Overcoming anabolic resistance for the older man and the hardgainer

What is anabolic resistance?

Anabolic resistance is the phenomenon in which muscle does not respond to stimulus with normal muscle protein synthesis, but rather a reduced response. The stimuli that would elicit such a response are resistance training, as the academics call it, and ingestion of protein. In young, healthy people, these stimuli cause increased muscle synthesis, and over the longer term this means bigger muscles, as they adapt to continued stimulus.
Sarcopenia and the “hard gainer”

In sarcopenia, that is muscle wasting, which is most often seen in older people, basal muscle anabolism and catabolism can be normal, but the muscle fails to respond properly to stimulus, namely resistance training and protein consumption.

In younger men, we find the phenomenon of the so-called “hard gainer”, the guy who lifts and lifts and eats and eats, but can’t seem to put on much muscle, or at least finds it much more difficult than others to do so.

The cause of anabolic resistance

Anabolic resistance has actually been studied a fair amount because it’s a common condition in older people that leads to sarcopenia. Since sarcopenia often leads to disability, the inability to care for oneself (nursing homes) and ultimately death (from falls leading to hip fractures and the like), anabolic resistance is actually a major public health problem.

Researchers often focus on ways to fix it, but as to the cause, they are often reduced to saying that it’s just “age”. Sure, we know detailed cellular mechanisms of resistance, but why age causes these is another story.

However, I’ve come to the rescue, since I know what causes anabolic resistance. In a nutshell, inflammation, which increases greatly with age. Inflammation is also a cause of insulin resistance, also more common with age, and the two are related. It follows that with less inflammation and greater insulin sensitivity, anabolic resistance will diminish.

A large clue to how all this works is the fact that omega-3 fatty acids from fish oil are anabolic. For example, Omega-3 polyunsaturated fatty acids augment the muscle protein anabolic response to hyperinsulinaemia-hyperaminoacidaemia in healthy young and middle-aged men and women. In this study, fish oil caused a ~30% increase in muscle protein synthesis, and a ~50% increase in mTOR phosphorylation.

Even better results were seen in the elderly: Dietary omega-3 fatty acid supplementation increases the rate of muscle protein synthesis in older adults: a randomized controlled trial.

Fish oil can also help treat a condition that’s similar to sarcopenia, cachexia: Eicosapentaenoic acid (EPA, an omega-3 fatty acid from fish oils) for the treatment of cancer cachexia.

How does fish oil decrease anabolic resistance?

Fish oil decreases anabolic resistance probably by two different means: it decreases inflammation, and restores normal fluidity in cell membranes, allowing receptors to work properly. Fish oil has clinically important anti-inflammatory effects.

How to overcome anabolic resistance
There are several ways that anabolic resistance may be overcome.

1. Fish oil: by decreasing inflammation and increasing insulin and other receptor sensitivity.

2. Increased protein consumption. In younger people, 20 grams of protein in one meal may be enough to promote maximum protein synthesis. Older people may need more. In one study, older men undergoing resistance training had better muscle protein synthesis when they ingested 40 grams of whey protein as opposed to 20.

3. Exercise itself reduces anabolic resistance.

4. “Faster” protein: the protein in meat, eggs, and the like digests slowly, and amino acids in the bloodstream therefore do not rise to as high a level as they do with a protein that digests faster, such as whey. The level of amino acids in the blood is a crucial determinant of anabolism. Therefore, taking a fast protein such as whey, whether with a workout or without it, will cause greater anabolism, other things being equal, such as quantity.

5. BCAAs and leucine: BCAAs, particularly leucine, crucially determine the amount of muscle protein synthesis. So ingesting protein high in BCAAs / leucine will cause greater anabolism. Whey has the highest fraction of BCAAs of any protein.

6. In older people, resistance training. It appears that sarcopenia may arise from a combination of inflammation (“inflammaging”) or just disuse. Older people typically have good responses to resistance training, even into their 90s.

Don’t let age be an excuse

There you have it. It is not “age” that causes anabolic resistance, but various metabolic derangements that accompany it. If you’re older, or you’re a hard gainer, you can use some of these methods I outlined to overcome anabolic resistance.

P.S.: I was asked what type of whey I like, and the answer is NutraBio, which is cold-processed and undenatured. Best one available, IMO.

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**N-acetylcysteine increases endurance performance**

Production of free radicals is a determinant of performance and fatigue

One of the crucial determinants of fatigue is the production of radical oxygen species (ROS, also known as free radicals) and internal antioxidant status, the latter mainly consisting of total, reduced, and oxidized glutathione. Glutathione is a tripeptide consisting of three amino acids, and the rate-limiting amino acid – the bottleneck to production – is cysteine. So, if more cysteine is provided, more glutathione will be produced. N-
acetylcysteine, the cheap over-the-counter supplement, provides cysteine, which cannot be taken in its native form due to high potential for oxidation.

When one performs any kind of intense or prolonged exercise, a large quantity of ROS is generated, and it’s mainly glutathione that mops them up and keeps the body from entering a condition of oxidative stress. Glutathione can be thought of as an exercise buffer. But when it is depleted, the body is overwhelmed with ROS, and fatigue ensues.

**N-acetylcysteine increases glutathione**

The main function of n-acetylcysteine (NAC) is to increase glutathione levels. When ingested, it is rapidly taken up by cells, de-acetylated to cysteine, and then used in glutathione production. Since NAC does this, and since glutathione is a determinant of fatigue, it follows that NAC should increase exercise performance.

**N-acetylcysteine significantly increases endurance and time to fatigue**

Lo and behold, NAC does work this way: N-acetylcysteine enhances muscle cysteine and glutathione availability and attenuates fatigue during prolonged exercise in endurance-trained individuals. In this study, trained cyclists who received NAC increased their endurance performance, that is, time to fatigue, by a remarkable 26%. NB: the cyclists received a lot of NAC, in fact a constant IV infusion.

Another study that used a special type of whey as a cysteine donor found increased peak power and 30-second work capacity: Effect of supplementation with a cysteine donor on muscular performance.

And in a study on rats, those that had a glutathione deficiency had a 50% reduced endurance performance.

**Fatigue of any kind is related to glutathione levels**

In my book on chronic fatigue, I discuss at some length the relation between chronic fatigue and glutathione levels, which is critically important for those suffering from long-term fatigue from any cause. NAC can be of help in that condition as well. So we see that fatigue, whether from unknown cause, illness, bad nutrition, or prolonged exercise is related to glutathione. This is not the sole determinant of fatigue, but an important one.

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**Ketosis extends lifespan**
Ketosis and ketone bodies

Ketone bodies are the small molecules that are produced by the liver when the body is in a state of ketosis. These can be readily used by the body and, most notably, the nervous system, and one of their functions is to spare lean tissue during ketosis, since with the burning of ketones, the body does not have to break down muscle in order to make blood glucose.

The state of ketosis is readily entered when severely restricting carbohydrates in the diet for just a short while; for instance, if someone goes on the Atkins diet, or generally keeps carbs below 50 grams a day. (If one exercises a lot or is otherwise physically active, one can eat more carbs, say up to 100 grams, and remain in ketosis.)

Ketosis extends lifespan in *C. elegans*

It turns out that in the roundworm *C. elegans*, one of the ketone bodies, beta hydroxybutyrate, extends lifespan: D-beta-hydroxybutyrate extends lifespan in *C. elegans*.

- βHB supplementation extended mean lifespan by approximately 20%. ... βHB did not extend lifespan in a genetic model of dietary restriction indicating that βHB is likely functioning through a similar mechanism. βHB addition also upregulated ΒHB dehydrogenase activity and increased oxygen consumption in the worms.

So, the ketone functioned similarly to dietary restriction, increased lifespan by 20%, and caused increased metabolism.

It looks like being in ketosis much of the time could be, gasp, good for you.

The probable future Nobel Laureate Cynthia Kenyon discovered that a mutation in insulin signalling in *C. elegans* caused radically increased lifespan. When she made that discovery, she herself went on a low-carbohydrate diet.

So, add all this to the evidence for the healthiness of [a low-carbohydrate diet](#).
Activate the stress response for health and long life

A pesticide extends lifespan in C. elegans

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

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

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

Stress response mechanisms are the key to health and long life

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

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

It’s thought that the level of activation of Nrf2 plays perhaps the key role in differences in longevity between species.
Longevity promoting effects are due to activation of stress response

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

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

Daily doses of good stress for health

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

Testosterone for muscle gain: it works

Steroids used for athletics have two functions: androgenic and anabolic. Androgenic signifies that it increases male sexual characteristics, and anabolic that it builds muscle. Steroids are essentially testosterone mimics with qualities that athletes want, such as longer half-life, more potent anabolic effects, and so on.

How does testosterone itself perform in that regard? Pretty well.

In a study of testosterone replacement therapy in hypogonadal men – that is, they had low T – they had an average 20% gain in muscle mass over 6 months. In other words, huge. Even better, they also had a loss of fat mass of 11%.

So, maybe testoserone’s anabolic affects have an upper limit, that is, what about supraphysiologic doses in men who already have normal T? Yes, that works too: The Effects of Supraphysiologic Doses of Testosterone on Muscle Size and Strength in Normal Men. In this study, young men were given high doses of T, a 600 mg injection once weekly. They also did resistance training 3 days a week, and ate a diet with enough protein to support optimal muscle growth, 1.5 grams per kilogram body weight, or about 0.7 grams/lb.

Results: those in the T + exercise group gained 6 kg, or over 13 pounds, over 12 weeks, and it was all muscle. But to show the power of T: even those who did not lift weights gained 3.2 kg of muscle.
One lesson here is that if you’re having difficulties in the gym with putting on muscle, a test for your T level would seem to be in order, whether you’re young or old. Should your T levels be suboptimal, then comes the harder part: convincing your doctor to prescribe T for you. Granted, if you’re youngish and in good health, some other strategies may work for increasing T, such as fat loss, ensuring adequate zinc in your system, and certain posture exercises, as shown here. Weightlifting itself, as well as a HIT exercise program, also improve T levels, so keep at it.

Chocolate can extend lifespan and improve cognitive performance, in rats, anyway, and there’s little reason to doubt that it would in humans. In the following study, the researchers used a special form of cocoa powder, Acticoa, which has been processed in such a way as to preserve a high content of flavanols. Acticoa is made in Switzerland and as far as I can see is not available in the U.S. Effects of long-term administration of a cocoa polyphenolic extract (Acticoa powder) on cognitive performances in aged rats.

Numerous studies have indicated that increased vulnerability to oxidative stress may be the main factor involved in functional declines during normal and pathological ageing, and that
antioxidant agents, such as polyphenols, may improve or prevent these deficits. We examined whether 1-year administration of a cocoa polyphenolic extract (Acticoa powder), orally delivered at the dose of 24 mg/kg per d between 15 and 27 months of age, affects the onset of age-related cognitive deficits, urinary free dopamine levels and lifespan in old Wistar-Unilever rats. **Acticoa powder improved cognitive performances in light extinction and water maze paradigms, increased lifespan** and preserved high urinary free dopamine levels. These results suggest that Acticoa powder may be beneficial in retarding age-related brain impairments, including cognitive deficits in normal ageing and perhaps neurodegenerative diseases. Further studies are required to elucidate the mechanisms of cocoa polyphenols in neuroprotection and to explore their effects in man.

The rats fed cocoa lived 11% longer than controls, which I would say is a huge increase in lifespan from the mere addition of cocoa to their food.

The rats received 24 mg/kg of body weight. To convert to a human dose, multiply by 6/37 (see [here](#)), which comes to about 4 mg/kg. So, for a 75 kg (165 lb) man, the daily dose of cocoa would be about 300 mg. Keep in mind that this was a concentrated form of cocoa (Acticoa). According to their website, Acticoa has 5 or more times the amount of flavanols than regular cocoa powder, so adjust accordingly.

Another study found that the mere addition of epicatechin, one of the major flavonoids in cocoa, to the diets of diabetic mice, radically reduced the death rates from 50% in controls, to 8% in the epicatechin group. **Dietary epicatechin promotes survival of obese diabetic mice and Drosophila melanogaster.** What this tells me is that a hormetic response can protect against diabetes. There’s good evidence that lack of hormesis contributes to diabetes: [Resistance to type 2 diabetes mellitus: a matter of hormesis?](#)

Despite the fact that even people who should know better refer to substances like epicatechin as antioxidants, in reality they are not. They work via hormesis, that is, by providing low doses of toxins to which the body mounts an anti-stress response. In the case of diabetes above, the flavonoids acted as hormetic agents and thus prevented diabetic mice from dying. That’s my interpretation.

Also, **cocoa has far more flavonoids, 2 to 4 times more**, than tea or red wine. I have to remind myself to eat more chocolate.
Lithium Extends Lifespan

Lithium is an essential nutrient

Most people know lithium as the “drug” given to bipolar patients. In reality it is not a drug but a mineral, and in bipolar disorder it’s given in high doses: the target dose is usually 900 to 1,800 mg a day.

However, lithium is a required nutrient. “The available experimental evidence now appears to be sufficient to accept lithium as essential; a provisional RDA for a 70 kg adult of 1000 μg/day is suggested.” (1000 μg = 1 mg.)

This is, as can be seen, much lower than the dose given in bipolar.

Furthermore, low levels of lithium in drinking water have been associated with violence, suicide, and homicide. See, for example, Lithium in Tap Water and Suicide Mortality in Japan.

Lithium increases lifespan in humans and animals

A study looked at epidemiological evidence of an effect of lithium on human lifespan, and found it. Low-dose lithium uptake promotes longevity in humans and metazoans. Mortality rates were inversely associated with lithium concentrations in tap water; furthermore, the lower mortality rate remained after adjusting for suicide, showing that lithium provides some other health
benefit not strictly related to mental health.

Since this association does not show causality, the same authors used low-level lithium, at about the same concentration found in the tap water, and tested it on the worm *C. elegans*. It extended their lifespan, showing causality.

**Lithium promotes autophagy**

Lithium seems to extend lifespan by promoting autophagy, the cellular self-cleaning process that rids cells of junk and is crucial to lifespan extension. It does this by an mTOR-independent mechanism, meaning that it does not depend on fasting. Through autophagy, lithium has been found to delay progression of amyotrophic lateral sclerosis.

**How much lithium do you need?**

As stated above, about 1 mg a day is a suggested RDA for lithium. Dose for bipolar patients are hundreds or thousands times higher, but there’s considerable risk of toxicity at those doses, while there appears to be little for low doses. A common formulation, lithium orotate, provides 5 mg lithium.

I generally take one 5 mg tablet of lithium orotate once every few days.

**Could intermittent fasting save you from a heart attack?**
Intermittent fasting is merely going without food for a set period of time, for 12 hours, 16 hours, or more. It increases the process of autophagy, and this may very well protect against heart attacks.

**The rise and fall of coronary heart disease**

Myocardial infarction – heart attack – is an important cause of death and disability. While we know that the immediate cause is due to arterial blockage, the longer term causes are less decided. The idea that it may be caused by high cholesterol due to high fat diets can safely be consigned to the garbage bin of history.

Furthermore, the rise and decline of coronary heart disease cannot be fully explained. My own guess would be that a combination of smoking, trans fat consumption from hydrogenated oils (like Crisco and margarine), and perhaps sugar consumption played a role.

**Autophagy declines with aging**

Autophagy is the process of controlled degradation of cellular components which is crucial to normal function, and it declines with aging. Whether the decline is causative of aging is an open question, but lifespan extension through calorie restriction or fasting requires autophagy, so there’s obviously a close relationship between autophagy and aging. “[A]utophagy may act as a central regulatory mechanism of animal aging.”

**Autophagy and myocardial infarction**

A recent study took a look at the expression of autophagy genes in peripheral leukocytes of patients with myocardial infarction. This simply means that the researchers looked at white blood cells obtained with a simple blood test. Patients who had suffered a heart attack were much more likely to have decreased expression of autophagy genes. This of course doesn’t prove anything about causation. It could be simply a marker of increased aging, with which decreased autophagy is associated. We know that older people are much more likely to have heart attacks. Could this be due to decreased autophagy?
Intermittent fasting strongly increases autophagy

Autophagy increases in response to amino acid starvation. The body has very limited storage ability for dietary protein, which is composed of amino acids. What this means in practical terms is that, once protein in the diet has been digested, and the human or animal is no longer in the “fed” state, but is now fasting, muscle is broken down to provide the necessary amino acids in the bloodstream. Autophagy is the mechanism that does this. Normally, autophagy increases after a simple overnight fast. Longer periods of fasting strongly increase autophagy. “[A] growing body of literature suggests that fasting periods and intermittent fasting regimens can trigger similar biological pathways as caloric restriction (i.e., increased autophagy and mitochondrial respiratory efficiency), which can result in a host of beneficial biological effects including increased circulation and cardiovascular disease protection, and modulation of reactive oxygen species and inflammatory cytokines (Lee and Longo, 2011), periods have also been shown to have antimutagenic, antibacterial, and anticarcinogenic effects (Lee and Longo, 2011).” (Fasting or caloric restriction for Healthy Aging.)

Fasting may protect the heart

So, we know that both myocardial infarction and aging are associated with decreased autophagy, and that fasting retards aging and increases autophagy. In animal studies, intermittent fasting protects the heart from ischemic injury, which is the type of injury heart attacks cause. (Beneficial effects of intermittent fasting and caloric restriction on the cardiovascular and cerebrovascular systems.) This shows a plausible mechanism by which autophagy protects against injury to the heart.

There’s little downside to regular periods of intermittent fasting, and a using an 8-hour feeding window followed by 16 hours of fasting is easily done and will increase autophagy, due to deprivation of amino acids. Will it protect against a heart attack? It just might.
Intermittent fasting for fat loss or anti-aging?

Lots of people, even including those wanting to build muscle, are doing intermittent fasting (IF) these days. The goal for these people is to lose body fat and, hopefully, retain muscle or build muscle at the same time.

Others practice IF as an anti-aging method. This has solid science behind it, and it may even be more beneficial for anti-aging purposes than calorie restriction, heretofore the most effective strategy for inhibiting or reversing aging.

Branched-Chain Amino Acids

Many of those in the first camp (lose body fat, retain muscle) use branched-chain amino acids (BCAAs), or leucine (one of the BCAAs) or perhaps whey
(which is rich in BCAAs) during their fast. BCAAs are powerful signals that tell cells to ramp up muscle protein anabolism and to decrease muscle protein catabolism. So the use of BCAAs while fasting is the practice that will give one the best shot at retaining or even building muscle, even while doing regular, periodic IF.

However, one thing that BCAAs, whey, or leucine do is to stop autophagy, the cellular self-cleaning process. This process is radically enhanced by fasting, and it is responsible for the beneficial effects of calorie restriction and fasting. No autophagy, no anti-aging benefit from fasting. One of the ways (not the only one) that BCAAs increase muscle protein synthesis is through increased insulin levels. Insulin suppresses autophagy.

So, if you practice IF for the purpose of anti-aging, you must not take any BCAAs, nor, if you are in the habit of taking small amounts of food during a fast, must you ingest any protein or carbohydrates, which raise insulin and stop autophagy, which is the central component of the anti-aging effect of IF.

Avoiding Intermittent Fasting Sabotage

However, fat, or in any case small amounts of it, do not raise insulin and do not signal the metabolic machinery to stop autophagy. Therefore you won’t sabotage an anti-aging fast with small amounts of fat. The best thing to do here, if needed, is to drink coffee or tea with cream; the fat in the cream will help satisfy the appetite, and the caffeine in coffee or tea will also decrease hunger.

That’s why you should be clear on what your intermittent fasting purpose is. If it is for fat loss, by all means use BCAAs to decrease muscle breakdown. If your purpose is anti-aging, you should avoid BCAAs.

Correlation between low sperm quality and soda consumption

Sugar-sweetened beverage intake in relation to semen quality and reproductive hormone levels in young men. The authors found that

SSB intake was inversely related to progressive sperm motility. Men in the highest quartile of SSB intake (≥1.3 serving/day) had 9.8 (95% CI: 1.9,17.8) percentage units lower progressive sperm motility than men in the lowest quartile of intake (<0.2 serving/day) (P, trend = 0.03). This association was stronger among
lean men (P, trend = 0.005) but absent among overweight or obese men (P, trend = 0.98). SSB intake was unrelated to other semen quality parameters or reproductive hormones levels.

If you’re dealing with male infertility, the lesson here is don’t drink sugar-sweetened beverages. In any case, it’s not a good idea to drink them no matter what.

The results could be, in my view, due to increased oxidative stress from dietary sugar. Ox. stress comes with diabetes and is at least one of the causes of its complications. “Oxidative stress can be reduced by controlling hyperglycemia and calorie intake.” Link. Diabetics have lower sperm counts and semen volume. So, to avoid this fate, keeping blood sugar and insulin levels normal by refraining from SSBs would be a good idea.

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**N-acetylcysteine Treats Fatigue and ADHD of Lupus**

**Systemic lupus erythematosus**

The cheap, over-the-counter supplement n-acetylcysteine treats fatigue and ADHD of lupus. Systemic lupus erythematosus, often known just as lupus (from the Latin for “wolf”) is a serious and debilitating autoimmune disease, characterized by the production of anti-nuclear antibodies.

The most common symptoms of lupus are:
- chest pain when taking a deep breath
- fatigue
- fever of unknown origin
- malaise
- hair loss
- mouth sores
- sensitivity to sunlight
- butterfly rash on the face
- swollen lymph nodes.

Lupus is often treated with corticosteroids like prednisone – often in high doses – and immunosuppressant drugs. It can cause serious complications, including kidney failure. The drugs themselves have a high incidence of unwanted and adverse side effects.

**N-acetylcysteine (NAC)** is an over-the-counter supplement that delivers cysteine, an essential amino acid. NAC is cheap and safe.

In a trial of n-acetylcysteine in lupus, the patients significantly improved. **“N-acetylcysteine reduces disease activity by blocking mammalian target of rapamycin in T cells from systemic lupus erythematosus patients: A randomized, double-blind, placebo-controlled trial.”**

Systemic lupus erythematosus patients exhibit T cell dysfunction, which can be regulated through mitochondrial transmembrane potential and mammalian target of rapamycin (mTOR) by glutathione (GSH). This randomized, double-blind, placebo-controlled study was undertaken to examine the safety, tolerance, and efficacy of the GSH precursor N-acetylcysteine (NAC). …

This pilot study suggests that NAC safely improves lupus disease activity by blocking mTOR in T lymphocytes.

So far, so good. NAC proved to be safe, although one third of those taking 4.8 g/d developed reversible nausea. That's quite a high dose however at 8 capsules a day.

**N-acetylcysteine does not need a prescription and is much cheaper than conventional lupus drugs**

From the discussion section of this study:

The therapeutic importance of NAC for SLE is reflected by the achievement of **clinical improvement within 3 months**, as assessed by 2 validated disease activity scores; diminishing fatigue (21), which is considered the most disabling symptom in a majority of SLE patients (22); the absence of significant side effects; and the affordability of this medication. **A monthly supply of 600-mg NAC capsules (120–240 capsules) costs $15–30 on the retail market. This**
sharply contrasts with the estimated average annual direct medical costs of $22,580 per patient in 2009. Thus, the cost of NAC at $180–360/year would be negligible compared to the overall expense to society caused by the disease and the expected benefit in reducing the need for vastly more expensive medications burdened with potentially serious side effects.

This explains why you won’t be hearing much about NAC for lupus treatment: cost of $180 to $360 a year, as compared with over $22,000 a year for regular lupus medications. Drug companies have no reason for promoting such a cost-saving, profit-eating, effective supplement.

The pharmaceutical industry drives conventional medical treatment, and that’s the case with lupus.

**N-acetylcysteine increases glutathione and reduces DNA damage**

An interesting point in this study is that NAC increased glutathione — which is its main mechanism of action — and by doing so inhibited mTOR (mammalian target of rapamycin), the chief driver of growth and a promter of aging.

This suggests that n-acetylcysteine may have potential as an anti-aging supplement.

A study reported that NAC reduced levels of DNA damage and “may have anti-immunosenescent potential in T cells” — an important immune system component. In other words, it prolongs the reproductive potential of the T-cells and prevents their senescence.

**N-acetylcysteine treats neuropsychiatric symptoms**

Another report by the same authors as the lupus study states that ADHD and other neuropsychiatric symptoms are prominent in lupus, and that NAC treats it: **Attention Deficit and Hyperactivity Disorder Scores Are Elevated and Respond to N-Acetylcysteine Treatment in Patients With Systemic Lupus Erythematosus**.

**Objective**

To investigate whether attention deficit hyperactivity disorder (ADHD) may serve as a marker of neuropsychiatric disease and as a target for N-acetylcysteine (NAC) treatment in patients with systemic lupus erythematosus (SLE).

**Conclusion**

In patients with SLE, elevated ASRS scores reveal previously unrecognized and clinically significant symptoms of ADHD that respond to NAC treatment.
Would NAC successfully treat ADHD from other causes? That wouldn’t be surprising.

N-acetylcysteine may treat fatigue and ADHD from other causes

If NAC treats fatigue and ADHD caused by lupus, it stands to reason that it may do so when caused by other illnesses. To the extent that these illnesses correlate with a depletion of cellular glutathione, then NAC should be able to treat them.

In fact, we do see this in depression and bipolar disorder (neuropsychiatric disorders), and I discuss NAC and how it can ameliorate fatigue in my book on chronic fatigue.

You can get NAC at Amazon.

PS: Get my book, Smash Chronic Fatigue.

PPS: Check out my Supplements Buying Guide for Men.

Subscribe and get my free book on fat loss

Does overtraining exist, or is it an
Strangely enough, I’ve seen lots of denials that overtraining exists, that it’s not a real phenomenon, on sites devoted to weightlifting and bodybuilding. The attitude seems to be that, since there’s no such thing as overtraining, you’re a wimp or lazy if you don’t want to, or can’t, hit the gym four, five, or more days a week. The guys that say this also seem to be young. Much of this comes from users of anabolic steroids, one of the main effects of which is to allow better exercise recovery and hence more exercise without overtraining. Of course most of these users don’t admit to using steroids; they’re “fake naturals”, they don’t reveal the secret of their remarkable staying power in the gym, but denigrate those who don’t have their powers of recovery.

Overtraining doesn’t exist for users of anabolic steroids

Androgenic anabolic steroids, such as testosterone and trenbolone cause increased rates of muscle protein synthesis, and as a consequence allow for better exercise recovery. Through increased insulin sensitivity, they also allow lifters to eat more without getting fat. If a lifter on steroids feels overtrained, he can up his dose and proceed back to the gym.

Overtraining does exist if you don’t use steroids

On the contrary, coaches and elite athletes in just about every sport know very well that overtraining exists, because they need to guard against it if they’re going to win competitions. Take a look at a PubMed search for “overtraining”: 727 items returned. Overtraining is real.

How can you tell if you’re overtraining?

An article at Men’s Fitness lists 12 signs of overtraining, and they include fatigue, depression, insomnia, reduced immune function (you get sick a lot), and constant muscle soreness.

For the average gym rat, among whom I include myself, you feel reluctant to head to the gym, and if you do get there, lifting seems much more difficult. You will be unable to match your usual weights, sets, or reps.
Muscle soreness is common, and by that I don’t mean the usual delayed onset muscle soreness (DOMS) that invariably follows a good gym session, usually in a day or two. In overtraining, one feels heavy and just sort of achy all over.

Mood takes a hit also. One feels a lack of ambition, and a kind of anhedonia.

**Overtraining hits women harder and more frequently than it does men**

Interestingly, female athletes seem even more likely to suffer from overtraining, since they are more likely not to eat enough, and especially of the right foods. They are less likely to eat enough meat, which is a potent source of iron, and they need more iron than men. Meat is of course a great source of protein, which athletes need to repair their tissues – whether they’re a strength athlete or not – and if women don’t eat enough meat, they’ll suffer from that as well.

**Chronic fatigue and overtraining are similar**

Those who have had chronic fatigue understand what it feels like to be overtrained, as they are similar in many ways. One of the most prominent symptoms of chronic fatigue, in fact used to diagnose it, is exercise intolerance. The person who has chronic fatigue takes far longer to recover from an exercise bout that a healthy person – assuming he can do it in the first place. When I had chronic fatigue, I usually managed to take a daily walk. But too fast a pace, or walking an extra 15 minutes, could set back my energy levels for days. So one way to look at overtraining is as a form of chronic fatigue. It is. (For more on this, see my book, *Smash Chronic Fatigue*.)

**How you can treat overtraining**

So what do you do about it? The first thing is, of course, lots of rest. If you’re genuinely overtrained, don’t go back into the gym (or run, or whatever other intense exercise training you do) until you feel completely well. For weightlifters, you need to have the ability to perform at your maximum weight and/or number of reps and sets for each exercise. If you can’t (unless you’re just having an off day), you need more rest.

**Use nutrition to prevent and treat overtraining**

But nutrition can play a large role in recovery from overtraining. Consider the following: [*Contrasting plasma free amino acid patterns in elite athletes: association with fatigue and infection* (pdf)]. The authors looked at three groups of athletes: Group A were track and field athletes with no signs of overtraining; Group B were judo athletes who reported heavy fatigue at night but who recovered with a night’s sleep; and Group C, track and field athletes with chronic fatigue from overtraining who were unable to train at their normal levels. The study analyzed free amino acids in their blood, and found contrasting patterns.

Most germane to the analysis is that the persistently fatigued, often ill, and overtrained group had low plasma glutamine levels. The researchers
advised some of them – leaving others that they did not advise as controls –
to increase their protein intake, “to consume additional protein (an average
or larger helping of lean meat, fish, cheese, or soya), at least once on most
days a week, and to supplement protein intake with skimmed milk powder in
cereals and drinks.” This was additional protein of “a minimum of 20-30 g
protein a day”.

Most of the overtrained, fatigued athletes then recovered quickly, within
three weeks, and their amino acid patterns returned to normal.

**How much protein do you need to recover from overtraining?**

So, to recover from and prevent overtraining, make sure that you get enough
protein in your diet. The authors suggest that elite athletes in maintenance
training need at least 1.6 g protein per kg bodyweight daily. That amounts to
about .75 grams per pound of bodyweight.

So for example:

Bodyweight 200 pounds, you need about 150 grams of good quality protein
daily.
Bodyweight 150 pounds, you need about 112 grams a day.

That’s a fair amount, and you may not get that without supplementation. Whey
protein is the best way to supplement, as it’s high in leucine and cysteine,
two of the most critical amino acids for athletes.

The best whey is cold-processed and undenatured, like NutraBio’s.

I normally take one 25 gram whey shake a day. If you eat enough high quality
protein at your regular meals, this may be more than enough to get you up to
the optimum protein intake per day. If for some reason you can’t get enough
protein at your regular meals, you may need a couple shakes a day. Higher
protein intakes are perfectly healthy.

If you practice intermittent fasting, a whey shake is a good way to mark the
end of your fast, ensuring that you get your protein intake up to speed and
get that muscle protein synthesis moving.
Daily intermittent fasting prevents obesity

The illustration is from *Time-Restricted Feeding without Reducing Caloric Intake Prevents Metabolic Diseases in Mice Fed a High-Fat Diet*.

While diet-induced obesity has been exclusively attributed to increased caloric intake from fat, animals fed a high-fat diet
(HFD) ad libitum (ad lib) eat frequently throughout day and night, disrupting the normal feeding cycle. To test whether obesity and metabolic diseases result from HFD or disruption of metabolic cycles, we subjected mice to either ad lib or time-restricted feeding (tRF) of a HFD for 8 hr per day. Mice under tRF consume equivalent calories from HFD as those with ad lib access yet are protected against obesity, hyperinsulinemia, hepatic steatosis, and inflammation and have improved motor coordination. The tRF regimen improved CREB, mTOR, and AMPK pathway function and oscillations of the circadian clock and their target genes’ expression. These changes in catabolic and anabolic pathways altered liver metabolome and improved nutrient utilization and energy expenditure. We demonstrate in mice that tRF regimen is a nonpharmacological strategy against obesity and associated diseases.

These mice underwent a common form of intermittent fasting, namely a daily 8-hour feeding window followed by 16 hours of fasting. Despite eating the same amount of calories, they did not develop obesity, unlike the ad lib fed mice.

Ad lib eating could be a major cause of obesity in humans, in fact, the biggest cause. Before the obesity epidemic started, fast food was not as widely available, and certainly not 24 hours a day. People normally ate a regular dinner and then nothing until breakfast, resulting in a natural, daily cycle of 12 hours or so of intermittent fasting.

Along with low-fat diets, the modern paradigm also recommended frequent meals and snacking (“grazing”), which keeps insulin levels elevated and actually increases hunger. This was done on the dubious grounds of keeping blood sugar levels as some supposed optimum. Disastrous advice.

Perhaps the first thing to be done in obesity prevention, even before changes in type of food, is to limit eating to three (or fewer) meals a day. No snacking. To actually lose weight, intermittent fasting, such as the 16-8 schedule noted above, would be a good place to start.

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**Chronic Catabolism in Illness and Fatigue**

Here’s a paper from Wulf Droge (et al.), who has done pioneering work in amino acid metabolism, *Role of cysteine and glutathione in HIV infection and other diseases associated with muscle wasting and immunological dysfunction*.

The combination of abnormally low plasma cystine and glutamine levels, low natural killer (NK) cell activity, skeletal muscle
wasting or muscle fatigue, and increased rates of urea production defines a complex of abnormalities that is tentatively called “low CG syndrome.” These symptoms are found in patients with HIV infection, cancer, major injuries, sepsis, Crohn’s disease, ulcerative colitis, chronic fatigue syndrome, and to some extent in overtrained athletes. The coincidence of these symptoms in diseases of different etiological origin suggests a causal relationship. The low NK cell activity in most cases is not life-threatening, but may be disastrous in HIV infection because it may compromise the initially stable balance between the immune system and virus, and trigger disease progression. This hypothesis is supported by the coincidence observed between the decrease of CD4+ T cells and a decrease in the plasma cystine level. In addition, recent studies revealed important clues about the role of cysteine and glutathione in the development of skeletal muscle wasting. Evidence suggests that 1) the cystine level is regulated primarily by the normal postabsorptive skeletal muscle protein catabolism, 2) the cystine level itself is a physiological regulator of nitrogen balance and body cell mass, 3) the cyst(e)ine-mediated regulatory circuit is compromised in various catabolic conditions, including old age, and 4) cysteine supplementation may be a useful therapy if combined with disease-specific treatments such as antiviral therapy in HIV infection.

For a more complete explanation of how cysteine, glutamine, and leucine levels regulate muscle mass and protein catabolism and anabolism, see Droge’s Oxidative stress and ageing: is ageing a cysteine deficiency syndrome? These three are all amino acids – the products of protein catabolism – and are thus all highly amenable to nutritional manipulation. In particular, whey protein is cysteine-rich, and will thus help replenish glutathione and ameliorate oxidative stress. Also, n-acetylcysteine is another cheap and safe method of replenishing glutathione.

Note that the authors of the paper say that “low plasma cystine and glutamine levels, low natural killer (NK) cell activity, skeletal muscle wasting or muscle fatigue” are common to a number of conditions, including “HIV infection, cancer, major injuries, sepsis, Crohn’s disease, ulcerative colitis, chronic fatigue syndrome”. This condition can be described as a chronic catabolic state, that is, a state of constant breaking down of muscle and other tissue. Discovering that a chronic catabolic state existed in chronic fatigue was in fact a key point for me in figuring out how to cure my own chronic fatigue, and forms an essential part of the method I describe in my book to overcome it. The connection with poor nutritional practices, including vegetarianism and high carb, low fat, low protein diets should be clear: if you don’t give your body high-quality protein, rich in cysteine and leucine, you encourage your body to break down muscle and other tissue to provide the constant level of amino acids in the bloodstream that it requires, and you leave yourself deficient in glutathione, leading to wasting and fatigue.

Sarcopenia, or muscle wasting, is also seen in aging, and this may be due to
several things: high levels of inflammation and oxidative stress, as well as poor protein nutrition and lack of exercise. (These can also lead to other pathologies of aging, including osteoporosis and dementia.) N-acetylcysteine and whey protein are also quite useful here, preventing chronic catabolism in aging.

As we get older, and as we develop “inflammaging” due to continuous exposure to antigens and pathogens, oxidative stress and inflammation increase. As also with the above conditions (HIV, chronic fatigue, Crohn’s, etc.), chronic (and acute) illnesses increase oxidative stress and inflammation. These can be guarded against, and in my opinion often overcome, through proper nutrition and supplementation, including proper protein nutrition and supplementation with n-acetylcysteine, as well as branched-chain amino acids, most notably leucine. (Whey is also rich in BCAAs, as well as cysteine.)

I’ll also note here that oxidative stress and inflammation are features of many mental illnesses, including depression and bipolar.

To sum up: if you have one of the pathological conditions listed above, or are elderly, avoiding chronic catabolism engendered by oxidative stress and inflammation is important, and may indeed by the key to improved health. Normal levels of glutathione are a must for healthy functioning and avoidance of wasting. It should also be noted that overtrained athletes can have this condition, which provides both a refutation of some assertions I’ve seen that overtraining is a myth (it is not), as well as a means of dealing with and/or preventing overtraining.

For more on this, plus additional information on overcoming fatigue, see my book, Smash Chronic Fatigue. Also, NutraBio whey, which is undenatured and cold-processed, is the kind I recommend, along with this type of n-acetylcysteine.

Why these depression treatments don’t get more notice

Because they’re cheap, easy, and safe is the short answer – especially cheap, which means no profit. Hence, no promotion or notice.

Take a look at some recent papers by Michael Maes (et al.), a pioneer in the investigation of depression and other mental disorders as organic illnesses characterized by oxidative stress and inflammation. Role of Immune-Inflammatory and Oxidative and Nitrosative Stress Pathways in the Etiology of Depression: Therapeutic Implications. This paper (available in full on the net) cites n-acetylcysteine, aspirin, omega-3 fatty acids, and curcumin as possibly important adjunctive treatments in depression. Costs are nil.
Curcumin for the treatment of major depression: A randomised, double-blind, placebo controlled study. Curcumin showed some efficacy in treatment of depression, although more trials with greater statistical power are needed. Treatment is cheap.

Targeting the Inflammatory Pathway as a Therapeutic Tool for Major Depression.

In the last decades convergent findings from several lines of evidence has revealed a robust association between major depressive disorder (MDD) and inflammatory pathways. Despite this, the translation of these findings into new and better treatments for MDD has not occurred.

In my opinion, one reason these findings have not been translated into better treatment is money. So these ideas need to be widely disseminated so that, as with diet, people can make intelligent decisions on their own.

Sleep deprivation, also known as wake therapy (in its kinder, gentler version), is another practically cost-free treatment method for depression.

Elevated levels of oxidative stress in bipolar disorder

Altered plasma glutathione levels in bipolar disorder indicates higher oxidative stress; a possible risk factor for illness onset despite normal brain-derived neurotrophic factor (BDNF) levels

Background Oxidative stress and neurotrophic factors have been implicated in the pathophysiology of bipolar disorder. Our objective was to determine whether plasma glutathione or brain-derived neurotrophic factor (BDNF) levels were abnormal in bipolar disorder and therefore useful as possible biomarkers.

Results Compared with controls, bipolar patients had significantly lower levels of total glutathione and it was more oxidized. BDNF levels were not different. Age of illness onset but not current mood state correlated with total glutathione levels and its oxidation status, so that lower levels of total and reduced glutathione were associated with later onset of disease, not length of illness.

Conclusions Plasma glutathione levels and redox state detect oxidative stress even in subsyndromal patients with normal BDNF. It
may relate to the onset and development of bipolar disorder. Plasma glutathione appears to be a suitable biomarker for detecting underlying oxidative stress and for evaluating the efficacy of antioxidant intervention studies.

N-acetylcysteine will replenish glutathione levels, and has already shown efficacy in treating bipolar disorder. See The efficacy of N-acetylcysteine as an adjunctive treatment in bipolar depression: an open label trial, which concludes, “These open label data demonstrate a robust decrement in depression scores with NAC treatment. Large placebo controlled trials of acute bipolar depression are warranted.” NAC has also been found useful in schizophrenia, addiction, and compulsive and grooming disorders: N-acetylcysteine in psychiatry: current therapeutic evidence and potential mechanisms of action.

In general, it seems that oxidative stress is a central component of many mental health disorders, and NAC may have the ability to substantially ameliorate some of them. But, NAC is cheap and off-patent, so no one makes money off it. So doctors and Big Pharma won’t be promoting it.

Testosterone therapy associated with vastly lower rate of heart attack and stroke

Testosterone Therapy Is Not Associated with Increased Cardiovascular Risk in Study Registry. I can’t copy and paste, so you’ll have to go read it there, but T therapy was associated with an 8 times lower rate of heart attack and 18 times lower rate of stroke. This contradicts the recent study showing increased heart attack rates.

Vitamin D may elevate klotho

Vitamin D Sufficiency Status May Effect Circulating Levels of the Anti-Aging Protein Klotho

Purpose: Vitamin D insufficiency, serum 25(OH)D ≤ 33 ng/mL, is associated with increased disease risk and all-cause mortality in population-based studies. The study aim is to determine if
Correcting 25(OH)D insufficiency results in increased circulating levels of Klotho protein, an anti-aging biomarker, which is tightly involved in vitamin D homeostasis, and could potentially contribute to the health benefits of 25(OH)D sufficient status.

Results: ANOVA of matched pairs (n=29) showed significant (p<0.0001) between-group differences in 25(OH)D levels post treatment 69.3(4.3), compared to insufficient levels at baseline 20.9(1.2) and to sufficient controls 42.0(10.6). The results for Klotho showed a mean increase of 75.3 (33.0) circulating Klotho levels in the treatment group (p=0.03), which approached significance (p=0.07) after adjustment for multiple comparisons with Tukey's test, between-group differences all p>0.05. Non-significant changes in levels of 1,25-(OH)2D, Ca, Pi, PTH and FGF23 were also observed.

Conclusion: These results suggest a significant increase in 25(OH)D and an increase in circulating Klotho approaching significance, after 12 weeks of vitD3 supplementation and repletion of 25(OH)D. Interpretation of the results is limited because post-hoc analysis showed insufficient power to measure the observed effect. These findings represent the first evidence that correction of 25(OH)D insufficiency may effect the circulating levels of the anti-aging protein Klotho in humans.

Elevated klotho levels are associated with both lifespan and intelligence, so if you want both, ensure that you are vitamin D sufficient.