



## [Aspirin, a Life Extension Drug](#)

One of the most commonly used over-the-counter drugs, aspirin, has considerable potential as a life extension drug. While this has been known for awhile, at least in theory, some recent research adds support.

### **Aspirin deters the diseases of aging and civilization**

In previous articles, we've seen that [aspirin prevents cancer](#), including [lung](#) and [prostate cancer](#). Cancer strikes mainly older people, and some 90% of cancer deaths are in people 65 years old and up. Cancer is therefore a disease of aging, and since aspirin prevents cancer, it might qualify as an anti-aging drug if it prevented the other diseases of aging and civilization.

Heart disease / atherosclerosis is another big killer that increases in incidence with age. [Aspirin prevents heart attacks when used in primary prevention](#), that is, in people who have never had a previous heart attack, but, "In primary prevention without previous disease, aspirin is of uncertain net value as the reduction in occlusive events needs to be weighed against any increase in major bleeds." Worth noting here is that "the main risk factors for coronary disease were also risk factors for bleeding." Aspirin is of greater value in secondary prevention.

In diabetics, [aspirin at high doses dramatically decreases glucose \(-25%\) and triglycerides \(-50%\)](#), and improves glucose tolerance and insulin sensitivity.

The fact that aspirin affects all of these diseases of aging and civilization suggests a common mechanism that may be involved in life extension.

### **Aspirin recapitulates features of calorie restriction**

[Autophagy](#), the cellular self-cleansing process that breaks down and recycles proteins and cellular components, is critical to maintaining a youthful

state. Normally, autophagy declines to basal levels when an animal or human eats (is in the fed state) and increases when no food is available (in the fasted state). As we age, levels of autophagy decline and the process becomes more difficult to induce, and as a result, damage accumulates and cellular processes don't work as well. Arguably, the increase in malfunctioning components just is aging, with the body increasingly susceptible to breakdown and infection.

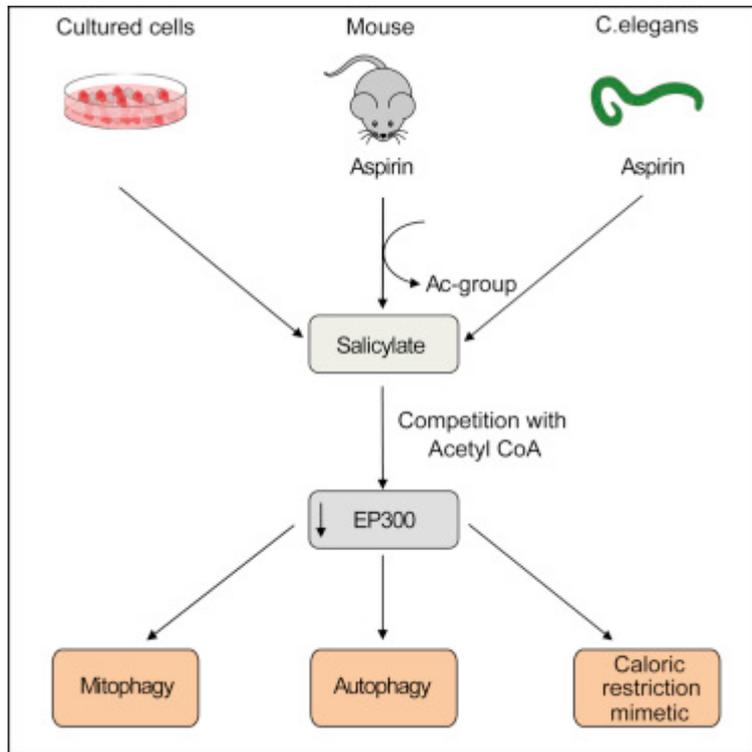
Calorie restriction and intermittent fasting strongly up-regulate autophagy. Since calorie restriction has been found to be the most robust and effective life extension intervention known to science, increasing the rate or frequency of autophagy extends lifespan. In fact, [mice that are genetically engineered to have higher rates of autophagy live longer than wild-type animals](#).

[Autophagy plays an essential role in lifespan extension](#), and may be not only necessary, but sufficient, for lifespan extension.

It turns out that [the effects of aspirin resemble those of calorie restriction](#), including the induction of autophagy.

The age-associated deterioration in cellular and organismal functions associates with dysregulation of nutrient-sensing pathways and disabled autophagy. The reactivation of autophagic flux may prevent or ameliorate age-related metabolic dysfunctions. Non-toxic compounds endowed with the capacity to reduce the overall levels of protein acetylation and to induce autophagy have been categorized as caloric restriction mimetics (CRMs). Here, we show that aspirin or its active metabolite salicylate induce autophagy by virtue of their capacity to inhibit the acetyltransferase activity of EP300... Altogether, these findings identify aspirin as an evolutionary conserved CRM.

EP300 is a cellular protein which functions as "a master repressor of autophagy". By binding to EP300, aspirin de-represses autophagy.



When aspirin is ingested, it is rapidly (minutes) [deacetylated and converted to salicylate](#), and in this case, the salicylate inactivates EP300, leading to increased autophagy.

Salicylate is one of the main components of willow bark, an ancient medicine. [An extract of willow bark has been shown to be the most powerful life extension substance known to science.](#)

So far, aspirin and/or salicylate look like potent life extension drugs.

One problem with using aspirin or salicylate for this purpose is the dose. Aspirin can cause stomach bleeding and bleeding in general, especially at high doses. While some patients such as those with rheumatoid arthritis may take large doses of aspirin, 3 grams or more daily (about 10 standard tablets), no one is going to recommend that to the general population. Many doctors even have misgivings about people taking low-dose (81 mg) aspirin due to its promotion of bleeding.

The above article states that “in patients taking up to 3 g aspirin/day, salicylate reaches 1–3 mM concentration in plasma, a dose range in which this molecule exhibits EP300 inhibitory and pro-autophagic properties, salicylate thus likely represents one of the principal metabolites responsible for aspirin activity.”

Given that we need a 1 mM concentration of salicylate to see any degree of EP300 inhibition, and that level isn't reached unless someone is taking a lot of aspirin, does the knowledge that aspirin is a calorie-restriction mimetic do us any good?

## Diflunisal

Possibly. [A different study found that salicylate inhibits p300 \(same as](#)

[EP300 above](#)) at about the same concentration, above 1mM. The study also found that diflunisal, a prescription anti-inflammatory drug and a salicylate derivative, inhibits p300 at much lower concentrations. Diflunisal showed activity at 100  $\mu$ M, and at 1 mM it cut the activity of p300 in half. Diflunisal appears to be a relatively safe drug given in doses of 500 to 1000 mg and doesn't appear to have the bleeding risk that aspirin does.

Both salicylate and diflunisal blocked the growth of cancer cells by inducing apoptosis, or programmed cell death, but diflunisal did so at concentrations less than 1/10 as high.

How else could the relatively high concentrations of salicylate required for life extension be overcome?

One way is potentiation.

## **Metformin potentiates aspirin, activates AMPK**

Salicylate, the metabolite of aspirin, activates [AMPK](#), the master regulator of lifespan, and it does this in common with exercise, fasting, metformin, polyphenols, and other interventions. [Metformin, the anti-diabetes drug that extends lifespan in lab animals \(and likely in humans\), potentiates the effects of salicylate.](#)

Aspirin, the pro-drug of salicylate, is associated with reduced incidence of death from cancers of the colon, lung and prostate and is commonly prescribed in combination with metformin in individuals with type 2 diabetes. Salicylate activates the AMP-activated protein kinase (AMPK) [with] a mechanism that is distinct from metformin... A hallmark of many cancers is high rates of fatty acid synthesis and AMPK inhibits this pathway... Salicylate suppresses clonogenic survival of prostate and lung cancer cells at therapeutic concentrations achievable following the ingestion of aspirin (<1.0 mM); effects not observed in prostate (PNT1A) and lung (MRC-5) epithelial cell lines. Salicylate concentrations of 1 mM increased the phosphorylation of ACC and suppressed *de novo* lipogenesis and these effects were enhanced with the addition of clinical concentrations of metformin (100  $\mu$ M)... Pre-clinical studies evaluating the use of salicylate based drugs alone and in combination with metformin to inhibit *de novo* lipogenesis and the survival of prostate and lung cancers are warranted.

Clinically achievable concentrations of salicylate and metformin killed cancer cells and activated AMPK.

Salicylate alone at clinically achievable levels, <1mM, activated AMPK and inhibited the growth of cancer cells, by blocking lipogenesis, the synthesis of lipid (fat) molecules necessary for growth of cancer. Metformin greatly potentiated the effect, such that, in my estimation, someone taking perhaps 2 standard aspirin tablets along with a standard metformin dose would achieve

concentrations of these drugs that would kill cancer, as well as promote life extension.

A major caveat of many studies which have utilized metformin to inhibit cancer growth is that millimolar (mM) concentrations have been used, despite maximum concentrations observed clinically being 50–100  $\mu$ M...

At clinical concentrations of salicylate achievable through the intake of regular strength aspirin (<1.0 mM) salicylate inhibited the survival of prostate and lung cancer cells by greater than 50%.

These data indicate that the salicylate-induced suppression of lipogenesis, taking place at **clinically relevant doses of the drug**, is mediated via the AMPK  $\beta$ 1 subunit...

We found that the IC50 for clonogenic survival was dramatically reduced in all cell types when metformin and salicylate were used in combination.

We find that salicylate at concentrations as low as 0.25 mM inhibited de novo lipogenesis in prostate and lung cancer cells and this was associated with the inhibition of clonogenic survival.

A dose of .25 mM might be achievable with a standard aspirin tablet or two.

Metformin and aspirin together also [significantly inhibit pancreatic cancer cells.](#)

## **Aspirin inhibits mTOR**

The mammalian (or mechanistic) target of [rapamycin](#), mTOR, regulates growth and aging, and is repressed by AMPK. Many consider the deactivation of mTOR as the Holy Grail of anti-aging, and it certainly seems about the most potent anti-aging mechanism that we know about currently.

[Aspirin inhibits mTOR](#), although the concentration here was 5mM, which is not clinically achievable.

Again, [aspirin and metformin together hold promise in treating pancreatic cancer by targeting AMPK and mTOR.](#)

A study that gets to the heart of the matter regarding mTOR and aspirin [directly compared aspirin's ability to inhibit mTOR with everolimus](#), an analog of rapamycin, the prototypical mTOR inhibitor. This study used tumor-bearing mice that were given low-dose or high-dose aspirin, or everolimus, or no treatment. Low-dose aspirin was 100 mg/kg, high-dose was 400 mg/kg.

The tumor growth inhibition rates induced by low and high-dose aspirin and everolimus were 19.6, 33.6 and 53.7% (P<0.05) in H22

hepatocarcinoma, and 25.7, 40.6 and 48.7% ( $P < 0.05$ ) in S180 sarcoma...

We have demonstrated that aspirin may inhibit mTOR signaling associated with anti-angiogenesis and promoting autophagy on the protein expression level. We intend to continue with further experiments on the genetic level. Our study has significant clinical reference value and may potentially lead to therapeutic treatment options for hepatoma or sarcoma and other types of cancer.

According to my calculations, the human equivalent dose for the high-dose aspirin given to the mice is about 2.3 grams for a 70 kg man. (Divide mouse dose by 12 to account for higher mouse metabolism.) Still, not many people (including me) want to take 2 grams of aspirin daily, although some people with pain do so. Metformin and aspirin appear to potentiate each other in deactivating mTOR.

Atenolol is [a beta blocker, a cheap, widely used anti-hypertensive drug which also promotes lifespan extension](#). Of interest, [atenolol, aspirin, and metformin together all potentiate each other and target cancer cells by deactivating mTOR](#). Use of beta blockers is associated with lower rates of cancer.

## **Aspirin promotes nitric oxide production and reduces erectile dysfunction**

[Aspirin promotes endothelial function](#). Endothelial cells are those that line the insides of blood vessels, and their dysfunction is important in promoting atherosclerosis. Part of the protective effect of aspirin on endothelial function is due to [its promotion of nitric oxide production, which relaxes blood vessel walls](#).

Possibly also due to increased nitric oxide production, [low-dose aspirin can help treat erectile dysfunction](#). Men who took 100 mg of aspirin daily for 6 weeks showed significant improvement in erectile function.

## **Aspirin inhibits cellular senescence**

Cellular senescence occurs when cells reach their growth limit (the Hayflick limit) and cannot divide any more. They go into a senescent state and emit inflammatory cytokines, which may be responsible for many of the ills of aging, and may promote cancer. [Getting rid of senescent cells may actually reverse aging](#).

Perhaps even better than eliminating senescent cells is preventing cellular senescence in the first place. [Aspirin delays endothelial cell senescence, increases nitric oxide, and reduces ADMA, a marker of atherosclerosis](#).

## Aspirin: dose matters

[Daily low-dose aspirin substantially decreases cancer risk.](#) However, what got me onto the line of thinking leading to this article is the following: [Aspirin Dose and Duration of Use and Risk of Colorectal Cancer in Men.](#)

After adjustment for risk factors, men who regularly used aspirin ( $\geq 2$  times per week) had a multivariate relative risk (RR) for colorectal cancer of 0.79 (95% confidence interval, [CI], 0.69–0.90) compared with nonregular users. However, significant risk reduction required at least 6–10 years of use ( $P$  for trend = .008) and was no longer evident within 4 years of discontinuing use (multivariate RR, 1.00; CI, 0.72–1.39). **The benefit appeared related to increasing cumulative average dose:** compared with men who denied any aspirin use, the multivariate RRs for cancer were 0.94 (CI, 0.75–1.18) for men who used 0.5–1.5 standard aspirin tablets per week, 0.80 (CI, 0.63–1.01) for 2–5 aspirin tablets per week, 0.72 (CI, 0.56–0.92) for 6–14 aspirin tablets per week, and **0.30 (CI, 0.11–0.81) for >14 aspirin tablets per week** ( $P$  for trend = .004). *Conclusions:* Regular, long-term aspirin use reduces risk of colorectal cancer among men. However, the benefit of aspirin necessitates at least 6 years of consistent use, with maximal risk reduction at doses greater than 14 tablets per week. **The potential hazards associated with long-term use of such doses should be carefully considered.**

The higher the dose and the longer the duration of use, the less colorectal cancer risk these men had, with 14 tablets a week conferring a 70% decrease in risk. While that's a large risk decrease, that's also a lot of aspirin, a dosage that no one will recommend to healthy men who don't need pain relief.

The other studies noted above suggest that lower doses can be effective, especially when used with metformin and/or beta blockers.

## Aspirin: the risk

Aspirin can cause gastrointestinal ulcers and it increases bleeding risk by acetylating the COX-1 enzyme in platelets, the small blood cells that promote blood clotting. Platelets are incapable of generating more COX-2, hence aspirin permanently disables them; platelets have a life of about 10 days. For the cardiovascular protection effect of aspirin, it must be taken daily.

The most serious possible consequence of taking aspirin is bleeding into the brain, which can be fatal or severely disabling. This is known as a cerebral hemorrhage, and accounts for 5-10% of all strokes. Most cerebral hemorrhages are caused by aneurysms in the brain, and it turns out that [aspirin could be protective against them](#). "... patients taking aspirin at least three times weekly had a significantly lower risk of SAH (OR, 0.27; 95% CI, 0.11–0.67;

P=0.03) compared with those who never took aspirin.”

What about in the population in general and in other forms of bleeding risk, such as gastrointestinal bleeding? The title of a study tells the story: [Systematic Review and Meta-Analysis of Randomised Trials to Ascertain Fatal Gastrointestinal Bleeding Events Attributable to Preventive Low-Dose Aspirin: No Evidence of Increased Risk.](#) Key to this is the word “fatal”.

Aspirin has been shown to lower the incidence and the mortality of vascular disease and cancer but its wider adoption appears to be seriously impeded by concerns about gastrointestinal (GI) bleeding. Unlike heart attacks, stroke and cancer, GI bleeding is an acute event, usually followed by complete recovery. We propose therefore that a more appropriate evaluation of the risk-benefit balance would be based on *fatal* adverse events, rather than on the *incidence* of bleeding... The majority of the adverse events caused by aspirin are GI bleeds, and there appears to be no valid evidence that the overall frequency of fatal GI bleeds is increased by aspirin. The substantive risk for prophylactic aspirin is therefore cerebral haemorrhage which can be fatal or severely disabling, with an estimated risk of one death and one disabling stroke for every 1,000 people taking aspirin for ten years. These adverse effects of aspirin should be weighed against the reductions in vascular disease and cancer.

The conclusion to the article:

Gastrointestinal bleeds constitute the majority of the adverse events caused by aspirin. The increase is about 60% overall, but there appears to be no increase in fatal GI bleeds attributable to low-dose aspirin, indeed prophylactic aspirin appear to be associated with a reduction in the fatality of GI bleeds. The undesirable effect of prophylactic aspirin which is of a severity comparable to a vascular disease event or a cancer is a bleed that leads to death, and low-dose aspirin appears to be associated with one death and one disabling haemorrhagic stroke per year in every 10,000 people taking low-dose aspirin. The available evidence makes it seem likely that these cerebral events would be reduced if hypertension is identified and adequately treated.

In addition, there will be one or two non-fatal GI bleeds per 1,000 people each year, but the frequency of these bleeds appears to fall rapidly, and there is no evidence of any increase in GI bleeds attributable to aspirin after three or four years of prophylaxis

All these conclusions are relevant to the risk-benefit balance of aspirin prophylaxis and should be communicated to subjects at risk of vascular disease and/or cancer, to enable them to make an informed decision about the protection of their own health.

Aspirin may not even really cause bleeding, hard as that may be to believe after the evidence laid out above. The bacterium *Helicobacter pylori*, which causes stomach ulcers, [could be the true culprit.](#) If *H. pylori* is eradicated via antibiotics, then possibly no bleeding would occur, and studies are ongoing to find out.

A number of people (on the Ray Peat Forum) appear to believe that taking vitamin K2 will mitigate the bleeding risk of aspirin. Unfortunately, anyone with actual knowledge of blood clotting (hemostasis) knows that won't work. Aspirin promotes bleeding by deactivating platelets, and vitamin K2 works by activating clotting factors, which are proteins, and the lack of which are responsible for disease like hemophilia. One won't mitigate the other.

## Aspirin may be under-used

One question about aspirin is whether there's a basis in reality for the near paranoia among doctors about promoting its use. After all, the same medical establishment is still reluctant to promote [a reasonable dose of vitamin D](#) for fear of toxicity, a reluctance which appears to me to have little basis.

[A study sought "to determine the long-term economic and population-health impact of broader use of aspirin by older Americans at higher risk for cardiovascular disease."](#)

**These data reveal a large unmet need for daily aspirin, with over 40% of men and 10% of women aged 50 to 79 presenting high cardiovascular risk but not taking aspirin.** We estimate that increased use by high-risk older Americans would improve national life expectancy at age 50 by 0.28 years (95% CI 0.08–0.50) and would add 900,000 people (95% CI 300,000–1,400,000) to the American population by 2036. After valuing the quality-adjusted life-years appropriately, Americans could expect \$692 billion (95% CI 345–975) in net health benefits over that period.

Expanded use of aspirin by older Americans with elevated risk of cardiovascular disease could generate substantial population health benefits over the next twenty years and do so very cost-effectively.

The average increase in life expectancy if everyone who should use aspirin did use it is only 0.3 years, but that figure is for the entire population, i.e. everyone, even those who don't take aspirin. You can be sure that if aspirin prevents a cancer or fatal heart attack, the number of years that life is lengthened will be longer, measured in years more likely.

At one time, [the then oldest living person credited his long life to taking aspirin.](#) He was 112 at the time.

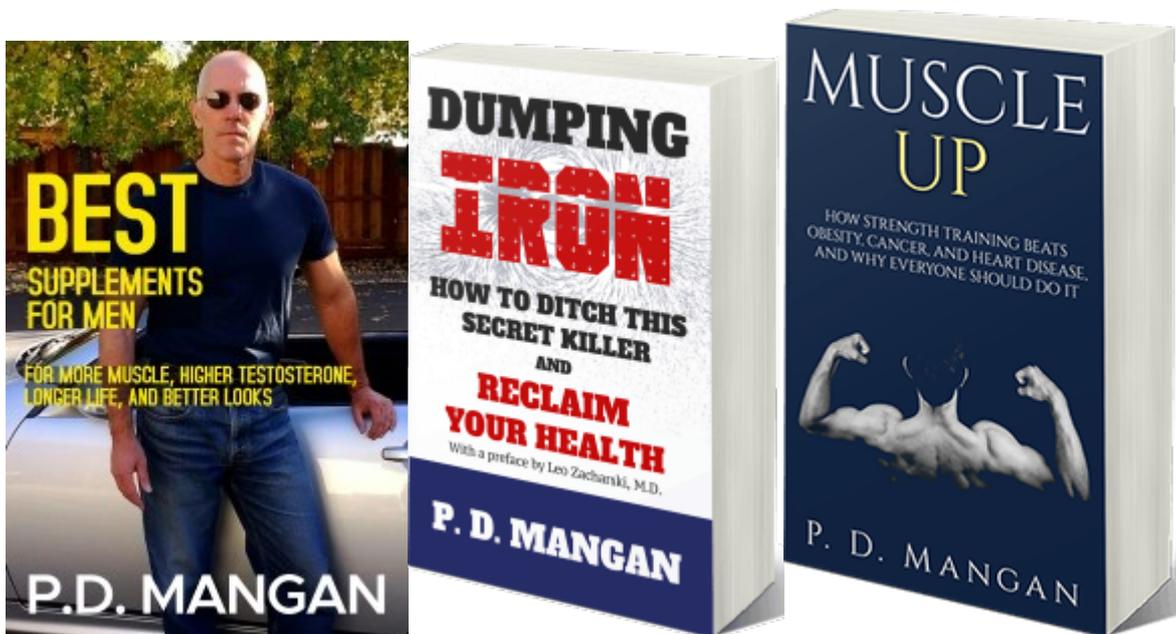
## Conclusion

Aspirin is staring us in the face as a cheap life extension drug. In combination with metformin and/or beta blockers, it may have great potential against cancer and in promoting longer life.

Aspirin is not without risks, and long-term use should be done in consultation with a physician to determine whether the benefits outweigh the risks for a given individual. For the record, I'm not promoting indiscriminate use of aspirin.

The noted scientist Mikhail Blagosklonny [mentions aspirin in his list of proposed anti-aging drugs](#), along with rapamycin, metformin, beta blockers, and [PDE5 inhibitors](#).

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