence that GlcN [glucosamine] extends lifespan in evolutionary distinct species by mimicking a low-carbohydrate diet.

So, this is further evidence: reducing glucose metabolism increases lifespan.
You could take glucosamine, or you could just cut out the middleman and reduce your carbohydrate consumption.

**Calorie restriction extends lifespan and reduces glucose metabolism**

*Calorie restriction* (CR), that is, the reduction in food given to lab animals or humans, is the most reliable and robust life-extension intervention there is, extending lifespan in rodents as much as 50%. The greater the restriction, the longer the life extension.

As one might expect, massive amounts of research has been done on CR attempting to pin down the means by which it counteracts aging. CR effects many biochemical/physiological changes, and some or all of these may be important to its benefits. One thing CR does is to decrease the metabolism of glucose, and to increase fat burning.

A key metabolic change during CR is a shift from carbohydrate metabolism to fat metabolism.

Once again, AMPK is involved, which coordinates a series of biochemical effects, including the shift to fat metabolism.

**Carbohydrate restriction lowers insulin and IGF-1**

CR lowers levels of both insulin and IGF-1 (insulin-like growth factor), and this is thought to play a large role in lifespan extension. Animals that have modified insulin signaling live longer, and IGF-1 is important in the development of cancer.

Humans that eat a carbohydrate-restricted diet see a large drop (50%) in plasma insulin, and about a 30% decrease in plasma IGF-1. This happened on a diet that contained 5% carbohydrate, as opposed to 60% before. Of interest, protein is thought to be important to IGF-1 levels, and this diet increased protein, to 35%, and IGF-1 still dropped, although muscle IGF-1 increased.

To what extent does carbohydrate restriction mimic calorie restriction? Probably a fair amount: restricting carbohydrate alone is responsible for about 70% of the benefits of intermittent fasting.

**Conclusion: Burning fat instead of glucose increases lifespan**

The evidence above suggests that less metabolism of glucose and more of fat increases lifespan.

If you want to implement a low-carbohydrate, high fat diet, here’s what you can eat ([source](source)):
### ‘Green list’: recommended foods on a Banting (low-carbohydrate high-fat) diet

<table>
<thead>
<tr>
<th>Animal protein</th>
<th>Dairy</th>
<th>Fats</th>
<th>Nuts and seeds</th>
<th>Vegetables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eggs</td>
<td>Cottage cheese</td>
<td>Olive oil</td>
<td>Almonds</td>
<td>All green leafy vegetables, cruciferous vegetables or above ground vegetables</td>
</tr>
<tr>
<td>Meats</td>
<td>Cream</td>
<td>Avocados</td>
<td>Flaxseeds</td>
<td></td>
</tr>
<tr>
<td>Poultry</td>
<td>Full-cream</td>
<td>Coconut oil</td>
<td>Macadamia nuts</td>
<td></td>
</tr>
<tr>
<td>Game</td>
<td>Greek Yogurt</td>
<td>Macadamia nut oil</td>
<td>Pecans</td>
<td></td>
</tr>
<tr>
<td>Seafood</td>
<td>Cheeses</td>
<td></td>
<td>Pine nuts</td>
<td></td>
</tr>
</tbody>
</table>

Adapted, with permission, from Noakes et al. Fruits are also recommended, but in controlled quantities based on carbohydrate content and the patient’s level of IR.

PS: For more on fighting aging, read my book, *Stop the Clock*.

PPS: Check out my Supplements Buying Guide for Men.
The Truth About the Blue Zones

The so-called Blue Zones are regions where there’s a high proportion of very old people, nonagenarians and centenarians. Is that really the truth about the Blue Zones?

The number of Blue Zones depends on whom you ask, but on the “official” site, there are five:

- Barbagia region of Sardinia
- Ikaria, Greece
- Nicoya Peninsula, Costa Rica
- Seventh Day Adventists – Highest concentration is around Loma Linda, California.
- Okinawa, Japan

Do Blue Zones even exist?

That’s a strange question to ask, one might think, but given past hype about allegedly long-lived people that turned out not to be true, it might pay to be skeptical.

How much do the Blue Zones have in common with gerrymandering or redistricting? In the United States, a ruling political party often redraws congressional and other districts to make them full of people who will elect that political party. It’s easy to do, just by drawing lines on a map. Have researchers drawn lines on a map that includes high numbers of centenarians and then dubbed them Blue Zones?

I have no evidence that they did that, but it reminds me of how numerous, above-average cases of leukemia or other cancers have been found in certain locations, only to find out later they were statistical flukes.
A problem, as I see it, in this research, is that people tend to see what they want to see.

**Why are some groups included and not others?**

Take the Adventists of Loma Linda, California; male Adventists live about 7 years longer than other white Californians, and this is ascribed to their lifestyle. The Adventist church recommends being vegetarian, although not all Adventists follow that stricture.

But Mormons in California and Utah appear to have about the same increase in life expectancy as the Adventists, and they are not vegetarians. So why aren’t Mormons on the Blue Zone list? Is it because of an agenda? Not sure what that might be, since Adventists are looked at as almost equally “weird” – not by me, just saying that’s the perception.

Maybe there are other places in the world where people live a lot longer, but because they don’t fit an agenda, they’re not included. I’m not accusing anyone of cooking the books, just noting that biases are everywhere, and our own biases are the hardest to see.

The above chart shows differences in life expectancy in the U.S. by religion. (Source.) Why not Jews in the Blue Zones? I’ll speculate that it’s because Jews have no special health practices (that I’m aware of), but live longer because of intelligence, education, and income. You can’t really point out a long-lived group and say “be like them” if being like them is impossible.

**The Blue Zones are not in Western Europe**

The Blue Zones all lie outside Western Europe, and except for the Adventists, none of the people inhabiting them are Western European. To a great extent, the factor that unites all of these groups is either being less touched by modernity, or actively rejecting it.

Western Europe is characterized by the nuclear family, which consists of
parents and children to the exclusion of other relations. Outside Western Europe, households are more likely to include grandparents, aunts, uncles, cousins, etc., or in any case they all live quite near each other.

Observers have noted that social cohesion is a common factor in the Blue Zones. Even among the Adventists, who are mainly of European origin, their minority religious status ensures that they stick together. Church attendance is also associated with longer life.

How would social cohesion make people live longer? Probably by giving older people a sense of purpose and belonging, leading them to actively participate in family and society.

The average American over the age of 65 watches television more than 7 hours a day. What would that do to their sense of belonging and purpose, much less the amount they spend in physical activity? Television viewing time independently raises the risk of death; each 1 hour of viewing associates with an additional 4% risk of death. Whether that’s due to lack of physical activity, decreased social cohesion, genetic confounds, or demoralization from crap TV shows, can’t be determined. But it seems doubtful that people in the Blue Zones are watching TV that much.

Food and the Blue Zones

What you eat is undoubtedly important for health, but whether it’s important enough to get a larger fraction of people to live to very old ages is another matter. Most non-scientific commentary on the Blue Zones emphasizes that they eat a lot less meat than others.

The Okinawan diet has been perhaps the most studied. Okinawans in 1949, representing the cohort that was long-lived, ate a high-carbohydrate diet, low in fat and protein, and low calorie too. Okinawans ate about 15% fewer calories than in mainland Japan. Of interest, most of their diet consisted of sweet potatoes, and they only ate half as much rice as in Japan. They ate about 1% of calories as fish, and < 1% as meat, compared to 4% and < 1% respectively for mainland Japan.

So what’s the magic ingredient for Okinawan longevity?

They ate the same amount of meat as in Japan, although quite a bit less fish. Hard to see how meat could be a factor.

They ate a lot less rice, a food with a high glycemic index. Nearly 70% of their calories came from sweet potatoes, compared to 3% for mainland Japan. The sweet potatoes look like this:
Looks very high in beneficial polyphenols.

In animals, calorie restriction is the most robust lifespan-extension intervention. And the Okinawans ate a lot less.

Here’s how the Okinawan diet has been characterized:

- Relatively high consumption of unrefined, low GI carbohydrates: principally vegetables, legumes, and fruits.
- Moderate fish and marine food consumption.
- Lower intake of meat with emphasis on lean meats.
- Liberal use of medicinal plants, herbs, spices or oils.
- Regular tea consumption and moderate alcohol consumption.

The secret to Okinawan longevity could be

- less food overall
- less fish
- less rice
- more sweet potatoes
- hormetic phytochemicals
- something else or a combination of the above.

I can state for a fact that Okinawans in 1949 watched zero television.

Many but not all of the Adventists are vegetarians, and the residents of other Blue Zones appear to eat less meat than others.

**Iron**

*Metals in plasma of nonagenarians and centenarians living in a key area of longevity.* This study shows that in one of the Blue Zones, in Sardinia, nonagenarians and centenarians had much lower levels of iron than middle-aged controls – almost 40% less. The important health risk factor of iron may be a key point in longevity in the Blue Zones.
No one discusses this. Few people know it. See my book, *Dumping Iron*.

**Adding longevity factors**

An article about the Adventists in JAMA Internal Medicine, *Ten Years of Life: Is It a Matter of Choice?*, says that the average Adventist man lives 7.3 years longer than other men in California. The article looks at the risk factors to see what are the most important driving the difference. See chart below.

![Chart showing expected age at death by risk factors](chart.png)

Risk factors for Okinawans could be similar when compared to mainland Japan. Okinawans probably smoked a lot less, since they were poor, and they probably weighed less, since they ate less. They may have been more physically active, since many of them were farmers or fishermen.

**Conclusion: How to Live Long, and the Truth About the Blue Zones**

The factors that make for a long life in the Blue Zone people could be one or
a combination of

- less smoking
- lower body weight
- less food
- lower body iron stores
- less meat eaten
- less refined carbohydrates eaten
- more plant foods eaten
- higher social cohesion
- religious attendance
- importance of family
- greater physical activity
- less modern life (TV, cars, alienation)

My money would be on the first four: smoking, body weight, food, and iron.

Although the Okinawans eat substantially less food than in Japan, the other Blue Zones may not be similar.

In Nicoya, Costa Rica, men at age 60 have a life expectancy of 24 more years, reportedly the highest in the world currently. Male Nicoyans apparently have the same rate of cancer as other Costa Ricans; their mortality advantage is due to less heart disease. If that statistic is true for those in other Blue Zones, then that helps us zero in on the important factors. Of course, cancer and heart disease have lots of overlapping causes.

I'm skeptical that eating less meat has much if anything to do with it, although lower iron levels may point to it as a factor.

The truth about the Blue Zones, as I see it, is that there's a lot more here than meets the eye.

Living a long time requires a confluence of factors coming together.

Even though I see certain risk factors as more important, I don’t dismiss any of them. For example, it seems clear to me that being well-integrated with your own family as you get older is very important for health, and so is being well-integrated with society and with a church.

**PS:** See my books for more on how to live a long time.

**PPS:** You can support this site by purchasing through my Supplements Buying Guide for Men.
New Young Blood Study Implicates Iron in Aging

Executive Summary

- Surgically joining the circulatory systems of a young and an old mouse may rejuvenate the old mouse
- A new study finds that benefit to the older mouse are much smaller than harm to the younger
- In the younger animal, beta 2 microglobulin increased and brain neurogenesis decreased
- The fact that a single exposure to old blood causes harm implicates some factor in old blood
- My hypothesis is that that factor is either iron or bacterial lipopolysaccharides

Scientists have studied aging by surgically joining the circulatory systems of two mice, one young, one old, and then looking at changes in either mouse. This process, known as heterochronic parabiosis, allows the exchange of circulating blood factors between the two mice, and these factors are presumed to promote either rejuvenation or aging. A new young blood study implicates iron in aging, either directly or through bacterial lipopolysaccharides.

In previous studies, scientists have thought that delivery of a protein, GDF11, from young blood to old, causes rejuvenation of muscle in the old animals. Others have cast doubt on this, and asserted that GDF11 inhibits muscle regeneration in old mice.

Other scientists have noted that this procedure may not be solely about circulating factors. When two mice are joined together, the old mouse has
access not only to the blood of the young animal, but to its organs as well, since blood circulates through them. Access to a young heart, or lungs, or other organs could have rejuvenating effects on their own.

To get around the sharing of organs and study circulating factors alone, the team of scientists headed by Irina Conboy at the University of California, Berkeley, developed a new procedure using microfluidic technology. The new procedure allows the animals to be joined for a few hours, their blood to circulate together and mix, and then the animals can be disconnected. This procedure effectively isolates blood as a source of any changes seen.

The new study, “A single heterochronic blood exchange reveals rapid inhibition of multiple tissues by old blood”, found that old blood was much more damaging to young mice than young blood rejuvenated old mice. Several new discoveries in this study implicate iron as one of the causative factors in old blood that damage the young mice. (The scientists don’t say this; that’s my interpretation, and I’ll explain.)

**Effects on muscle**

Old mice transfused with young blood showed better recovery from muscle injury. Young mice transfused with old showed worse recovery.

Young blood showed a rejuvenating effect. But – the researchers note, “The positive effects of young blood could also be explained by dilution of old blood, and not necessarily by young factors.”

If that’s correct, then there’s no rejuvenating factor in young blood, but there’s something in old blood that is associated with aging and causes harm. More on that below.

**Brain effects**

Genesis of new neurons in the brain, specifically in the hippocampus, was “severely” curtailed in young mice after only one transfusion of old blood, and there was no rejuvenating effect in old mice from young blood.

**Increase in beta 2 microglobulin**

Beta 2 microglobulin (B2M) is a protein that forms part of the major histocompatibility complex in cell membranes and as such is important in immune function. Transfusion with old blood increased B2M in young mice.

“Moreover, our studies demonstrate a rapid increase in beta-2 microglobulin (B2M) in young tissues by old blood; and this phenotype is not from elevated circulating B2M in old mice (as there is none), suggesting that another age-specific systemic molecule raises B2M in the young organs.”

This increase in B2M is an important clue as to what transfusion of old blood does and what causes it.
Potential causes: iron and lipopolysaccharides

In rats, iron accumulates in tissues with aging. Calorie restriction, which is known to extend lifespan, markedly suppresses the accumulation of iron.

Yeast (Saccharomyces cerevisiae, or brewers’ yeast) are used as a model organism to study aging, since the mechanisms of aging are evolutionarily conserved in all eukaryotic organisms. They, too, massively accumulate iron with aging, 4 to 5 times as much as when young. The increased iron is associated with damage to cellular proteins.

“The pro-oxidant effects of such increased iron concentration would account for the damage observed.”

Calorie restriction curtails both the iron and the damage. Decreased accumulation of iron could be an important way in which calorie restriction extends lifespan.

Lipopolysaccharides (LPS) are fragments of bacterial cell walls, and are extremely toxic – they’re often referred to as “endotoxins”.

In aging, the lining of the gut wall deteriorates, allowing LPS to enter the circulation, where they cause a chain reaction of deleterious events. Mice show both a change in gut microbes in aging and an increase in LPS in the circulation. This causes increased inflammation, a characteristic of aging.

Can these components of old blood, iron and LPS, cause deleterious changes when given to young animals?

Douglas Kell, an expert in this field, wrote, “...there is overwhelming evidence for the involvement of iron in this neurodegeneration [in Parkinson’s disease]”.

With regard specifically to the hippocampus, the region of the brain studied in this young-old transfusion experiment, iron accumulates in it in Alzheimer’s disease in humans and correlates highly with the severity of disease.

When a specific toxin that induces Parkinson’s disease is given to lab animals, iron chelators protect against damage. What appears to occur is that the toxin causes accumulation or iron in the brain and/or causes the release of free iron from ferritin; free iron is what causes damage, and iron chelators mop up free iron and remove it.

As for LPS, they play a central role in increasing inflammation and promoting cell death. They may come either from increased bacterial translocation from the gut or from the revival of dormant bacteria in the blood.

Bacteria, like virtually all living things, require iron; withholding iron from bacteria is one of the first lines of defense in immunity. Bacteria and primates are involved in an ongoing evolutionary arms race in a battle for iron.
Exposure to LPS increases iron levels and oxidative damage in endothelial cells, and iron chelators prevent the damage.

**The Mechanism**

Kell and Pretorius write,

“Given the well-established facts (i) that microbial growth in vivo is normally strongly limited by the (non-) availability of free iron, and (ii) that bacterial components such as lipopolysaccharide (LPS) are strongly inflammatory, such an analysis leads to the recognition that the iron-related inflammatory diseases also have a major microbial component involving the resuscitation of dormant organisms and their shedding of inflammatory molecules, and especially of cell wall components such as LPS.”

Older animals have higher levels of both free iron and LPS. If old blood is transfused into young animals, they receive both of these. Either the high iron in the blood of old mice revives dormant bacteria in the young animals, or the LPS in old blood causes massive inflammation in young mice, and prevents neurogenesis.

As we noted above, tissue beta 2 microglobulin increased dramatically in young animals after old blood transfusion, as much as 3-fold in brain and 8-fold in muscle.

One of the most important functions of beta 2 microglobulin is the regulation of iron. B2M knockout mice, which lack genes for B2M, become iron-overloaded and are in fact used as a mouse model of hemochromatosis, or pathological iron loading.

Increased iron or LPS in old blood could cause the rise of B2M in the tissue of young mice. That, however, is speculative, as I’ve been unable to find any data on what increases B2M in tissue. Since B2M regulates iron, it stands to reason that high iron could cause an increase in it, in order to down-regulate iron. In any case, in these young mice, something clearly increases B2M.

Important to note that, while B2M has been recognized as an important pro-aging factor that circulates in old blood, and injection of it causes cognitive deficits, the present study found no increase in circulating B2M in old blood.

**Conclusion**

The evidence indicates that some factor in old blood causes damage when given to young animals.

That factor may be iron and/or bacterial lipopolysaccharides.

Old blood is more harmful to young animals than young blood is a benefit to old animals.
That would seem to dash hopes of any large benefit of young blood in older people.

If my analysis is correct, it shows that controlling iron and bacterial LPS are important to aging. (We already know this; this report just supplies more evidence.)

In regard to iron, controlling both total body iron stores, as represented by ferritin, and the release of free iron, are important. The former can be controlled in a number of ways, and the latter by iron chelators.

For control of bacterial LPS, oral and gut integrity are important. Since bacteria require free iron, measures that keep it low also help prevent increased LPS.

PS: For more on iron and aging, check out my book, Dumping Iron.

PPS: You can support this site by purchasing through my Supplements Buying Guide for Men. No extra cost to you.

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**Targeting Hypercoagulation for Anti-Aging**

Coagulation (clotting) of the blood is an important process that keeps us from bleeding by stopping blood flow in a timely fashion. It’s intricately regulated by dozens of proteins, with positive and negative feedback loops. Hypercoagulation refers to the abnormally high tendency of the blood to clot, and there’s a marked association of hypercoagulation and aging. Here we’ll
discuss targeting hypercoagulation for anti-aging.

One of the most important of the proteins that promotes blood clotting is fibrinogen, and it markedly increases with age. Higher levels of fibrinogen are associated with heart disease and cancer.

Fibrinogen forms fibrin, which in turn forms a blood clot. Dissolution of fibrin is as important as its formation; clots that form too quickly or don’t dissolve soon enough can cause heart attacks, strokes, and deep vein thrombosis.

Why do fibrinogen levels rise with age? It may be due to inflammation, since fibrinogen is an acute phase reactant.

Noteworthy also is that fibrinolysis, the process of breaking down a blood clot, decreases with age. “[T]he increasing hypercoagulability observed with aging may account for the higher incidence of thrombotic cardiovascular disorders in the elderly”.

So, we have increased fibrinogen, possibly due to greater inflammation in aging, and decreased fibrinolysis, both of which tend toward the formation of blood clots, which increase the risk of heart attacks, cancer, and stroke, and probably lots of other diseases.

**Why blood clots won’t break down**

In fibrinolysis, the breaking down of blood clots, enzymes designed for that purpose act on fibrin. If something alters the molecular structure of fibrin, clot-dissolving enzymes can’t function as well, or even at all.

What could alter the fibrin structure?

Iron, for one. Iron enhances the generation of fibrin, and makes it harder to break down.

Here, we show by means of electron microscopy that iron ions added to human blood dramatically enhances fibrin fibers formation with thrombin, and significantly delays fibrinolysis during spontaneous clotting of native blood. Iron ions caused the appearance dense matted fibrin deposits, similar, if not identical, to those observed in plasma of patients with stroke. These results may explain a known relationship between thrombotic diseases and the increased body concentrations of free iron and/or hemoglobin derivatives. We conclude that any action resulting in the inhibition of hemostatic abnormalities, as well as in the reduction of body free iron and scavenging of hydroxyl radicals (e.g., by polyphenols) can potentially prevent pathological reactions associated with consequences of stroke.

Iron, through its ability to generate hydroxyl radicals (OH¯), changes the
structure of fibrinogen, and the fibrin formed by it, and makes it difficult to break down.

The mechanism of this phenomenon is very likely based on hydroxyl radical-induced modification of fibrinogen tertiary structure with the formation of insoluble aggregates resistant to enzymatic and chemical degradations.

It’s even suggested that the presence of iron-induced fibrin clots may be the cause of the inflammation that raises fibrinogen, and could be very important for causing heart disease.

Accumulating evidence within the last two decades indicates the association between cardiovascular disease (CVD) and chronic inflammatory state. Under normal conditions fibrin clots are gradually degraded by the fibrinolytic enzyme system, so no permanent insoluble deposits remain in the circulation. However, fibrinolytic therapy in coronary and cerebral thrombosis is ineffective unless it is installed within 3-5 hours of the onset. We have shown that trivalent iron (FeIII) initiates a hydroxyl radical-catalyzed conversion of fibrinogen into a fibrin-like polymer (parafibrin) that is remarkably resistant to the proteolytic dissolution and thus promotes its intravascular deposition. Here we suggest that the persistent presence of proteolysis-resistant fibrin clots causes chronic inflammation. …We argue that the culprit is an excessive accumulation of free iron in blood, known to be associated with CVD. The only way to prevent iron overload is by supplementation with iron chelating agents.

Iron appears to be the biggest culprit in the increased fibrinogen and decreased fibrinolysis seen in aging, and may therefore be largely responsible for increased rates of heart disease and cancer seen in older people.

Iron also increases with age, which gives us another piece of evidence in the chain: aging → more iron → greater tendency to clotting → heart disease, stroke, cancer.

Iron is well-known to be involved in Alzheimer’s disease, and the ability of iron to enhance clot formation may be one of the reasons.

Amyloid hypothesis of Alzheimer’s disease (AD) has recently been challenged by the increasing evidence for the role of vascular and hemostatic components that impair oxygen delivery to the brain. One such component is fibrin clots, which, when they become resistant to thrombolysis, can cause chronic inflammation. It is not known, however, why some cerebral thrombi are resistant to the fibrinolytic degradation, whereas fibrin clots formed at the site
of vessel wall injuries are completely, although gradually, removed to ensure proper wound healing. This phenomenon can now be explained in terms of the iron-induced free radicals that generate fibrin-like polymers remarkably resistant to the proteolytic degradation… In addition, iron-induced fibrin fibers can irreversibly trap red blood cells (RBCs) and in this way obstruct oxygen delivery to the brain and induce chronic hypoxia that may contribute to AD.

Iron: is there anything (bad) it can’t do?

How to avoid the hypercoagulation of aging

Avoiding the hypercoagulation of aging would be a potent strategy for fighting aging and remaining free of the diseases of aging. There are a few ways to do this.

1. Keep iron in the low normal range, via blood donation and/or iron chelators. Both can be useful, since blood donation targets total body iron, while iron chelators mop up any excess free iron.
2. Magnesium can help dissolve fibrin-red cell aggregates. It’s therefore no surprise that magnesium reduces death rates in heart attack patients, and deficiency is associated with stroke.
3. Polyphenols like EGCG (from green tea) and curcumin protect against hypercoagulation. No accident that they also chelate iron.
4. Aspirin enhances fibrinolysis. This may be one of its modes of action that protects against both heart attacks and cancer. Long-term aspirin use also results in lower levels of iron.

Conclusion

The hypercoagulation of aging represents an important target for any anti-aging and life-extension regimen. Even middle-aged men should pay attention to it, since they have a high rate of heart attacks — as well as high iron, which is why they have the high rate of heart attacks.

Unfortunately, no one is talking about this. While it’s well known that blood clots can precipitate heart attacks, the idea that hypercoagulation may be a (or the) root cause of heart disease is barely even considered. (Instead, we get all that cholesterol nonsense.)

Even less discussed is the role of iron, whether it’s increasing fibrinogen, decreasing fibrinolysis, causing infections, cancer, or any number of other things, including aging itself.

PS: Read my book Dumping Iron.
Self-Stereotypes and How to Overcome Them

Stereotypes are empirical generalizations, and they are largely true. That’s how they got to be stereotypes. As such, they can be useful guides when dealing with other people, even other things. But stereotypes can be so pervasive that they affect how you perceive yourself, and one of the most pervasive of stereotypes is that pertaining to age. In this article we’ll look at self-stereotypes and how to overcome them.
Stereotypes of age

Stereotypes of age are generalizations about what someone usually is or does, or what they should be or do, at certain ages.

The structure of society reinforces these stereotypes, and they are so common to our patterns of thought that they can be like water to a fish: the fish doesn’t even know that he’s in water and swimming. It’s just natural – just as we don’t give much thought that we’re at the bottom of the atmosphere.

For instance, mandatory elementary education means that children and teenagers from ages 6 to 18 are expected to be in school. If they are not, we see that as a glaring exception that must have some reason.

But my grandfather quit school at age 13 on the death of his father so that he could support his family. A laudable act, no doubt, but he was probably expected to do this at the time in which he lived.

These days, it’s becoming more expected that high school grads will attend college, and therefore if a young person between 18 and 24 or so is not in college, he’s expected to have a good reason for it, especially if under pressure from parents.

So the stereotypes roll on. After college, we’re expected to get married, buy a house, have children. It’s highly expected that you’ll drive a late model, expensive car.

Going against the grain in all of this, should you want to, can be tough, especially if you yourself expect that you’re supposed to do these things.

As you get older, you’re expected to be and act older. The approach of Social Security, when you’ll get money to stay away from work, reinforces the notion that you should stop working. And wait for death.

Why you should care about age stereotypes

I got to thinking about this topic because in theory I could start collecting Social Security next year, when I turn 62.

Given what kind of shape I’m in – excellent – and given my interest in anti-aging, the idea that I’m ready to stop doing what I do because I’m too old to do it seems ludicrous.

Perhaps more importantly, I believe I could have many decades of healthy life ahead of me. I could get a PhD, work on my business or any number of other projects and still be able to enjoy the fruits of my work.

Yet, the actuaries tell me that in 21 years, I have a 50% chance of being dead. I don’t believe it, but – those are the facts: 50% of men my age will be dead in that time. Barring, in one direction, nuclear war, and in the other, some vastly powerful life extension technology.
So, even though I consider myself an independent thinker, I face the reality of what science actually says.

Personally, I think I’ll be deadlifting 320 when I’m 82. But who knows. I’ll be trying anyway.

What I’m getting at is that the stereotypes can keep you from doing what you want, or what you think best. For instance, if I thought I could get that PhD and work as a scientist for the next 50 years, I might do it. The stereotype of my age says that no one does this.

When I look back on my life at the decisions I made and the course my life took, I see that much of it was dictated by stereotypes. Education, marriage, work, how I dressed and behaved. I’m not saying it was all bad by any means; as I noted above, stereotypes can be useful.

But you must realize when you’re acting out a stereotype even when you don’t realize it. Otherwise you’ll end up doing things just because everyone else is doing them, or everyone expects you to do them.

When you’re 20, don’t go to college because everyone else is, or your parents expect you. By all means, go if that will help you get ahead. (But choose wisely, not many people should attend college in my opinion; the return on investment is abysmal on average.)

Don’t get married because you’re at the age when people normally do so. You need a much better reason than that. (In my opinion, the same strictures apply to marriage as for college.)

And, if you’re around my age, don’t believe the stereotypes that it’s acceptable to be fat and out of shape, to spend your time watching television, or in general just to lack ambition and be unworthy of attention.

I struggle myself with the idea that my life is supposed to be 75% over. Not out of a fear of death, but from a fear that I’ll stop trying to achieve anything, that I may as well just hang it up because there’s not much time left.

**Conclusion**

The late historian and cultural critic Jacques Barzun wrote dozens of books and kept at it all his life. At the age of 93, he published the 800-page *From Dawn to Decadence*, his only best-seller and widely considered his best book. He continued to write until he was 103, and died at 104.

I doubt that Barzun paid much attention to stereotypes; if he had, he would have spent his twilight years playing golf and watching TV. His inattention to stereotypes led him to do his best, most creative work long after others would have quit.

I know an important scientist who is still working at age 80, and another who still keeps his hand in at 95. I doubt they pay much attention to stereotypes...
My own mother, who taught singing all her life, founded a community chorus at age 65 and directed it until the age of 91.

Chuck Berry is 90, and his new album will be out soon.

On a different level, take a look at Mike Cernovich, a lawyer and writer who looks like he’s having quite an influence on the upcoming presidential election. He’s in his late 30s, and he’s violating just about every life stereotype that you can imagine. He could have been satisfied to be a lawyer, make decent money, settle down and keep quiet. But he seems to be having the time of his life, in no small part because he refuses to abide by stereotypes.

As for myself, I’m going to ignore what the actuaries say, and what the media and culture say, about what I’m supposed to do with my life.

**PS:** Strike back against stereotypes by gaining some muscle with my book, Muscle Up.

**PPS:** You can support this site by purchasing through my Supplements Buying Guide for Men. (You pay nothing extra.)

Subscribe and get my free book on fat loss

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How Iron and Bacteria Combine to Promote Aging
Microbes in normally sterile body sites

One of the more remarkable developments in recent years in the field of health and aging is the recognition that bacteria and other microbes such as fungi can be found in many body sites that were formerly considered to be sterile – the bloodstream for instance, or the brain. In this article, I’ll discuss how iron and bacteria combine to promote aging and disease.

I covered this idea in a book review on how bacteria may be largely responsible for many of the ills of aging.

Many body sites are normally covered or filled with bacteria: the gut, the skin, the mouth and throat, for example. But these sites can all be considered to be outside the body. The gut and skin barriers and mucus membranes function to keep bacteria where they belong and to prevent bacterial and fungal illness.

When microbes penetrate to normally sterile body sites, such as the bloodstream, they can cause illness, a fact which has been known at least since the time of Louis Pasteur and Robert Koch.

What current research is uncovering is that apparently healthy people often – maybe always – carry bacteria in normally sterile sites, and that they may be the cause of diseases previously thought non-infectious – heart disease and Alzheimer’s disease, to name two.

Bacteria and other microbes can be placed into one of three categories with regard to their infectiousness: pathogens, opportunistic pathogens, and non-pathogens.

- **Pathogens**: The pathogens are well-known, for example *Yersinia pestis*, which causes the plague, or *Francisella tularensis*, which causes tularemia. Both of these can cause fatal disease in an otherwise healthy human, and generally you don’t want to be anywhere near them.
- **Opportunistic pathogens** are organisms like *E. coli* or *Staphylococcus aureus*, which live in and around healthy people and normally cause no problems. But if they get into body sites where they don’t belong, such as beneath the skin, in the bloodstream, or in the urinary tract, or in people who have compromised immune systems, they can cause disease.
- **Non-pathogens** live on humans, or in soil and water, and do not cause disease.

The story of microbes in normally sterile sites as the cause of aging and disease is largely the story of non-pathogens and/or normally sterile sites like the bloodstream. We already knew about the disease-causing effects of other bacteria, and we knew that blood is not supposed to have microbes in it.

Microbes as the cause of chronic disease

How do we know that bacteria and other microbes cause chronic disease? Are they just bystanders or actual perpetrators?
Take the case of Alzheimer’s disease. Bacteria and fungi have been found in the brains of Alzheimer’s patients, but not in those of controls.

This begins to satisfy the first of Koch’s postulates: the organism must be present in all cases of the disease. Until recently, culturing the microbes, the second of Koch’s postulates, has been difficult, but scientists are working on that.

Culturing the microbes may be difficult. It’s estimated that less than 1% of bacteria can be cultured, which has become known as “the great plate count anomaly”. What this means is that most of the bacteria seen under a microscope cannot be grown in a laboratory, whether because they are dead, non-viable, dormant, or just don’t thrive in laboratory culture media and conditions.[1. Grice, Elizabeth A., et al. “A diversity profile of the human skin microbiota.” Genome Research 18.7 (2008): 1043.]

So, only until the advent of DNA probes has it been discovered that many body sites formerly considered sterile are in fact loaded with microbes.

One of the key factors in Alzheimer’s and other diseases of aging, and of aging itself, is inflammation – an activation of the immune system.

Bacteria and other microbes activate the immune system – that’s what the immune system does, it activates to protect the body from invaders.

Other lines of evidence of a microbial cause of Alzheimer’s include:

- the fact that it only strikes old people, and they have weakened immune systems

**Iron and microbes**

Virtually all living things require iron to grow, metabolize, and reproduce, and bacteria are no exception.

A key factor in the successful bacterial invasion, colonization, and/or infection of an organism is its ability to get enough iron. If it can’t do so, then it may remain dormant and unsuccessful, as it’s unable to commandeer enough iron to grow.

Because bacteria and other invading microbes require iron, organisms including humans have evolved a number of means of withholding iron from invading microbes. Perhaps the most important is the protein molecule ferritin, which encloses and holds iron atoms tightly in its core and makes
it unavailable to microbes that need it.

In turn, microbes have evolved ways to get that iron, and these ways are often very important to a microbe’s pathogenicity — its ability to invade an organism and cause disease.

It’s an **evolutionary arms race** between host and microbe.

Microbes have developed methods of destroying iron-containing molecules and grabbing the iron within, or have developed their own molecules with a high affinity for iron, and these latch on to any free iron within the organism.

Free iron is the key factor, the bottleneck, that microbes need.

It’s well established that **iron supplementation causes infections**. In recent years, the seeding of iron in the oceans has been proposed as a method of fighting global warming. In essence, dumping free iron in the form of iron powder eliminates the iron bottleneck for microbial growth, and algae and plankton grow abundantly. This is a good analogy for what happens in the human body when too much iron is available.

Physiological insults can also increase the amount of free iron inside the body and set the stage for microbial infection. Oxidative stress, which increases in aging, causes the release of free iron from ferritin. Solar radiation causes release of free iron in the skin, and this is critical to the mechanism of sun-caused skin damage.[4. Bissett, Donald L., Ranjit Chatterjee, and Daniel P. Hannon. “CHRONIC ULTRAVIOLET RADIATION-INDUCED INCREASE IN SKIN IRON and THE PHOTOPROTECTIVE EFFECT OF TOPICALLY APPLIED IRON CHELATORS 1.” *Photochemistry and photobiology* 54.2 (1991): 215-223.]

Limiting the amount of free iron is crucial in thwarting infections.

If Alzheimer’s and other chronic diseases are caused by infections, then controlling iron could stop them. Indeed, decreasing the amount of iron in the body either through phlebotomy (bloodletting) or iron chelators has been proposed as a method to treat Alzheimer’s.[5. Dwyer, Barney E., et al. “Getting the iron out: Phlebotomy for Alzheimer’s disease?.” *Medical hypotheses* 72.5 (2009): 504-509.]

Douglas Kell and colleagues, who have done important work in this area, have recently proposed that iron activates dormant bacteria in the brain to cause Alzheimer’s.[6. Pretorius, Etheresia, Janette Bester, and Douglas B. Kell. “A Bacterial Component to Alzheimer’s-Type Dementia Seen via a Systems Biology Approach that Links Iron Dysregulation and Inflammasome Shedding to Disease.” *Journal of Alzheimer’s Disease* Preprint (2016): 1-20.] They write:

> The progression of Alzheimer’s disease (AD) is accompanied by a great many observable changes, both molecular and physiological. These include oxidative stress, neuroinflammation, and (more proximal to cognitive decline) the death of neuronal and other cells. ... We review the evidence that **iron dysregulation is one of the central causative pathway elements here**, as this can cause each
of the above effects. In addition, we review the evidence that dormant, non-growing bacteria are a crucial feature of AD, that their growth in vivo is normally limited by a lack of free iron, and that it is this iron dysregulation that is an important factor in their resuscitation. Indeed, bacterial cells can be observed by ultrastructural microscopy in the blood of AD patients. A consequence of this is that the growing cells can shed highly inflammatory components such as lipopolysaccharides (LPS). These too are known to be able to induce (apoptotic and pyroptotic) neuronal cell death... This integrative systems approach has strong predictive power, indicating (as has indeed been shown) that both natural and pharmaceutical iron chelators might have useful protective roles in arresting cognitive decline, and that a further assessment of the role of microbes in AD development is more than highly warranted.

Alzheimer’s disease is a signature malady of aging, and if iron is implicated in it, then we may justifiably speculate that iron is involved in other diseases of aging, and in aging itself.

Indeed, iron has been implicated in heart disease, cancer, and diabetes, to name but a few diseases.

While free iron catalyzes harmful chemical reactions that damage cellular components and proteins, its role as a catalyst for bacterial growth, which then causes the diseases of aging, lends a new perspective on how iron causes aging.

Kell et al. also argue that many other chronic, inflammatory diseases are caused by infectious microbes, and that iron may be involved in their successful invasions of human tissue.[7. Potgieter, Marnie, et al. “The dormant blood microbiome in chronic, inflammatory diseases.” FEMS microbiology reviews (2015): fuv013.]

Where do these microbes originate? Humans have protective barrier functions designed to keep microbes where they belong; as noted, the skin, the gut barrier, and mucus membranes do this.

But these barriers are not perfect, and microbes can slip through them on occasion, or in certain pathological states.

In most cases, DNA sequencing has found that most of these disease-causing microbes that are present in normally sterile sites originate in the gut, and secondarily from the oral cavity.

Leaky gut is the condition in which gut microbes, or their constituent parts such as lipopolysaccharides (LPS), slip past the gut barrier and into the body, there to cause damage or infection. In periodontitis, bacteria from infected gums and bone sheds into the bloodstream.

Kell and colleagues note that tiny amounts of LPS interact with fibrinogen, a blood-clotting protein, and cause hypercoagulability, the tendency of blood
to clot faster than normal. This in turn increases the risk of blood clots in veins and arteries, as well as stroke and heart attack.

Hypercoagulability is characteristic of aging. If iron revive dormant bacteria, which then produces LPS and activates the coagulation system, then here’s another way that iron and bacteria synergize to cause disease.

**Conclusion**

The study of bacteria and other microbes in sites that were formerly thought sterile is, if not in its infancy, relatively new. Much more remains to be learned about their disease-causing effects, how they got there, what types of microbes they are, and how to prevent their occurrence.

It is well-known, however, that bacteria need iron to thrive, and without it they wither away, become dormant, or die.

Therefore, as documented in my book *Dumping Iron*, keeping iron levels low and well-controlled can stave off the ravages and illnesses of aging. In my view, iron is a critical factor in aging that so many scientists are overlooking. Whether it is so by virtue of its high reactivity with biological structures, by its role in feeding microbes, or both, remains to be seen.

(NB: As this is a huge topic, not all possible references have been included, but many of them are found in my other articles which are linked above.)

**PS: For much more on the role of iron in aging and disease, see my book, *Dumping Iron: How to Ditch This Secret Killer and Reclaim Your Health.*

**PPS: Check out my Supplements Buying Guide for Men.** Includes iron chelators!
The Garbage Catastrophe of Aging and How to Avoid It

Aging just is damage accumulation

Aging is the accumulation of damage and nothing more. As the level of damage rises, cells and the tissue made from them function poorly, and this in turn causes increased risk of disease and death. This is the garbage catastrophe of aging.

What causes this rising level of damage? If we can answer that, we know what causes aging.

(Note that this is a different question from asking whether aging is programmed by evolution or not.)

When we, or any organisms, are young, our cells can repair damage, but as we get older, the damage repair mechanism is itself damaged. This leads to rising levels of damage and an inability to fix it.

The main mechanism for damage repair is autophagy, from the Greek for “self-eating”. Autophagy is the cellular self-cleansing process in which cellular organelles such as mitochondria and proteins within the cell are broken down and their components recycled for making new organelles and proteins.

Autophagy is a daily occurrence – or should be – with peaks and troughs of activity. The absence of food strongly increases the rate of autophagy, so that in young organisms at least, its rate rises dramatically overnight. Fasting even longer than overnight further increases the rate of autophagy.

Other interventions besides fasting also increase autophagy, for instance, exercise and certain drugs and supplements.

But in older organisms, the capacity for increasing autophagy in response to fasting or other stimuli decreases. This leads to a rising level of damage that interferes with cell function and is characteristic of aging.

Autophagy is crucial for the organism. Treatments that prolong lifespan, for example calorie restriction, fasting, or even genetic manipulation of insulin signaling, require the organism to possess an intact autophagy mechanism to work.[1. Jia, Kailiang, and Beth Levine. “Autophagy is required for dietary restriction-mediated life span extension in C. elegans.” Autophagy 3.6 (2007): 597-599.]

No autophagy, no lifespan extension.

What leads to declining autophagy and a rising level of damage?
Accumulating damage itself leads to declining autophagy

When cellular organelles and proteins that are past their expiration date are broken down and recycled during autophagy, it turns out that some of the material cannot be completely disposed of. Much of this material is composed of lipofuscin, the toxic waste of aging.[2. Terman, Alexei. “Garbage catastrophe theory of aging: imperfect removal of oxidative damage?.” Redox Report (2013).]

Lipofuscin is all but non-degradable, and it accumulates with age.

Autophagy takes place inside cellular vesicles, called lysosomes, which are formed for that specific purpose. The inside of the lysosome is kept at an acidic pH, so that the autophagic enzymes will function optimally. These enzymes are inserted into the lysosome, along with the material that is to be broken down, and autophagy proceeds.

Some fraction of the material is impervious to breakdown, however, and this forms lipofuscin.

As lipofuscin builds up in the lysosomes, it impedes the process of autophagy. The cell continues to pour autophagic enzymes into the lysosome, but these are increasingly ineffective, as lipofuscin absorbs them and renders them useless. The entire process of autophagy becomes weaker.

Why autophagy is necessary

Most people understand that the constituents of our bodies turn over regularly, being broken down and rebuilt on a constant basis. Most of the cells and material in our bodies are not the same as they were earlier, so that it can be truthfully said that we literally are not the same person we were a few years before.

For example, red blood cells have a lifespan of about 120 days. If you were to take a blood sample from a person and determine the age of each red blood cell, you would find few to none that were older than that.

All of the red blood cells in your body were created within the last four months.

Why does this happen, and why is it necessary?

The constituents – cells, their organelles, and structural proteins and lipids – are subject to wear and tear. The most important source of wear and tear is due to metabolism, i.e. life itself.

When cells burn energy sources in order to power the processes of life, this burning releases byproducts, called free radicals, and these can and do damage to surrounding cell components. Think of it as the exhaust from a power plant, the pollution of which can cause damage to the surrounding area.
Cells have developed ways of coping with the byproducts of burning cellular fuel. One way is to contain and control them with internal antioxidants, such as glutathione, catalase, and superoxide dismutase. These may be likened to scrubbers in the exhaust stacks of a power plant.

The other way that cells have developed to cope with the inevitable damage caused by fuel-burning is to periodically replace the damaged components. Hence the process of autophagy.

**Mitochondria and aging**

Mitochondria are the cellular organelles commonly called “the powerhouses of the cell”, because most of the fuel-burning takes place in them.

As such, mitochondria are subject to greater damage from oxidation – fuel-burning – than other cell components.

Mitochondria are critical in aging. Older organisms have larger and more poorly functioning mitochondria, which pour out greater amounts of oxidizing free radicals, causing more and more damage.[3. Weber, Tobias A., and Andreas S. Reichert. “Impaired quality control of mitochondria: aging from a new perspective.” Experimental gerontology 45.7 (2010): 503-511.]

Since mitochondria are so subject to damage, they wear out, and cells use autophagy to eliminate damaged mitochondria, which are then replaced with new ones. This process must proceed efficiently for the cell to retain its full youthful function. Quality control of mitochondria is essential.

So, as organisms age and autophagy declines, older and poorly functioning mitochondria become prevalent.

To maintain youthful, fully functional, and efficient mitochondria, autophagy must work properly. Yet as we’ve seen, autophagy declines with age.

**Aging as a garbage catastrophe**

The inefficient and incomplete breakdown of cellular organelles and other components leads to increasing amounts of waste inside lysosomes, and it never goes away. This is the garbage catastrophe of aging. (See reference 2.)

From this perspective, it might be predicted that:

(i) suppression of oxidative damage would enhance longevity;

(ii) accumulation of incompletely digested material (e.g. lipofuscin pigment) would interfere with cellular functions and increase probability of death;

(iii) rejuvenation during reproduction is mainly provided by dilution of undigested material associated with intensive growth of the developing organism; and
(iv) age-related damage starts to accumulate substantially when development is complete, and mainly affects postmitotic cells and extracellular matrix, not proliferating cells.

There is abundant support for all these predictions.

Prevention of the formation of lipofuscin, i.e. cellular garbage, and/or removal of it when it exists, is crucial to slowing or stopping aging. For that purpose, it may not only be necessary, but sufficient.

Consider that when a cell divides, any waste material inside that cell is now cut in half. This may be the mechanism by which stem cells, which can divide throughout the lifespan of an organism, maintain perpetual youth. The dilution of waste material through cell division may also be the reason why even aged organisms always give birth to young progeny. By diluting the waste contents of gametes (sperm and eggs) continually, they’re maintained in a youthful state, with no aging damage.


Unfortunately for us, most of our cells do not divide continually. Heart cells and neurons, for example. So we’re stuck with cells that accumulate damage, because they can’t dilute it by passing it to numerous daughter cells.

**Lipofuscin**

What is lipofuscin anyway? If we can determine its composition, we may be able to understand how to prevent it and how to eliminate it.


Iron-containing proteins, such as ferritin, are subject to the normal turnover of cell components, and are broken down inside the lysosome. When this happens, free iron reacts with proteins and lipids, forming lipofuscin.

The enzymes that normally break down proteins and lipids inside the lysosome are not capable of breaking the chemical bonds formed in this reaction and that characterize lipofuscin.

Another important source of lipofuscin is so-called AGE, or advanced glycation end-products.[6. Yin, Dazhong. “Biochemical basis of lipofuscin, ceroid, and age pigment-like fluorophores.” Free Radical Biology and Medicine
AGEs are formed by the non-enzymatic reaction of sugars with proteins, and they can be broken down by the cell with difficulty or not at all. They occur in everyone but are higher in diabetes, which is characterized by high blood sugar. [7. Kalousova, M., J. Skrha, and T. Zima. “Advanced glycation end-products and advanced oxidation protein products in patients with diabetes mellitus.” *Physiological Research* 51.6 (2002): 597-604.]

Both iron and sugars are necessary for the formation of lipofuscin.

**The garbage catastrophe theory and the evidence**

Does everything outlined above agree with other evidence on aging and longevity? Consider the following.

1. Calorie restriction and fasting promote longevity, and they both are associated with increased autophagy.
2. Decreased insulin signaling promotes longevity, and it too is characterized by increased autophagy.
3. Substances that promote longevity also increase autophagy, for example resveratrol, metformin, berberine, curcumin, and lithium.
5. Some animals don’t age. The Hydra, a non-aging animal, continually renews its cells, i.e. it has no post-mitotic cells, thus diluting all its cellular damage, resulting in no aging. [9. Martinez, Daniel E. “Mortality patterns suggest lack of senescence in hydra.” *Experimental gerontology* 33.3 (1998): 217-225.]

The scientist Alexei Terman, of Linkoping University in Sweden, writes (reference 2):

> Clearly, if all damaged structures were renewed with perfect accuracy, aging would not occur. But the inevitability of aging suggests that the biological mechanisms of removal and re-synthesis are not perfect. Of these two processes, the one most suspect in the progression of aging is that of inefficient removal.

Full understanding of the nature of aging, therefore, requires an explanation of the reasons why the renewal process is imperfect, even under the most favorable conditions. As argued here, the basis of this imperfection may be in the incomplete removal of damaged biological material, which is necessary to make room for newly synthesized structures. This, in turn, may derive from the unfortunate fact that some of these damaged products are difficult or impossible to digest, particularly by the lysosomal compartment.
How to prevent and/or slow aging

Iron

I've argued that iron is the primary driver of aging, and looking at aging from the standpoint of the garbage catastrophe lends new support to this idea. Why?

Because iron is required for the formation of lipofuscin, the cell’s toxic waste.

Therefore, to slow the formation of lipofuscin, keep iron levels in the low normal range. Ferritin is the body’s main iron-storage molecule, and the more you have of it, the more will be turned over on lysosomes and the more iron will be left there, creating lipofuscin and catalyzing chemical reactions that damage cell structures.

Intermittent fasting

Intermittent fasting (and calorie restriction, which few people are willing to do over the long term) activates autophagy potently. Therefore fasting increases the clearance of damage. In older people, whose cells are clogged with garbage that inhibits autophagy, fasting may bring the rate of autophagy back to youthful levels.

Autophagy boosters

Certain substances/drugs can boost autophagy. These include resveratrol, hydroxycitrate, curcumin.

Exercise

Exercise increases autophagy and thus the clearance of cellular damage.

Normal blood sugar

Keeping blood sugar in the low normal range will help to prevent the formation of advanced glycation end-products (AGE), one of the constituents of non-degradable cellular garbage.

Experimental treatments

There have been a few reports of substances that can clear lipofuscin from cells. If these were to pan out, they could turn out to be potent anti-aging interventions.

One such substance is a form of cyclodextrin, which is a cheap safe molecule that is already used as an excipient in medicines.[10. Song, Wensi, et al. “2-Hydroxypropyl-β-cyclodextrin Promotes Transcription Factor EB-mediated Activation of Autophagy IMPLICATIONS FOR THERAPY.” Journal of Biological Chemistry 289.14 (2014): 10211-10222.]

PS: You can read more about these issues in my books Dumping Iron and Stop the Clock.

Follow me on Twitter.

Check out my Supplements Buying Guide for Men, where you’ll find many of the anti-aging supplements mentioned in this article.

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**Cracking the Aging Code: The Science Book of the Year**

In his new book, *Cracking the Aging Code: The New Science of Growing Old and What It Means for Staying Young*, Josh Mitteldorf, who has studied aging for decades and writes about it at his website, explores the science of aging and sets forth his own theory as to why we, and virtually all organisms above the level of bacteria, age. (The book has a co-author, Dorion Sagan, but the theory is Mitteldorf’s, and in any case, perhaps because I’ve been an avid reader of his website, the author’s voice seems like Mitteldorf’s alone.)

This is the science book of the year, the best I’ve read in quite awhile.
Mitteldorf is an expert in evolutionary theory (he used to be an astrophysicist), and deftly and skillfully expounds and criticizes the several current theories of aging. He then proposes his own radically different theory. And he’s very convincing. Whatever the fate of his theory, he brings enough evidence to bear both in its favor and against the other theories that, it seems to me, his theory must be reckoned with.

**A thorn in the side of evolutionary theory**

Aging has been a thorn in the side of evolutionary theory since the beginning. Even Darwin knew and understood this and could not see a way to incorporate aging into the theory of evolution.

Aging poses a conundrum for evolutionary theory because aging manifestly decreases biological fitness, causing lower reproduction and greater mortality. Why wouldn’t evolution have abolished it, or not allowed it to come into existence?

If an organism didn’t age, it would seem to have an advantage: it would never die of aging and it would continue to reproduce throughout its lifetime; hence the longer an organism lived, the more offspring it would leave, and the fitter in evolutionary terms it would be.

Indeed, we do see this in some organisms. Lobsters, for example, apparently do not age, but grow bigger and more fertile with the passage of time. (The record weight for a lobster was 44 lbs.) Mitteldorf describes some species of long-lived shellfish that are almost nothing but feeding and egg-laying machines, cranking out a million eggs daily.

But humans and most animals do age. Animals in the wild have a greater chance of death from predators and infections the older they are. Why hasn’t evolution put a stop to this?

One older idea, that of Peter Medawar, is that the force of natural selection declines with age. If an organism has aged and then dies, any genes that contributed to aging and death have already been passed to its offspring. The idea is that some genes that may cause aging are also necessary for growth and reproduction. Therefore natural selection is unable to eliminate the genes for aging.

Medawar’s idea led to the three main modern theories of aging.

**Mutation Accumulation**: Genetic mutations are always present in a population; in other contexts, this is known as genetic load. If a mutation is not severe enough to cause death, but causes only, say, a 1% decreased level of fitness, then these genes can stick around in a population for a long time. Essentially, natural selection has not had enough time to get rid of them. An example might be the ApoE4 gene, which raises the risk of dementia and heart disease.

But even a 1% difference in fitness is, as Mitteldorf says, “far from being invisible to natural selection”. Aging animals do not die of senescence.
usually, but they die at a much greater rate from disease and predators than younger animals. In some arctic species, 60% of deaths in the wild can be attributed to aging. Natural selection should be capable of eliminating the genes that cause this huge death toll, and to be able to do it quickly.

**Antagonistic Pleiotropy:** Some, maybe most, genes have multiple functions, and this theory says that genes with important functions in youth cannot be weeded out when they cause aging. An example of this might be the hormone IGF-1, which is involved in both growth and aging. Mice without it die shortly after birth — but high levels in older people are associated with cancer and higher mortality.

Mitteldorf describes the work of Michael Rose, who bred fruit flies for longevity in order to see what would happen to fertility. In theory, if he selected long-lived flies and bred them for longevity, their fertility should decrease, given antagonistic pleiotropy. But that’s not what happened; their fertility went up. So there seems no reason that nature can’t separate the function of fertility from aging.

**Disposable Soma:** Resources, usually in the form of food energy, are always in short supply, so this theory says, so that organisms must allocate these resources to different needs. Damage repair at the cellular level is one of those needs and is an important component of aging, since if the body can repair all of its damage, aging will not occur. So if resources are lacking, the organism allocates them preferentially to growth and reproduction, and essentially allows itself to age.

The huge counter to this theory is calorie restriction, the most robust life-extending intervention in lab animals. When they are literally starving, animals can live 50% longer than normally fed animals. If resource scarcity were causing aging, we could expect to see the opposite. If you ate more, you would live longer; but such is manifestly not the case. Eat more, die younger — and this holds true for virtually every species of organism which has been put to the test.

Same is true for exercise: if damage and repair are crucial for aging, exercise would make you age faster. Exercise causes damage — yet it makes animals, including humans, live longer.

**Hormesis**

Both calorie restriction and exercise are examples of *hormesis*, in which the application of a stress or toxin causes better health and longer life. The organism doesn’t just repair the damage, but becomes stronger and healthier than before.

Hormesis is central to Mitteldorf’s theory of aging. As he says, it looks as if the organism already has potent anti-aging capabilities that, in normal, “easy” times, it does not use. The organism is fully able to slow aging, when the conditions are right.

Aging is not damage that the body can’t control or that natural selection
can’t abolish. It isn’t due to lack of resources or pleitropic genes. No.  

**Aging is programmed.**

**Programmed Aging and Group Selection**

The theory of programmed aging clashes directly with the neo-Darwinian theory of evolution, which is the theory that represents current thinking in biology.

Neo-Darwinian theory states that natural selection takes place at the level of the gene, and only benefits individuals carrying that gene.

Mitteldorf’s theory of programmed aging relies on *group selection*, a notion that most evolutionary scientists say cannot exist.

Hence my description of Mitteldorf’s theory as radical, since it takes on the entire neo-Darwinian synthesis, and the scientists that back it.

In this light, it’s of more than passing interest that Mitteldorf’s mentor has been another proponent of group selection, David Sloan Wilson, the author of the masterful book *Darwin’s Cathedral: Evolution, Religion, and the Nature of Society*.

The programmed theory of aging sees aging as a “suicide program”, one that is of no benefit to the individual but which is of great benefit to the group. The organism dials up genes that cause inflammation and other forms of damage, leading to aging and death. Aging is a deliberate effort on the part of the organism, not something it tries to avoid.

Why would organisms do this? The benefit to the group would have to be a very powerful one in order to override the harm to the individual. And indeed it is, according to Mitteldorf.

Organisms age in order to avoid extinction.

In any successful group of organisms, it seems easily possible for the group to overshoot its environment and to succumb to famine or other causes.

All animals are predators in some way or other, depending on other life forms for sustenance, and if the animals are too successful, they risk famine or epidemics and subsequent extinction of the entire group.

Aging is the organisms’ way of buffering the population. In good times, with plentiful food, organisms age and some of them die, thus keeping the group within its environmental limits and in tune with its ecology. The group thrives.

In bad times, with fewer available resources, aging slows. The species does not want every member to die at once, of famine or some other cause. It wants to avoid extinction, an event which means the demise of every gene carried by the species. When the crisis is over, aging resumes.
Criticism

Mitteldorf supplies abundant evidence for his theory, and it makes for fascinating reading. While reading it, I thought of a few objections, which wasn't easy, as the author is convincing. Note that I am not an evolutionary biologist.

Aging seems too messy a process to be a “suicide program”. If you think of all the ways that aging causes damage, illness, and death, how could multiple sources of these things arise? One gene that caused death would be a lot simpler, and the fact that aging apparently has multiple genetic roots makes one wonder how it could arise by natural selection.

Admittedly, this objection is probably more a matter of taste than of empirical backing.

Another objection is that the mere passage of time seems involved in some aspects of aging, for example, in the accumulation of iron or exposure to antigens.

Iron seems a good example of pleiotropic effects: it’s necessary for growth and reproduction, but causes aging. Furthermore, natural selection might be unable to eliminate its effects on aging. Women with higher iron are more fertile, which might swamp the effect of natural selection on iron causing aging after a person has already had children.

Antigen exposure comes from infectious agents, and is a primary cause of inflammation in aging. The longer we live, the more antigens we’re exposed to, and in fact those exposed to more diseases die younger, i.e. they age faster. But perhaps the organism can’t dial down inflammation, since we need it to fight off pathogens.

Conclusion

Cracking the Aging Code is the best book I’ve read this year, and should be required reading for anyone interested in aging or indeed evolution and biology. Mitteldorf skillfully wends his way through evolutionary theory, its history, and the biology of aging – he even knows his chops when it comes to field biology and ecology.

At the end of the book, he discusses the prospects for anti-aging research as well as what he believes are the best means of slowing aging that we have right now.

His ideas about slowing aging are, I’m happy to say, very much in tune with what I’ve expounded on this site: exercise, intermittent fasting, supplements like berberine and curcumin, aspirin, and more. (He should have mentioned iron.) On the horizon are technical developments like telomerase therapy, which hold great promise in getting to the root mechanisms of aging.

So go read this book.
PS: I cover some of the same ground as to the best way to fight aging in my book, *Stop the Clock: The Optimal Anti-Aging Strategy*.

PPS: Check out my Supplements Buying Guide for Men.

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**The 80/20 Rule in Fighting Aging and Obesity**

Vilfredo Pareto first formulated the rule named after him, the Pareto Principle, or as it’s now often known, the 80/20 Rule. The rule states that in many phenomena, 20% of the inputs generate 80% of the results — so as a practical matter, you should be focusing on those 20% of inputs, whether you are studying them or want to improve them. We can usefully apply the 80/20 rule in fighting aging and obesity.

**Aging and obesity**

A recent review paper noted that aging and obesity share many biological hallmarks. (1) This indicates that they share common mechanisms.

The hallmarks shared by obesity and aging include:

1. Excess adipose (fat) tissue
2. Inflammation
3. Multi-organ damage
4. Cognitive dysfunction
5. Insulin resistance
6. Impaired muscle function
7. Immune dysfunction
8. Osteoporosis — a high fraction of fractures in the elderly occur in the
In addition, calorie restriction, the most robust life-extending intervention known, has obvious implications for both obesity and aging. One reason calorie restriction works is by causing lower fat mass.

In a nutshell, obesity accelerates aging.

Given the shared characteristics of obesity and aging, staying lean could be one of the most effective anti-aging strategies currently available.

**Muscle and bone loss**

Loss of muscle and bone are hallmarks of aging, leading to sarcopenia and osteoporosis respectively. Both result in loss of function and frailty – the inability to perform daily activity without assistance.

Strong bones, a high muscle mass, and leanness are all characteristics of youthful people, whether men or women.

Aging means less muscle, weaker bones, and more fat, all wrapped up in a stew of insulin resistance, inflammation, and oxidative stress.

**The 80/20 Rule**

What are the 80% of outputs that we want in order to stay in a youthful condition? For instance, how much do we care about grey hair or wrinkles? Sure, it’s great not to have these, but we don’t want to concentrate our efforts on avoiding them, which is elusive in any case.

Our main outputs of interest will be less fat tissue, higher muscle mass, and along with these, less inflammation, greater insulin sensitivity, less oxidative stress, better autophagy.

Less fat tissue and more muscle mass are your 80% of desirable outputs.

Therefore, your 20% of causative inputs are those that most lead to less fat and more muscle.

Taking muscle first, weight lifting is the most effective means of increasing muscle. While all exercise is beneficial, for the twin purposes of remaining youthful and fat loss, weightlifting is the way to go. Aerobic exercise doesn’t come close in either category.

For fat loss, diet is much more important than exercise. And when you eat is as important as what you eat. I’m a partisan of both low-carb high-fat diets (LCHF) and intermittent fasting. Even if you’re already lean, a LCHF diet can keep you that way, and periodic intermittent fasting boosts the anti-aging process.

The most important 20% of inputs that fight aging and obesity are:
1. Weight lifting
2. LCHF diet
3. Intermittent fasting

Once you are lean and muscular, you should continue to practice these.

After you have your desired 20% of inputs in place, you can look at the other 80%. These include supplements, keeping iron low, exposure to natural settings, love and friendship, optimal levels of sex hormones, and quite a few others.

**PS:** For more, see my books, *Muscle Up, Stop the Clock*, and *Dumping Iron*.

**PS:** Check out my Supplements Buying Guide for Men.

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**Do Microbes Cause Aging?**

Microscopic organisms – bacteria, fungi, protozoa, and viruses – are extremely abundant on the planet; the estimated number of bacteria alone is ~5 x 10^30, and their total content of carbon, nitrogen, and phosphorus weighs more than all plants put together.¹

Many of these organisms are capable of either living in or on humans, and some of them cause disease when they do so.

Humans and indeed all organisms possess more or less elaborate means of protecting themselves from microbial invaders. We normally think that certain sites of our bodies are meant to be off-limits to microbes, and other sites to be loaded with them. The human mouth, gut, and skin are loaded with microbes, but generally other body sites are supposed to be sterile – the
blood, for instance.

But scientists have recently discovered that the blood of healthy people (blood donors) contains an abundance of bacteria and viruses.(2)

These microorganisms get into the blood presumably through breaches in the tight junctions in the gut, through the lungs, and the skin.

What they’re doing there is anyone’s guess just now. It was formerly thought that any bacteria in the bloodstream caused disease – sepsis – but apparently not.

The blood of patients with cardiovascular disease is higher in bacteria than in healthy controls, from 40- to 70-fold higher, which suggests that there could be a link between these bacteria and heart disease.(3) It’s already known that periodontal disease increases the risk of heart disease, apparently even when controlling for socioeconomic status.(4) It could be that the pockets of oral infection shed bacteria into the bloodstream, leading to increased heart disease risk.

A new book by Michael Lustgarten, PhD, Infectious Burden: The Cause of Aging and Age-Related Disease, makes the case that these new discoveries show that microorganisms are intimately involved in aging and in fact may cause aging. (The book is free for the next several days.)

Lustgarten shows that microbes are involved in many diseases that increase with age, such as heart disease, cancer, and Alzheimer’s.

Older people get many infections

As people get older, their susceptibility to infections increases due to declining immune function.

So is the increased number of infections due to aging, or do the bacterial, viral, and fungal agents of infection cause aging?

Certainly, finding that bacterial numbers are greatly increased in heart disease, and that bacteria (Treponema) and fungi may be important to Alzheimer’s disease is important.

Do these increased numbers result from a lack of immunity?

In most infections, the agents causing the disease are pathogens, i.e. they are capable of causing disease when they invade a host. Think of Salmonella, for instance, which may be normal flora in some animals but causes serious illness in humans.

In other infections, the organisms are opportunistic, causing disease only in debilitated subjects (e.g. pneumocystis pneumonia in AIDS patients), or causing disease when they get somewhere they don’t belong (e.g. E. coli and urinary tract infections).

Therefore, it’s not a simple matter to say when an organism is causing a
disease and when it just happens to be there. Everyone has bacteria on their skin, for instance, but few people have skin infections.

Likewise, if healthy people have bacteria in their bloodstreams, but no apparent illness, what’s going on?

So, we already know that elderly people are subject to increased infections; we may yet confirm that microorganisms are causative in heart disease and Alzheimer’s. But are these microbes causing aging, or these diseases, or is a great part of their power that they hit aging and/or debilitated people?

Older people have increased amounts of iron in their bodies, and more of it is unregulated, i.e. not bound to ferritin. And iron increases infections. Microorganisms require iron for growth, and usually have a hard time getting it; having a lot of it around is just giving pathogens what they need.

So if bacteria and fungi are in the brains of Alzheimer’s patients, what’s causing the Alzheimer’s, iron or pathogens?

Alzheimer’s has also been characterized as type 3 diabetes, and in diabetes, blood sugar levels are high, again providing pathogens with a required nutrient. Diabetics have up to a 10-fold increased incidence of urinary tract infections for that reason: glucose in the urine feeds bacteria.(4)

My judgment on whether microbes cause aging is that the case is very provocative but not proven.

What to do about microbes and aging

In his book, Dr. Lustgarten makes a number of suggestions as to what to do about microbes as they relate to aging. For example, he suggests using soaps that do not raise the pH of skin (most of them do), so as to maintain the skin barrier function. (He didn’t suggest going all the way and not using soap at all. That’s for us radicals.)

He also suggests ways to maintain the barrier function of the gut, which is indeed important, as well as ideas for promoting good oral health.

However, bacteria are everywhere, and while you can keep the numbers of those that get into the body way down, you can’t keep them out entirely.

Good oral hygiene has been shown to decrease the number of incidents of pneumonia in the elderly who live in nursing homes, but will it do the non-elderly and reasonably healthy any good?

It’s a good question. While infected gums are associated with heart disease, is this just an association? People with infected gums and missing teeth are very likely to neglect their health in other ways.

And if healthy people have bacteria in their blood but no heart disease or other illness, what does that mean? Will keeping bacteria out of your body help you at all?
We simply don’t have all the answers yet.

My take on prevention is that a sound and healthy immune system is the best defense. While you don’t want huge numbers of even allegedly non-pathogenic bacteria pouring into your bloodstream, it appears that it may be next to impossible to keep them all out.

A healthy immune system is the result of everything else that makes for good health: diet, exercise, sleep, supplements, etc.

Infectious Burden presents a provocative thesis, and we will undoubtedly learn much more about the role of microbes in aging in the years to come.


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**Weightlifting Is Anti-Aging**

In my book Muscle Up, I gave a host of reasons why strength training – which most people accomplish through lifting weights – is a uniquely healthful exercise and much better than aerobic or endurance exercise. Among these reasons are lower risk of heart disease and cancer, and a far better record at fat loss than endurance exercise. And weightlifting is anti-aging.

As an anti-aging intervention, weightlifting fights the loss of muscle (sarcopenia) that starts early in life, in the thirties, and maintains high insulin sensitivity, the loss of which is a main cause of the maladies of age.
Telomeres

Telomeres are the caps on the ends of chromosomes, and they shorten with age. Dr. Michael Fossel, one of the world’s foremost scientists in the field of aging research (whom I interviewed), believes that telomere shortening is the key process in aging: prevent telomere shortening, and you prevent aging.

Interventions that promote good health, such as exercise and fasting, lead to slower telomere shortening, and those that promote poor health, such as obesity and smoking, lead to faster telomere shortening.

**Weightlifters have longer telomeres**

Endurance athletes who are suffering from fatigue and overtraining have shorter telomeres.(1) These people have arguably passed to the wrong side of the hormetic U-shaped curve, and got to the point where too much exercise was harming them, just as Ryan Hall did, formerly America’s fastest runner, who retired due to chronic fatigue and low testosterone.

Endurance athletes who do not overtrain appear to have normal telomeres.

What about weightlifters?

An analysis was done using a group of power lifters with an average of 8 years of training behind them, and comparing them to a group of “healthy, active subjects with no history of strength training.”(2)

The authors of the study say that wanted to understand “whether long-term practice of sports might have deleterious effects on muscle telomeres.”

Result: not only did power lifting not have deleterious effects on telomeres, but the power lifters’ telomeres were longer than the non-strength-trainers.

Even more interesting, telomere length in the power lifters was strongly correlated with maximum lifts in the deadlift and squat.

The more weight the power lifters were able to lift, i.e. the stronger they were, the longer their telomere lengths.

**Correction:** Commenter Tom pointed out that I got some of this this wrong, and indeed I did.

The article I linked says, “There was no abnormal shortening of telomeres in PL. On the contrary, the mean (P = 0.07) and the minimum (P = 0.09) TRF lengths in PL tended to be higher than in C.” OK, so far so good, telomere lengths tended to be higher in the power lifters than in healthy, active controls.

But, “In PL, the minimum TRF length was inversely correlated to the individual records in squat (r = -0.86; P = 0.01) and deadlift (r = -0.88; P = 0.01).” In the measurement of telomere lengths, distinctions must be made, because they’re not all the same length in different cells in the same
person. So, minimum telomere length is of interest, and these significantly correlated to max lifts in the power lifters, i.e. the more they could lift, the shorter the minimum telomere lengths.

Since power lifters tended to have longer telomeres overall, it’s not clear to me how the minimum telomere length bears on their health and longevity. The article states, “These results show for the first time that long-term training is not associated with an abnormal shortening of skeletal muscle telomere length. Although the minimum telomere length in PL remains within normal physiological ranges, a heavier load put on the muscles means a shorter minimum TRF length in skeletal muscle.”

More muscle, less obesity

An animal experiment (in mice) found that overexpression of a certain gene that leads to more muscle hypertrophy (growth) “can regress obesity and resolve metabolic disorders in obese mice”.(3)

The results included

- atrophy of visceral adipocytes (fat cells)
- regression of fatty liver
- improved insulin sensitivity (an important aging correlate)
- lower levels of glucose, insulin, and leptin

All of this occurred with no changes in food intake.

In Muscle Up, I cited many studies in humans that showed that weightlifting produced far better results in terms of fat loss than endurance training. In essence, weightlifting works, endurance training doesn’t.

The cited study above on mice gives us a biochemical and physiological rationale for how more muscle means less fat. By changing the hormonal milieu, the body sheds its fat, and strength training produces the desired hormonal changes.

The nub of the matter

Weightlifting leads to less shortening of telomeres, and more muscle leads to hormonal changes that conduce to less fat tissue and better insulin sensitivity.

All of these are important to any anti-aging program.

Weightlifting is a unique component of such a program, since its benefits are not matched by endurance training, and it confers benefits that even the best dietary program won’t give you.

Of course you need to eat right to slow aging, but if weight training is not in your anti-aging rotation, you’re missing a major aspect of slowing aging.
How I Plan to Reach 110 Years of Age

It’s strange. At 61 years old, according to statistics and common knowledge, I’m supposed to be getting to the point where age-related diseases start to
Aside from the usual, dreaded ones like cancer and heart disease, there’s also obesity, arthritis, and sarcopenia waiting for me. And I’m supposed to feel tired and out of it.

But I don’t feel old at all. While comparisons are difficult, when I was 18, I was out-of-shape and smoked cigarettes, and I certainly feel better now.

My hair is even getting darker. (I should write a separate post on that.)

So, far from feeling like I’m about to hit old age, I feel like there’s no reason I can’t get another 50 years out of my brain and body.

One often reads about centenarians and how they reached that age. The vast majority I would characterize as lucky: they have the right genes.

Most of them appear to have done little in the way of health interventions. The longest-lived person ever, Jeanne Calment, who died at the age of 122, smoked cigarettes most of her life. That’s not to say that some haven’t inadvertently done some good things for their health; for instance, when you read of someone who eats bacon and eggs every day but avoids donuts, or only eats one meal a day instead of eating around the clock.

Jack LaLanne, fitness buff extraordinaire, reached 96. His brother Norman, who apparently didn’t much take care of his health at all, made it to 97.

But did Jack LaLanne do everything right? While he certainly did many things right, he was fond of juicing, which adds a lot of sugar if it’s fruit juice, he took liver tablets, which are high in iron, and he ate a low-fat diet. Not criticizing him at all, but one must have proper knowledge, and he was mainly flying by the seat of his pants, or so it appears.

Hopefully we have a little better knowledge now. We also have to keep an open mind to new things, and to revise our beliefs if necessary. (Harder to do than it looks.)

So how do I plan to make it to 110? Here’s how.

**Weightlifting**

Muscle loss begins at age 30 (though barely perceptible then) and by the time someone is 80, they’ve typically lost half their muscle. Muscle loss leads to insulin resistance, obesity, and debility.

To live healthily to an old age, it’s essential to build and keep muscle, and to keep fat tissue off.

The average old person is, physically, a mess, with lost of muscle loss and plenty of fat tissue to replace it.(1) Too much fat is detrimental to long life.(2)
Low-carbohydrate paleo diet and intermittent fasting

High-carbohydrate diets speed aging through insulin and IGF-1 signaling. Low-carbohydrate diets, and intermittent fasting, slow aging. Fasting results in improved mitochondrial function and number, making it strongly anti-aging.

Paleo diets avoid destructive food elements even more so. Omega-6 fatty acids from vegetable oils, for instance, and sugar.

So I’m planning to maintain a low-carb paleo diet, with intermittent fasting days, the rest of my life.

Polyphenols

Polyphenols are plant-derived chemicals found abundantly in coffee, tea, chocolate, red wine, fruits (especially berries) and vegetables. They are associated with markedly better health and lower death rates. They extend life in lab animals.(3)

I’m covered. I have no intention of ever giving up coffee, tea, and red wine. Or chocolate. I also supplement with resveratrol, green tea extract, and curcumin, all of which are polyphenols.

Iron

Iron accelerates aging, leads to heart disease, cancer, Alzheimer’s, and infections, and lots of other nasty things. I’ve lowered my ferritin to, at last check, 77, and plan to go lower. Keeping iron low is the most underrated factor in health. Read my book, Dumping Iron, to find out the several ways you can keep iron in the low normal range.

Vitamin D, magnesium, fish oil, and zinc

Fortunately, vitamin D is now no longer as obscure as it was just a few years ago. It is a must for avoiding premature death.

Magnesium is the nutrient most people are most likely to be deficient in, and it’s required for good health. It prevents sudden cardiac death, raises T levels, and promotes mental health.

Fish oil, with its high content of omega-3 fatty acids, helps prevent heart disease and keeps your brain in working order.

Zinc is important for immune function, and can reverse thymus atrophy, an important cause of immune decline in older people.
Sense of purpose

Here’s where we come to a more nebulous input. Too many older people, but especially the men, appear to have little sense of purpose, and use their time watching television or with other aimless pursuits. Forget about retirement. Read good books, write, lift weights, start a business, go into politics – anything but the dreaded years of sitting on your backside and watching yourself head towards death.

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PS: Check out my Supplements Buying Guide for Men

Ten Questions and Answers with Dr. Michael Fossel

Michael Fossel, M.D., PhD, is the author of The Telomerase Revolution, The Immortality Edge, and Cells, Aging, and Human Disease. He is the president and co-founder of Telocyte, a company that aims to use telomerase therapy to cure Alzheimer’s.

Dr. Fossel believes that the shortening of telomeres, the caps on the ends of chromosomes, is the fundamental process behind aging, and his most recent book makes a convincing case for it. You can read an explanation of the telomere theory of aging here. In essence, as telomeres become too short after repeated cell divisions, the cell is unable to clear damaged molecules, and ultimately enters a state of senescence, and this is responsible for aging.

As I read the book, a number of questions came to mind, and Dr. Fossel agreed
to answer them.

If the theory holds true and the technology is successful, we could be on the verge of a huge breakthrough in aging. Dr. Fossel asserts in his book that within a decade or two, we will be able to extend human life to up to several centuries in length.

Below are my questions with Dr Fossel’s answers. I thank Dr. Fossel for responding to my questions.

1. Some components of an aged cell appear to be very difficult or impossible to degrade, for example lipofuscin. How would the resetting of telomeres solve this problem?

A. Actually, lipofuscin, like almost all molecules, is NOT a molecule that passively and gradually accumulates, but rather represents a dynamic pool in which it is continually being produced (anabolism) and broken down (catabolism). The reason that it increases in some cells is that the overall rate of turnover (both anabolism and catabolism) decreases and permits the gradual increase in the percentage of denatured molecules. Parallels are found in all other molecular pools (such as beta amyloid), both intracellularly and extracellularly, as well as in cell populations themselves (such as occurs in the dynamic turnover of bony matrix via osteoblasts v osteoclasts). In short, we need to remember that lipofuscin is not simply “garbage” that accumulates passively, but is actually a reflection of slower cell product “recycling”. The rate of that recycling is directly correlated to telomere loss: the shorter the telomeres, the slower the rate of molecular and cellular turnover. Once we increase telomere length, we increase gene expression, increase molecular turnover, and bring lipofuscin levels back to those typical of “young” cell function.

2. You write in your book about how the shortening of telomeres changes gene expression so that molecular turnover becomes slower and damaged molecules accumulate. Yet the pattern of gene expression changes, not merely slows, with some gene products becoming more abundant with age, for example TNF alpha. Why does a change in the pattern and not merely the rate of gene expression contribute to the accumulation of damage?

A. It always depends on the gene in question. In the case of most inflammatory gene products, for example, the result in increasing (and increasingly inappropriate) gene responses. Overall, most enzymes, for example those involved in DNA repair, show a decrease and almost all protein and other molecular pools (lipids and glycoproteins, for example) show a slower rate of turnover. In the case of many markers, however, such as inflammation, ROS (production, leakage, and concentration), the levels rise, often due (as with ROS issues) to the slower turnover rates of the enzymes responsible for those levels. The key is that gene expression CHANGES and while almost all direct changes are to lower gene expression, indirect changes are legion. If I, for example, lower the gene expression of one gene, it may well induce a secondary increase in the expression of a second gene.
That’s the beauty and the complexity of epigenetic (as opposed to genetic) relationships.

3. Perhaps the most accepted theory of aging at the moment concerns the pro-
aging effects of insulin and IGF-1 signaling. Can that be reconciled with the
telomere theory? What are its shortcomings, if any, in your opinion?

A. That’s not a theory, has no logical supportive data, and is naïve. They
look at a small segment of biology and (unsuccessfully and with internal
contradictions) try to paste together a theory. It’s no better than trying to
explain aging by reference to hormones or ROS alone: it fails to explain
anything but the most myopic selection of data, clinical facts, or
interventive predictions. Phlogiston was a better basis for physics and
humors a better basis for medicine than is the attempt to explain all of
aging on the basis of insulin and IGF’s.

4. Another theory has it that aging is a “quasi-program” (Blagosklonny), a
continuation of the development program. Do you think this is
plausible/correct? Does it conflict with the telomere theory?

A. Aging certainly isn’t merely something that “happens”, but I have a hard
time fitting it into a single teleologically loaded word such as “programmed”
or even “quasi-programmed”. Once we pick a loaded word like that, people (on
both sides of the argument) stop thinking. It reminds me of the problem that
occurs when we label (for example) penicillin as an “antibiotic”. We then
stop thinking reasonably and begin to assume that it can’t be an anti-viral,
anti-chlamydial, or anti-fungal agent. As you may know, penicillin is an
excellent agent for causing seizures if applied to the vertebrate brain after
removal of the meninges, yet no one thinks of it that way. In regard to
aging, however, I would say that aging is NOT a continuation of “the”
developmental program that takes an organism from zygote to adult. I would,
however, say that aging has advantages to species adaptation and survival.
Once again, however, I deprecate the use of the word “programmed” simply
because it carries unintentional denotational baggage and misleads the
discussion into the idea of teleology, as though nature “chooses” to have us
age. Nature has no “intentions” and doesn’t “program” what happens to
biological systems. That is wobbly thinking of the worst sort and makes me
suspect that humans are incapable of facing reality at all. Nature simply is:
aging occurs because some species that age are a bit more likely to survive
(as species) that others that don’t. Things that survive, survive. That’s all
there is to evolution.

5. What would you say would count as evidence against the telomere theory of
aging?

A. There is no evidence against the telomere theory of aging, but there are a
great many people who don’t understand the telomere theory of aging. They 
start with naïve misunderstandings, erroneously attribute them to “the 
telomere theory of aging”, find irrelevant counter-examples, and then declare 
victory. The most common example is telomere length. People note that some 
mouse varieties have longer telomeres and shorter lifespans than humans and 
conclude that the telomere theory of aging is wrong. The telomere theory of 
aging would actually say that telomere length per se has absolutely nothing 
to do with aging in cells or otherwise. Cell aging is NOT related to telomere 
lengths but to CHANGES in telomere length. In my book, I’ve cited several 
other examples of naïve criticisms, often based on either an ignorance of the 
theory or an ignorance of human pathology, but there are several other 
similar “strawman arguments” made that are not so much “evidence against the 
telomere theory of aging” as they are evidence against the knowledge and the 
logical abilities of those who espouse them.

6. Would you agree that interventions that result in good health, for example 
exercise or fasting, result in slower telomere shortening, and that 
conditions that cause worse health, say obesity or smoking, increase telomere 
shortening?

A. Yes.

7. You state in your book that within the next decade or two, we will be able 
to lengthen the human lifespan to perhaps several centuries. What is the 
ground for such optimism?

A. Theory, cell data, tissue data, and organism data. That includes both 
animal and human studies.

8. Is there currently a good way to lengthen telomeres or activate 
telomerase? Is there good evidence that TA-65 works?

A. There is fair evidence (not “good”, just “fair”) that TA-65 works in 
humans.

9. It seems to me that interventions that increase autophagy, such as 
intermittent fasting or the use of autophagy promoters like hydroxycitrate or 
resveratrol, are the best way we currently know to increase turnover of 
damaged molecules and hence to counteract the aging process. Would you agree?

A. No.

10. You emphasize in your book that cell division and not passage of time 
causes aging. Yet the accumulation of iron (and to a lesser extent other 
metals) promotes aging and disease, an effect which could be ascribed to the 
passage of time. The human body has no means of excreting excess iron. 
Wouldn't this issue need to be dealt with in addition to lengthening 
telomeres?

A. Not true. The human body DOES excrete iron, it just has no ACTIVE 
mechanism for excretion and it can’t excrete excess iron beyond a fixed
amount. There is passive excretion in both menses and stool, which roughly balance intake over the lifetime, but there is an overall imbalance if the menses are too great (iron loss) or if iron intake is even slightly too high (iron gain). In most healthy adults (even in old age) the passive loss of iron is sufficient to prevent an overall iron saturation.

Notes: Calorie restriction is currently the most robust means of increasing lifespan, and much of its efficacy appears to be due to increased autophagy, which breaks down and recycles damaged molecules. (Question 9.) Unfortunately, men and post-menopausal women do not have menses, and many adults have far too much body iron, as documented in my book. (Question 10.)

Iron Shortens Telomeres and Damages DNA

I’ve been reading the new book by Michael Fossel, The Telomerase Revolution: The Enzyme That Holds the Key to Human Aging and Will Soon Lead to Longer, Healthier Lives. I think anyone who finds the material on this site to be of interest will find the book an enlightening, enjoyable read.

Fossel’s thesis in the book is that telomeres are the ultimate cause of aging. Telomeres are caps on the ends of chromosomes, and with each cell replication, the caps become shorter. Once the telomeres become short enough, all kinds of cellular malfunction occurs, and ultimately the cell becomes senescent. Since all aging and the diseases associated with it are ultimately caused at the cellular level, shortening of telomeres provides a mechanism for the phenomenon of aging.
**Shorter telomeres mean lower cell turnover**

Aging is associated with the accumulation of cellular damage. When we’re young, the constituents of our cells turn over at a high rate; essentially, the constituents — proteins, lipids, organelles — are broken down and replaced often. As we age, this process slows, allowing for the accumulation of damaged cell parts, and they don’t function as well. Fossel ascribes this to shortened telomeres leading to changes in gene expression, in turn leading to lower turnover of cell constituents.

Several companies are at work researching how to lengthen telomeres. One product (that I’m aware of) has been developed: **TA-65**, an expensive supplement that activates telomerase, the telomere-lengthening enzyme. (For what it’s worth, many of the Amazon reviewers say it works well. I’m tempted to try it.)

Meanwhile, what can you do to keep telomeres from shortening at a faster rate than normal?

For starters — and maybe the most important thing — keep iron levels low.

**Oxidative stress shortens telomeres**

Oxidative stress caused by iron is known to shorten telomeres(1, 2), and iron is probably the most important cause of oxidative stress.

While users of multivitamin supplements had about a 5% longer telomere length than non-users, those who took iron supplements had 9% shorter telomeres.(3)

People with iron overload also have shorter telomeres.(4)

**Iron damages DNA**

Excess iron, and in fact, probably any level of iron, also causes DNA damage. Since telomeres are made of the same bases as DNA, damage to DNA not can cause cancer or other diseases of aging, but directly promote aging itself.

It’s been shown that body iron stores are highly correlated to the amount of DNA damage.(5) See the chart below, taken from the paper that found this result. Urinary 8-OHdG is a measure of DNA damage.
Of more than passing interest in this paper, the subjects were divided into tertiles (thirds) of ferritin levels. Among fertile women, the lowest tertile was a ferritin of <17, the highest >36; among men, the lowest tertile represented those with a ferritin of <98, the highest >180. This shows the much greater levels of iron that men normally have, and is connected to their higher rates of disease and earlier death than women.

So, for now, it looks like the best thing to keep telomeres longer is to keep iron low. We already know that iron is a strong driver of aging, and shortening of telomeres could be the proximate cause.

Of interest, if the way that telomere shortening causes aging is through decreased turnover of cellular constituents, speeding up the turnover to more youthful levels may counteract this effect. The best way to do that is through intermittent fasting, which promotes autophagy, the cellular self-cleansing process, and speeds turnover of damaged cellular constituents.

Both fasting and exercise, as well as a low-carbohydrate diet, improve insulin sensitivity, and worse insulin sensitivity (high insulin resistance) is associated with shorter telomeres.(6)

**PS:** To learn how to use supplements to lower iron, see my Supplements Buying Guide for Men, as well as my new book, Dumping Iron.
How to Make Cheap Anti-Aging Supplements

There are a number of supplements that are marketed as having anti-aging activity, and that are expensive. The two that are best-known to me are Protandim and Longevinex. But let’s see how to make cheap anti-aging supplements.

Protandim and Nrf2

Protandim is marketed as “The Nrf2 Synergizer”, since it up-regulates the cellular stress defense mechanisms via the Nrf2 (nuclear erythroid factor 2) system.(1) When Nrf2 is activated, the so-called phase 2 enzymes are produced; these include catalase, superoxide dismutase, and various enzymes that catalyze metabolism of xenobiotics, including drugs. Notably included in the phase 2 group is ferritin, which captures free iron and prevents it from doing damage. They prevent oxidative stress, cancer, and probably lots of other maladies of aging.(2)

The Nrf2 system is up-regulated by contact with foreign molecules that need detoxifying. Hence it can be seen that this system is involved in hormesis, in which low doses of a toxin or other input such as exercise or fasting produce beneficial health effects.

The ingredients in Protandim promote hormesis. They include milk thistle extract, bacopa extract (whatever that is), ashwaghanda, turmeric extract (i.e. curcumin), and green tea extract.

As it happens, I’m already taking two of these, curcumin and green tea extract, which is what inspired this post.

Protandim retails at Amazon for just under $35 for 30 capsules, or a one-
month supply. Seems to me that this could be done a lot cheaper.

**Longevinex and calorie restriction**

*Longevinex* is another supplement in the same arena. It claims to be designed to mimic *calorie restriction*, the robust life extension intervention. (Many of the benefits and few of the downsides of calorie restriction can be obtained through *intermittent fasting*.)

The ingredients of a capsule of Longevinex are vitamin D3 (1000 IU), and 244 mg of a proprietary blend of resveratrol (at 100 mg per capsule), unknown quantities of *inositol hexaphosphate (IP6)*, *quercetin*, chlorogenic acid, green tea extract, and “nucleotides”.

Longevinex *retails for about the same price* as Protandim, or about $34 for a 30-day supply. Their new product, Advantage, retails for $50 a month.

Let’s say I wanted to both activate my Nrf2 system and mimic calorie restriction using these premium products. That could cost me a minimum of $70 a month, or $840 a year. Also keep in mind that most people buying these products don’t know much or even anything about their ingredients, and probably think of these products as unique or magical. (Not that they aren’t backed by science; they are.)

**My cheap anti-aging supplements**

As it happens, in my rotation of supplements I have curcumin, green tea extract, IP6, and resveratrol, providing many of the ingredients of both of these. Chlorogenic acid, an ingredient of Longevinex, is found abundantly in *coffee*, and may provide many of its benefits. And I do drink coffee.

Many of these are cheap. *IP6 in bulk is about $20 for 250 grams* (over half a pound); at 500 mg a day, that will last 500 days. *Green tea extract is $14 for 250 capsules*, and since I don’t take one even every day, that should last a year.

I could go on, but you get the idea. Curcumin is the only one that’s relatively expensive, but even here, at *$26 for 120 capsules*, and not taken every day, that will last quite awhile.

It’s worth noting that neither proprietary supplement contains *aspirin*, which not only may be the most potent anti-aging drug available, but is dirt cheap. I take aspirin too.

So, we see that expensive, proprietary anti-aging supplements can easily be, if not duplicated, at least reasonably imitated with cheap OTC, generic supplements.

Is it possible that we’re not getting all of the benefits of Protandim and Longevinex because some of the ingredients are missing? Sure, it’s possible. I’m not taking milk thistle, ashwagandha, or quercetin.
But is it likely we’re missing any of the benefits? That seems highly doubtful to me.

For one thing, I already practice an intervention that mimics calorie restriction, namely intermittent fasting. I also exercise, another hormetic process.

Maybe more importantly, I drink coffee, tea, and red wine, and eat chocolate, which provide high levels of dietary polyphenols and greatly lower disease risk. I have difficulty believing that the other ingredients in the two proprietary supplements would add anything of value to what I already do.

I also eat vegetables, especially broccoli, onions, peppers, and the like, which strongly up-regulate the Nrf2 system. Broccoli and other cruciferous vegetables are known to have a strong anti-cancer effect. Again, given my intake of these and other dietary components high in hormetic constituents – like the aforementioned coffee, etc. – it’s doubtful that Protandim and/or Longevinex would add in any appreciable way to the health benefits I already get.

So, instead of spending beaucoup bucks on Protandim and Longevinex, consider doing it my way, the cheap way. It will likely provide more and better anti-aging effects anyway.

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

PS: Check out my Supplements Buying Guide for Men.

Iron Chelators More Effective Than
Rapamycin for Life Extension

The scientist Mikhail Blagosklonny is best-known for his advocacy of the “quasi-program” theory of aging. What this means is that aging is the continuation of the development program; certain genes that are absolutely necessary for organism development, when continued after maturity, cause aging. Therefore aging is quasi-programmed into the genome. Blagosklonny is an advocate of rapamycin, yet are iron chelators more effective than rapamycin for life extension?

In a recent article in Oncotarget (of which he is one of the editors-in-chief), Blagosklonny sums up the evidence for what he believes is the triumph of his theory. In this theory, the cellular nutrient-sensing pathway and growth promoter mTOR (mammalian target of rapamycin) plays a key role. Inhibition of mTOR can prolong life. The continued operation of mTOR pushes cells into the senescent state.

It was recently shown that an analog of the drug rapamycin, which inhibits mTOR, increased immunity in elderly human volunteers.

How does rapamycin work? Well, as can be seen by its name, it works on the target of rapamycin (TOR), and inhibits it.

But how do cells become senescent? Is it really because mTOR pushes them into it? Lacking here is any mechanism or theory as to why more growth would make cells senescent.

On the other hand, iron causes damage even at minimal levels, and iron is a growth factor.

Consider the following facts.

Age-dependent mitochondrial accumulation of iron “may increase mitochondrial dysfunction and oxidative damage, thereby enhancing the susceptibility to apoptosis [cell suicide]”.

Oxidative stress induced by hydrogen peroxide can induce cell senescence. Iron is a well-known catalyst of oxidative damage and stress.

So, we know that iron can lead to damage and is associated with cellular senescence.

What about mTOR?

It turns out that iron chelators can inhibit mTOR. The addition of iron to the medium prevented cancer cell death, showing either that iron activates mTOR or is a necessary cofactor for it.

Treatment of transplant patients with rapamycin (sirolimus) can cause iron deficiency anemia by interfering with iron homeostasis.
The reduction in iron levels [with rapamycin treatment] together with the stable ferritin serum concentrations may suggest a condition of functional iron deficiency, partially resembling that observed in the inflammation-related anemia.

Therefore, rapamycin may inhibit mTOR by modifying iron metabolism.

Iron has the hallmarks of a pro-aging function: it’s necessary for growth and development, and it accumulates with age. It causes molecular / cellular damage, and is known to cause diseases such as cancer. (Which is characterized by high growth, mTOR activation, and iron accumulation.) Iron in lipofuscin is a major source of cell aging and damage and senescence.\(^8\)

The lifelong accumulation of iron activates mTOR, causes cellular damage, and increases aging. Iron is intimately involved in both the growth and aging aspects of mTOR.

Calorie restriction extends life and results in far less iron accumulation.\(^9, 10\) Inhibition of iron absorption from food extends lifespan.\(^11\)

Addition of iron promotes aging in C. elegans.\(^12\)

Iron promotes aging, and inhibition of iron slows aging.

Inhibition of iron accumulation or decreasing iron levels is just not a sexy scientific topic. Drugs like rapamycin and metformin garner attention from scientists and doctors alike – and from people, who want to pop a pill and make no further effort.

Yet iron comes from without – it’s not a constituent of the cell in the same way that mTOR is. Therefore it’s much easier to slow or prevent aging by dealing with iron.

Iron is a much better candidate for a prime driver of aging than is mTOR.

End of science part, and on to how to use this to benefit your health and longevity. It’s simple: prevent iron accumulation and/or decrease high body iron stores by donating blood, using iron chelators, inhibiting iron from food, or a low-iron diet. read about it in my new book, **Dumping Iron**.

Check out our Supplements Buying Guide for Men.
The Most Potent Life Extension Substance Ever

Plant extracts more potent than metformin and rapamycin

Recently, a research group screened a number (37 to be exact) of plant extracts to see what effect they might have on slowing aging and extending life. They say they've found the most potent life extension substance ever.

The screening was done by adding these substances to the growth medium of the yeast *Saccharomyces cerevisiae*, which is the same yeast used to make wine and beer, and which is often used in aging studies. Yeast cells have biochemistry similar to mammalian cells, they age and die similarly to mammalian cells, their lifespans can be increased by calorie restriction, they are cheap experimental animals, and their lifespans are short, all of which make them ideal for aging experiments and especially, screening of a large number of compounds. The paper is “Discovery of plant extracts that greatly delay yeast chronological aging and have different effects on longevity-defining cellular processes”, published in Oncotarget.(1)

An news write-up in Science Alert (2) stated:

“In total, we found six new groups of molecules that decelerate the chronological ageing of yeast,” said biologist Vladimir Titorenko from Concordia University.

As the authors report in *Oncotarget*, one of these compounds – a specific extract of willow bark (*Salix alba*) – is the most potent longevity-extending pharmacological intervention ever described in scientific literature. In testing, the willow bark extract
increased the average chronological lifespan of yeast by 475 percent and the maximum chronological lifespan by 369 percent. If these findings can be replicated in something other than yeast, it’s a major discovery, outperforming the anti-ageing effects of both rapamycin and metformin. And in addition to slowing ageing, the compounds may also have beneficial effects on cellular processes when it comes to preventing related diseases, such as cancer, the researchers say. The other extracts come from Cimicifuga racemosa, Valeriana officinalis L., Passiflora incarnata L., Ginkgo biloba, and Apium graveolens L.. [My emphases.]

These compounds may be much more potent than the two most widely touted anti-aging drugs, rapamycin and metformin.

**Willow bark was the most potent extract, extending lifespan 5-fold**

What really caught my eye was that the most potent substance they found was an extract of willow bark. This the same source from which aspirin was derived.

Willow bark contains salicin, which when metabolized in the body becomes salicylate, an anti-inflammatory and pain-killing chemical. In the new paper, the potent life-extending willow bark extract contained “>25% salicin”.

The technical name for aspirin is acetyl salicylic acid (ASA). When metabolized, the acetyl group is split off, and the active pain-killing substance, salicylate, is generated. (Aspirin has two modes of action: the anti-platelet (“blood-thinning”) action comes from the acetylation of platelets; the pain-killing mode from salicylate.)

So, we see that there’s a huge point of similarity between aspirin and the willow bark extract that extended lifespan. Of course, there may be other compounds in willow bark besides salicin that are important – we just don’t know at this point. There’s even a possibility that salicin is irrelevant to the extract’s effects, though that seems very unlikely, as I’ll explain.

How much did this extract with >25% salicin extend yeast lifespan? See the following chart.
In the chart, the willow bark extract is PE21, at the bottom. The top, black bar is the control yeast, with no plant extract added to the medium. Willow bark extract extended yeast lifespan by almost 5-fold, making it the most potent life-extending substance yet found, eclipsing metformin and rapamycin.

Importantly, as the chart shows, the yeast were grown in 2% glucose, i.e. were not food restricted. When cells were grown in calorie-restricted conditions – 0.5% glucose – all the extracts were much less or even not at all effective. This shows that a major mode of action of these substances is by mimicking calorie restriction, presumably by activating the same biochemical pathways.

**Aspirin extends lifespan**

If salicin in willow bark is wholly or partially responsible for its life-extending power, then aspirin could also be one of the most potent life-extending drugs known.

We already know that aspirin extends lifespan in mammals (mice) and in *C. elegans* (a worm). So the fact that salicin was involved in the present study is unlikely to be a fluke.

Aspirin also extends lifespan in another experimental animal, the cricket.\(^3\) Not only did it extend lifespan, but it was much more potent than metformin in doing so, and showed very few life history trade-offs in life extension. In other words, metformin, while it extends lifespan, also significantly impairs growth and rate of maturity, while aspirin does not.

Unlike the reigning dietary restriction paradigm, low aspirin conformed to a paradigm of “eat more, live longer.” In contrast, metformin-treated females were only ~67 % of the mass of controls. Our results suggest that hormetic agents like metformin may derive significant trade-offs with life extension, whereas health and longevity benefits may be obtained with less cost by agents like aspirin that regulate geroprotective pathways.
How does aspirin increase lifespan? It’s anti-inflammatory, but that just moves the question a step further back. It turns out that aspirin chelates iron, which could account for its anti-inflammatory property.⁴

These results may help to explain the interaction of nonsteroidal anti-inflammatory drugs with free radicals and the anti-inflammatory properties of these agents, inasmuch as accumulating evidence indicates that much of the injury observed during inflammatory disorders may be mediated by oxidative stress frequently induced by iron-dependent reactions.

Iron

It follows from this that control of iron may be the proximate mechanism of action of salicin, aspirin, and calorie restriction, or that control of iron operates through the same biochemical pathways to extend life. I discussed this at length in my new book, Dumping Iron.

Aspirin could be one of the most potent anti-aging drugs. We might see more research on it except for the fact that pharmaceutical companies can’t make big profits from it, as it’s dirt cheap and over-the-counter.


PS: Check out our Supplements Buying Guide for Men.