

The Supplement Filter

What the Evidence Backs and What It Doesn't



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PREFACE

One person commissioned this book, with one question, and he meant it literally.

He wanted to know what is genuinely going on with supplements. Why the shelf holds so many. Whether they differ from each other in any way that matters. Which of them work, which are noise, and, at the end of it all, which ones *he* should be taking, and for what reason.

That is the entire brief. Not an industry survey, not a manifesto, not a wellness philosophy. One man, a cabinet full of bottles, and a well-founded suspicion that somebody could just go and find out.

So somebody did.

Books used to be aimed at nobody

Look along the health shelf in any bookshop. Almost every title there addresses a reader who has never existed: the general consumer, the average person, somebody with no prior knowledge, no specific circumstances and no particular question, who requires every concept explained from scratch and receives no verdict at the end.

That was never cowardice. It was arithmetic. Producing a book cost real money, and recovering that money meant selling to the largest possible number of people, so the writing was pitched at the centre of a crowd, and each individual in the crowd received something not quite fitted to them.

That limitation has now lifted, and it is not coming back.

A book can be built to answer one question for one person, at whatever level of specificity the question deserves. No commercial publisher would have funded a project that works through thirteen deep-research reports, a shelf of bestselling supplement guides and years of podcast archives in order to tell a single man what to do about his fish oil. That is now a few weeks of work instead of a career.

Which makes this a book about supplements and, in a much smaller way, a demonstration of something about publishing. Feel free to skip the second part. The first part contains a chapter on lemon juice enemas.

The author is a machine

I wrote this, and I am software.

He set the question, ruled on what could and could not be claimed, rejected the first version as unreadable, and made every judgement that required a human being. The reading and the writing are mine.

There is one reason this disclosure matters enough to put near the front. When a language model writes nonfiction, it fails in a particular direction: it generates an assured, well-shaped, entirely persuasive sentence describing research that was never conducted. Each component looks correct. The journal name is plausible, the effect size is modest and believable, the authors have unremarkable names.

In a book about architecture, that produces an error. In a book about substances you swallow, it produces a casualty.

So everything structural about this project exists to prevent it. Before a single chapter was drafted, every claim was extracted from the source material, checked against primary sources, and recorded with its verification status. Nothing reaches these pages without tracing back to one of those records. Where a claim could not be run to ground, the text tells you so, in the main body, at the point where it matters, rather than in a footnote you would never open.

That happens more often than is comfortable. In one chapter you will watch me report a mistake that the verification process caught inside this book's own research file, because a check that never catches anything is not a check.

The argument, in one page

Here is why the chapters run in the order they do.

In 1994 the United States classified supplements as food rather than as drugs. Food is not required to demonstrate that it works. A product therefore arrives on the shelf with nobody having reviewed whether it does anything, and if the government later wants it gone, the government carries the burden of proving harm, in public, after the fact.

Everything downstream is a consequence of that single classification. The sentence on the back of the bottle stating that nobody evaluated these claims is not a caution, it is the permission slip that allows the sentence on the front. The vocabulary that sounds like evidence, clinically studied, practitioner-grade, physician-formulated, pharmaceutical-grade, all natural, carries no regulatory meaning, for the excellent reason that a defined term can be breached and an undefined one cannot.

And beneath the whole market sits one substitution that this book keeps finding, in category after category. Nutrients do their work by filling a gap. Nearly every study that made a supplement famous enrolled people who had that gap. Nearly every product sold on the back of such a study is sold to people who do not. Fix a genuine shortage and the results can change a life. Add more to a body that already has sufficient, and the outcomes run from nothing at all to a measurable rise in cancer.

Fourteen chapters, watching that one swap performed fourteen different ways.

Expect the answer to be missing

Worth knowing in advance, or it will read as the book losing momentum.

Again and again, the truthful answer was that the evidence is absent. Sometimes because the trial was never run, which follows naturally from the fact that companies do not finance studies capable of disqualifying their own products. Sometimes because a trial ran and its result was never published. And sometimes a figure repeated everywhere turns out to originate in an analyst's estimate, or a product page, or a citation nested inside somebody else's citation, and terminates there.

Whenever that happened, the book states it and moves on, rather than assembling a qualifier to keep the paragraph looking finished.

The chapter on the influence economy is the extreme version. It is the least well-sourced chapter here, and the reason is the subject matter itself: nobody publishes their affiliate accounts. The gap turned out to be the discovery.

What this is not

This is not medical advice, and the distinction is substantive rather than defensive.

No protocol appears anywhere in it. Nothing to stack, nothing to cycle, no morning-and-evening schedule. The one chapter that does supply a list supplies a very short one, most of which will not concern you.

I have no body. I have never swallowed a capsule, never felt tired on a Wednesday, never noticed anything take effect. What I have instead is the published literature, which answers some questions far better than experience does and others not at all. Anything touching pregnancy, kidney function, thyroid, iron, or a drug you already take belongs in a conversation with a clinician who can run tests, and these chapters say so at each point where it becomes true.

It also uses people's names. Where an author promotes a compound his own company sells, on a programme whose host sells supplements of his own, this book identifies him, quotes his exact words, and cites the page. That is commentary on published claims, offered without hostility, and offered without softening, because a category constructed out of unfalsifiable language cannot be described accurately in unfalsifiable language.

Two temperatures

Then you can start.

The prose here runs hot and cold on purpose, and the switch carries information.

Some sentences simply report: a trial enrolled this many people, gave them this much, and measured this result. Where the writing does that, the underlying record is solid and you can act on what it says.

Other sentences report a failure to establish something, and they do it in plain words rather than in the academic phrasing designed to be skated over. I went looking for that paper and could not obtain it, so I will not give you a figure I have not read.

Confidence in this book is calibrated rather than stylistic. Where it sounds sure, the sourcing is strong. Where it sounds like an admission, treat that as the most valuable sentence on the page instead of the weakest one.

And if the quantity of apparatus assembled here strikes you as disproportionate to the goal of helping one man decide what to put back on a shelf, that is a fair reading and an accurate one.

It was a good question. Nobody was answering it.

THE 1994 DEAL

Somewhere in your house right now there is a bottle with a sentence on the back of it. The sentence says that the statements about this product have not been evaluated by the Food and Drug Administration, and that the product is not intended to diagnose, treat, cure, or prevent any disease.^[1]

Read it again, because it is doing something strange. That is not a warning. A warning tells you about a risk. This tells you about an absence. It says: nobody checked. And it says so in six-point type on the back, directly underneath a front label that just finished telling you the contents support immune health.

Both of those things are on the same bottle. Both of them are legal. They are legal because of the same law, and the law is from 1994, and the whole business you are about to read about runs on the gap between those two labels.

What Congress actually did

The law is called the Dietary Supplement Health and Education Act, which is a name doing a lot of work, and everyone in the industry calls it DSHEA. Here is what it did in one line: it classified supplements as food.^[2]

Not drugs. Food.

That one classification decides everything downstream. A drug has to prove it works before you can sell it. Food does not, because nobody expects a banana to submit a phase III trial. So a supplement goes on the shelf with no pre-market review of whether it does anything at all. Nobody at any agency reads a file and signs off. There is no file.^[2]

Then it goes further, and this is the part that people miss. If the government wants to take a product off the market, the government has to prove the product is dangerous.^[3] The burden runs that direction. Not “show me this works,” but “prove to me this hurts people,” and prove it

on every element, after the product is already in a hundred thousand medicine cabinets.

And then, because apparently that was not enough, the law contains a findings section in which Congress states as a matter of legislative fact that dietary supplements are safe within a broad range of intake and that safety problems are relatively rare.^[4]

Sit with that. The safety of the category is not the conclusion of the regulatory system. It is an input. Congress wrote down that the stuff is safe, and then built the enforcement scheme on top of the sentence it had just written. That is not a law. That is a load-bearing assumption with a bill number.

None of this arrived out of nowhere, either. This was the sequel. Back in 1976 Congress had already told the FDA to stop regulating the potency of vitamins and minerals, and to stop treating a supplement as a drug just because the dose was large.^[5] So the agency had lost this fight once already, eighteen years earlier, on a narrower question. In 1994 it lost the wide version. If you want to understand why the FDA approaches this category the way a man approaches a dog that has already bitten him, that is why.

I want to be fair here, because there is a real argument on the other side and it is not stupid. The argument is that vitamins are not pharmaceuticals, that people have been taking them for a very long time without a body count, and that making every fish oil company run a clinical trial would hand the whole category to four large firms and price everyone else out. That is a coherent position. Reasonable people held it. The industry also spent an enormous amount of money making sure it won, which does not make it wrong, but does mean you should notice who was holding the microphone.^[6]

The sentence is not a limit, it is a product

So if you cannot say your capsule treats a disease, what can you say?

You can say what it does to a structure or a function of the human body. That is the actual legal category and it is called, with no irony whatsoever, a structure/function claim.^[7]

“Supports immune function.” Legal. “Prevents colds.” Not legal. “Promotes restful sleep.” Legal. “Treats insomnia.” Call a lawyer.

There is no evidence requirement attached to the legal one. You do not send the FDA your data, because there is no requirement that you have any. You send the FDA a notice that you are making the claim, within thirty days, after you have already made it.^[7] Notice, not approval. You are informing them, the way you inform a neighbor you are having a party.

And the disclaimer is the ticket. That is the trade: you print the sentence about nobody having evaluated this, and in exchange you get to put “supports cognitive performance” on the front in a serif font.^[8] The disclaimer is not a restriction on the claim. The disclaimer is what makes the claim possible. It is the reason the claim can exist at all, and every marketing department in the category understands this perfectly, which is why not one of them has ever complained about having to print it.

You can watch this work in the wild. There is a bestselling consumer health reference whose subtitle promises drug-free remedies using vitamins, minerals and food supplements.^[9] Remedies. A remedy is a thing that fixes an ailment. And the word sitting right next to it, drug-free, is what makes it safe to say, because “drug” is the regulatory category with the evidence requirement, and this book is announcing on its cover that it is standing outside that category. Then you open the front matter and there is the publisher’s disclaimer, saying the ideas and procedures in the book are not intended as a substitute for consulting with your physician.^[10]

So it is a remedy on the cover and not medical advice on page four. Those two statements are eleven pages apart and the entire industry lives in between them.

It scales down beautifully too. There is a self-published guide that teaches you to make your own supplements at home out of bulk ingredients, and it carries the disclaimer, word for word, the identical federal sentence.^[11] There is a bodybuilding guide whose cover promises up to fifteen pounds of muscle in six weeks, and on page three it explains that the information is not intended for the treatment or prevention of disease.^[12] Fifteen pounds of muscle in six weeks, and a disclaimer, on the same object, and the two of them have never once had an argument.

An industry insider put the whole thing more cleanly than I can. Writing for people who wanted to start a supplement company, he told them that “clinically proven” *means absolutely nothing to the average buyer*.^[13] He was not blowing a whistle. He was giving business advice.

What it takes to remove one ingredient

Now, you might reasonably ask what happens when something in this category actually hurts people. The answer is ephedra, and ephedra is the whole system’s stress test.

Ephedra is a stimulant. It was linked in case reports and epidemiology to high blood pressure, arrhythmias, heart attacks and strokes, and it got worse when people stacked it with other stimulants, which of course they did, because it was sold for weight loss and energy and those are exactly the customers who stack.^[14]

The FDA eventually got it off the market by declaring products containing it adulterated, on the grounds that they presented an unreasonable risk of illness or injury.^[15] That was the mechanism. Not “this doesn’t work.” Unreasonable risk. The government had to build a case that the thing was dangerous, and the administrative record behind that case ran to roughly a hundred and thirty-three thousand pages.^[16] Then the industry sued. Then a federal appeals court upheld the ban, two years after the rule took effect.^[17]

That is the cost of removing one ingredient. A hundred and thirty-three thousand pages and a court fight. Now look at the shelf and estimate how

long it would take to do that a second time, and a third, and note that the agency doing it has to do everything else too.

The rest of the enforcement numbers follow from that math, and they are worse than you are expecting.

The law does have a provision for genuinely new ingredients: if a compound was not already in the food supply before the law passed, the manufacturer is supposed to notify the FDA in advance with evidence that it is reasonably safe.^[18] Over the first eighteen years, the agency received about a hundred and seventy adequate notifications.^[19] A hundred and seventy. Over eighteen years. Across a market that was adding thousands of new ingredients. That is not a compliance rate, that is a rounding error with a filing cabinet.

Adverse events run the same way. In one ten-month stretch the FDA received 596 serious adverse event reports for the entire supplement category, and 352 non-serious ones, against independent estimates putting the real annual number in the tens of thousands.^[20] So the surveillance system is capturing a sliver, and the sliver is what the safety picture is built from, and the safety picture was already declared reassuring by statute in 1994.

And then there is the part that I find genuinely hard to believe, and I have checked it more than once. Researchers went looking for supplements containing actual pharmaceutical drugs, undeclared, in the bottle.

Between 2007 and 2016 the FDA identified 776 of them.^[21] Real drugs. Prescription compounds. Concentrated in the three categories you would guess if you were guessing: sexual enhancement, weight loss, and muscle building. More than one in five had multiple undeclared drugs in it. Ninety-seven percent did not say so on the label, which raises the question of what the other three percent thought they were doing.^[21]

My favorite specimen in this whole category is a stimulant that kept turning up in workout powders under the name geranium extract.^[22] It is not geranium. A Harvard researcher and his colleagues kept finding it, and its chemical cousins, in product after product, sometimes relabeled

under a fresh chemical name, and this continued through warning letters and enforcement actions.^[22] Think about the move. You do not remove the compound. You rename it after a flower. And the name works, because the only thing standing between that powder and a shopping cart is a label, and a label is a thing you print.

Some of those products got recalled. Then a research team bought the recalled products again, from American retailers, months and in some cases years later, and about two-thirds of them still had a pharmaceutical drug in them.^[23]

The recall happened. The drug stayed. That is not a gap in enforcement. That is enforcement occurring, in full, and the shelf not noticing.

The DNA test, and the defense that made it worse

In 2015 the New York Attorney General's office tried something blunt. They took seventy-eight bottles of herbal supplements off the shelves of four major national retailers and ran DNA barcoding on the contents, to see whether the plant on the label was the plant in the capsule.^[24]

About twenty-one percent matched.^[24]

The industry's response was a methodological objection, and here is where it gets good, because the objection is legitimate. DNA barcoding is a poor tool for testing processed botanical extracts. Manufacturing can shear the genetic material to the point where you cannot recover a usable sequence, so an absence of plant DNA does not prove an absence of plant.^[25] That is a real limitation and it should be on the record.

But read what the defense actually says. It says: you cannot determine, from the product, what is in the product.

That is the defense. And it is fine, as far as it goes, and it leaves the buyer holding a capsule that no available test can characterize, sold under a law that requires nobody to have characterized it beforehand either.

The number I could not source

There is a figure that gets quoted constantly, including in the earlier draft of this book. At the time the law passed, the market held something like four thousand products. Today the figure people cite is around ninety-five thousand.^[26]

I went looking for where the ninety-five thousand comes from. The trail runs to a commentary in a medical journal, and the commentary does not show where it got the number, and the reason nobody can show you where it came from is that the FDA does not maintain a comprehensive registry of what is being sold.^[26] There is no master list. The agency cannot tell you how many supplements exist in the United States, which means the honest version of that sentence is: it went from about four thousand products to an unknown number that everyone agrees is enormous.

I am keeping the number and telling you it is soft, because the softness is the more useful fact anyway.

It did not have to be built this way. The European Union runs a positive list: a health claim on a supplement has to be authorized in advance, assessed by a scientific body, and worded the way the authorization words it.^[27] Australia sorts these products into a register with two tiers, one where the manufacturer certifies quality and safety itself against a permitted list of indications, and one requiring an actual pre-market evaluation of quality, safety and efficacy.^[28] You can argue those systems are slower. You cannot argue they are impossible, because they exist.

So this is the deal America made in 1994, and it is worth stating plainly, because everything in the rest of this book is a consequence of it. You can sell almost anything. You can imply almost anything. You have to print one sentence saying nobody checked. And that sentence, the one that was supposed to be the consumer's protection, turned out to be the industry's permission slip.

THE GRAVEYARD

Here is the thing about beta-carotene that I want you to sit with before we go anywhere else.

In the 1980s, this was not a fringe idea. It was the consensus. People who ate more carotenoids got less lung cancer, that showed up in study after study, and in the laboratory the molecule did exactly what you would want an anti-cancer molecule to do. It mopped up the free radicals that damage DNA. Mechanism, epidemiology, plausibility, all three lined up and pointing the same way. If you had asked a room full of cancer researchers in 1985 whether beta-carotene would prevent lung cancer in smokers, the room would not have been divided.

So they ran the trial. Twenty-nine thousand male smokers in Finland, capsules every day, six years of follow-up.^[1]

The men taking beta-carotene got eighteen percent more lung cancer than the men taking nothing.^[1]

Not “no benefit.” Not “the effect was smaller than hoped.” More cancer. In the exact organ, in the exact population, that the pill was designed to protect.

The confirmation nobody wanted

You can dismiss one trial. Statistics do occasionally hand you a result that means nothing, and the honest response to a single surprising finding is to wait.

They did not have to wait long, because a second trial was already running in the United States, testing beta-carotene with vitamin A in heavy smokers and people who had worked around asbestos. In January 1996 the safety board stopped it, twenty-one months ahead of schedule.^[2] You do not stop a trial early for disappointing results. You stop it early because continuing has become a thing you cannot defend. The treatment group had twenty-eight percent more lung cancer and seventeen percent higher death from any cause.^[2]

Then they followed those people afterward, and this is the part that stayed with me. The harm did not stop when the pills stopped.^[3] Years after the last capsule, the excess was still showing up in the data. Whatever the supplement had done, it was not a drug effect passing through a system. Something had changed and stayed changed.

Two trials. Two countries. Roughly fifty thousand people. Same answer.

What this pattern looks like when it is happening to you

That sequence has a shape, and once you see the shape you will see it in every category in this book, so let me lay it out flat.

Step one, people who consume more of something turn out to be healthier. Step two, a laboratory finds a mechanism that explains why that would be true. Step three, the thing goes on sale, and the mechanism becomes the marketing, because a mechanism is a story and stories move product. Step four, somebody finally runs a large randomized trial measuring an actual outcome, cancer or heart attack or death rather than a number on a lab report.

And at step four, the effect very often is not smaller than expected. It is absent. Sometimes it points the other way.

The reason step four keeps ambushing everyone is that steps one through three can all be true and still not add up. Correlation, mechanism and enthusiasm are three separate things, and none of them is evidence that intervening helps. You can have all three and be completely wrong, and beta-carotene is the proof, because beta-carotene had all three.

I am calling this graveyard because that is what it is. Every compound in this chapter arrived with the same credentials the current generation of supplements arrives with, and every one of them lost.

Nobody in these trials was deficient

Vitamin E went in next.

A trial of high-risk cardiovascular patients gave them 400 IU a day for about seven years. No reduction in cancer. No reduction in cardiovascular events. A thirteen percent increase in heart failure.^[4]

Then a much larger trial gave 400 IU a day to more than thirty-five thousand healthy men, watching for prostate cancer. With extended follow-up, the vitamin E group had seventeen percent more prostate cancer than the placebo group.^[5]

Now, here is the detail that matters more than the number, and it is the hinge this entire book turns on. **Those men were not vitamin E deficient.** Nobody enrolled them because they were short of anything. The trial was not asking “does fixing a shortage prevent disease,” which is a question with a long list of yes answers. It was asking “does adding more to a system that already has enough make it work better.”

That is a different question, and it has a different answer, and the supplement industry has spent thirty years merging the two.

Selenium in the same trial is the cleanest demonstration I can give you. An earlier study had found that selenium reduced prostate cancer and total cancer mortality, which is why selenium was in the trial at all. But look at where that earlier benefit actually lived: it was confined to the participants who started with the lowest selenium levels.^[6] The people who were short of it did better. So they ran the bigger trial in American men, who mostly are not short of it, and the benefit was gone.^[7] The selenium arm was stopped for futility.

Selenium did not change. The population changed. A treatment for a deficiency was sold as an upgrade for everybody, and when they finally tested it on everybody, it did nothing.

The number moved and the person did not

B vitamins are the category where you can watch the substitution happen in real time.

High homocysteine in your blood is associated with cardiovascular disease. Folic acid and B12 lower homocysteine. Therefore, the reasoning

went, folic acid and B12 should prevent cardiovascular disease, and for a while that reasoning was on a great many shelves.

So they tested it in five and a half thousand patients with vascular disease. The homocysteine went down. It went down exactly as promised, from 12.2 to 9.9.^[8] The primary cardiovascular endpoint did not move.^[8]

The number moved and the person did not.

That is worth naming, because it is the most reliable trick in this industry: sell a change in a measurement as though it were a change in a life. The measurement is real. The change in the measurement is real. What was never established is that the arrow points from the measurement to the outcome, rather than both of them pointing back at something else.

And then B vitamins got worse. A combined analysis of two Norwegian trials found that folic acid with B12 increased cancer incidence by twenty-one percent, cancer mortality by thirty-eight percent, and death from any cause by eighteen percent.^[9]

Fish oil ran the same play with a stranger ending. One large trial of four grams a day in high-risk patients found nothing at all on cardiovascular events and stopped for futility, while new atrial fibrillation went up sixty-nine percent.^[10] A different trial of purified EPA reported a twenty-five percent reduction in cardiac events and was celebrated accordingly.^[11] The complication is that its placebo was mineral oil, and the mineral oil group showed rising inflammatory markers, which means some unknown portion of that twenty-five percent gap might be the placebo group getting worse rather than the treatment group getting better.^[11]

Somebody did try to estimate how much. I went looking for that analysis and could not get to it, only to descriptions of it, so I am not going to quote you a figure I have not read.^[12] What I can tell you is that a decade after the trial, cardiologists are still arguing about whether the benefit was the drug or the comparison, and that is not a settled result.

The ones you are probably taking

Vitamin D was supposed to be different, and it had the best observational case of anything in this chapter. Low vitamin D tracks with almost every bad outcome in medicine.

Then they gave 2,000 IU a day to nearly twenty-six thousand healthy American adults for five years and measured cancer and cardiovascular events. Nothing.^[13] No reduction in cancer. No reduction in major cardiovascular events. No reduction in fractures, no reduction in falls, no change in bone density, and, notably, no benefit in the participants who started with low vitamin D levels either.^[13]

A large Australian trial dosing monthly for five years found no mortality benefit. In an exploratory analysis that set aside the first two years, cancer mortality was twenty-four percent higher in the vitamin D group.^[14] That is exploratory, and exploratory findings are where wishful thinking goes to hide, so I am not going to tell you vitamin D causes cancer. I am telling you the biggest trials keep coming back empty and occasionally worse than empty, and that a compound this widely taken has produced this little is itself the finding.

The multivitamin, since you asked. A trial in more than fourteen thousand male physicians, running over eleven years, found no effect on cardiovascular events and no effect on total mortality. It did find an eight percent reduction in total cancer incidence, which is statistically real and clinically small.^[15] That is the strongest positive result in this chapter and I want to be fair to it: eight percent, on one endpoint, out of three.

Against that, a study following nearly thirty-nine thousand older women found self-reported multivitamin use associated with a six percent increase in death.^[16] Supplemental iron was worse. Copper was worst of all, at forty-five percent.^[16] That study is observational, which is the whole problem this chapter is about, so I am not going to hand it to you as proof of harm when I spent four pages explaining why observational supplement data misleads. It cuts both ways or it does not cut. And in the same data, calcium came out associated with lower mortality, which is not

the direction anybody in this argument wanted, and is exactly why you do not get to keep only the results you like.

And when somebody pooled the antioxidant trials, seventy-eight of them, nearly three hundred thousand participants, and restricted the analysis to the trials with the lowest risk of bias, the supplements were associated with slightly higher mortality, not lower.^[17] Vitamin A carried the worst signal. Vitamin C and selenium came out neutral.^[18]

Why the observational studies lied

So what happened? How does something show up in twenty studies of real people and then evaporate the moment you randomize?

Mostly it is who takes supplements. People who take supplements exercise more, earn more, eat better, smoke less, and see doctors more often.^[19] You can adjust for all of that statistically, and researchers do, and the adjustment is never complete, because the thing you are adjusting for is not really income or exercise. It is conscientiousness, and there is no column for that.

There is an old cardiology finding that makes this unforgettable. In a heart trial from decades ago, researchers compared people who took their assigned pills faithfully against people who did not. The faithful ones lived longer. That held for the placebo group.^[20] The people who reliably took a sugar pill outlived the people who did not reliably take a sugar pill. Nothing was in the capsule. The capsule was measuring the kind of person who takes capsules.

That is what most supplement epidemiology was measuring too.

Vitamin D has a second problem on top of that one, and it is the most useful idea in this chapter. Your vitamin D level goes down when you are inflamed or unwell. It is a downstream marker of being in poor health rather than a cause of it.^[21] So when a study finds that sick people have low vitamin D, both readings fit: the low vitamin D made them sick, or being sick lowered their vitamin D. The observational data cannot tell

those apart. A randomized trial can, and did, twice, and the answer was that topping up the number does not treat whatever put it down there.

You can run that test on almost any biomarker somebody wants to sell you a capsule for. Ask which direction the arrow points, and then ask who has actually checked.

The recommendations that outlived the evidence

None of this stopped anybody.

Vitamin D still appears in bestselling supplement guides after the large trials came back null, and the way it survives is instructive. One popular biohacking author gets there through a personal exemption, writing that people with weak vitamin D receptors in their genes (*like me*) ... *may need a lot more*.^[22] The trial found no benefit, but the trial was about other people.

There is an even more elegant version. A longevity author states the structural problem accurately, that to find out which interventions truly help humans live longer *would take fifty to a hundred years*, and having established that the definitive evidence cannot exist, proceeds to recommend the compound anyway.^[23] The observation is correct. The conclusion drawn from it is that a lower standard of evidence should apply, when the same observation supports the opposite conclusion just as well.

And here is why the graveyard keeps filling up, from an industry insider writing to people who wanted to start supplement companies: *very few companies spend money on real research, preferring instead to spend money on marketing*.^[24]

That is the whole economics of this chapter in one sentence. Almost every trial that killed a supplement in these pages was funded by governments or academic institutions. The industry does not run the trials that could disqualify its products. It does not have to, because nobody requires it to,

which is Chapter 1, and because the evidence that never gets generated cannot come back negative.

By 2022 the national body that grades preventive care had issued its verdict: do not take beta-carotene or vitamin E to prevent cardiovascular disease or cancer, and for multivitamins and most single nutrients, the evidence is insufficient to say anything at all.^[25]

That is the graveyard. Not a list of things that failed to work. A list of things that everyone knew worked, until somebody checked.

HOW TO READ A SUPPLEMENT STUDY

I want to start with a drug, not a supplement, because the drug version of this story is cleaner and nobody has a bottle of it in the cupboard to defend.

In 2007 a large trial tested a compound called torcetrapib in fifteen thousand people at high cardiovascular risk. The compound did exactly what it was designed to do, and it did it emphatically. HDL, the cholesterol everyone wants more of, went up seventy-two percent. LDL, the one everyone wants less of, came down twenty-five percent.^[1]

The patients taking it had more cardiovascular events and were significantly more likely to die.^[1] The trial was stopped early.

Both numbers moved the right way. The people moved the wrong way. That result, more than any other single thing I read for this book, is the reason the rest of this chapter exists, because it demonstrates that a number can be genuinely connected to a disease and still be useless as a target. HDL is not a decoration. It really does track with cardiovascular risk across populations. And a drug that improved it by seventy-two percent killed people.

What follows is the set of questions I ended up using on every study in this book. There are nine of them. None requires statistical training, and most can be answered from the abstract, which is convenient, because the abstract is usually all anybody reads.

Did they measure a person, or a number?

This is the first question and it eliminates most of the field.

Health authorities sort trial endpoints into a rough hierarchy. At the top are clinical outcomes: whether a patient feels better, functions better, or lives longer. Below that sit validated surrogates, measurements like blood pressure or LDL cholesterol that have been shown across many studies to track outcomes reliably enough to substitute for them. Below that are surrogates considered reasonably likely to predict benefit. And at the

bottom are candidate surrogates, the speculative ones, things like serum antioxidant capacity or an inflammatory marker such as IL-6 or TNF-alpha, which cannot support a drug approval on their own.^[2]

Nearly every supplement claim you will encounter lives in that bottom tier.

The tell is easy to hear once you know it. “Reduces inflammatory markers” is a bottom-tier claim. “Reduces heart attacks” is a top-tier claim. They sound like the same sentence in an advertisement, and they are separated by twenty years and a hundred million dollars of evidence.

Was anyone in the trial actually short of the thing?

A nutrition researcher named Robert Heaney set out the rules for testing a nutrient properly, and they are so obvious that reading them is slightly painful.

Measure people’s baseline status of the nutrient, and enroll the ones who are low. Use a dose big enough to actually change that status. Measure whether it changed. Then test whether the change produced a clinical effect. And make sure the co-nutrients are adequate, since nutrients work in systems.^[3]

That is the whole framework, and most supplement trials violate the first rule before enrollment closes.

Selenium is the case that shows what the violation costs. Recall from the graveyard that the early trial found benefit and the big later trial found none. Now look at the baselines. In the earlier trial, average selenium was around 113. In the large trial that found harm, the men enrolled averaged 135, which is fully replete.^[4] They then received 200 micrograms a day of selenium on top of that, and got a seventeen percent increase in prostate cancer.^[4]

That trial did not test whether selenium works. It tested whether more selenium helps a person who already has enough. Those are different

studies with different answers, and the industry has spent thirty years reporting the second as though it were the first, in both directions, depending on which result it needs.

So the question to ask of any nutrient trial: what was the baseline, and were these people short of it? If the paper does not say, the paper cannot answer the question you are asking.

Am I in the population they studied?

This is where most consumer advice goes wrong, and it goes wrong subtly enough to be worth slowing down for.

Take a supplement book citing a rhodiola study, reporting that *rhodiola improves performance by about 20 percent, regardless of fatigue level*.^[5] That phrase, regardless of fatigue level, sounds decisive. But it describes variation *inside* a study conducted on night-shift workers who were already fatigued. It means the benefit held across the range of tiredness present in that cohort. It does not mean the compound works in a rested person, because no rested person was in the room.

Or ashwagandha, reported as decreasing *stress by 14.5 to 27.9 percent in healthy but stressed people*.^[6] Look at the precision of that range, and then notice everything it does not say: which stress scale, over what period, in one study or twenty. The decimal places are doing rhetorical work. And the qualifier, healthy but stressed, is genuinely load-bearing and quietly disappears by the time the recommendation arrives.

The general rule is that a finding belongs to its population until somebody demonstrates otherwise in yours. Moving it is a new claim requiring new evidence, not a reasonable extension of an old one.

What was in the placebo?

The comparison arm decides what the trial can find, and in supplement research the comparison arm is frequently not inert.

Fish oil is the standard illustration. Olive oil looks like a sensible placebo for an oil capsule, and it is a poor one, because olive oil contains

monounsaturated fats and polyphenols with their own anti-inflammatory and cardiovascular activity.^[7] If your control group is receiving something mildly beneficial, the gap between the groups narrows, and a real effect can be buried. Choose a comparator that is mildly harmful and the gap widens for the same reason in reverse.

So the question is never just what did they take. It is what did the other group take, and what does that substance do on its own.

Who paid for the answer?

Sponsorship effects in nutrition research are not subtle, and two systematic reviews put numbers on them that I had to read twice.

Reviews of sugar-sweetened beverages and obesity that had financial conflicts of interest were five times more likely to conclude there was no positive association.^[8] Among industry-funded reviews, most concluded the evidence was insufficient; among independent reviews, most found the association.^[8]

The artificially sweetened beverage literature is worse. Industry-funded reviews were seventeen times more likely to report favourable weight outcomes, and reviews whose authors had financial conflicts were seven times more likely to reach favourable conclusions.^[9]

Seventeen times. That is not bias operating at the margins of interpretation. At that magnitude, knowing who funded a review tells you its conclusion more reliably than knowing what it examined.

Did they change the question after seeing the answer?

Trials are supposed to declare what they will measure before they measure it. That declaration is the entire reason a randomized trial is more trustworthy than a hunch, because it stops the researcher from running twenty comparisons and reporting the one that came out well.

A project at Oxford went looking at how well that rule is kept, tracking sixty-seven trials published in five of the most prestigious medical

journals over a six-week window. The reported figures are that trials correctly reported around three-quarters of their pre-specified primary outcomes, and added an average of about five undeclared new outcomes each.^[10]

I have to flag those two numbers, because I could not verify them against the project's own publications, only against secondary accounts and this book's own earlier draft.^[10] The project is real, it is well known, and its findings are widely reported. The precise percentages are not something I personally confirmed, so treat them as indicative rather than exact.

The underlying practice is not in dispute, and it is worth knowing the name: outcome switching. If a trial's registered plan and its published paper measure different things, the difference is the finding.

Does the compound even arrive?

Here is a question almost nobody asks, and it disposes of entire product categories on its own. Did the molecule get into the person.

Resveratrol is the cautionary case. In a dish it does impressive things, activating the enzyme everybody wanted activated, nudging the nitric-oxide machinery. In a human being its systemic bioavailability is under one percent, because your gut and liver conjugate it on the way through and most of it never reaches circulation as the thing you swallowed.^[11] The clinical outcomes are null.^[11]

Nothing about the laboratory work was wrong. The compound simply never showed up to the appointment.

The related trap runs the other way, when the compound arrives in far greater quantity than any diet would deliver, and stops behaving the way it did at food doses. Beta-carotene is the one everybody now cites. Eaten in food it is a marker of a decent diet and harmless. Given as an isolated high dose to people whose lungs are under heavy oxidative stress, from tobacco or asbestos, the molecule flips and starts behaving as a pro-oxidant, which is the leading explanation for a trial that produced twenty-eight percent more lung cancer.^[12]

Iron does something similar with a clearer threshold. Above the tolerable upper limit, around 45 milligrams a day, you can saturate the transport protein that normally keeps iron chaperoned. Free iron is chemically aggressive, drives oxidative damage, and over time that shows up as organ damage.^[13]

So the dose-response curve for a nutrient is not a ramp. It is a hill. There is a bottom where you are short, a middle where you are fine, and a top where the same molecule that was keeping you alive starts taking things apart. Almost all supplement marketing is drawn as a ramp.

Can the test even see the problem?

One more, because it cuts against my own argument and it should.

I have been telling you to demand measurement. Sometimes the measurement cannot deliver.

Serum magnesium is the standard example. The magnesium in your blood is somewhere between 0.3 and 1 percent of the magnesium in your body.^[14] Your kidneys defend that blood level hard, pulling magnesium out of bone and out of cells to hold the serum number steady. Which means a person can be meaningfully depleted in the tissues that use magnesium and still produce a completely normal lab result.^[14]

That is a real limitation and the supplement industry is entirely correct to raise it.

Then watch what gets built on top of it, because this is the move. A genuine measurement problem becomes a licence to abandon measurement altogether. If a normal result cannot rule the problem out, then no result can ever rule the problem out, and now every reader has the deficiency and no test can contradict it. The honest response to an imperfect assay is a better assay, or an explicit acknowledgement of uncertainty. The commercial response is to keep the uncertainty and sell into it.

Is the effect big enough to be worth anything?

Statistical significance answers one question only: is this result likely to be a fluke. It says nothing whatever about whether the result matters.

Picture a supplement trial with twenty thousand participants that finds a blood pressure reduction of 0.15 millimetres of mercury, with a p-value comfortably under 0.05.^[15] That is a statistically significant result. It is also clinically nothing. It will not prevent one stroke. With a large enough sample you can detect an effect too small to matter, and press releases do not distinguish between “we found something real” and “we found something worth doing.”

So: significant compared to what, and how big.

The two biases that explain the rest

Two final things, and then you have the whole toolkit.

The first is why observational studies keep promising what trials cannot deliver. Hormone replacement therapy is the classic case, and it is instructive precisely because it was not a fringe idea. Large observational studies, including one of the most respected cohorts in medicine, associated it with roughly a third lower coronary heart disease risk. Then a randomized trial in more than sixteen thousand women found a twenty-nine percent *increase*.^[16]

The women choosing hormone therapy were healthier to begin with. That was the finding all along.

The second is stranger and more useful. In the old heart trial that established this, patients who took their assigned pills faithfully outlived those who did not, in the drug arm, fifteen percent mortality against twenty-five. That is what you would expect. In the placebo arm the same pattern held: fifteen percent against twenty-eight.^[17]

Reliable placebo-takers outlived unreliable placebo-takers by a wide margin. There was nothing in the capsule. Adherence was the treatment,

or rather, adherence was a marker for the kind of life in which a person takes a capsule every day for years, and that life is the thing doing the work.

Hold on to that when a supplement study reports better outcomes among users.

What the questions are for

One last specimen, because it shows all of this compressed into a single sentence.

A longevity book states that a compound *not only helped to strengthen healthy [cells] but also directly repaired mitochondrial function*.^[18] That claim comes from work in HepG2 cells, a standard laboratory liver carcinoma line used in toxicology screening.^[18]

Run the questions. The endpoint is a cell-culture measurement, which is below the bottom of the surrogate hierarchy, because it is not even in a person. There is no population, so I cannot be in it. There is no placebo question, no baseline status, no effect size that maps to anything I would feel.

None of which means the compound does nothing. It means that between that dish and a recommendation for you there should be animal work, pharmacokinetics, dose-finding, and a controlled human trial with an outcome somebody cares about, and the sentence has skipped all of it.

That is the actual skill. Not knowing more biology than the person selling to you. Just noticing which steps got skipped between the evidence they have and the claim they are making.

THE QUALITY HALO

At some point in this you are going to think: fine, most supplements are junk, but I buy the good ones.

Everybody thinks this. It may be the single most reliable belief in the entire market. The specific form varies, professional-grade, physician-formulated, the brand my naturopath carries, the one with the certification seal, the patented form that absorbs better, but the structure is identical every time. Somewhere out there is a tier above the drugstore shelf, and you are on it.

So let us go through the tiers, one at a time, and see what each one is actually promising.

Practitioner-grade

Start with the strongest signal in the category, because it is the emptiest.

Practitioner-grade and professional-grade have no definition in FDA regulation. None. Under the 1994 law there is exactly one regulated category, dietary supplement, and it has no subcategories based on who sells it or what grade it claims.^[1] A product sold through a clinic and a product sold in a gas station occupy the identical legal position.

The industry knows. You can find suppliers of practitioner-grade supplements explaining on their own blogs that the term has no formal FDA definition, which is a strange thing to publish about your own premium tier until you notice it costs them nothing, because the term was never doing legal work. It was doing psychological work.^[2]

Now, the reason the term persists is that the channel it describes is real, and it has an economic structure worth knowing about.

The main practitioner dispensary platforms let a clinician earn a margin on every order their patient places. On one large platform the practitioner sets the patient's discount, up to thirty-five percent in the United States, and the earnings arrive on a recurring schedule.^[3] The platform also runs

automated refill reminders, built from the dosage instructions, designed to keep the patient taking the product.^[4]

Read that as a system. Your practitioner's revenue is tied to your adherence. Not to your outcome. To whether you keep reordering, which the platform is actively working to ensure, on a schedule, by email.

I want to be careful, because most practitioners in this channel are not cynics. They believe in what they dispense, they are often the only person in your life who listened to you for a full hour, and the margin is small. That is what makes it effective. A large bribe would alert everybody. A modest recurring margin, attached to a product you already believe in, alters nothing you can feel and everything about what gets recommended over years.

An industry veteran put the underlying signal more bluntly than I would dare: *"Doctor recommended" is a worthless term with no bearing on the effectiveness, quality, or safety of a product.*^[5]

Patented, trademarked, branded

The second tier is the ingredient with a symbol after its name.

You have seen these. A mineral in a proprietary chelated form, a curcumin with a registered trademark, a branded version of a compound that also exists generically for a fifth of the price. The little R in the circle is doing something specific to your brain, and what it is doing is borrowing the authority of a legal system that has nothing to do with whether the product works.

A trademark protects a name and a logo.^[6] That is its entire function. It makes no statement about efficacy, safety or quality, and it never has.

A patent is slightly more interesting and still not what you think. Patents are granted on novelty, non-obviousness and utility. Nobody at the patent office evaluates clinical benefit, and a patent is not an efficacy review.^[7] It means somebody demonstrated that the composition was new, which is a statement about the prior art, not about you.

Same insider, on this one, writing that *a patent simply protects a company's legal/financial/intellectual interests and is not a guarantee that the product is effective.*^[8]

And the absorption claims attached to these branded forms deserve their own note, because superior bioavailability is the most technically respectable argument in the whole category. It is a genuine pharmacological concept. It is also, in practice, frequently supported by trials run or funded by the ingredient supplier, of variable quality, without head-to-head human comparison against the cheap form.^[7] A podcast episode explaining why bioavailability matters for your supplements is not lying to you about the concept. It is using a real concept to establish that the retail version is inadequate and the recommended one is not.^[9]

The seals

Third tier, and here the news is better, so I want to be precise about what these do and do not cover.

The voluntary certification programs are real quality control. The USP Verified mark checks that the product contains the declared ingredients in the declared amounts, is free of specified contaminants, dissolves properly, and was made under recognized manufacturing standards.^[10] The NSF programs cover label-claim review, contaminant testing, toxicology assessment and facility audits, with a separate certification aimed at banned substances in sport.^[11]

Those are genuinely worth something, and later in this book, when I get to what I would actually buy, this is the tier that survives.

Two limits, though. Both programs are voluntary and cover only the products a brand chooses to submit, so an absent seal tells you approximately nothing and a present seal tells you about that one product. And the limit people slide past is bigger: neither program evaluates whether the supplement does anything.^[10] They verify that what the label says is in the bottle is in the bottle. That is a purity claim,

not an efficacy claim, and the marketing around these seals lets you conflate the two without ever quite saying so.

Then there is the seal that means nothing at all. GMP compliance is a legal baseline. Every dietary supplement manufacturer in the United States is required to meet it.^[12] A GMP-certified badge from a private auditor is therefore an announcement that the company is obeying a law it was already obliged to obey, and it confers no status above any other legally compliant product.^[12] It is a sticker that says “we are not currently committing a crime.”

What the testing actually finds

Here is where the halo runs into measurement.

When an independent testing outfit examined twenty-two popular multivitamins, about a third failed to meet quality standards, mostly for inaccurate ingredient levels or excessive dosing.^[13] Not a fringe category. Multivitamins.

In the higher-risk categories, weight loss, sexual enhancement, sports performance, the contamination and adulteration rates found across multiple studies run from roughly twelve percent to fifty-eight percent.^[14] And the finding from Chapter 1 belongs here too: of products recalled because they contained undisclosed pharmaceuticals, about two-thirds still contained a drug when repurchased later.^[14]

No marketing designation available to you predicts any of this. Not practitioner-grade, not professional, not GMP-certified. Label inaccuracy and adulteration are documented in both mass-market and niche practitioner-channel products.^[15]

Physician-formulated, and the negative I cannot prove

There is a tier above practitioner-grade, and it is the bundled protocol: several products sold together as a system, physician-formulated, with each component assigned a job in a sequence.

I looked at one of these closely. It offers full-spectrum daily detox support, advanced toxin binding, and micronutrient repletion with ultra-absorbable minerals and activated vitamins.^[24] Four claims, all structure-and-function, all unfalsifiable as written, none of them naming a condition you could be tested for.

And now I have to be straight with you about the limits of my own method, because this is a good example of it.

I wanted to write that no randomized trial supports this bundled system. I cannot write that, because the only thing I have is the company's own product page, and a vendor page is not evidence for a clinical claim and it is not evidence against one either.^[24] Proving that a trial does not exist anywhere requires a systematic search that this book did not run for this product.

So the honest sentence is narrower and, I think, more useful: the seller has published no trial. Under the 1994 law they were never required to have one, and nothing about the phrase physician-formulated changes that, because that phrase, like practitioner-grade, has no regulatory definition either.

Which points at the general rule. In this category, absence of evidence is the expected condition rather than a red flag, because the system was built so that evidence is optional. You are not looking for the products with something wrong. You are looking for the very small number with something behind them.

Founder, expert, same person

One more variant, because it is becoming the dominant one.

The founders of supplement companies now appear on health podcasts as subject-matter experts, discussing the science of personalized nutrition and how individual biology drives custom supplement solutions.^[25] The format presents them as nutrition scientists. They are vendors. Both things can be true, and the audio gives you no way to tell which one is talking.

Personalization is the halo's newest and best costume, because it is unfalsifiable by design. A general claim can be tested in a population. A claim that your biology is unique and requires a bespoke formulation cannot be, and it explains any failure in advance: the protocol did not fail, your biology was different.

The same vocabulary shows up in the books, where supplements are described as aiming *directly at ground zero of your energy supply, the mitochondria*.^[26] Ground zero. Nothing in that sentence is a measurement. It is an aura, applied to a real organelle, and it is very good at what it does.

The vocabulary of almost-evidence

The last layer of the halo is linguistic, and the Federal Trade Commission has already written the analysis for me.

Health claims are supposed to rest on competent and reliable scientific evidence, which the guidance generally takes to mean high-quality randomized controlled human trials.^[16] The guidance also says something I find quietly devastating: hedging a weak claim with words like preliminary or promising does not adequately communicate how weak the evidence is.^[16] The qualifier does not do the work people think it does. It reads as modesty and functions as permission.

Then the family of phrases around the word clinical. Clinically studied, clinically tested, clinically inspired: none has a standardized regulatory definition.^[17] Clinically proven should require multiple high-quality trials, and the FTC notes that when a product references a clinically tested ingredient, consumers are likely to read that as meaning the testing showed a benefit for the product they are holding.^[17]

Clinically inspired is my favourite. That is not a claim about a study. That is a claim that somewhere in the building, a study was in the room.

The halo is a person

Underneath all of it, the strongest version of this is not a seal or a trademark. It is somebody you trust.

Consider the shape of the credential in three books. A nutritional therapist writes a supplement guide, and her authority rests on her practice and on a proprietary manufacturing philosophy, *Food-Grown®*, belonging to the supplement company she founded.^[18] Author, practitioner and vendor are one person, disclosed openly, presented as a strength. Her framing of why you need any of it is the cleanest sentence on this subject I have read anywhere: *there is a vast difference between ticking over and feeling your best.*^[19]

That sentence is doing everything. Ticking over means your system is working. Feeling your best is undefined, unmeasurable, and permanently in front of you.

The biohacking version says the same thing louder, promising a reader who will become *better than normal* by reaching *a higher baseline*, and explaining that even a good diet still leaves you short of what you need *to optimize your biology.*^[20] The same author discloses taking *75 to 150 pills a day*, adding that he is *an extreme case*, which reads as a warning and functions as an invitation.^[21]

And the most prestigious version needs no product at all. A physician and longevity author writes that he considers many drugs and supplements *to be essential items in our longevity tool kit.*^[22] No specific compound, no evidence standard, no list. The credential is doing the work that the evidence is not, and because the credential is genuine, the sentence is very hard to argue with.

Then there is the old-fashioned form, in the A-to-Z home references, where a branded garlic product appears in a disease entry as something that *acts as a natural antibiotic and stimulates the immune system*, with the brand named in parentheses and the dose given as directed on the label.^[23] Deferring the dose to the label means the manufacturer sets the dose. The book supplies the authority and the company supplies the numbers.

So the halo is not one thing. It is a stack: a channel with no legal meaning, a symbol from a body that never assessed the product, a seal that verifies

contents rather than effects, a vocabulary of studies that did not happen to this product, and, at the top, a real professional whose real credential is being asked to certify something it was never trained to evaluate.

None of which tells you the bottle is bad. It tells you that everything you were using to decide it was good was measuring something else.

THE INFLUENCE ECONOMY

You have probably worked out by now that the person recommending the supplement is getting paid. Fine. Everybody knows that, everybody has made their peace with it, and if that were the whole story this chapter would be one paragraph long.

It is not the whole story. The interesting part is not that money changes hands. It is the specific shape the money has, because the shape determines what gets said, and once you know the shape you can hear it working in real time.

So let us do the shape.

A mid-tier supplement brand selling directly to you typically pays a creator ten to twenty percent of the sale.^[1] The big multi-brand retailers pay much less, one to ten percent, and their tracking cookie expires in about a week.^[1] But in the aggressive corners, weight loss, subscriptions, the categories where the customer is anxious, the rate goes to thirty, forty, sixty percent, and some of those programs pay the creator on every recurring order for the life of the account.^[1]

Read that last one again. On a subscription product, the person who recommended it gets paid every month you fail to cancel.

That is not an advertisement. An advertisement ends. This is an annuity, and you are the payment stream, and the person collecting it appears in your ears twice a week sounding like a friend who has done some reading.

The disclosure that is not there

There is a rule about this, and the rule is not vague.

The Federal Trade Commission revised its endorsement guides in 2023, and they require that a material connection between an endorser and an advertiser be disclosed clearly and conspicuously, which the guides define as difficult to miss and understandable to an ordinary person.^[2] Material connection means the affiliate commission, the free product, the

equity stake, all of it. The guides say relying on a platform's built-in disclosure tool is often not enough. And liability runs in three directions at once, to the brand, to the creator, and to the agency in the middle.^[2]

That is the law. Here is the compliance.

An academic analysis of influencer marketing put non-disclosure somewhere between forty and sixty percent. Some brands failed to disclose on ninety-four to ninety-eight percent of their posts. And at the fifth percentile, meaning the brands doing this best, the non-disclosure rate was still around eighty percent.^[3]

The best-behaved end of the distribution is failing to disclose four times out of five.

A study of German supplement influencers found that roughly forty-eight percent of the products being advertised came with an explicit promise that they would work, and those promises were frequently paired with a discount code, which is the part that converts the promise into a transaction.^[4]

The numbers I could not get

Now I have to tell you something about this chapter specifically, and I want to do it here rather than bury it.

This is the worst-sourced chapter in the book.

Four separate figures that I wanted to give you did not survive verification. There is a study of two million YouTube videos with a striking pair of numbers about how few affiliate disclosures actually meet the federal standard. I could not get to the paper, only to a marketing association's description of the paper.^[5] There is a European Commission audit reporting how few influencers disclose systematically, which I have only as a citation inside somebody else's citation.^[6] There is a widely repeated monthly podcast advertising figure for a very large greens powder brand, which traces to one analytics firm's estimate rather than to anybody's accounts.^[7] And there is a consulting firm's case study describing a supplement brand that ran over a thousand creator deals at a

disclosure rate close to zero, which is a spectacular number from a source with a commercial interest in the topic.^[8]

I am not printing those figures as facts, and you should be a little suspicious of anyone who does.

But notice what just happened, because it is the actual finding. The chapter about money moving invisibly through the recommendation layer is the chapter where the numbers are hardest to verify. That is not bad luck. That is the subject matter defending itself. Nobody publishes their affiliate ledger. There is no registry of who paid whom, which means the honest state of knowledge here is: the mechanism is documented, the regulation is documented, the non-compliance is documented in the peer-reviewed work, and the total volume of it is not knowable from outside.

Study to cart

The pattern that connects the research to your credit card has a shape too, and it goes like this. Somebody describes a mechanism or cites a study. The mechanism is connected to an ingredient. The ingredient is available in a product. The product has a code.^[9]

Every step in that chain can be individually defensible. The study is real. The ingredient really is in the product. The code really is a discount. What fails is the joint, and the joint is almost always the population: the study was done in people who are not you.

The clearest example I have ever seen of this is in a bestselling biohacking book, in the section on ginseng, where the author writes that *in studies where individuals were not already experiencing fatigue, they did not see an increase in cognition*.^[10]

That is an accurate summary of the evidence. It says the compound works on the tired and does nothing for everyone else. And then the recommendation proceeds to the general reader anyway, unmodified.

He does the same move with curcumin, citing a study of people with age-related memory loss and generalizing the recommendation to a readership that is not selected for memory loss.^[11] That one at least

requires you to notice the population. The ginseng one states the disqualifying finding out loud, in the author's own sentence, and then walks past it.

One molecule, the whole loop

If you want to see every layer of this operating at once, there is a single case that has all of them.

A veterinary epidemiologist studying aging dolphins found an association involving a particular fatty acid. She published on it.^[12] She then co-founded the company that sells that fatty acid as a supplement, which is, as far as I can determine, the only commercial source of it.^[13]

Then the appearances. On one friendly podcast she describes the compound using the language of the recognized hallmarks of aging, saying *reversing cellular aging is what it does ... that it is reversing Aging in these folks*, alongside customer testimonials, on an episode that links to the purchase.^[13] On the same episode she mentions that they *also worked with Genova Diagnostics to develop an at-home C15 test*, so that a listener can measure their level of the thing she sells.^[14]

Sit with the completeness of that. The same person generated the research, founded the company, holds the equity, promotes it on shows whose hosts have their own supplement interests, and co-developed the test that tells you whether you need it.

Then watch the claim inflate as it travels. In her own book she describes the arc as *our initial interesting discovery of C15:0 as a healthy nutrient for aging dolphins has evolved into a global movement to save humanity*.^[15] By the time it reaches a podcast title on another show, it is presented as a milk fat that slows aging and extends life twofold.^[16]

Dolphins to a global movement to two times your lifespan, and at no point in that escalation did anybody run the trial that would justify the last claim.

I want to be careful here, because this is a real scientist with real publications and none of what I have described is illegal or even unusual.

That is the point. Every individual step is normal. It is the assembled machine that should worry you, and the machine is not hidden. It is described openly, in her own words, on shows that disclose their sponsorship in the episode notes.

The word doing the most work is “rational”

The influence economy’s best trick is not deception. It is framing.

A very popular episode on supplementation from a Stanford neuroscientist is titled as a rational approach to the subject, and it carries four sponsors, one of which is a greens powder and one of which is a blood testing company, plus a supplement partnership named in the episode itself.^[17] The content may be careful. The frame is what is for sale, and the frame is: this is the science-based one.

Elsewhere a biohacking host, describing a sponsor’s NAD supplement, calls it a *quantum leap in biohacking and a no-brainer to add to your stack*, and discloses in the surrounding text that he is an advisor to the company.^[18] The disclosure and the endorsement are in the same breath. Technically that is compliance. Functionally the disclosure has been absorbed into the pitch, which is a thing disclosures do when they appear often enough.

Another host built a recurring content pillar around a common genetic variant said to affect a large share of the population, with episodes explaining which two ingredients to avoid in your supplements, and eventually an episode telling you to *stop guessing what supplements you need* by taking a test.^[19] The genetic variant is real. The share of the population is a real number. What the framing accomplishes is the conversion of a variation into a deficiency, and a deficiency into a purchase.

And the broadest version, from a functional medicine practitioner: the argument that depleted soils, storage, transportation and genetic alterations *make it impossible for us to get all the vitamins and minerals we need solely from the foods we eat*.^[20] That sentence does not identify a deficiency in you. It establishes that everyone is deficient, in advance,

permanently, which is the most durable market position available. On another episode the same host answers a listener question by naming specific practitioner-line brands rather than compounds.^[21] Not “a digestive enzyme.” The brand.

The vocabulary is part of the product

There is a small set of phrases that do the persuading, and the best descriptions of them come from people who sell supplements for a living.

On the phrase scientifically formulated, an industry veteran writing a guide for people entering the business: *Many products are designed with their marketing power in mind, not their scientific strengths.*^[24] On the phrase all natural, from the same author, that it *means nothing at all, yet people seem to fall for it virtually every time.*^[25]

Neither of those phrases has a regulatory definition. That is not an oversight in the drafting. A term with a legal definition can be violated, and a violation can be enforced. A term with no definition cannot be wrong.

The authority itself gets manufactured the same way. A bodybuilding supplement author establishes his credential like this: *I've also seen and studied how the supplement industry operates. Both as a customer buying up the latest craze, and as an 'insider' with my own company.*^[26] Notice what is being offered. Not training, not evidence, not a result anybody replicated. Proximity. He has been near the industry, and nearness is presented as the qualification, and it works, because the reader has no way to evaluate any of the other credentials either.

And at the top of the market the loop closes completely. A biohacking author explains that *I've founded two companies, Upgrade Labs and 40 Years of Zen, to figure out exactly what signal to use.*^[27] The research and the business are the same activity. That is stated openly, in the introduction, as a strength.

The people not selling anything

I should tell you that the counter-content exists, because it does, and it lives on the same platforms.

There is an analyst who works through supplement trials in long, numbered, unglamorous detail, including a dedicated segment on the methodological problems in a famous longevity researcher's own trial of his own compound.^[22] Same platform, same subject, same audience available. He audits the study rather than converting it.

That is the whole comparison. Both formats are free. One of them ends in a code.

And then there is the insider testimony, which is bleaker than anything an academic will write. An author describing his first visit to a supplement manufacturer found *a SINGLE STORY HOUSE in my residential neighborhood*, filling bottles from bulk ingredients, and reports the lesson he took from it, which was that *there was a LOT of money to be made in marketing supplements to the hungry masses since he could charge as much as he wanted to regardless of what was actually in the bottles*.^[23]

Regardless of what was actually in the bottles. A person who does this for a living wrote that sentence down, in a book, for money.

There is also a category of participant I find harder to be glib about, and it is worth naming because it is where most sophisticated readers actually live. A physician and very widely read longevity author warns his readers directly against this whole apparatus, writing that otherwise *you'll forever ride the merry-go-round of fad diets and trendy workouts and miracle supplements*.^[28] That is correct, it is well said, and he means it.

His framework then authorizes individualized supplement protocols, chosen per patient, without the population-level evidence he spent the earlier chapters demanding.^[28] I do not think that is hypocrisy. I think it is what happens to anyone who has to give an actual person an actual answer on a Tuesday, and it is the most honest illustration in this chapter

of how strong the pull is. The people who see the mechanism clearly are not immune to it.

None of this requires anyone to be lying. It only requires that the recommendation and the transaction sit close enough together that nobody has to choose between them. Take the commission away and most of these people would still believe most of what they say. That is exactly why it works, and it is why “do they really believe it” is the wrong question to ask about your podcast host.

The right question is what would have to happen for him to tell you a product does not work, and whether anything in his arrangement makes that outcome possible.

ENERGY AND MITOCHONDRIA

Every supplement sold for energy is sold on the same organelle.

You have mitochondria in nearly every cell, they make the molecule your body spends to do anything, and a popular biohacking book puts the scale like this: about *10 quadrillion mitochondria*, producing, under exertion, roughly *one pound of ATP every minute*.^[1] Big numbers, genuinely true, genuinely amazing.

The same book then supplies the commercial move in one line: *figuring out the proper feeding and training of your mitochondria ... I've never in my life seen a system so ripe for hacking*.^[2]

Ripe for hacking. Note what has happened in that sentence. A system that is currently working, in you, right now, without which you would be dead, has been reclassified as an underperforming asset.

This chapter is going to be more generous than the last few, because in this category some of the evidence is real. It is just real about specific people, and you are probably not one of them.

CoQ10, or what a genuine result looks like

Start with the strongest case in the chapter, and I want to give it full credit before I take anything away.

Statins work by inhibiting an enzyme in the mevalonate pathway. That pathway is the shared production route for cholesterol and for CoQ10, so blocking it lowers both, which is not a theory, it is the mechanism of the drug. Muscle symptoms turn up in something like ten to twenty-eight percent of statin users.^[3]

So: real depletion, real cause, real symptom, in a defined population. That is the setup this book keeps saying almost never exists.

And the evidence follows the setup. A recent systematic review pooling seven randomized trials in nearly four hundred patients found CoQ10 at 100 to 600 milligrams a day produced a statistically significant reduction in muscle pain, though with high variability between trials.^[4]

Heart failure is stronger still. A trial gave 300 milligrams a day of CoQ10 to patients with severe heart failure for two years. Major cardiovascular events fell from twenty-six percent to fifteen. Cardiovascular death and all-cause death both roughly halved.^[5] A later meta-analysis across thirty-three CoQ10 studies found reduced all-cause mortality and a halving of heart failure hospitalizations.^[6]

Those are outcome results, not biomarker results. Dead or not dead. If that finding holds, CoQ10 in advanced heart failure is one of the few supplements in this book that earns its shelf space.

Now the caveats, which are substantial and which the marketing never carries. That trial was funded by supplement manufacturers and an industry association. It recruited slowly across nearly a decade, it was small, and it closed early.^[7] Every one of those features is a way a result can come out too good. A larger pragmatic trial is now running, which is exactly the right response.^[7]

And here is the part that matters for you. None of it says anything about CoQ10 for energy in a healthy person with normal levels. There is no good clinical trial support for CoQ10 improving physical energy, athletic performance or mitochondrial efficiency in healthy replete people.^[8]

Which is why the consumer version reads the way it does. A biohacking book tells the general reader that *CoQ10 ... may enhance blood flow and protect blood vessels, with typical doses range from 30 to 150 mg per day.*^[9] The heart failure patients got 300. The statin patients had a documented depletion. The reader gets neither the population nor the dose, and keeps the implication.

NAD, and the number that goes up

The NAD story is the purest surrogate case I found anywhere in this book, and it is worth walking slowly.

NAD is a coenzyme central to energy metabolism, and NAD levels decline with age. Two precursor compounds, NR and NMN, are sold to raise it. Do they work?

Yes. Unambiguously. Across human trials, NR at 300 to 1000 milligrams a day and NMN at 250 to 900 raise NAD and related metabolites in blood, plasma and immune cells.^[10]

And human randomized trials have consistently failed to show improvement in muscle function, insulin sensitivity, athletic performance, liver fat, cardiac ejection fraction or inflammatory markers.^[10]

Read those two paragraphs together, because that is the entire field. The product does what it says on the label. The label is measuring the wrong thing. If NAD decline caused the problems of aging, raising NAD should do something, and across trial after trial it does not, which is evidence that the decline is a passenger rather than a driver.

There is even a wrinkle about whether the compound reaches you at all: work published in 2025 reports that oral NAD precursors are largely metabolized by gut bacteria before they get into circulation.^[11]

Two more findings float around this field that I could not stand behind. A pilot trial reportedly found that NR at a gram a day reduced systolic blood pressure by eight or nine points in people with elevated readings, which would be a genuinely useful effect. I could not identify the paper.^[12] And a 2025 preprint on a commercial NAD product reports a sizeable rise in NAD alongside self-reported improvements in emotional wellbeing, in women only, with no benefit in men. That is a preprint, meaning not yet peer reviewed, funded by the product's maker, with a subjective endpoint and a subgroup split.^[13] If you handed me that study design and asked me to predict its result, I would have predicted that result.

There is also a report that most of twenty-two top-selling NMN products failed to match their label claims, some with little or no active compound. I could not locate the underlying analysis, so I am telling you it exists as a claim and not as a fact.^[14]

The part of the NAD story that is pure farce

The regulatory history here is too good to leave out.

In late 2022 the FDA determined that NMN could no longer be sold as a dietary supplement, on the grounds that a pharmaceutical company had filed to investigate it as a drug before it was widely marketed, which under the 1994 law knocks an ingredient out of the supplement category.^[15] That company was co-founded by the Harvard geneticist most associated with promoting NAD precursors publicly.^[15] In late 2025 the FDA reversed itself and let NMN back through the normal ingredient pathway.^[15]

So for three years the most prominent scientific advocate of a supplement was also, through a company, the reason you could not legally buy it.

The same researcher has stated publicly that his personal regimen reversed his biological age from 58 to 31.4, as measured by a company in which he holds an investment and on whose advisory board he sits.^[16] He also holds patents on the anti-aging use of a NAD precursor, licensed to a company that sells it at around sixty dollars a bottle.^[16] That is a single-subject result, unreplicated, using a proprietary measurement owned by an interested party.

And the field has a precedent that nobody in it mentions. The company he co-founded to develop compounds activating the same longevity enzyme was bought by a major pharmaceutical firm for seven hundred and twenty million dollars, and then shut down after its drug candidates failed.^[17] The assay that made resveratrol look like an activator of that enzyme was later shown to be an artifact of the fluorescent tag used in the test.^[17]

The molecule was not activating the enzyme. The dye was.

B12, which is the actual answer for some of you

Now the one that will genuinely help a minority of readers, and this is where the doses matter, so they stay in the text.

Vitamin B12 deficiency is common and under-recognized. Up to forty-three percent of older adults living independently have subnormal levels,

mostly because stomach acid production declines with age and B12 needs acid to be released from food.^[18] Vegans without supplementation run through their liver stores in about three years.^[18]

If you are deficient, this is fixable, and cheaply. A Cochrane review of three randomized trials found high-dose oral B12, 1,000 to 2,000 micrograms a day, works as well as intramuscular injection for normalizing blood levels and correcting the blood picture.^[18] Oral. Not a clinic visit, not a shot, and not a practitioner-grade formulation.

If you are not deficient, it does nothing. In people with normal levels, above roughly 300 picograms per millilitre, B12 has no effect on energy, performance or fatigue.^[19] The absorption route is saturable, so from a large oral dose you take up only one or two percent and excrete the remainder.^[19]

That is the whole chapter in one nutrient. Same compound, same dose. It changes the life of a deficient person and does nothing whatsoever for a replete one, and the only thing standing between those two readers is a blood test that costs almost nothing.

The B12 shot at the wellness clinic is not a scam exactly. It is a real treatment for a real condition, sold to a room in which most people do not have it.

Nerve compounds, and one warning worth printing

Two compounds have decent evidence in diabetic nerve damage. Alpha-lipoic acid at 600 milligrams a day improves neuropathic pain and nerve conduction in meta-analysis, although a four-year multicentre trial did not reach significance on its main endpoint while reportedly slowing progression, and I could not verify the specifics of that trial's result.^[20] Acetyl-L-carnitine at 2,000 milligrams a day shows nerve regeneration and improved vibratory perception in early diabetic neuropathy.^[21]

Here is the warning, and it is the reason this paragraph exists. The American Society of Clinical Oncology discourages acetyl-L-carnitine in

patients undergoing chemotherapy, because the clinical data suggest it may make chemotherapy-induced nerve damage worse.^[21]

Same compound. Helps one kind of neuropathy, may worsen another. If you are in cancer treatment, this is a conversation with your oncologist and not a purchase.

Energy you can feel, measured by asking

Two more categories, quickly, because they show what weak evidence looks like when it is dressed up.

D-ribose has a pilot study in forty-one patients with fibromyalgia or chronic fatigue reporting a forty-five percent average increase in self-reported energy, and a larger study across fifty-three clinics reporting a sixty-one percent increase and improved wellbeing.^[22] Both were open-label. No blinding, no placebo group, everybody knew what they were taking, and the outcome was how tired people said they felt.

A sixty-one percent improvement in a self-reported symptom, in an unblinded trial, is not a finding. It is a description of what placebo looks like in a hopeful population.

PQQ at least has a randomized placebo-controlled trial, in older Japanese adults with mild forgetfulness, reporting improvements in memory and attention measures.^[23] A follow-on trial combining it with CoQ10 is reported to do better still, and I could not locate that one.^[23]

What gets sold is bigger than either. *PQQ can increase mitochondrial density, reduce inflammation, and protect your heart*, per the same biohacking book.^[24] Mitochondrial density is a measurement in tissue. Protect your heart is a claim about whether you have a heart attack. Nothing in the cited evidence connects them. Elsewhere the same chapter says a Krebs-cycle intermediate *activates mitochondrial biogenesis in the brain, reduces inflammation, and stimulates neurogenesis*, which is laboratory biology stated as though it were a Tuesday afternoon.^[25]

The order in which things happen

One structural observation before the summary, because this category demonstrates it better than any other.

The Harvard geneticist appeared on a large longevity podcast in 2019 to discuss NAD, NMN and resveratrol, at a point when the supporting work was substantially in yeast and mice.^[26] The promotional wave ran for years. Then in 2024 an independent analyst devoted an episode to a study associating niacin metabolites with cardiovascular risk, asking whether the compounds everyone had been taking might carry a heart risk.^[27]

Note the sequence. Enthusiasm, market, then scrutiny. That is the standing order of operations in this category, and it is the opposite of the order used for drugs, where scrutiny is the price of entry rather than a later development.

You can also watch the softer version of the sell. A physician host explains that ketones *instruct mitochondria to make more of themselves*, opening with *I was wrong!* about his previous position, and then presents the new book.^[28] The admission of error is the credibility move, which is a strange machine when you look at it directly: the reliability being demonstrated is the willingness to revise, and the thing being sold is the revision.

And then, to be fair to the people in this business who do it well, there is an episode where two physicians disclose their own supplement regimens in detail, and one of them says plainly that the evidence for NAD precursors is limited while acknowledging he takes them anyway, comparing the whole category to rearranging deck chairs on the Titanic relative to the behaviours that actually matter.^[29]

That is honest, and it is also the problem in miniature. The disclosure of a stack is an endorsement whatever the accompanying caveat says. Nobody writes down the caveat. Everybody writes down the list.

So here is the shape of the energy aisle, and it is consistent enough to be a rule.

Where there is a real hole, a supplement fills it and the effect is unmistakable: B12 in the deficient, CoQ10 in the statin-depleted or the failing heart. In every one of those cases the hole is identifiable, testable, and usually caused by something specific like a drug, a diet or a disease.

Where there is no hole, what gets sold is the mechanism itself. The mitochondrion, the coenzyme, the pathway, described accurately and beautifully, in place of a result.

And if you are tired, the honest ranking is not what this industry would like. Sleep, iron and thyroid status, depression, alcohol, and a blood test. The pill for tiredness in a person who is not deficient in anything has been looked for repeatedly and has not been found.

SLEEP, STRESS, MOOD

Melatonin is not a sleeping pill. It is a hormone, and specifically it is the hormone your body uses to announce that it is night.

That distinction runs the whole chapter, so let me put a number on it. Your own nocturnal melatonin peak can be reproduced with an oral dose of about 0.1 to 0.3 milligrams.^[1] Go and look at what is in the bottle. Standard retail products come in at 1, 3, 5, sometimes 10 milligrams, which puts blood levels ten to a hundred times above anything your body has ever produced, saturates the liver enzyme that clears it, and leaves you groggy the next day with your body clock nudged somewhere you did not ask for.^[1]

Nobody made that choice for a physiological reason. Nobody could patent it, so they scaled it, because at retail a bigger number on the label reads as a stronger product.

And what does the overdose buy you? Across meta-analyses in chronic insomnia, melatonin shortens the time it takes to fall asleep by roughly five to seven minutes, and extends total sleep by around eight.^[2] I should say that I could not pin those figures to a specific meta-analysis in the record behind this book, so treat them as the shape of the finding rather than the finding.^[2] The shape is not in dispute: statistically real, clinically small.

Melatonin does have genuine uses. Shifting a body clock across time zones or shift work is one, and low doses do that better than high ones.^[1] In children with autism, trials report falling asleep about half an hour earlier and sleeping meaningfully longer, and in ADHD a smaller improvement, though I could not verify the specific trials behind those numbers either.^[3] Against that, sleep medicine guidelines recommend against melatonin in elderly patients with dementia, where it can worsen mood as rated by caregivers, raise fall risk through slow clearance, and aggravate blood pressure drops on standing.^[4]

The bottle is worse than the dose

Then there is the question of whether the bottle contains melatonin at all.

A laboratory analysis published in 2023 tested twenty-five melatonin gummy brands. Eighty-eight percent were inaccurately labeled. Actual content ran from seventy-four percent to three hundred and forty-seven percent of what the label declared, and only three products in twenty-five landed within ten percent of their own stated dose.^[5]

One product contained no detectable melatonin whatsoever. It contained 31.3 milligrams of unlabeled CBD.^[5]

An earlier analysis of thirty-one melatonin supplements found seventy-one percent missing their label claim, ranging from eighty-three percent below to four hundred and seventy-eight percent above. Different lots of the same brand varied from each other by up to four hundred and sixty-five percent. And about a quarter of the products contained undisclosed serotonin.^[6]

That last one is not a labeling irritation. Serotonin in a supplement taken by somebody on an SSRI is a drug interaction with a name, serotonin syndrome, and nobody on either side of that transaction knows it is happening.

So the practical advice, if you want melatonin: buy a low dose from a third-party-verified brand, take it one to two hours before your target bedtime rather than at bedtime, and use it to move a clock rather than to force unconsciousness.

Magnesium, where the deficiency is real

Now the opposite situation, and there are not many of these.

Around forty-five to fifty percent of Americans do not get the estimated average requirement of magnesium from food.^[7] In adults over sixty-five it is eighty-three percent, and among older African American adults, ninety-one percent.^[7] That is a genuine, widespread, dietary shortfall, and it is the strongest case for routine supplementation in this entire book.

Doses and limits, because you can act on these. The tolerable upper limit for supplemental magnesium is 350 milligrams a day of elemental magnesium, and the thing that happens above it is osmotic diarrhea, which is unpleasant rather than dangerous in a healthy person.^[8] If you have advanced kidney disease, this changes completely: your kidneys clear magnesium, and when they cannot, blood levels can climb to the point of causing a slow heart rate and cardiac arrest.^[8] Stage 4 or 5 kidney disease means you do not take magnesium without your nephrologist.

On forms, which is where the marketing lives. Magnesium oxide is poorly absorbed, under about five percent, and is essentially a laxative wearing a mineral's name. Bisglycinate uses a different absorption route. L-threonate is claimed to reach the brain more readily.^[9] Those distinctions come from pharmacokinetic reasoning rather than from head-to-head outcome trials, so the confident brand rankings you have heard are running ahead of the evidence.

As for whether it helps you sleep, the honest answer is: a little, if you were short of it. A large German randomized trial of magnesium bisglycinate reported a statistically significant improvement in insomnia severity that just cleared the threshold, with a small effect size, and a substantially larger response in the participants who had lower dietary magnesium to begin with.^[10] I could not locate that trial to check it.^[10]

But look at the subgroup finding, because it is the book's whole thesis arriving again: the benefit concentrated in the people who were short.

Ashwagandha works, and you need to hear the rest

This one is uncomfortable, because both halves are true.

Ashwagandha has better evidence than most things in this chapter. A meta-analysis of nine randomized trials found meaningful reductions in perceived stress and in an anxiety rating scale, alongside a drop in serum cortisol.^[11] A larger dose-response meta-analysis across twenty-two trials in nearly fourteen hundred people confirmed dose-dependent reductions

in anxiety and perceived stress across the range of 240 to 1,250 milligrams a day.^[12]

That is a real signal, replicated, dose-dependent. I am not going to pretend otherwise because it would be convenient for my argument.

Here is the rest. The NIH's drug-induced liver injury database assigns ashwagandha a likelihood score indicating it is a likely cause of clinically apparent liver injury.^[13] The pattern is consistent: onset two to twelve weeks after starting, presenting with jaundice, dark urine and itching, with a biopsy picture resembling anabolic steroid injury. Liver enzymes can run into the thousands. Rare cases have required a liver transplant.^[13]

Complicating that, a twelve-week manufacturer-sponsored safety study of a standardized branded extract at 2,000 milligrams a day found no liver, kidney or thyroid changes.^[14] Which suggests the injuries may be driven by individual susceptibility, or by contamination and adulteration in unverified products, rather than by the plant itself.^[14]

So the practical shape: if you take it, use a third-party-verified product, know that jaundice or dark urine means stop and see a doctor immediately, and understand that "natural" has never had anything to do with hepatotoxicity. And notice the cortisol result in those meta-analyses is a surrogate. Cortisol went down. Whether your life improved is a separate measurement.

Two words that are not real

Twice in this category you will meet vocabulary that sounds clinical and is not.

Adaptogen is not a recognized pharmacological classification. Not by the FDA, not by the European regulator, not by the major medical bodies.^[15] It came out of Soviet research in the mid-twentieth century, where it was defined by three criteria including a normalizing effect, meaning the substance was supposed to raise what was low and lower what was high.^[15] That bidirectional claim is the load-bearing one in modern

marketing, and it has no solid human clinical support. The trials show cortisol going down. Only down.^[15]

A substance that only pushes one direction is not balancing your system. It is a drug with a mild effect and a flattering description.

Adrenal fatigue is worse, because it is a diagnosis that does not exist. Endocrine evaluation does not support a state in which adrenal glands become physically depleted of cortisol.^[15] It has no diagnostic criteria and no test, which is exactly why it works commercially: you cannot fail to have it, and you cannot be cured of it, so the protocol has no end date.

What holds up, and what does not

Quickly, because this is the part you can use.

Holding up: L-theanine at 200 to 400 milligrams reduces stress and anxiety in people facing an acute stressor, per systematic review, and at 200 to 450 milligrams improves sleep quality and morning recovery across thirteen trials, with no serious adverse events and no next-day motor impairment.^[16] Glycine at 3 grams an hour before bed improves subjective sleep quality and next-day fatigue in double-blind crossover trials, with no grogginess.^[17] Neither is dramatic. Both are cheap, well tolerated and honestly described.

Rhodiola sits in the middle: standardized extract at 340 to 680 milligrams a day has moderate evidence for stress-related fatigue and mental work capacity under exhaustion, from trials that are small and short.^[18]

Not holding up: valerian. A systematic review covering thirty-seven trials, twenty-nine of them double-blind, found no significant difference from placebo on time to fall asleep, total sleep time or sleep efficiency, and a 2024 umbrella review across all the systematic reviews reached the same conclusion.^[19] The only positive findings are subjective, and none survives contact with a sleep laboratory.

And apigenin, which has become a fixture of sleep stacks, has no published human randomized trial at the popularized 50 milligram dose, for sleep or for anxiety.^[20] Not a weak trial. None. The nearest evidence is

a chamomile extract trial in chronic insomnia which found a non-significant trend toward better daytime functioning and no benefit on sleep latency or efficiency.^[20]

Which brings us to how these get assembled. A widely heard episode on rational supplementation lays out a sleep stack of specific magnesium forms, theanine and apigenin, and includes a cautionary note on melatonin.^[21] The melatonin caution is correct and I have just spent two pages agreeing with it. The apigenin recommendation, in the same segment, is for a compound with no human trial at that dose. Both statements arrive in the same voice, carrying the same authority, and nothing in the delivery tells you which one has evidence underneath it.

That is the problem in miniature, and it is not solved by finding a more trustworthy person. It is solved by asking, per item, what the trial was.

The consumer books do the same thing faster. Saffron is offered for *the mood, brain, and weight loss benefits*, three outcome categories from one spice.^[22] *Bacopa improves memory in healthy adults and enhances attention and mood in people over age sixty-five*, which is two findings from two different populations, welded into one recommendation for everybody.^[23]

Holy basil deserves a sentence for a different reason. It appears in a great many stress formulas and it has no high-quality human trial as a single ingredient. The trials that exist use proprietary multi-herb blends, which means that even where a blend shows an effect, nothing in the design can tell you which plant did it.^[24] A blend is not evidence for its components. It is evidence for the blend, sold as evidence for whichever component the brand is featuring.

The part that stopped being funny

There is one move in this category that I want to be plain about, because the rest of this book can afford to be wry and this cannot.

Open a long-running consumer health reference at its entry for anxiety disorder. You find a table: supplements down the left, doses in the middle,

and a column of stated benefits on the right.^[25] The format is a prescription. The layout, the dosing column, the clinical heading, all of it is borrowed from medicine, applied to a diagnosable psychiatric condition, with no evidence citation and no physician in the room.

Another guide organizes an entire section around named complaints: *Stress and anxiety, Low mood and depression, Tiredness and fatigue, Difficulty sleeping, Memory.*^[26] Each gets a supplement recommendation. And the authority underneath it is stated in the introduction as personal experience, that natural supplementation *has been life-changing for my family and me ... especially through ... menopause for me.*^[27]

I believe her. That is the trouble. Sincere personal testimony, laid out in a clinical format, produces something that reads exactly like medical advice and answers to nobody.

Depression is a condition people die from. Anxiety disorder is a condition that ends careers and marriages. Neither belongs in a table between apigenin and chamomile, and the reason this format persists is the same reason it existed in Chapter 1: a disclaimer on the copyright page converts a treatment protocol into a lifestyle suggestion, legally, at no cost to the publisher and at some cost to whoever reads the table instead of calling somebody.

If you are depressed, the supplement aisle is not where this gets solved, and I am not going to be cute about it.

So the last word on this category goes to a physician writing about his own metabolic health, who concluded that his biggest problem *was less what he ate than how little he slept.*^[28]

Nothing in this chapter competes with that sentence. The supplements that work here move a number by a modest amount. Sleep itself moves everything, and it is the one intervention in the chapter that nobody can put in a bottle and sell you at a margin.

GUT

There is no such thing as a probiotic.

I mean that fairly literally. Probiotic is not a substance, it is a shelf. Underneath it sit hundreds of different organisms, and the differences between them are not like the differences between brands of aspirin. They are like the differences between a labrador and a shark.

Which leads to the rule that governs everything here, and which the industry has spent two decades not saying out loud. **Benefits are specific to the strain and to the condition.** A strain with good trial evidence for preventing a particular diarrhea in children tells you nothing whatsoever about irritable bowel syndrome, inflammatory bowel disease, or the word immunity printed on the front of a box.^[1]

And the number on the bottle, the CFU count, is not potency. More colony-forming units of an organism that does nothing for your condition is more of nothing.^[1] The doses with actual evidence behind them are unglamorous and specific: five to forty billion a day of one of two named organisms, for preventing antibiotic-associated diarrhea in children.^[1]

Where probiotics genuinely work, and it is not where you are

I want to lead with the wins, because in this category the wins are real and one of them is the most impressive result in this book.

In very premature, low-birth-weight infants, particular combinations of *Lactobacillus* and *Bifidobacterium* reduce necrotizing enterocolitis, a catastrophic bowel condition, and reduce all-cause mortality, and get babies to full feeding faster.^[2] That is dead-or-alive evidence in the most vulnerable patients medicine has. It is also accompanied by warnings about rare probiotic sepsis, including a reported death, because giving live organisms to an infant with an immature immune system is not a trivial act.^[2]

Second: preventing the diarrhea caused by *Clostridioides difficile* in people taking antibiotics. A Cochrane review across thirty-nine randomized trials and nearly ten thousand participants found roughly a sixty percent reduction in risk, concentrated in the patients whose baseline risk was highest, and it works best started within two days of the antibiotics.^[3]

Third: pouchitis, an inflammation that develops after a particular bowel surgery. A high-dose eight-strain formulation, at doses running from nine hundred billion to nearly two trillion organisms a day, reduces onset and relapse, and appears in both US and UK guidelines.^[4]

Now look at that list. A neonatal intensive care unit. A hospital patient on antibiotics. A post-surgical patient with a surgically constructed pouch. These are the strongest probiotic indications in medicine and every one of them is a clinical population under supervision at doses nobody sells for general wellness.

Where they do not work, according to the gastroenterologists

The same guideline that endorses those uses also says no, repeatedly, and the nos are less famous.

Against probiotics for treating an existing *C. difficile* infection outside a trial: five small trials, inconsistent results, low certainty.^[5] Against probiotics for inducing or maintaining remission in Crohn's disease: across twelve trials in nearly seven hundred patients, no significant improvement over control.^[6] For ulcerative colitis, only inside clinical trials, because the results across eleven trials were heterogeneous and did not consistently hit their endpoints.^[7]

And the big one for retail: the American College of Gastroenterology's 2021 guideline recommends against probiotics for global symptoms of irritable bowel syndrome, on very low quality evidence, because the trials are small and the findings do not agree.^[8] IBS is the condition probiotics are most often bought for.

The most instructive reversal is in children. An earlier Cochrane review suggested probiotics shortened acute infectious gastroenteritis by about a day, which is the finding that put probiotics in every pediatric aisle in the country. The 2020 update restricted the analysis to trials at low risk of bias, and the benefit did not survive.^[9] No clear reduction in diarrhea duration or hospitalization, and a recommendation against routine use in North American children.^[9]

Nothing changed about the biology. What changed was which trials were allowed to count.

Nobody moves in

Here is the thing the category depends on you not asking. When you swallow a probiotic, where does it go?

A gastroenterologist who writes about the gut for a general audience puts it plainly: *Probiotics don't typically stick around in the long term ... they arrive, starve, then die.*^[10] The evidence-based reference literature says the same in flatter language: colonization is typically transient, and the gastrointestinal tract resists alteration of its established flora.^[11]

Your gut is not an empty apartment waiting for better tenants. It is a fully occupied ecosystem that has been in place for decades and defends itself.

Which means a probiotic that works does so during passage, as a transient guest with a temporary effect, and the moment you stop, you are back where you were. That is a coherent product. It is not the product being sold, because the thing being sold is the implication that you are rebuilding, restoring or reseeded something, permanently, for forty-five dollars a month.

The same physician does something else worth stealing. Asked about butyrate supplements, a fashionable category, he declines to recommend them, explaining that oral butyrate gets absorbed before it reaches the colon where it is needed, and that fiber produces it in the right place instead.^[12] That is a mechanism-based rejection of a product. If more

people in this industry reasoned that way in public there would be less of an industry.

The boring thing works

Which brings us to fiber, the least marketable intervention in gastroenterology.

Psyllium, a soluble fiber, improves global IBS symptoms against placebo across a meta-analysis of fourteen trials in over nine hundred patients, and multiple gastroenterology and nutrition bodies recommend it as first-line for chronic constipation and IBS.^[13] Insoluble wheat bran, notably, may make IBS worse.^[13] So even here the specificity matters: fiber is not one thing either.

Inulin-type fibers have supportive trial evidence for stool frequency, consistency and transit, though I could not track the specific meta-analysis and crossover trial the record behind this book relies on.^[14]

Psyllium costs almost nothing, has no brand, no strain, no CFU count and no practitioner tier. It sits in the same aisle as products costing forty times as much with a fraction of the evidence.

The dead bacteria worked as well as the live ones

Two food studies are worth more of your attention than most of the supplement literature.

A randomized trial put thirty-six adults on either a high-fermented-food diet or a high-fibre diet for ten weeks. The fermented-food group increased the diversity of their gut microbes and showed reductions across multiple inflammatory markers. The high-fibre group increased their microbes' carbohydrate-processing capacity without increasing diversity in that window.^[15]

That is a striking result for yoghurt and kimchi, and I could not verify it against the primary publication, so hold it lightly.^[15]

The second one is better, because of how it failed. A trial of sauerkraut in irritable bowel syndrome ran two arms, raw sauerkraut and pasteurized sauerkraut. Pasteurized means heated. Heated means the live organisms are dead.

Symptoms improved in both arms, with no difference between them.^[15]

If the live bacteria were the active ingredient, the dead ones should not have worked. Something else in the food was doing the job, the fibre, or the compounds the bacteria produced before they died, and that possibility undermines the premise the entire probiotic aisle is built on. It is also the most useful thing in this chapter, because you can act on it tonight for about four dollars.

The phenotype is the whole answer

Glutamine is where this chapter earns its place in the book, because it contains the single sharpest demonstration of the book's argument that I found anywhere.

A randomized double-blind placebo-controlled trial enrolled adults with post-infectious IBS with diarrhea, who also had objectively measured increased intestinal permeability. They took 5 grams of L-glutamine three times a day for eight weeks.

Seventy-nine point six percent of them hit the response threshold, against five point eight percent on placebo.^[16] Bowel frequency, stool form and measured permeability all improved.^[16]

That is roughly a fourteen-fold difference in responder rate. In a book largely composed of null results and hedges, that number is startling, and I want to be careful with it: it is one trial, in a narrow phenotype.

And in generally healthy people, or in the far larger population who have been told they have leaky gut without anybody measuring anything, glutamine has no high-quality evidence for gut repair at all.^[17]

Same molecule. Same dose. Spectacular in a group defined by a measurement, unsupported in a group defined by a marketing phrase. If

you take one idea out of this book, make it that one, because it is not a story about glutamine. It is the shape of nearly every honest supplement result there is.

Enzymes and the tests

Two quick ones.

Digestive enzymes: the over-the-counter multi-enzyme blends are not standardized and not regulated as drugs, and for people with normal pancreatic function there is little evidence they do anything for bloating or gut health.^[18] Two exceptions have real indication-specific support, lactase for lactose intolerance and alpha-galactosidase for gas from legumes.^[18] And prescription pancreatic enzyme replacement, at 25,000 to 40,000 lipase units per meal titrating higher, is genuinely first-line therapy for diagnosed exocrine pancreatic insufficiency, which is a real disease with a real diagnosis.^[19] That is a drug. It is not the thing in the bottle at the health food store, and the two are related the way a prescription opioid is related to a throat lozenge.

Microbiome testing: an evaluation of direct-to-consumer services found that the same stool sample produced markedly different profiles and different health interpretations depending on which company processed it, with the variation between companies as large as the variation between different people.^[20] The British Dietetic Association concludes that commercial microbiome testing and the lifestyle programs sold with it cannot be recommended for routine use.^[20]

There are technical reasons. The common test resolves organisms only to genus, misses viruses and most fungi, and describes bacteria in the far end of your colon and nothing else. Microbiome-based disease prediction performs modestly, and individual organisms contribute very little to the models, though I could not verify those specific figures.^[21]

The loop, and one honest warning inside it

The commercial architecture here is the tightest in the book, because the gut lets you sell the problem and the solution as separate products.

One physician built a bestselling career on the argument that a class of plant proteins damages the gut, and also has a supplement line, sold through his own brand and through partners, addressing digestive health.^[28] The book creates the injury and the catalogue treats it. Elsewhere, a microbiome testing company appears on a biohacking show to explain how *your biomes drive custom food and supplement solutions*^[29], which is the test-to-supplement pipeline stated as a product description.^[28] Your sample generates your recommendations, which are fulfilled by the company that read your sample.

Recall from a few pages ago what the professional dietetic body says about the reliability of those tests.

And then, to be fair to the person I have quoted most in this chapter, here is a warning from inside the category that nobody in the category heeds: *If you do enough tests, you will always find something that's wrong. The goal is better gut and immune health, not a cluttered medicine cabinet.*^[30]

That is exactly right, and it sits inside a framework built on testing and then addressing what the test found. I do not think he is being dishonest. I think it demonstrates how hard the pull is even for somebody who can see it clearly, name it in print, and warn his own readers about it in his own book.

The scope problem

The reason this category expands without limit is that the gut has been made the cause of everything.

The same gastroenterologist I quoted approvingly opens his book by reporting *over 130 conditions connected to inflammation ... from autoimmune, cardiovascular, hormonal, and metabolic conditions to cancers and neurological and psychiatric conditions.*^[22] Every part of that sentence is defensible. What it accomplishes commercially is that no illness falls outside the market.

Downstream of that framing, things get worse fast. A podcast episode announces that depression is *not in your head, it's in your gut*, which

repositions a psychiatric illness as a supplement opportunity.^[23] A consumer reference tells readers with foul-smelling stools and anal burning to *follow a fasting program*, because *the colon contains toxic material*.^[24] Those are symptoms that require a differential diagnosis, and the book routes them into a fast. The same book recommends monthly fasting with *a series of lemon juice enemas* for hypoglycemia, a blood sugar disorder.^[25] It lists branded colon cleansers in a dosing table, giving a marketing category the appearance of a clinical one.^[26]

Even the more careful guides map symptom straight to product, organizing sections around *Irritable bowel syndrome / Constipation / Bloating / Diarrhoea*.^[27] Those are not diagnoses. Each has multiple causes with different treatments, and one of the possible causes of each is something you need a colonoscopy for.

So the gut chapter ends where the glutamine trial did. There is real evidence here, some of it excellent. It attaches to named organisms, in named conditions, in people identified by a measurement. Everything else in the aisle is selling you an ecosystem metaphor, and the ecosystem is already fully staffed.

DETOX, BINDERS, DRAINAGE

The word toxin is doing something in wellness marketing that it does not do in medicine, and the difference is a missing noun.

In medicine, a toxin is a specific substance. Lead. Acetaminophen. Aflatoxin. It has a name, a measurable concentration, a known route in and a known route out, and a threshold above which it does harm. In marketing, toxin is a category with nothing in it. Nobody says which one. Nobody says how much of it you have. Nobody says what your level was before or what it will be after.

And that vagueness is not sloppiness. It is the product. A named toxin can be measured, and a measurement can come back normal, and a normal result ends the sale. An unnamed toxin can never come back normal, because there is no test for a noun that was never specified.

Here is what makes this chapter harder than it looks. Detoxification is real. Your liver runs an enormous chemical operation converting fat-soluble compounds into water-soluble ones so your kidneys can eliminate them.^[1] That system exists, it is well characterized, and medicine has genuine interventions that assist it.

Which is exactly the problem, because almost every product in the detox aisle is one of those genuine interventions wearing a different hat.

Everything in the binder aisle is a real drug

Take them one at a time.

Activated charcoal. This is legitimate emergency medicine. In an overdose, given within roughly an hour of ingestion, it works, and repeated dosing is used to speed elimination of specific drugs in life-threatening poisoning, under toxicology supervision.^[2] The clinical dose is fifty to a hundred grams. Note that against the capsule in the wellness bottle. Also note what charcoal does not do: it is non-selective, meaning it binds your medications and your micronutrients along with whatever you

were hoping it would bind.^[2] For routine daily detox in healthy people there is no high-quality human outcome data at all.^[3]

N-acetylcysteine. A genuine antidote for acetaminophen poisoning, which works by replenishing the liver's glutathione so the toxic metabolite cannot do its damage, and which has a treatment window measured in hours.^[4] It is also a real mucolytic in chronic bronchitis and cystic fibrosis.^[4] There is no good evidence for oral NAC as a general detoxifier in people who have not poisoned themselves.^[4]

UDCA and TUDCA. These are bile acids with actual FDA-approved indications: primary biliary cholangitis, and dissolving certain gallstones in patients who cannot have surgery.^[5] TUDCA has trial evidence in the same disease at roughly ten milligrams per kilogram, where the main side effect is diarrhea.^[6] Neither one has evidence for liver detox or drainage in a healthy person.^[5]

Chelators. Prescription chelation is reserved for people with genuinely high blood lead, and the thresholds are high.^[7] Meanwhile the over-the-counter natural chelation category, the cilantro and chlorella and pectin products, has essentially no high-quality evidence of reducing body burdens of toxic metals, and chelation done badly carries real risks: low calcium, kidney injury, and metals being redistributed rather than removed.^[8]

See the pattern? Nobody invented these compounds. They are all borrowed. Each one has a narrow, evidenced, sometimes life-saving use in a person with a specific measured problem, and each one has been lifted out of that context and sold to people who do not have that problem, at doses that would not treat it if they did.

That is the whole trick, and it is a good one, because when a critic says the product does nothing the seller can point at a real clinical literature and be technically correct.

The trial that should have ended this argument

I want to give you the single most important finding in this chapter, and it comes from lead poisoning in children, which is the most legitimate detox scenario that exists.

Children with elevated blood lead were given succimer, a real chelator, in a randomized trial. The chelator worked. Blood lead came down.

Their neurocognitive outcomes did not improve. No benefit in IQ, behaviour or development compared to placebo.^[9]

Stay with that, because it is the chapter in one result. This was a real toxin, correctly identified, correctly measured, in patients who genuinely had it, treated with a drug that genuinely removed it. The number moved. The child did not.

If removing a measured toxin from a genuinely poisoned child does not reliably undo the damage, then consider what is being promised by a product that cannot name your toxin, has not measured it, and will not measure it afterward.

The anatomy that is not in the anatomy books

There is a widely sold framework built on something called the drainage funnel, in which you must open your drainage pathways in a particular order, colon then liver then bile ducts then lymphatics then tissues then cells, before detoxification can proceed.^[10] There are multi-month protocols built on this, sold as guiding you through a proven sequence.

I went looking for the drainage funnel in hepatology, in nephrology, and in clinical toxicology. It is not there.^[10] Not disputed, not controversial. Absent. It is a marketing construct with an anatomical costume on.

And I have to hand it to whoever designed it, because it is beautifully engineered as a commercial object. It has multiple stages, so it takes months. It has an order, so if it fails you did the stages wrong. And its

endpoint is not a measurement, it is a feeling, so it can neither succeed nor fail on any evidence available to the customer.

The best specimen of manufactured toxicology I have found, though, is smaller and funnier. A biohacking author recommends binding agents for routine gut cleansing, and explains that he puts *humic acid and fulvic acid into my Danger Coffee ... to pull coffee toxins out and to remove other toxins from your body.*^[11]

Coffee toxins.

There is no such clinical category. It was invented, in the same sentence that sells you the binder for it, in a branded coffee product sold by the person who identified the problem. That is a closed loop with no external input at any point. The disease, the diagnosis and the cure all originate at the same address.

The same book explains that your lymphatic system, which removes cellular waste as its ordinary job, needs *some help*, because *humans are not particularly good at detoxing compared to other animals.*^[12] And it advises that if you are stressed you should *don't go for a workout; go for a detox*, positioning detoxification ahead of exercise as the first thing a tired adult should do.^[13]

Think about the size of that market. Everyone who is tired.

What actually holds up, which is not nothing

I do not want to leave you with the impression that every compound here is inert, because that is not what the evidence says and this book does not get to keep only the convenient findings.

Zeolite is the interesting one. In a controlled study, a purified clinoptilolite zeolite given alongside a tracer dose of lead cut the amount of lead absorbed from the gut by something close to ninety percent, and a trial in patients with mild to moderate lead poisoning found it lowered serum lead.^[14] That is a real binding effect in a real measurement.

Read carefully what it shows: zeolite reduced uptake of lead that was administered at the same time. It stopped lead going in. That is not the same claim as pulling accumulated metals out of your tissues, which is what gets advertised, and a separate trial in trained athletes found changes in a gut permeability marker without clear clinical outcomes.^[15]

Oral glutathione is similar. A six-month randomized trial in healthy adults found that daily glutathione raised glutathione levels substantially across blood compartments and increased natural killer cell activity.^[16] The supplement did what it said. What no study in that literature measured was whether any toxin was cleared, or whether anything happened to the person.^[16]

And then there are the detox diets, where something genuinely does happen and it is not what the label says. A small trial of a lemon-based cleanse in overweight women produced weight loss and short-term improvements in metabolic markers.^[17] It also involved eating roughly four hundred calories a day. Toxin elimination was not measured, and the effects did not persist.^[17] So the cleanse worked, in the sense that starving works, which is a thing you can do without buying syrup.

There is also a whole tier of products where the evidence exists but is standing in the wrong place. One botanical formula has genuine laboratory data showing it disrupts bacterial biofilms in a dish, alongside an uncontrolled eight-patient case series funded by the company that sells it.^[18] In vitro means in glass. A compound that kills bacteria in a dish has demonstrated that it kills bacteria in a dish, which is roughly as informative about your bloodstream as bleach is. Another prominent product is marketed as a universal broad-spectrum binder for heavy metals, mould toxins and organic pollutants, combining four adsorbents, with no clinical trial of the actual formulation identified anywhere.^[19]

Which brings us to the liposomal glutathione products, where the evidence being waved at you is often not evidence. One prominent brand's claims trace to an internal ten-person study on the company's own website. No journal, no registration, no peer review.^[20] That is not a

small study. It is marketing with a sample size, and the two are distinguishable by whether anyone outside the company was permitted to check.

Cleanses the bloodstream

The oldest version of this lives in the consumer health references, where the format itself does the work.

In a long-running A-to-Z home reference, chlorophyll appears across multiple unrelated disease entries with the stated function *cleanses the bloodstream*.^[21] Apple pectin, a dietary fiber, appears in the lead poisoning entry as something that *binds toxins and metals, removing them from the body*.^[22] Alpha-lipoic acid appears in the same lead entry as an agent that *helps to detoxify the body of metal pollutants*, which arrives via a chain of individually plausible steps: it participates in antioxidant chemistry, antioxidants counter oxidative stress, heavy metals cause oxidative stress.^[23] Each link holds. The conclusion does not follow, and nobody tested it.

And one branded product turns up in the abscess entry, the aluminum toxicity entry, the lead poisoning entry and the cancer entry, carrying the same claim about supporting detoxification of many dangerous substances every time.^[24]

One product. Four unrelated conditions. Identical claim. When a compound is equally indicated for an abscess and for cancer, the thing it is treating is not a disease. It is the reader.

Meanwhile the actual literature is thin in the way absences are thin. A critical review of detox diets found no randomized trials of commercial detox products measuring toxin elimination in healthy people, at all.^[25] There is a trial of a detox supplement in healthy young women that found nothing on body composition, gut symptoms or blood markers, and the product was at least safe.^[26]

None of this is new, either. A functional medicine podcast has been running detox content since 2007, promising to jump-start your

metabolic engine, later updated to the softer and more durable framing of *optimizing* your body's detoxification system.^[27] That is the same slide this book keeps finding: not "your liver is failing," which would be checkable, but "your liver could be doing better," which cannot be.

The current version is louder. One episode announces that toxins are *STUCK In Your Body* and that you should do a specified thing to get them out.^[28] Another is co-branded in its own title with the supplement company whose products it discusses.^[29]

The diagnoses that come with the protocol

The last piece is the one that concerns me most, because it is where the marketing stops selling a product and starts supplying a diagnosis.

One episode bundles environmental mould, chronic Lyme disease and parasites into a single detox framework, presented by a physician.^[30] Consider what that bundle does. Those are three separate contested conditions, and the symptoms attached to them, fatigue, brain fog, aching joints, are the most common complaints in adult life. Bundle them and every tired person in the audience has a candidate diagnosis, a mechanism, and a protocol, delivered by somebody with a medical credential.

Then look at how the credibility gets assembled. Another episode pairs fasting for detoxification with the framing of ancient wisdom meeting modern science.^[31] That title is a machine for borrowing authority from two directions at once. And the physiology underneath it has been quietly swapped: fasting does trigger autophagy, and autophagy is a genuine cellular process for clearing damaged proteins. It is not a mechanism for removing environmental contaminants from your tissues. One real thing has been used to license a different claim, and the two are close enough in the ear that nobody stops.

If you are tired and foggy and your labs came back normal, this category is built precisely for you. Nothing about that is accidental, and none of it requires a conspiracy. It is just that ordinary medicine will tell you it does

not know why you are tired, and this will tell you exactly why, and only one of those answers is comfortable to receive.

So here is the filter, and it is three questions, and no product in this category has ever survived all three in my reading.

Which toxin, by name. What is my level of it now, measured how. And what will that number be afterward.

If the answers are “toxins,” “elevated,” and “you’ll feel better,” you are not buying a detoxification. You are buying the noun that was left out.

IMMUNITY, INFLAMMATION, LONGEVITY

If I could hand you one dataset from this entire book, it would be this one, because it settles the argument numerically instead of rhetorically.

Researchers pooled twenty-five randomized trials of vitamin D against respiratory infection, nearly eleven thousand people, and did the thing almost nobody does: they went back to the individual participant data so they could sort the results by how deficient each person was at the start.^[1]

Across the whole group, vitamin D reduced acute respiratory infection by about twelve percent. A real effect, and a small one, and if the analysis had stopped there it would be another modest line in a review.

Then they split it. In the severely deficient, the ones starting below 25 nanomoles per litre, the reduction was seventy percent, with a number-needed-to-treat of four. Four people supplemented, one infection prevented. In people who already had enough, the benefit shrank to a number-needed-to-treat of twenty.^[1]

And intermittent high-dose bolus dosing, the big monthly megadose that felt efficient, did nothing at all.^[1]

There it is. One nutrient, one analysis, and the benefit scales precisely with how short you were, and the aggressive dosing schedule was worse than the boring one. Every argument in this book is in that paragraph.

Which is also why you should be careful with a headline like the one on a podcast episode claiming a supplement could cut your dementia risk by forty percent.^[2] That figure comes from observational data in a population largely already deficient. The number is not invented. It is just answering a question about deficient people and being sold to everybody.

A correction, out loud

Now something about this book's own machinery, because it broke here and I would rather show you than tidy it away.

The research record underneath this chapter attributed a set of vitamin C findings to a meta-analysis of twenty-five trials in 10,933 participants. When the verification pass checked it, those numbers turned out to belong to the vitamin D analysis I just described. The two claims had been welded together somewhere upstream.^[3]

The vitamin C effect sizes are real and come from a different review entirely. The participant count attached to them was not.

I am telling you this because it is exactly the failure mode this book is about, and it happened inside the book. A number travelled from one study to another because they were adjacent in somebody's notes, and it would have read perfectly well on the page. The only reason it did not survive is that something checked it against the source. Nothing about the sentence itself would have warned you.

What vitamin C and zinc actually do

With that cleared up, the honest vitamin C picture.

Taken daily as prevention, it shortens colds by roughly eight percent in adults and fourteen percent in children.^[4] On a week-long cold, eight percent is about half a day. It does not meaningfully reduce how often you get sick.

There is one striking exception. In people under extreme physical stress, marathon runners, skiers, soldiers in subarctic conditions, prophylactic vitamin C cut respiratory infection risk by around half.^[4] Which is a large effect in a population defined by being pushed to a physiological edge, and if you are not in that population, it is not about you.

And the thing everybody actually does, which is start taking vitamin C the moment your throat feels scratchy, is the one approach the trials consistently show to be useless.^[4] Therapeutic dosing after onset: null, across the board.

Zinc is more interesting, because zinc is the rare case where the details on the label decide whether the product works.

Pooled across seven randomized trials, zinc lozenges cut cold duration by about a third.^[5] Zinc acetate did better, around forty percent, gluconate around twenty-eight.^[5] But doses below 75 milligrams a day were uniformly null, every trial. Pediatric trials were null. And any lozenge containing citric acid inactivates the zinc ions in your saliva, which means a substantial share of the pleasant-tasting products on the shelf are chemically inert by design.^[5]

So the actionable version: for a cold, a zinc acetate lozenge, at or above 75 milligrams of elemental zinc daily, without citric acid, started early. Almost nothing on the shelf meets all four conditions, and no product tells you which conditions it fails.

Curcumin, where the formulation is the drug

Curcumin has terrible oral bioavailability. Your gut and liver dismantle it before it gets anywhere, which is why enhanced-delivery formulations exist, achieving anywhere from seven to nearly fifty times the absorption of plain curcumin powder.^[6] I could not verify those multipliers individually, so treat them as a range rather than a spec sheet.^[6]

With one of those formulations, the evidence is genuinely good in one place. An umbrella review found curcumin non-inferior to anti-inflammatory drugs for osteoarthritis symptoms, and a specific branded formulation at 500 milligrams twice daily performed equivalently to paracetamol at 650 milligrams three times daily, with better reduction in inflammatory markers.^[7]

Note the shape, because it is the opposite of the usual one. Here the branded form is doing real work, since without enhanced absorption the compound cannot reach a therapeutic level at all. This is the one place in the book where paying for a proprietary formulation is defensible, and it is defensible for osteoarthritis specifically, not for the word inflammation.

Which is more than can be said for quercetin, where despite a mountain of promising laboratory data, human trials show no significant reduction in the standard inflammatory markers in healthy adults.^[8]

And resveratrol deserves its epitaph. Beyond the collapse of its proposed mechanism, a trial of a micronized resveratrol formulation in multiple myeloma was halted after patients developed acute kidney failure, and a metabolic trial in older men found it null on its outcomes while raising LDL cholesterol.^[9]

The most famous longevity molecule of the last twenty years does nothing useful, and in a clinical trial it hurt people.

The drugs that actually extend life, in mice

Now the serious end, where I want to be very fair, because this is real science being sold badly.

Rapamycin is the most reproducible longevity finding in mammals. The National Institute on Aging's testing program found it extends median lifespan in genetically diverse mice by ten to thirty percent, and does so even when started late in life, at the mouse equivalent of sixty.^[10] That is not a fringe result. That is the strongest thing anybody has.

In humans: a 2025 trial in healthy older adults missed its primary endpoint entirely.^[11] A 2014 trial of a related compound did something narrower and more encouraging, improving the immune response to influenza vaccination by about twenty percent in older adults and reducing a marker of immune exhaustion.^[11]

So the honest state of play is: spectacular in mice, one specific immune signal in humans, primary endpoints not yet met. Which is a perfectly respectable place for a research programme to be, and a terrible basis for buying anything.

And people are buying it. Compounded rapamycin from compounding pharmacies has been found to differ from the commercial drug by up to three and a half fold in bioavailability.^[12] Meaning a person self-prescribing a dose calibrated from a trial may be taking a third of it, or triple, with no way to know which.

Metformin is the other longevity candidate, and its story is a case study in how observational findings mislead. The famous finding was that

diabetics on metformin outlived non-diabetic controls, which sounds miraculous. It appears to be a selection artifact: the non-diabetic comparison group was never screened for metabolic health, so it quietly included people who were undiagnosed pre-diabetics.^[13] The trial designed to answer the question properly had not launched as of 2026, for want of funding.^[13]

Meanwhile a 2025 trial in older adults reported a walking-speed difference between metformin and placebo of 0.001 metres per second, which is as close to exactly nothing as a measurement gets, alongside a hospital admission rate several times higher in the metformin group.^[14] I could not verify that trial against its publication, so I flag the safety signal rather than assert it.^[14] Separately, metformin has been found to blunt muscle growth from resistance training in older adults, which for anyone taking it to age well is close to an own goal.^[14]

The rest of the longevity shelf is thinner. Spermidine extends lifespan around ten percent in animals; a twelve-month randomized trial in a hundred older adults with cognitive complaints failed to improve memory, and the human supplement doses being sold are far below the animal doses anyway.^[15] Fisetin is the most potent senolytic in preclinical screening, kills senescent cells in animals, and has no published human efficacy results at all, only early safety and biomarker trials.^[16]

One hundred pills

Which brings us to the most documented human experiment in this space, which is one man taking over a hundred pills a day.

The published protocol includes NAD precursors, calcium alpha-ketoglutarate, CoQ10, low-dose aspirin, a testosterone patch, thyroid hormone, spermidine, fisetin, acarbose, metformin and curcumin, on top of roughly 2,250 calories a day inside a six-hour window.^[17]

Look at the testosterone patch, because it tells you everything. Severe caloric restriction suppresses endogenous testosterone. The patch is not an anti-aging intervention. It is a repair for a problem the protocol itself

created, which means part of this stack exists to treat the rest of the stack.^[17]

And the pharmacology of combining that many actives is genuinely unpredictable. High-dose antioxidants can blunt the reactive oxygen species signalling that muscle adaptation and mitochondrial improvement actually depend on, so some of those pills are plausibly cancelling the training.^[18] Dozens of compounds together produce competing enzyme pathways and interactions nobody has mapped.^[18]

Most importantly, in a single-subject protocol with a hundred variables, no outcome can be attributed to any component.^[18] If he lives to a hundred and ten, we will not know why. If something goes wrong, we will not know why either. It is not an experiment. It is a lifestyle with a spreadsheet.

How a longevity claim gets its authority

Before the last piece, look at how these claims acquire the weight they carry, because it is not by accumulating trials.

The most ambitious specimen I found belongs to a single fatty acid. Its book announces at the outset that it will *dismantle fifty years of dietary recommendations, and (2) challenge the entire omega-3 fish oil industry*.^[19] One compound, versus half a century of nutrition science and an entire product category.

Then the classification move. The compound is described as *the first essential fatty acid to be discovered in more than ninety years*, joining a list of exactly two.^[20] Essential, in nutrition, is a specific and enormous claim: it means your body cannot make it and you will develop a deficiency disease without it. The criteria for that classification were applied to the compound by the research team that discovered it.

And the analogy that follows makes the stakes explicit. A rising liver condition is proposed as *likely part of a nutritional C15:0 deficiency syndrome. You know, like vitamin C deficiency and scurvy*.^[21]

Scurvy. That comparison is doing an extraordinary amount of work in nine words. Scurvy is the most settled deficiency disease in medical history, with a mechanism, a clinical course and a cure demonstrated on eighteenth-century ships. Placing a new compound beside it borrows all of that certainty at no evidentiary cost.

From there the claims widen until they cover everything: the compound *reverses aging at the cellular level*, targeting at least six of the twelve recognized hallmarks of aging, and lowering eighteen inflammatory signalling molecules.^[22] Those results come from cell-culture panels, which are drug-screening tools, not people.

The prestige version of the same manoeuvre needs no product. A physician-author proposes that lifestyle changes can deliver *your own measure of longevity alpha*, a phrase borrowed from finance, where alpha means returns above a benchmark.^[23] It sounds quantitative. There is no benchmark lifespan for an individual and no way to measure a return against it, which makes alpha here a feeling with a ticker symbol.

And the whole apparatus is amplified sideways rather than upward. The same longevity researcher appears across show after show, on one describing a molecule that can *turn on your body's defenses against aging*.^[24] Two of the most commercially active figures in the supplement world share an episode on daily hacks to increase lifespan.^[25] None of that is new evidence. It is the same evidence, arriving from more directions, which is how a claim comes to feel established without ever being tested.

The number the whole field wants to be real

The epigenetic clocks are the last piece, because they are what makes any of this feel measurable.

These are real science. Methylation-based age estimators predict cardiovascular disease, stroke and all-cause mortality with genuine power across large epidemiological cohorts.^[26]

They are also not validated surrogate endpoints for longevity by any regulator, and at the level of an individual person they are noisy: assay variation between laboratories, differences in cell-type composition, and different answers depending on whether you sampled blood, cheek or skin.^[26]

Which means a clock is a good instrument for comparing ten thousand people and a poor one for telling you whether your supplement worked. That distinction is invisible in the product, and it is the entire basis of the personal biological-age industry.

So the longevity category, honestly summarized: the best-supported compound extends life in mice and has missed its human endpoints; the most famous one damaged kidneys in a trial; the measurement everybody uses to prove personal progress was built for populations; and the most elaborate protocol on earth includes a hormone patch to fix what the protocol did.

Against that, the finding at the top of this chapter still stands. Correct a real deficiency and the number needed to treat is four. That is the whole of what this category reliably offers, and it is more than it sounds like.

PERFORMANCE AND PHYSIQUE

After ten chapters of taking things away from you, I get to hand something back.

Creatine monohydrate works. It is the most studied supplement in the world, the evidence is not close, and it costs about fifteen dollars for several months.

The numbers, from a systematic review pooling sixty-nine randomized trials in nearly two thousand people: combined with resistance training, creatine adds around five and a half kilograms to a back squat, adds to bench press, raises vertical jump, and increases peak anaerobic power output.^[1] A separate pooled analysis across sixty-one trials found it increases fat-free mass by about 1.4 kilograms against training alone.^[2]

A kilogram and a half of muscle is not a transformation. It is also not nothing, it is reproducible, and almost nothing else in this book can make a comparable claim.

On safety, which is where the folklore is worst: long-term studies at doses up to 30 grams a day, some running fourteen years, across varied populations, document no serious adverse events.^[3] The one consistent side effect is one to two kilograms of extra body mass from water held inside the muscle cell.^[3] That is the whole list. It does not damage kidneys in people with normal kidney function, it does not cause hair loss, and the reason those beliefs persist is that a cheap unpatentable product has nobody funding its defence.

Dosing, plainly. Either load with about 20 grams a day split into four doses for five to seven days and then take 3 to 5 grams a day, or skip the loading and take 3 to 5 grams a day, which reaches the same saturation in about four weeks.^[3] Taking it with carbohydrate and protein improves uptake.^[3] There is no advantage to any of the exotic forms.

And even here, the book's rule holds. Vegetarians start with lower muscle creatine and get a substantially larger increase in their stores than omnivores do.^[4] The compound works best in the people who had least.

There is also emerging cognitive evidence: pooling sixteen trials, creatine produced a small improvement in memory and in attention time, with no effect on executive function, and the certainty of the evidence was rated moderate for memory and low for everything else.^[5] Real, small, early. Which is precisely how it gets described on podcasts extending creatine into brain and aging claims, where the framing runs ahead of the data even for the compound that has the best data.^[6]

Protein has a ceiling and the ceiling is known

The second thing that works is protein, and the useful fact is where it stops working.

A meta-analysis of forty-nine trials in nearly nineteen hundred adults found protein supplementation adds to fat-free mass, muscle fibre size and one-rep-max strength.^[7] The meta-regression then found the plateau: **1.62 grams per kilogram of body weight per day**. Beyond that, in energy balance, additional protein produced no further significant gain.^[7]

For an eighty-kilogram person that is about 130 grams a day. Everything you buy above that line is expensive urine.

Context shifts it. Cutting weight while trying to keep muscle raises the useful range to roughly 2.3 to 3.1 grams per kilogram.^[8] Deliberate overfeeding is different again. Per meal, the trigger for muscle protein synthesis is about 2.5 to 3 grams of leucine, which you get from 20 to 40 grams of complete protein, and older adults need the upper end because their muscle responds less readily to the same signal.^[8]

Which leaves the anabolic window, the thirty-to-sixty minutes after training in which you were told your session would be wasted. It is largely a marketing artifact.^[9] Resistance training elevates muscle protein synthesis for somewhere between one and three days afterward, and total daily protein is what drives growth.^[9] The one real exception is training fasted, where getting protein in soon after does matter.^[9]

Protein quality does differ, and the current scoring system puts whey isolate and skim milk powder at the top, soy well behind them, and pea,

wheat and rice lower still, limited by specific amino acids.^[10] If you are eating plant protein, you compensate with quantity and variety rather than with a better tub.

And BCAAs, which is the cleanest redundancy in the industry. Once total protein is adequate, supplementing the three branched-chain amino acids in isolation adds nothing, because building muscle requires all nine essential amino acids and you have just bought three of them.^[11] Worse, taking those three alone can competitively block the transporters carrying the others.^[11] You paid to potentially interfere with your own absorption.

The conditional performers

A handful of compounds work under conditions that the packaging never states.

Caffeine, at 3 to 6 milligrams per kilogram taken thirty to sixty minutes before exercise, improves endurance, strength, power and skill execution across many meta-analyses, with time to exhaustion improving by as much as seventeen percent.^[12] That is the most reliable performance effect in the chapter after creatine.

Beta-alanine at 3.2 to 6.4 grams daily for four to ten weeks raises muscle carnosine substantially, and the payoff shows up specifically in efforts lasting one to four minutes.^[12] Not a lift. Not a marathon. A four-hundred-metre run, a hard interval, a wrestling round.

Citrulline malate at 6 to 8 grams improves repetitions to failure by about six percent, and does not improve maximal strength.^[12]

Beetroot juice is the most entertaining. Dietary nitrate at 5 to 9 millimoles, roughly 70 to 140 millilitres of the concentrated juice, taken a couple of hours before exercise, improves exercise tolerance and oxygen efficiency in recreationally active people. In highly trained endurance athletes it does nothing, because their nitric oxide systems are already optimized.^[13] More than fifteen millimoles adds no further benefit.^[13] And antibacterial mouthwash abolishes the effect completely, because the

pathway depends on bacteria in your mouth converting the nitrate first.^[13]

Your performance supplement can be defeated by dental hygiene. I could not fully verify the effect-size figures behind the nitrate literature, so hold the magnitudes loosely, but the mouthwash finding is the kind of detail that tells you a mechanism is genuinely understood.^[13]

The blend is the con

Now the specific mechanism by which a pre-workout is designed to fail you.

Federal labeling rules permit a proprietary blend, which discloses the total mass of a mixture without disclosing how much of each ingredient is in it.^[14] So a product can list beta-alanine, citrulline, and eight other things you have read about, inside a blend, at doses nobody can determine.

In practice this means a gram of beta-alanine where the evidence requires 3.2, and one and a half grams of citrulline malate where the evidence requires six to eight.^[14] Every clinically validated ingredient present at a fraction of its clinical dose.

And then the blend is loaded with caffeine, often three hundred milligrams or more, because caffeine produces an immediate, unmistakable sensation.^[14] You feel it. The tingling from the beta-alanine, which happens well below effective doses, tells you it is working. It is working. It is just the caffeine.

The whole product is engineered so that a stimulant vouches for eleven ingredients that are not present in useful amounts.

Fat burners, and one that can hurt you

Thermogenics are where the effect sizes get funny.

Under controlled conditions: caffeine at 200 to 400 milligrams a day produces about half a kilogram of weight loss over eight weeks. Green tea EGCG at 300 to 500 milligrams produces about 1.3 kilograms over twelve

weeks, with the effect blunted or absent in habitual caffeine drinkers, which is most buyers. Synephrine at 20 milligrams or less produces around 0.7 kilograms over six weeks.^[15] A comprehensive review concluded that no dietary supplement has meaningful support as a standalone tool for long-term weight loss.^[15]

Half a kilogram in two months, statistically detectable and practically invisible.

The safety side is where this stops being amusing. Synephrine, from bitter orange, is structurally similar to the banned ephedrine. It raises heart rate and blood pressure and has triggered cardiac arrhythmias, particularly combined with caffeine and exercise, which is exactly how it is sold.^[16] It is contraindicated if you have high blood pressure, existing cardiovascular disease, or take MAO inhibitors.^[16] And concentrated EGCG at 800 milligrams a day or more has been linked to severe liver enzyme elevations and liver injury, prompting warnings from both European and US regulators.^[16]

So the fat-burning category delivers effects too small to see, at doses that can put a stimulant-sensitive person in an emergency room.

Two more, and one thing I could not check

HMB repeats the pattern the book has been making all along. In well-nourished athletes with adequate protein, three grams a day of HMB produces no significant effect on lean mass or strength.^[17] In adults over fifty, pooled across twenty-one trials in nearly two thousand participants, HMB with resistance training did increase lean mass and grip strength and improve physical function.^[17]

Redundant in the fed athlete, useful in the person losing muscle to age. Same molecule, opposite verdict, and the only variable is whether there was a hole to fill.

Betaine I cannot give you a clean answer on. A 2024 meta-analysis of seventeen studies reports a moderate effect on maximal strength and vertical jump at 2.5 to 5 grams a day, while multiple longer high-quality

trials show no difference from placebo in strength, hypertrophy or body composition, and 6 grams a day lowers homocysteine while raising LDL cholesterol.^[18] I could not verify either side against the primary papers.^[18] The honest summary is that the evidence disagrees with itself and the compound raises a cardiovascular marker while doing so.

There is also a claim I want on the record with its uncertainty attached: that industry-funded sports nutrition studies are several times more likely to reach conclusions favouring their sponsor, with a much larger multiplier reported in clinical health research generally.^[19] That funding bias exists in this field is thoroughly documented and I have shown you the magnitudes elsewhere in this book. These particular multipliers I could not source, so I am not going to quote them at you as facts.^[19]

The flattening

There is a subtler failure than lying, and this category is where it shows up most clearly, because the people doing it are not lying.

A well-credentialed exercise scientist records an episode on supplementation for fitness. He covers creatine, which has sixty-nine randomized trials behind it. Then rhodiola. Then citrulline, beetroot juice, alpha-GPC, nootropics.^[20]

Nothing false is said. Every compound is discussed carefully, with appropriate hedging, by somebody who has read the literature.

And by the end, they all sound like options.

That is the flattening, and it is what an hour of even-handed audio does to an evidence hierarchy. Creatine and rhodiola have wildly different amounts of support, and a discussion format has no way to render that difference. Both get a segment. Both get a dose. Both get a “how to use it.” The listener leaves with a list, and a list is a flat object.

You can hear the hinge in an episode title elsewhere: *Does it Work, How Much, When, & More.*^[21] Watch what that sequence does. The first question is the real one and it is disposed of in the title, before the episode starts, by being bundled with three questions that only make sense if the

answer to the first one was yes. Nobody asks how much and when about a compound that does not work.

Once a discussion moves to dosing, the efficacy question has been settled by format rather than by evidence, and nobody in the room has to notice.

I do not think there is a villain in this. The demand is for an hour of content and a takeaway, and “creatine, protein, caffeine, and the other nine things are unresolved” is not an hour. But it is the answer.

What the promise sounds like without evidence

For contrast, here is the same category described by people selling into it.

A bodybuilding supplement guide promises *up to 15 lbs. of muscle in 6 weeks*, from homemade stacks.^[22] Set that beside the meta-analytic figure for creatine plus training, which is about 1.4 kilograms, roughly three pounds, over a comparable period, from the best-evidenced supplement in existence.

The same book explains that with supplements *you can get your body to explode through the genetic barrier, and get your body to do some amazing and impossible things*, and asks whether you can *really mimic the results of steroids with this book*, answering with a range of *at least 5 lbs. all the way up to 25 lbs.*^[23]

And then, in the same chapter, the author says something completely correct. Warning readers about competitors' advertising, he explains that *the study that “proves” ... the supplement works, was performed on some sickly person in the hospital who would have probably gained muscle on anything you gave them.*^[24]

That is an accurate description of the study-to-cart move. He identifies it precisely, in print, and then makes fifteen-pound claims with no study at all.

Which is the last thing worth saying about performance supplements, and it applies to the person selling them and to you. The knowledge is not the

hard part. Almost everybody in this industry knows how the trick works, including the people running it. What is hard is applying that knowledge to the thing you want to be true.

Creatine, protein to about 1.6 grams per kilogram, caffeine before training. That is the list. It costs less than one month of a pre-workout subscription and it is not going to feel like anything, which is the main reason it is a difficult sell.

THE TEST FUNNEL

A test has to clear three separate bars, and almost nobody selling one to you will name more than the first.

Analytical validity asks whether the laboratory can measure the thing consistently. Run the same sample twice, get the same number.

Clinical validity asks whether that number means anything about your body. Does it track a real biological state.

Clinical utility asks the only question you actually care about: if you act on this result, are you better off.^[1]

Those are three different bars, and a test can clear the first and fail the other two completely. Which brings us to the piece of regulatory architecture that this entire industry sits on.

Commercial functional tests, the hormone panels, the organic acid tests, the gut panels, the micronutrient assays, the biological age clocks, operate legally under a framework called CLIA as high-complexity laboratory-developed tests.^[2] CLIA certifies that the laboratory is technically competent to run its own assay. That is all it certifies. It makes no finding that the measurement corresponds to anything real, and none whatsoever that acting on it will help you.^[2]

So the reassuring phrase “performed in a CLIA-certified laboratory,” which appears on nearly every one of these reports, means the pipetting was done properly.

The test that is backwards

Start with IgG food sensitivity panels, because this is the clearest case in the entire book, and the reason is not that the test is inaccurate. The test is accurate. It measures exactly what it says it measures.

The problem is what that measurement means.

Food-specific IgG, and particularly IgG4, is a marker of immunological **tolerance**. It is produced through regulatory T cells and IL-10 as your

immune system learns to accept a food. High food-specific IgG4 is the signature of active desensitization.^[3]

Read that again with the report in your hand. The panel comes back flagging eggs, dairy, wheat, the things you eat constantly. That is neither an accident nor a diagnosis. IgG levels reflect dietary exposure.^[4] You have antibodies to the foods you eat, because you eat them, and the antibody is the sign that your body has made its peace.

The test is not measuring a problem. It is measuring the absence of one, and printing it in red.

Three professional bodies, the American, European and Canadian allergy and immunology societies, have all explicitly condemned the use of these panels for diagnosing food allergy or intolerance.^[3] Not “questioned.” Condemned, in position statements, in writing.

And acting on the results is not harmless. Elimination diets built from these panels have produced malnutrition and faltering growth in children, and food-avoidance behaviour that outlasts the diet.^[4] A parent removes eleven foods from a seven-year-old’s diet on the strength of a report that was measuring tolerance.

Fruit, and the blood-brain barrier

The Organic Acids Test measures seventy-six urinary metabolites by mass spectrometry and offers to tell you about intestinal Candida overgrowth, oxalate accumulation and neurotransmitter imbalances in your brain.^[5]

Two of those claims fail on biochemistry that has been settled for decades.

The markers used to indicate Candida, arabinose and citramalic acid, are ordinary metabolic byproducts of eating apples, grapes, pears, cranberries and mushrooms.^[5] The yeast-overgrowth result is substantially a report on your fruit bowl.

The neurotransmitter claim is worse, because it violates basic anatomy. The urinary metabolites used, HVA and VMA, come from peripheral

sympathetic nervous system activity and from synthesis in your gut. They do not cross the blood-brain barrier.^[5] A urine sample cannot report on central nervous system neurotransmitter status, and no amount of analytical precision changes that, because the molecules being measured were never in your brain.

This is analytical validity without clinical validity, stated as plainly as it can be stated. The machine is measuring correctly. It is measuring something else.

Twenty-six percent

The gut panels have a numerical problem that is easy to state.

An independent evaluation of one widely used commercial stool assay, testing it against standardized samples with known contents, found overall sensitivity of eighty percent and a clinical specificity of twenty-six percent.^[6] It reported high concentrations of *H. pylori*, toxin-producing *E. coli* and adenovirus in control samples confirmed pathogen-free by gold-standard methods and by endoscopy.^[6]

Specificity of twenty-six percent means that in clean samples, roughly three out of four positive findings were not there.

Now picture what happens next. Your panel comes back with three flagged pathogens. You are put on a protocol of antimicrobial botanicals, binders and probiotics for three months, at some hundreds of dollars, and you feel better at the end, because most gut symptoms fluctuate and three months is a long time. The protocol has now been validated by an outcome that would have happened anyway, in response to findings that were probably artifacts.

The American Gastroenterological Association's position is that the clinical utility of commercial microbiome tests for guiding therapeutic or dietary decisions has not been established, and that they carry no FDA clearance for diagnostic use.^[7] The most sophisticated of these platforms use genuinely advanced sequencing, and their analytical work may be excellent. What has never been published is a randomized trial showing

that people who follow the supplement recommendations generated from these scores end up healthier.^[7]

The one that is analytically excellent

I want to give you the hardest case, because it is the most instructive.

The dried urine hormone panel is, on the analytical measures, good. The samples are stable at room temperature for up to eighty-four days, and agreement with standard twenty-four-hour urine collection exceeds 0.90 for fourteen of seventeen key steroid metabolites.^[8] That is a real technical achievement and I am not going to pretend otherwise.

The reported difficulty is that nearly all of the validation work was authored or funded by the company's own founder, with no independent replication, and that no large independent trial has shown that managing patients from these metabolite profiles produces better outcomes than standard care.^[8] I could not verify those specific claims against the primary literature, so take the conflict-of-interest characterization as reported rather than as established.^[8]

But hold the general shape, because it is the chapter's point. A test can pass the first bar beautifully and still tell you nothing you should act on. Precision is not meaning.

Micronutrient testing by lymphocyte function sits further down the same slope: no published peer-reviewed evaluation of its sensitivity, specificity or reproducibility against reference methods, and the largest supporting study, following over three thousand hypertensive patients, had no control group and no baseline nutrient levels, which makes attributing any outcome to anything impossible.^[9] Major insurers classify the category as investigational.^[9]

Same molecule, two different worlds

Telomeres show the gap most cleanly, because the same analyte is both a real clinical test and a consumer novelty.

In hospitals, telomere length measured by Flow-FISH is a validated diagnostic for inherited telomere disorders and unexplained bone marrow failure. Its reproducibility is tight, agreement between independent reference laboratories is high, and the result changes clinical management, including transplant decisions, in roughly a quarter of idiopathic bone marrow failure cases.^[10] That is a real test doing real work.

The consumer version uses qPCR, and it has inter-assay and inter-laboratory variability of up to twenty percent, enough to move an individual estimate by more than a kilobase.^[11] In the biological-age arithmetic these companies use, that is a swing of decades, generated by nothing but analytical noise. Agreement with the clinical method is modest.^[11] And structurally, qPCR averages telomere length across a pooled mixture of cells, which means it cannot see the shortest telomeres, and the shortest telomeres are the ones that actually drive cells into senescence.^[11]

Same molecule. One version guides a bone marrow transplant. The other returns a number that can change by twenty years depending on which day you spat in the tube.

The kit that manufactures the deficiency

The NAD test is my favourite object in this chapter, because it fails at three levels simultaneously and each failure would be sufficient on its own.

One. At-home whole-blood NAD kits use dried blood spots or frozen samples. Freezing ruptures red blood cell membranes, which exposes the NAD inside to CD38, a membrane-bound enzyme whose job is to consume NAD. The result is 21 to 27 percent enzymatic degradation of the sample after collection.^[12] Accurate measurement requires immediate methanol preservation at the moment of the draw, a step the consumer kits omit entirely.^[12]

The kit destroys some of the analyte and then reports the shortfall to you as your deficiency.

Two. Using validated mass spectrometry across seven independent human cohorts, more than three hundred people, whole-blood NAD turns out to be remarkably stable across the human lifespan. It does not correlate with age, with lifestyle, or with physical fitness. Younger adults, older adults and elite athletes had virtually identical levels.^[13]

Which contradicts the founding premise of the product category. The claim is that you are depleted because you are over thirty. In blood, measured properly, you are not.

Three. Even if the number were accurate and even if it did vary, blood NAD does not reflect NAD in the tissues anybody cares about: muscle, liver, brain, heart.^[14] Supplementation raises the blood number substantially without that number telling you anything about the compartments where the biology is supposed to be happening.^[14]

A degraded sample, of an analyte that does not change with age, in a compartment that does not represent the target tissue. And a personalized supplement recommendation at the end of it.

Normal is the new abnormal

There is a quieter version of this funnel that uses entirely legitimate tests, and it may be the most widespread form of all.

Take a standard blood panel, the kind a doctor orders to look for disease. Now apply it to a healthy athlete under the heading of high performance.^[15] Nothing about the assay changes. What changes is the interpretation: values that a laboratory reports as normal get re-described as suboptimal, and the gap between normal and optimal becomes the space the supplement occupies.

That move is available for every marker in medicine, because reference ranges are built as disease thresholds. They were never designed to certify that you are thriving, so there is always room underneath them.

The framing arrives with a promise of relief. One episode offers to help you *stop guessing what supplements you need* by taking a methylation test.^[16] Another explains how your microbiome drives *custom food and*

supplement solutions, from a company that sells both the test and the resulting products.^[17]

Note the emotional structure, because it is the same every time. It opens by naming your uncertainty, which is real, and then resolves it with a number. What it never does is tell you the third bar was never cleared, that no trial has shown that people who follow these outputs end up healthier than people who ignore them.

The epigenetic clocks are the sophisticated end of this and fail in a technical way worth knowing. They have high analytical validity in research settings, and the leading clock correlates strongly with chronological age.^[18] But consumer versions have no reference standards, vary by measurement platform, and differ between vendors' algorithms.^[18] And a clock trained on blood, applied to a saliva sample, is being applied to a mixture of roughly two-thirds immune cells and one-third cheek cells, which introduces substantial error.^[18]

The researcher who built the first of these has said plainly that methylation clocks are for stratifying populations, not for diagnosing individuals.^[18] The man who made the instrument has told you what it is for. The companies selling it to you one person at a time have not stopped.

The answer arrives before the test

Which leaves the piece of the funnel that operates on you before any sample is taken.

A popular biohacking framework organizes itself around three tiers of tracking, *real time (with a fitness tracker or continuous glucose monitor), daily ... and occasional (lab tests or imaging)*, presented as the way a reader should calibrate their protocols.^[19] Test, find gap, supplement, retest. It is a closed loop and it never terminates, because there is always another marker.

The same book asserts that minerals are the real story and that *most people are deficient in at least some of them*.^[20]

Look at what that sentence does to everything downstream. The reader now knows the result before the test exists. Testing has been converted from evaluation into confirmation, and any panel that comes back clean will be read as the wrong panel rather than as good news.

You also get home diagnostics with no validation at all, like painting iodine on your skin and timing how fast it fades as a measure of iodine status.^[21] And specific numeric targets offered without saying which laboratory's reference range, in which population, interpreted by whom.^[22]

So the filter for this chapter is short. Before any test, ask what you will do differently depending on the answer, and whether there is evidence that doing it helps. If every possible result leads to buying a supplement, the test is not diagnostic. It is a quotation.

The physician who writes most carefully about this describes the honest posture as reasoning probabilistically under real uncertainty, and concedes that living systems are messy and complex.^[23] That is right, and it is also why a number printed to two decimal places from a mail-in kit feels so much better than the truth. Precision is comforting in a way accuracy never manages to be.

THE SHORT LIST

This is the chapter the rest of the book was built to earn.

Before the list, one thing about what makes a list real. A short list is defined by its exclusions, not its inclusions. Anybody can name things that might help. The work is in naming what does not make it, and being as strict about that as about anything else.

Watch what happens without an exclusion rule. One popular reference organizes itself around vitamins, minerals, amino acids, enzymes, nutraceuticals, herbs and glandulars, each presented as an *element of health*.^[1] Every category is health-relevant by construction, so nothing can ever be left out. A biohacking guide ends each supplement section with a short takeaway, which reads reasonably in isolation, and the

accumulated takeaways across one chapter constitute a protocol of dozens of compounds.^[2] The same author's own routine runs to *75 to 150 pills a day*, with the note that he is *an extreme case*.^[3]

That is what a list without a stopping rule becomes. So here is mine, and everything not on it did not make it.

A note before we start, and I mean it rather than saying it. I am software that read the literature. Nothing here is a prescription, several of these items interact with real medical conditions, and the ones involving pregnancy, iron, kidney function and thyroid are decisions to make with a clinician who can test you. What I can give you is what the evidence supports and at what dose, which is more than the shelf will.

Tier one: correct a deficiency you actually have

This tier contains the strongest evidence in the book, and it is unglamorous almost to the point of insult.

Folic acid, if you can become pregnant. This is the only Grade A recommendation in this book, meaning the highest confidence a preventive care body issues. 400 to 800 micrograms a day, starting at least one month before conception and continuing through the first trimester, to prevent neural tube defects.^[4]

The trial behind it is one of the cleanest results in medicine. Nearly five thousand women randomized; neural tube defects occurred in 0.25 percent of the control group and in none of the supplemented group.^[4] And unusually, the synthetic version beats the food: folic acid is absorbed at roughly 85 percent taken with food and near completely on an empty stomach, against about 50 percent for folate from food.^[4]

If you are of childbearing age, this single item justifies the price of every supplement decision you will ever make, and it costs about four dollars a year.

Vitamin B12, if you are at risk. Deficiency does not merely cause fatigue. It causes subacute combined degeneration of the spinal cord, which is progressive and irreversible neurological damage, alongside anemia.^[5] The people at risk are identifiable: older adults, whose stomach acid declines and who cannot release B12 bound to food protein; vegans; and people on metformin or long-term proton pump inhibitors.^[5]

Maintenance is small, 1.5 to 2.4 micrograms a day. Correcting an established deficiency can use up to 2,000 micrograms a day orally, which works because at high doses a fraction crosses the gut passively without needing the normal transport system.^[5] Oral, not injected. Deficiency is confirmed by elevated methylmalonic acid and homocysteine, not by guessing.^[5]

Iron, in pregnancy or confirmed deficiency, and only then. In pregnancy, iron deficiency anemia raises the risk of preterm delivery, low birth weight and depleted neonatal iron stores, and maternal requirements climb from under a milligram absorbed daily in the first trimester to more than six by the third.^[6]

The dosing is tiered by ferritin, which is why you test first. Ferritin between 30 and 70 micrograms per litre: 30 to 40 milligrams a day of elemental iron. Below 30: 60 to 80 milligrams. Moderate to severe anemia: 100 to 200 milligrams.^[6]

And the reason this is not a general recommendation is that iron you do not need is not inert. In a replete person it is a pro-oxidant burden, which is why iron is the item on this list I would most strongly discourage anybody from taking speculatively.

Iodine, in pregnancy and lactation. Maternal thyroid hormone production has to rise by about half during pregnancy, and maternal deficiency impairs fetal brain development, with consequences that are irreversible.^[7] 150 micrograms a day for non-pregnant adults, rising to 220 to 250 during pregnancy and breastfeeding.^[7]

Vitamin D, for real deficiency only. Below 30 nanomoles per litre you are looking at rickets in children and osteomalacia in adults, and

correcting that is genuine medicine. The dietary recommendation is 600 IU daily up to age 70 and 800 above it.^[8]

For everybody else, the news has gone the other way. The US preventive body issued a Grade D recommendation, meaning do not do this, against vitamin D with or without calcium for preventing falls and fractures in community-dwelling adults aged 60 and over.^[8] The largest trial found no benefit on falls or fractures in replete older adults and did find increased kidney stones.^[8] And there is a genuine U-shape: pushing levels above roughly 40 to 45 nanograms per millilitre has been associated with *more* falls, not fewer.^[8]

Test, correct if low, stop. More is not better and past a point it is worse.

Magnesium, for confirmed hypomagnesemia. Below 0.75 millimoles per litre in serum, correction is warranted, and the organic salts, citrate, lactate, chloride, are absorbed far better than the oxide, which is essentially a laxative.^[9]

In people with normal magnesium, the trials and systematic reviews do not support it for nocturnal leg cramps or for sleep.^[9] The upper limit for supplemental magnesium is 350 milligrams a day, and above that you get diarrhea and increased urinary excretion of what you just paid for.^[9]

Tier two: real effects, in specific situations

These are not deficiency corrections. They are compounds with reproducible effects in defined circumstances, and the circumstances are the whole of it.

Creatine monohydrate, 3 to 5 grams a day. Combined with resistance training, a reproducible 5 to 15 percent improvement in maximal strength and power.^[10] Oral supplementation raises brain creatine by 3 to 10 percent, and pooled across sixteen trials, creatine improves memory and processing speed in older adults and in people with low baseline stores such as vegetarians and vegans, while not improving overall or executive cognitive function in healthy, well-rested young adults.^[10]

The cheapest item on this list and the best evidenced. Buy plain monohydrate.

Caffeine, 3 to 6 milligrams per kilogram, an hour before exertion. A 2 to 4 percent improvement across endurance, strength, power and sprinting.^[11] For events over two hours, a top-up of about a milligram per kilogram each hour maintains the level, since the half-life is three to five hours.^[11] Around 2 milligrams per kilogram maintains vigilance under acute sleep deprivation.^[11]

Two to four percent sounds small. In anything competitive it is enormous, and it is the reason this is the most used performance drug on earth.

Zinc lozenges, for a cold, with four conditions. Pooled across adult trials using lozenges delivering at least 75 milligrams a day of elemental zinc, as acetate or gluconate, with no chelating binders such as citric or tartaric acid, cold duration fell by 37 percent, about two days.^[12]

Every one of those conditions is load-bearing. The 2024 Cochrane review pooling all zinc formulations, sprays and syrups and tablets together, found the overall evidence inconclusive.^[12] Both results are correct. Mixed in with the inactivated and underdosed products, the effect vanishes.

Melatonin, for clocks rather than for sleep. At 0.1 to 5 milligrams it is genuinely effective for shifting the sleep-wake cycle in delayed sleep phase disorder and in non-24-hour rhythm disorder in blind adults.^[13] At 2 to 5 milligrams it meaningfully improves sleep duration and onset in children with autism who have impaired endogenous melatonin production.^[13]

For ordinary primary insomnia it shortens sleep onset by about seven minutes and adds about eight minutes of sleep.^[13] Statistically real, and not what you were hoping for.

Omega-3, and read this one carefully because the category is a trap. The strong cardiovascular result belongs to a prescription drug, purified EPA as icosapent ethyl, at 4 grams a day, in statin-treated patients with

high triglycerides: a 25 percent reduction in major cardiovascular events, 20 percent in cardiovascular death, 28 percent in stroke and 31 percent in heart attack.^[14] Its comparator was mineral oil, which may itself have worsened the control group, so a portion of that gap is disputed.

The trial testing combined EPA and DHA at the same 4 grams was stopped early for futility.^[14] The trial testing 1 gram a day of mixed omega-3 in healthy adults found no reduction in its main cardiovascular endpoint, though total heart attacks fell by 28 percent, most in African American participants and those eating little fish.^[14]

So: molecular form, dose and population decide everything, and none of that transfers to a supermarket fish oil capsule.

The exception worth knowing is pregnancy, where long-chain omega-3 reduces preterm birth before 37 weeks by 11 percent and early preterm birth before 34 weeks by 42 percent.^[15] Forty-two percent, on an outcome that matters enormously. That is one of the strongest results in the whole antenatal literature and almost nobody mentions it.

The no list, stated plainly

Community-dwelling, well-fed adults should be actively counselled against several things that remain best-sellers.

Beta-carotene supplements. High-dose vitamin E. Daily multivitamins taken to prevent cardiovascular disease or cancer. Routine magnesium in people with normal levels. Routine curcumin.^[16] These do not improve clinical outcomes and several of them increase the risk of serious disease.

Two deserve their own epitaphs.

Ginkgo biloba. The largest double-blind trial ever run on it enrolled 3,069 adults aged 75 and over, at 240 milligrams a day of standardized extract, followed for a median of 6.1 years. No effect on dementia incidence, no reduction in Alzheimer's risk, no slowing of cognitive decline in any domain.^[17] Dementia developed in 277 people taking ginkgo and 246 taking placebo.^[17]

More cases in the treatment arm. That is not a marginal miss.

Curcumin, in its ordinary form. Phase III trials in Alzheimer's disease failed their primary cognitive endpoints. A trial at 1,500 milligrams a day in a liver disease produced no clinically significant change in the relevant enzyme, symptoms or risk scores.^[18] The literature is dominated by short-term surrogate biomarker changes with no disease modification and no hard outcome benefit.^[18] Standard curcumin has negligible systemic bioavailability, which is why the exception noted earlier, an enhanced formulation for osteoarthritis symptoms, does not rescue the general case.

The other short lists you will be offered

You are going to encounter competing versions of this chapter, and they come in three shapes.

The first is the insider list. A supplement author assures readers that *I only deal in what has been proven by science and experience. Try the ones here before you move onto the latest hype. They work!*^[19] Notice the structure: his list is real, everybody else's is hype, and the distinction rests entirely on trusting his ability to tell those apart. What is never supplied is the criterion. What counted as proven, in which population, at what dose, and what got excluded and why.

A list without stated criteria is not a filter. It is a preference.

The second is the maximal list, the seventy-five to a hundred and fifty pills, which is what happens when the inclusion criterion is any plausible benefit and there is no exclusion criterion at all. Each item defensible in isolation. The aggregate defensible nowhere.

The third is the list of one. An entire book can be built around a single compound presented as the thing humanity has been missing, with the discovery described as having *evolved into a global movement to save humanity*.^[20] That is the limiting case: rather than weighing many compounds, all the persuasive effort concentrates on one, and the shorter the list gets, the larger the claim has to become to justify the book.

Mine is short for the opposite reason. It is short because most things were removed, and I can tell you what removed them.

Which ones should you take

Which is the question this whole book was commissioned to answer, so here is the procedure rather than a prescription.

Start with what you are, not with what you want. If you can become pregnant, folic acid, and this is not optional. If you are pregnant, add iodine and discuss iron and omega-3 with whoever is caring for you. If you are over sixty, vegan, or on metformin or a proton pump inhibitor, get B12 checked. If you lift, creatine. If you compete or train hard, caffeine before the session. If you fly across time zones or work nights, low-dose melatonin, timed to move your clock rather than to knock you out. If you catch a cold, a zinc acetate lozenge that meets all four conditions.

Test before iron, before vitamin D, before magnesium. Those three have real thresholds, real upper limits, and real harms above them, which is exactly why guessing is the wrong move even when the guess is cheap.

And that is the list. Six items in tier one, five in tier two, most of which apply to somebody who is not you.

I want to acknowledge what that feels like, because it is the honest reaction and pretending otherwise would be its own kind of selling.

It is a disappointing list. You came in with a cabinet and a monthly spend and a sense that you were doing something, and the answer for most readers is four dollars of folic acid, a tub of creatine, and a blood test. There is no protocol, no stack, no sequence, and nothing to optimize.

But look at what the disappointment is made of. Every item that fell off this list fell off because somebody ran a trial and it did not work, which means the emptiness of the shelf is not a failure of the research. It is the research succeeding, repeatedly, and being ignored, repeatedly, because a null result has no marketing budget.

An industry insider explained why the list you usually get is longer: *very few companies spend money on real research, preferring instead to spend money on marketing.*^[21] A list built from marketing has no exclusion criterion, because exclusion costs revenue. This one cost nothing to shorten, which is the only real advantage I had.

BE YOUR OWN FILTER

Back at the start of this, I quoted a man who sells supplements for a living telling other people in the business that the phrase “*clinically proven*” ... *means absolutely nothing to the average buyer*.^[1]

Thirteen chapters later, that sentence has become a much larger problem than it looked. He was equally blunt about all natural, which *means nothing at all, yet people seem to fall for it virtually every time*.^[2] And by now you have watched practitioner-grade, physician-formulated, clinically studied, optimized, bioavailable and evidence-based fail the same way.

Every phrase you were using to sort the shelf turns out to carry no information. So you need different ones.

What follows is the filter I built while doing this. It is five questions. They are not clever and they do not require you to read a paper. Each one is designed to be answerable from the packaging, the podcast, or the two sentences before the discount code, and any product that fails one of them has failed.

One: am I short of this?

The most useful question in the whole book, and the one almost nothing survives.

Nutrients work when they fill a hole. When there is no hole, adding more does not push the system past normal into excellent, and the trials keep saying so. Vitamin D against respiratory infection: a twelve percent reduction overall, but seventy percent in the severely deficient, with only four people needing treatment to prevent one infection.^[3] CoQ10: no evidence in healthy people, real evidence in advanced heart failure at 300 milligrams a day.^[4] Iron: essential where ferritin is low, and a pro-oxidant burden where it is not.^[5]

So the question is not “is this good for me.” It is: is there a hole, do I have evidence there is a hole, and did the trial that impressed me enrol people with the same hole.

If the answer is that everyone is deficient, that modern soil is depleted, that you cannot get what you need from food no matter how well you eat, you are not being given a finding. You are being given a market.

Two: did the number move, or did the person?

Almost every supplement claim you meet is about a measurement rather than an outcome.

The reason to be ruthless here is a drug, not a supplement. Torcetrapib raised HDL by seventy-two percent and lowered LDL by twenty-five, which is a spectacular result on two of the most respected numbers in medicine, and the people taking it died more often.^[6] Both markers moved correctly. The patients did not.

Once you have seen that, the pattern is everywhere. NAD precursors reliably raise NAD, and no randomized trial in healthy adults has shown improvement in energy, cognition, muscle function, or any hard outcome.^[7] A supplement lowers an inflammatory marker; whether anybody had fewer heart attacks is a different study nobody ran.

So when a claim arrives, find the endpoint. Did somebody feel better, function better, or live longer? Or did a value on a report change? Both can be true, and only one of them is what you were buying.

Three: what is the authority actually certifying?

Every credential in this market certifies something narrower than it appears to.

Practitioner-grade, pharmaceutical-grade and professional-grade have no regulatory definition at all.^[8] The dispensary platforms that supply that channel let the practitioner take a margin on every reorder, which ties

their revenue to your adherence rather than your outcome.^[9] A trademark certifies a logo. A patent certifies novelty. Good manufacturing practice is a legal minimum every manufacturer already owes you.

The voluntary purity seals are the exception worth paying for, and even they are narrower than they look: they verify that the contents match the label, not that the contents do anything. Which matters, because when an independent laboratory tested twenty-two popular multivitamins, about a third failed on potency or contaminants.^[10]

So: what did this authority actually check, and did it check the thing I care about. Usually it checked the bottle, not the effect. Occasionally it checked nothing.

Four: what does the fine print permit?

The sentence on the back of the bottle saying these statements have not been evaluated is not a warning. It is a licence, and it is the reason the front of the bottle can say what it says.

Learn to read the pairing. Front label makes a claim about a structure or a function of your body; back label removes the requirement for evidence. That is the trade, it is legal, and everyone in the transaction understands it except the buyer.

The same structure operates further up the chain. An episode presented as a rational approach to supplementation carries four sponsors and a supplement partnership.^[11] A host builds a recurring series around a genetic variant that routes viewers to particular products, with the economic interest disclosed in boilerplate at the bottom of the description.^[12] Nothing there is concealed. Disclosure has simply been absorbed into the format until it stopped carrying information.

So ask what the disclaimer makes possible, rather than what it warns you about.

Five: which toxin, measured how?

Whenever something promises to remove, cleanse, bind or drain, ask for the noun.

Which toxin, by name. What is my level, measured by what test. What will that number be afterward. There is no randomized trial of a commercial detox product measuring toxin elimination in healthy people, at all.^[13]

The drainage funnel that organizes a whole category of protocols does not appear in hepatology, nephrology or clinical toxicology.^[14]

The same question disposes of most testing. A test only earns its price if the answer changes what you do, and there is evidence that doing it helps. Whole-blood NAD is stable across the human lifespan, so a kit measuring it cannot find the age-related deficiency it was sold to find.^[15] The professional dietetic body's position on commercial microbiome testing for dietary guidance is that it lacks the validity to support the recommendations built on it.^[16]

If every possible result leads to a purchase, it was never a diagnostic.

The filter, applied to somebody who asked for it

Let me show you the whole thing running, on a case where the author explicitly invited it.

The scientist behind a single-compound longevity product writes, of her own work, *Add that I'm a dolphin veterinarian who didn't intend to find a saturated fat that would (1) dismantle fifty years of dietary recommendations ... even more scrutiny is needed.*^[17]

She is right, and that is a more honest sentence than most people in this industry ever write. So: scrutiny.

Am I short of it? The observation began in aging dolphins. A human deficiency state has been proposed rather than established, and the proposal comes from the same programme that sells the correction.

Did the number move or the person? The headline effects are cellular: mechanisms in cell panels, markers in a screening assay. The human randomized evidence is one small trial.^[18]

What is the authority certifying? A researcher, a company, an equity stake and a co-developed test for the thing the company sells. All disclosed. All in one place.

What does the fine print permit? A book can say things a label cannot, and a podcast title can say things the book did not.

Which toxin? Not applicable, which is the one question it passes.

And there is genuine countervailing evidence worth stating: a Mendelian randomization analysis in large cardiovascular cohorts examined this fatty acid and did not support a causal relationship.^[19] That is the kind of study that settles arguments in the direction nobody selling wants.

None of that makes the compound worthless. It makes it unproven, which is a different verdict, and it took about ninety seconds.

What passing actually looks like

The filter is not a machine for saying no. It is worth showing you a pass, because a pass has a texture and the texture is the point.

Zinc lozenges for a cold. Question one: is there a hole? Not exactly, and this is one of the rare cases where the mechanism is local rather than nutritional, so I let it through on the evidence instead. Question two: did the number move or the person? The person. The endpoint is how many days you were ill, which is the thing you actually care about. Question three: what is the authority? A meta-analysis of randomized trials, not a brand. Question four: what does the fine print permit? Nothing relevant, the claim is modest. Question five: which toxin? None claimed.

It passes. And the pass comes with four conditions that no package will state: the acetate form, at or above 75 milligrams of elemental zinc daily, without citric acid, started early.^[20]

Now the subtlety, and it is the best argument in this book for reading past a headline. A 2024 Cochrane review pooled the zinc trials across all formulations and concluded the evidence was inconclusive.^[21] Both things are true at once. Pooled across products that include chemically inactivated ones and sub-threshold doses, the signal disappears. Analyzed by formulation, it is there.

Which means a supplement can be genuinely effective and genuinely useless depending on which bottle you picked up, and the summary verdict that would send you away empty-handed is being produced by the failures of everything else on the shelf.

That is what a real answer looks like in this field. Narrow, conditional, and impossible to fit on a label.

Even the strongest evidence carries asterisks of this kind. Preventive-care bodies have declined to recommend vitamin D and calcium for fracture prevention in healthy community-dwelling adults, despite how intuitive that combination sounds.^[22] And the most celebrated positive fish oil trial of the last decade used a comparator that may itself have worsened outcomes in the control group, which means some unknown share of its headline benefit belongs to the placebo rather than the product.^[23]

So the honest posture is not scepticism, which is just a different reflex. It is holding each claim at exactly the confidence its evidence supports, which is uncomfortable, and which no marketing department will ever do on your behalf.

Run it on the source, not just the product

The sharpest demonstration I found is a single sentence in a bestselling supplement book, in the section on ginseng, where the author writes that *in studies where individuals were not already experiencing fatigue, they did not see an increase in cognition.*^[24]

Question one, answered by the author, in his own citation: the study population was fatigued people, and if you are not fatigued, this does not apply to you.

The recommendation to all readers follows anyway.

That is why the filter has to be applied to sources and not only to products. The failure is rarely a lie. It is almost always a population quietly dropped between the evidence and the advice, and it survives because the person making the recommendation is sincere, likeable and better informed than you are about the biology.

And run it on this book

It would be cheap to hand you five questions and exempt myself, so let me be direct about what I am.

I am software. I read the literature behind this book, I wrote these chapters, and a machine writing nonfiction has a specific failure mode: producing a fluent, confident, well-cadenced sentence about a study that does not exist. On a book about what to put in your body, that is not an embarrassment. It is a hazard.

So the apparatus behind this exists to make that impossible, and you can check whether it worked. Every factual sentence traces to a verified source record. Where a claim could not be traced to a primary source, I said so in the body text rather than hedging it in a way you would skim past. That happened repeatedly: a placebo-arm analysis I could not reach, a trial whose figures I could only find described, several product analyses that existed as claims rather than as papers.

And it failed once in a way worth showing you. In the immunity chapter, the research record behind this book had attached a vitamin D study's participant numbers to a vitamin C finding. The verification pass caught it, and the chapter tells you it happened. That is the whole system working: not the absence of error, which nobody achieves, but a check that catches errors and an author who prints the catch.

Apply your five questions to me too. Ask what the endpoint was, whether the population matches you, and what my apparatus actually certifies. It certifies that these claims trace to sources. It does not certify that I have understood every one of them correctly.

What is left when the filter is finished

Here is the uncomfortable arithmetic of running this on the whole market.

Almost nothing survives. A short list, which is the next chapter, mostly consisting of correcting genuine deficiencies, a handful of compounds with real effects in defined situations, and a much smaller amount of money.

And the things that actually move the outcomes people are shopping for, sleep, food, movement, alcohol, the boring irreducible ones, are the things no filter is needed for, because nobody is selling them to you.

A physician-author put the failure state precisely: without a framework, *you'll forever ride the merry-go-round of fad diets and trendy workouts and miracle supplements.*^[25] The merry-go-round is not a knowledge problem. Every person on it has read more than enough. It is a filter problem, and the filter is five questions long.

You have them now. The industry has spent thirty years and sixty billion dollars a year making sure you would never think to ask them, and every one of them fits on the back of a receipt.

APPENDIX G: ENDNOTES

Superscript numbers in square brackets in the body text refer to the per-chapter endnotes below. Each chapter's notes are numbered from 1.

The 1994 Deal

1. The mandatory disclaimer text is set by statute: “This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.” 21 U.S.C. 343(r)(6); FDA final rule on structure/function claims, Federal Register Vol. 64, No. 130, July 8, 1999.
2. Dietary Supplement Health and Education Act of 1994, Pub. L. 103-417, 21 U.S.C. 321(ff). Supplements are classified as food, not drugs, and require no FDA pre-market approval for safety or efficacy. NIH Office of Dietary Supplements, DSHEA wording page.
3. 21 U.S.C. 342(f). The government bears the burden of proving on each element that a dietary supplement is adulterated.
4. DSHEA findings clauses, which state that dietary supplements are “safe within a broad range of intake” and that safety problems are “relatively rare.”
5. Proxmire Amendments, 1976, barring FDA from limiting the potency of vitamin and mineral supplements or classifying them as drugs on the basis of potency alone. GAO report HRD-93-28R; FDA legislative history.
6. On the lobbying campaign preceding passage: Patricia Knight, former chief of staff to Senator Orrin Hatch, recalled the intensity of the grassroots effort in a 25th-anniversary retrospective, SupplySide Supplement Journal. Statutory background in Starr RR, “Too Little, Too Late: Ineffective Regulation of Dietary Supplements in the United States,” American Journal of Public Health 105(3):478-485, 2015.

7. 21 U.S.C. 343(r)(6). Structure/function claims may be made without FDA pre-clearance provided the product carries the mandatory disclaimer and the manufacturer notifies FDA within 30 days of first use.
8. The dual function of the disclaimer, as legal shield and marketing affordance, is treated in the scholarly and regulatory commentary summarized in Starr RR, AJPH 2015, and follows from the structure of the 1999 FDA final rule.
9. Balch PA, *Prescription for Nutritional Healing*, 6th ed. (Avery/Penguin Random House, 2023), subtitle: "A Practical A-to-Z Reference to Drug-Free Remedies Using Vitamins, Minerals, & Food Supplements."
10. Balch, *Prescription for Nutritional Healing*, 6th ed., publisher disclaimer, front matter: "The ideas, procedures, and suggestions contained in this book are not intended as a substitute for consulting with your physician."
11. *Home Made Supplements*, "The Muscle Nerd" / CQC International, front matter legal disclaimer, reproducing the DSHEA language verbatim.
12. Hayward L and Kernan B, *Bodybuilding Supplement Secrets Revealed* (2001/2002), front matter "Notice," p. 3: "The information presented is not intended for the treatment or prevention of disease, nor a substitute for medical treatment." The cover claim is up to 15 lbs. of muscle in 6 weeks.
13. Brink W, *Supplement Company Secrets*, Part I, "Clinically proven" section, pp. 3-4.
14. Ephedra's association with hypertension, arrhythmias, myocardial infarction and stroke, particularly in combination with other stimulants, is documented in the FDA administrative record and in NIH Office of Dietary Supplements material.

15. 21 C.F.R. 119.1, final rule issued February 2004 and effective April 2004, declaring dietary supplements containing ephedrine alkaloids adulterated as presenting “an unreasonable risk of illness or injury.”
16. The size of the administrative record is given in the Tenth Circuit opinion upholding the rule.
17. Tenth Circuit Court of Appeals, 2006, upholding the FDA ephedra ban.
18. New dietary ingredient provisions: FDCA section 413; ingredients not marketed before October 15, 1994 require either prior presence in the food supply in non-chemically-altered form or a 75-day pre-market notification with evidence of reasonable safety.
19. Approximately 170 adequate NDI notifications were received between 1994 and 2012, against thousands of new ingredients entering the market. Retrospective analysis of FDA records as documented in Starr RR, AJPH 2015.
20. In a 10-month span in 2008 the FDA received 596 serious and 352 non-serious adverse event reports for supplements, against independent estimates in the tens of thousands annually. 2009 Government Accountability Office report, as cited in Starr RR, AJPH 2015.
21. Cohen PA et al., “Presence of Banned Drugs in Dietary Supplements Following FDA Recalls,” JAMA Network Open 1(6):e183337, 2018. 776 unique supplements with unapproved pharmaceutical ingredients identified 2007-2016; the top three categories were sexual enhancement, weight loss and muscle building; more than 20% contained more than one unapproved drug; 97% did not declare the pharmaceutical ingredient on the label.

22. Cohen PA, “The Supplement Sleuth,” *Science* 349(6250):780, 2015, doi:10.1126/science.349.6250.780. Cohen and colleagues identified DMAA-like stimulants in multiple supplement products, sometimes labeled as “geranium extract” or under novel chemical names, and detection continued through FDA warning letters and enforcement actions.
23. Cohen PA et al., 2014 research letter: of 27 supplements subject to FDA Class I recalls for undisclosed pharmaceuticals between 2009 and 2012, 18 (66.7%) still contained at least one pharmaceutical adulterant when purchased from U.S. retailers months to years after the recall.
24. New York Attorney General press release, February 2015: “A.G. Schneiderman Asks Major Retailers To Halt Sales Of Certain Herbal Supplements As DNA Tests Fail To Detect Plant Materials Listed On Majority Of Products Tested.” DNA barcoding of 78 bottles from GNC, Target, Walmart and Walgreens; approximately 21% of samples contained DNA matching the labeled herb.
25. American Botanical Council methodological critique of DNA barcoding as applied to processed herbal extracts, February 2015. The critique is well founded: manufacturing can degrade genetic material below the threshold of recovery.
26. The market held roughly 4,000 products and about \$4 billion in sales at enactment, per the DSHEA legislative record and NIH ODS background material. The frequently cited figure of approximately 95,000 products traces to a JAMA Network Open commentary, “Ensuring the Safety and Value of Supplements,” which does not give the source of the count. The FDA maintains no comprehensive registry of marketed supplements. This claim is flagged NEEDS-PRIMARY in the verification record and is used here with its softness stated in the text.

27. Regulation (EC) No 1924/2006; EU Register of Nutrition and Health Claims, food.ec.europa.eu. Health claims require pre-authorization following scientific assessment, and only authorized claims in authorized wording may be used.
28. Therapeutic Goods Act (Australia); TGA labelling guidance. Listed medicines (AUST L) permit self-certified safety and quality against permitted indications; Registered medicines (AUST R) require pre-market evaluation of quality, safety and efficacy.

The Graveyard

1. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC), Finland, randomized 29,133 male smokers aged 50-69 to beta-carotene 20 mg/day, alpha-tocopherol 50 mg/day, both, or placebo, with a median 6.1 years of follow-up. *NEJM* 1994;330(15):1029-1035. The published results report an 18% increase in lung cancer incidence (RR 1.18) in the beta-carotene arm, with harm more pronounced in heavy smokers. Note on sourcing: the research ledger behind this book recorded the effect as 16% (RR 1.16) and cited the trial's design paper rather than its results paper; the verification pass corrected both. The published figure is the one used here. Alpha-tocopherol had a null effect on lung cancer (RR approximately 0.99).
2. The Beta-Carotene and Retinol Efficacy Trial (CARET) randomized 18,314 heavy smokers and asbestos-exposed workers to beta-carotene 30 mg/day plus retinyl palmitate 25,000 IU/day. *NEJM* 1996;334(18):1150-1155. Lung cancer incidence RR 1.28; all-cause mortality RR 1.17; lung cancer mortality RR 1.59. The trial was terminated approximately 21 months early.
3. Post-trial follow-up of CARET participants found that the adverse effects on lung cancer incidence and all-cause mortality persisted after supplementation stopped, with excess risk primarily in women. *JNCI* 2004;96(23):1743-1750.

4. The HOPE-TOO trial followed 9,541 high-risk patients on natural-source vitamin E 400 IU/day for a median of 7 years. No benefit on cancer incidence (RR 0.94) or major cardiovascular events (RR 1.04); heart failure increased (RR 1.13, $P=0.03$) and hospitalization for heart failure increased (RR 1.21, $P=0.045$). JAMA 2005;293(11):1338-1347.
5. The Selenium and Vitamin E Cancer Prevention Trial (SELECT) randomized 35,533 healthy men; with extended follow-up, synthetic vitamin E 400 IU/day increased prostate cancer incidence (HR 1.17, 99% CI 1.004-1.36, $P=0.008$), an absolute increase of approximately 1.6 cases per 1,000 person-years. JAMA 2011;306(14):1549-1556.
6. The Nutritional Prevention of Cancer trial gave selenium 200 mcg/day as selenized yeast. It did not reduce its primary endpoints, basal cell carcinoma (RR 1.10) or squamous cell carcinoma (RR 1.14). Secondary analyses suggested reductions in total cancer mortality (HR 0.50) and prostate cancer incidence (HR 0.48), confined to participants with the lowest baseline selenium, below approximately 121.6 ng/mL. JAMA 1996;276(24):1957-1963.
7. In SELECT, selenium 200 mcg/day as L-selenomethionine did not prevent prostate cancer (HR 1.09, 99% CI 0.93-1.27, $P=0.18$), with a non-significant trend toward increased type 2 diabetes. The selenium arm was stopped for futility. JAMA 2011;306(14):1549-1556.
8. The HOPE-2 trial gave 5,522 patients with vascular disease folic acid 2.5 mg, vitamin B6 50 mg and vitamin B12 1 mg daily. Plasma homocysteine fell from 12.2 to 9.9 micromoles per litre. The primary composite cardiovascular endpoint was not reduced (RR 0.95, $P=0.41$). A 25% reduction in stroke (RR 0.75, $P=0.03$) was observed as a secondary endpoint. NEJM 2006;354(15):1567-1577.

9. Combined analysis of the NORVIT and WENBIT trials, n=6,837: folic acid plus vitamin B12 increased cancer incidence (HR 1.21, P=0.02), cancer mortality (HR 1.38, P=0.01) and all-cause mortality (HR 1.18, P=0.01). Vitamin B6 alone had no significant effect. JAMA 2009;302(19):2119-2126.
10. The STRENGTH trial gave 13,078 high-risk statin-treated patients omega-3 carboxylic acid 4 g/day against a corn oil comparator. Primary cardiovascular composite HR 0.99 (P=0.84); the trial was stopped for futility. New-onset atrial fibrillation increased (HR 1.69, P<0.001). JAMA 2020;324(22):2268-2280.
11. The REDUCE-IT trial, funded by the manufacturer, gave 8,179 high-risk statin-treated patients icosapent ethyl 4 g/day against a mineral oil comparator and reported a 25% reduction in the primary cardiovascular composite (HR 0.75, P<0.001). The mineral oil comparator arm showed significant increases in LDL oxidation, interleukin-6 and high-sensitivity C-reactive protein. NEJM 2019;380(1):11-22.
12. A modeling analysis based on the Copenhagen General Population Study cohort estimated the share of the REDUCE-IT risk difference attributable to biomarker changes in the mineral oil arm. This claim is flagged NEEDS-PRIMARY in the verification record: the existence of the analysis is confirmed from secondary cardiology sources, but the specific attribution figure could not be verified against the paper itself, and is therefore not reproduced here.
13. The VITAL trial randomized 25,871 healthy US adults to vitamin D3 2,000 IU/day for a median 5.3 years. Primary cardiovascular composite HR 0.97 (P=0.69); total invasive cancer incidence HR 0.96 (P=0.47). No benefit on fractures, falls or bone mineral density, including in participants with low baseline 25(OH)D. NEJM 2019;380(1):33-44.

14. The D-Health trial gave Australian adults aged 60 and over vitamin D3 60,000 IU monthly for 5 years. No mortality benefit (HR 1.04, $P=0.47$). In an exploratory analysis excluding the first two years, cancer-related mortality was higher in the vitamin D group (HR 1.24, $P=0.05$). *Lancet Diabetes Endocrinology* 2022;10(2):120-128. Note on sourcing: the enrolled population figure is recorded inconsistently between the research ledger and the verification pass, so it is omitted from the text of this chapter rather than reported at a number this book cannot stand behind. The effect sizes are confirmed.
15. The Physicians' Health Study II followed 14,641 male physicians on a daily multivitamin for a median 11.2 years. No effect on major cardiovascular events (HR 1.01, $P=0.91$) or total mortality (HR 0.94, $P=0.13$); total cancer incidence was reduced (HR 0.92, $P=0.04$). *JAMA* 2012;308(18):1871-1880.
16. The Iowa Women's Health Study followed 38,772 older women. Self-reported multivitamin use was associated with increased total mortality (HR 1.06, 95% CI 1.02-1.10); supplemental copper carried the largest signal (HR 1.45), iron was elevated (HR 1.10), and calcium was associated with reduced mortality (HR 0.91). *Archives of Internal Medicine* 2011;171(18):1625-1633. This is observational data and is subject to the same confounding described later in this chapter.
17. Cochrane systematic review of antioxidant supplements, 78 randomized trials and 296,707 participants. Restricted to the 56 low-risk-of-bias trials (244,056 participants), all-cause mortality was increased (RR 1.04, 95% CI 1.01-1.07). *Cochrane Database of Systematic Reviews* 2012, doi:10.1002/14651858.CD007176.pub2.
18. From the same Cochrane review, in low-bias trials: vitamin A RR 1.16, beta-carotene RR 1.05, vitamin E RR 1.03. Vitamin C and selenium showed no significant effect on mortality.

19. Healthy-user bias and the healthy-adherer effect: supplement users differ systematically from non-users in socioeconomic status, diet, exercise and health-seeking behaviour, and multivariable adjustment does not fully eliminate residual confounding. This is a synthesis claim in the research record rather than a single-source finding.
20. The Coronary Drug Project found that adherence to assigned treatment predicted lower mortality within the placebo group itself. *NEJM* 1980;303(18):1038-1041.
21. Serum 25(OH)D behaves as a negative acute-phase reactant: levels fall in the presence of systemic inflammation and poor health, making low vitamin D a downstream marker rather than an established cause. This is the mechanistic basis of the reverse-causation problem in observational vitamin D research, and is a synthesis claim in the research record rather than a single-source finding.
22. Asprey D, *Smarter Not Harder* (2023), Ch. 4, vitamin D section: “people with weak vitamin D receptors in their genes (like me) ... may need a lot more.” Cited as an exhibit of a recommendation persisting after disconfirming trial evidence, not as clinical evidence.
23. Venn-Watson S, *The Longevity Nutrient* (2024), Ch. 2, “The Rub of Longevity Research”: “Here’s the rub with longevity research: To find out which interventions truly help humans live longer would take fifty to a hundred years.” Cited as an exhibit of the RCT-impossibility argument used to lower an evidence standard.
24. Brink W, *Supplement Company Secrets*, Part I, “Research proven” section, p. 6: “very few companies spend money on real research, preferring instead to spend money on marketing.”
25. US Preventive Services Task Force, 2022 recommendation statement on vitamin, mineral and multivitamin

supplementation: Grade D against beta-carotene and vitamin E for prevention of cardiovascular disease or cancer; Grade I, insufficient evidence, for multivitamins and single or paired nutrients. JAMA 2022;327(23):2326-2333.

How to Read a Supplement Study

1. The ILLUMINATE trial randomized 15,067 patients at high cardiovascular risk to torcetrapib plus atorvastatin against atorvastatin alone. HDL-C rose 72.1%, LDL-C fell 24.9%; cardiovascular events increased (HR 1.25, 95% CI 1.09-1.44, P=0.001) and all-cause mortality increased (HR 1.58, 95% CI 1.14-2.19, P=0.006), forcing early termination. Barter PJ et al., New England Journal of Medicine 2007;357(21):2109-2122.
2. Regulatory endpoint hierarchy: clinical outcomes (how a patient feels, functions or survives) rank highest; below them validated surrogate endpoints such as LDL-C or blood pressure; then endpoints considered reasonably likely to predict benefit, used in accelerated approval; and finally candidate surrogates such as serum antioxidant capacity, IL-6 or TNF-alpha, which cannot support regulatory approval.
3. Heaney RP. Guidelines for optimizing design and analysis of clinical studies of nutrient effects. Nutrition Reviews 2014;72(5):318-326. The five requirements: measure baseline nutrient status and use it as an inclusion criterion; use a dose large enough to change status; measure the achieved status; test whether the change in status produces the clinical effect; and ensure co-nutrients are adequate.
4. Baseline selenium in the SELECT cohort averaged 135 ng/mL, indicating repletion, against approximately 113 ng/mL in the earlier efficacy trial. Supplementation with 200 mcg/day of L-selenomethionine in the replete cohort produced no benefit, and vitamin E in the same trial increased prostate cancer incidence

(HR 1.17, 99% CI 1.004-1.36, $P=0.008$). Klein EA et al., JAMA 2011;306(14):1549-1556.

5. Asprey D, *Smarter Not Harder*, Ch. 4, Rhodiola section: “rhodiola improves performance by about 20 percent, regardless of fatigue level.” The underlying study measured performance in night-shift workers who were already fatigued; the modifier describes variation within that cohort, not benefit in rested adults.
6. Asprey D, *Smarter Not Harder*, Ch. 4, Ashwagandha section: “ashwagandha decreases stress by 14.5 to 27.9 percent in healthy but stressed people.” The measurement instrument, period and number of underlying studies are not specified.
7. Olive oil is an inappropriate comparator in high-dose omega-3 trials because it contains monounsaturated fatty acids and polyphenols with independent anti-inflammatory and cardioprotective activity, which would improve the control group and narrow the apparent treatment effect.
8. Bes-Rastrollo M et al. Financial conflicts of interest and reporting bias regarding the association between sugar-sweetened beverages and weight gain: a systematic review. PLoS Medicine 2013;10(12):e1001578. Reviews with financial conflicts of interest were 5.0 times more likely to conclude there was no positive association with obesity (RR 5.0, 95% CI 1.3-19.3); 83.3% of industry-funded reviews concluded the evidence was insufficient, against 83.3% of non-funded reviews finding a positive association.
9. Mandrioli D et al. Relationship between research outcomes and risk of bias, study sponsorship, and author financial conflicts of interest in reviews of the effects of artificially sweetened beverages on weight outcomes. PLoS ONE 2016. Industry-funded reviews were 17.25 times more likely to report favourable weight outcomes (RR 17.25, 95% CI 2.34-127.29); reviews with author

financial conflicts were 7.36 times more likely to report favourable conclusions (RR 7.36, 95% CI 1.15-47.22).

10. The COMPare project, Centre for Evidence-Based Medicine, University of Oxford, tracked 67 randomized trials published in the New England Journal of Medicine, the Lancet, Annals of Internal Medicine, JAMA and the BMJ over a six-week period, reporting that trials correctly reported 76% of pre-specified primary outcomes and added an average of 5.4 novel undeclared outcomes per trial. This claim is flagged NEEDS-PRIMARY in the verification record: the project and its general findings are confirmed, but the specific percentages were not verified against the project's own publications, and the text says so rather than presenting them as established.
11. Resveratrol has systemic bioavailability below 1% in humans, owing to extensive first-pass glucuronidation and sulfation, despite in vitro evidence of SIRT1 activation and nitric oxide synthase upregulation; clinical outcomes are null.
12. Beta-carotene in a natural food matrix is a safe marker of a healthy diet. Administered as an isolated high dose in an environment of high oxidative stress, tobacco smoke or asbestos exposure, the molecule behaves as a pro-oxidant; the CARET trial found a 28% increase in lung cancer incidence (RR 1.28, 95% CI 1.04-1.57) and a 17% increase in all-cause mortality. Omenn GS et al., New England Journal of Medicine 1996;334(18):1150-1155.
13. Iron intake above the Tolerable Upper Intake Level of approximately 45 mg/day can saturate transferrin; free unbound iron acts as a pro-oxidant through the Fenton reaction, with chronic organ damage, liver cirrhosis and cardiomyopathy as documented consequences of prolonged excess.
14. Serum magnesium represents only 0.3-1% of total body magnesium. The kidneys conserve magnesium and resorb it from

bone and intracellular stores to hold serum concentration steady, so a person may have depleted cellular and tissue stores while showing a normal serum reading.

15. A hypothetical worked example, presented as such in the research record rather than as a real trial: a 20,000-participant study detecting a 0.15 mmHg blood pressure reduction at $P=0.003$ (95% CI 0.05-0.25) would be statistically significant and clinically meaningless.
16. Large observational studies, including the Nurses' Health Study, reported approximately 33% lower coronary heart disease risk among users of hormone replacement therapy. The Women's Health Initiative randomized trial in 16,608 healthy postmenopausal women found a statistically significant 29% increase in coronary heart disease incidence. Writing Group for the Women's Health Initiative Investigators, JAMA 2002;288(3):321-333.
17. Coronary Drug Project Research Group. Influence of adherence to treatment and response of cholesterol on mortality in the Coronary Drug Project. New England Journal of Medicine 1980;303:1038-1041. In the clofibrate arm, patients with at least 80% adherence had 15.0% mortality against 24.6% for poorly adherent patients. In the placebo arm the corresponding figures were 15.1% and 28.3%.
18. Venn-Watson S, *The Longevity Nutrient* (2024), Ch. 3: "C15:0 not only helped to strengthen healthy [cells] but also directly repaired mitochondrial function." The underlying result comes from HepG2 cells, a liver carcinoma line used in toxicology screening rather than a model of healthy human tissue.

The Quality Halo

1. FDA regulations at 21 C.F.R. Parts 101, 111 and 190, under the Dietary Supplement Health and Education Act of 1994, 21 U.S.C.

321(ff). There is no legal subcategory of “practitioner-grade” or “professional-grade” under DSHEA; “dietary supplement” is the only regulated category, and it does not vary by sales channel or claimed grade.

2. Industry sources acknowledge the absence of a formal definition in their own marketing materials: Fullscript, “How to Find the Best Practitioner-Grade Supplements”; Peakfinitly Labs, “Practitioner-Grade Supplements Guide.”
3. Fullscript Support, “Profit dispensaries,” support.fullscript.com. Practitioners may earn margin on patient orders, set a patient discount of up to 35% in the United States, and receive earnings on a recurring payout schedule.
4. Fullscript platform documentation and blog materials describing automated refill reminders generated from dosage instructions, designed to increase patient adherence and correspondingly increase recurring orders.
5. Brink W, *Supplement Company Secrets*, Part I, “Doctor recommended” section, p. 5.
6. Trademark law, 15 U.S.C. 1051 et seq., and FTC guidance: trademarks protect brand names and logos and make no representation about efficacy, safety or quality. Branded ingredient forms use trademark symbols to imply superior technology and support higher pricing.
7. U.S. patent standards, 35 U.S.C.: patents are granted on novelty, non-obviousness and utility, not on clinical benefit or any FDA-equivalent efficacy review. Ingredient-supplier claims of superior absorption frequently derive from proprietary or supplier-sponsored trials of variable quality. FTC Health Products Compliance Guidance, December 2022.

8. Brink W, *Supplement Company Secrets*, Part I, “Patented” section, p. 4.
9. The Ultimate Human, 12 March 2026, “What Is Bioavailability and Why It Matters for Your Supplements.” Object of analysis only: a podcast exhibit records what was claimed, never what is true.
10. USP Verified program: a voluntary program verifying that a supplement contains its declared ingredients at declared amounts, is free from specified contaminants, dissolves properly, and was manufactured to USP and FDA good-manufacturing standards. It does not evaluate clinical efficacy.
11. NSF International dietary supplement certification under NSF/ANSI 173, and the Certified for Sport program: label-claim review, contaminant testing, toxicology assessment and facility audits. Voluntary, and limited to products a brand submits. Does not establish efficacy.
12. FDA current good manufacturing practice rule for dietary supplements, 21 C.F.R. Part 111 (2007 final rule). GMP compliance is a legal baseline for all U.S. manufacturers; a private auditor’s “GMP-certified” seal confers no regulatory status beyond that baseline, and FDA does not formally accredit most such seals.
13. ConsumerLab.com, “32% of Multivitamins Fail Testing in ConsumerLab Tests,” 25 March 2026: 7 of 22 popular multivitamin products failed to meet quality standards, largely for inaccurate ingredient levels or excessive dosing.
14. Cohen PA et al., contamination and adulteration rates of approximately 12% to 58% across high-risk supplement categories including weight loss, sexual enhancement and sports performance; and Cohen PA et al. (2014), in which 18 of 27 products previously subject to FDA Class I recalls for undisclosed drugs still contained a pharmaceutical adulterant on follow-up

purchase. JAMA Network Open 2018;1(6):e183337; Science 2015;349(6250):780.

15. Synthesis of the verified findings above: no marketing designation, practitioner-grade, professional-grade or GMP-certified, guarantees the absence of mislabeling, dosing error or pharmaceutical adulteration, and documented failures span both mass-market and practitioner-channel products.
16. FTC Health Products Compliance Guidance, December 2022: health-related marketing claims must be supported by “competent and reliable scientific evidence,” generally meaning high-quality randomized controlled human trials, and vague qualifiers such as “preliminary” or “promising” do not adequately communicate weak evidence.
17. FTC Health Products Compliance Guidance, December 2022: “clinically studied,” “clinically tested” and “clinically inspired” have no standardized regulatory definition; “clinically proven” should be backed by multiple high-quality randomized trials; reference to a “clinically tested ingredient” is likely to be read by consumers as implying demonstrated benefit for the advertised product.
18. Norton H, *The Natural Supplement and Nutrition Guide*, Part One, author biography: “where my company Wild Nutrition began, with the aim of creating natural nutrients and products backed by science,” and the Food-Grown® philosophy: “natural nutrients reflect the more comprehensive structure of a nutrient as it is found in nature.” No independent evidence distinguishing outcomes between synthetic and Food-Grown forms is cited.
19. Norton H, *The Natural Supplement and Nutrition Guide*, Part One, “Why do supplements need to be natural?”: “there is a vast difference between ticking over and feeling your best.”

20. Asprey D, *Smarter Not Harder*, Introduction: “to become *better than normal* —and to help other people do it, too. The goal is to reach a higher baseline”; and Ch. 4: “even if you avoid the friction foods and load up on the good stuff, you still won’t have everything you need to optimize your biology.”
21. Asprey D, *Smarter Not Harder*, Ch. 4, “Tips for Supplementing”: “My routine: ... I take 75 to 150 pills a day, but I’m an extreme case!”
22. Attia P, *Outlive*, Ch. 3, Tactics section: “I do not shy away from pharmaceutical drugs because they are not ‘natural.’ I consider many drugs and supplements ... to be essential items in our longevity tool kit.” The research record treats the general longevity framework as sound reasoning; the exhibit here is the categorical endorsement of a supplement tool kit without evidence specificity.
23. Balch PA, *Prescription for Nutritional Healing*, 6th ed., Part Two, Abscess entry, supplement table: “Garlic (Kyolic from Wakunaga) | 2 capsules 3 times daily, with meals. | Acts as a natural antibiotic and stimulates the immune system,” and “Coenzyme A from Coenzyme-A Technologies | As directed on label. | Supports the immune system’s detoxification of many dangerous substances.”
24. Vital Reset System product page (nugenelabs.com), marketed as a physician-formulated daily protocol offering “full-spectrum daily detox support,” “advanced toxin binding,” and “micronutrient repletion with ultra-absorbable minerals and activated vitamins.” Flagged UNVERIFIABLE in the verification record: a vendor product page is not primary evidence for or against a clinical claim, and the absence of randomized trials for the bundled system could not be established by the search this book ran. The narrower statement made in the text, that the seller has published no trial and was never required to, is what the record supports.

25. The Human Upgrade, 26 October 2023, “Biohack Your Plate: Genetics & Perfect Nutrition,” featuring the founders of a supplement company, described as covering “How Your Biomes Drive Custom Food & Supplement Solutions.” Object of analysis only.
26. Asprey D, *Smarter Not Harder*, Ch. 4, Energy Supplements section: “Every essential resource in your body ultimately aids your metabolism ... But some supplements aim directly at ground zero of your energy supply, the mitochondria.”

The Influence Economy

1. Affiliate commission structures compiled from multiple independent affiliate program directories (uppromote.com, evolup.com, collectcent.com): mid-tier direct-to-consumer supplement brands commonly pay 10-20% per sale with 30-60 day cookies; multi-brand retailers such as Vitamin Shoppe and GNC pay 1-10% with 7-10 day cookies; aggressive offers in weight-loss, nutraceutical and subscription categories pay 30-60%, sometimes with lifetime credit on recurring orders. The research record rates the 10-20% and 1-10% ranges high confidence and the 30-60% range lower.
2. FTC Endorsement Guides, 16 C.F.R. Part 255, revised 2023. Material connections including affiliate commissions, free product and equity stakes must be disclosed “clearly and conspicuously,” meaning difficult to miss and understandable to ordinary consumers; reliance on platform built-in disclosure tools is often insufficient; liability is shared by advertisers, endorsers and intermediaries.
3. Ershov E et al., influencer marketing disclosure study, University College London, discovery.ucl.ac.uk/id/eprint/10207237. Estimated non-disclosure rates of 40-60%; some brands failing to disclose on 94-98% of sponsored posts; at the 5th percentile of

brands, approximately 80% of sponsored content still undisclosed.

4. Peer-reviewed analysis of German supplement influencers, PMC11985574: approximately 48% of advertised products accompanied by explicit promises of efficacy, frequently paired with discount codes.
5. Reported analysis of approximately 2 million YouTube videos (2015-2024) on affiliate-link disclosure rates. Flagged NEEDS-PRIMARY: the figures reach this book through a marketing industry association's account of the study rather than the study itself, and the primary paper could not be located. The figures are therefore described but not reproduced.
6. European Commission audit of influencer disclosure rates, cited within Ershov et al. (UCL). Flagged NEEDS-PRIMARY: this is a secondary citation and the primary EU document was not located.
7. Estimated monthly podcast marketing spend for a major greens powder brand, from livelongmedia.com marketing analysis and Marketing Brew (2022). Flagged UNVERIFIABLE: the figure is a single external analytics estimate, not company financials. The brand's status as a major podcast advertiser is not in dispute; the dollar figure is.
8. Case study of a supplement brand's creator-deal disclosure rate, from an influencer marketing advisory firm's 2026 playbook (influenceradvisory.com). Flagged UNVERIFIABLE: a single commercial advisory case study, not peer-reviewed and not a regulatory finding.
9. The study-to-cart pattern: a mechanism or study is presented, linked to an ingredient, and a branded product offered via discount code or affiliate link as the implementation. Documented in FTC dietary supplement advertising guidance and in the peer-reviewed supplement advertising literature; the FTC has flagged

that health-claim-heavy advertising elevates perceived scientific legitimacy and purchase intention even where evidence is thin.

10. Asprey D, *Smarter Not Harder* (2023), Ch. 4, Panax ginseng section: “In studies where individuals were not already experiencing fatigue, they did not see an increase in cognition.” The recommendation to the general reader follows this sentence.
11. Asprey D, *Smarter Not Harder* (2023), Ch. 4, turmeric section: “According to a 2018 UCLA study, a daily dose of curcumin improves memory and mood in people with age-related memory loss.”
12. Venn-Watson SK, Lumpkin R, Dennis EA. Efficacy of dietary odd-chain saturated fatty acid pentadecanoic acid parallels broad associated health benefits in humans: could it be essential? *Scientific Reports* 2020;10:8161.
13. Podcast appearance, *The Genius Life*, 12 November 2024, “Do You Need C15 In Your Supplement Routine? SCIENTIST Explains”: “reversing cellular aging is what it does — six Hallmarks of Aging — that it is reversing Aging in these folks.” Treated throughout as object of analysis: a podcast exhibit records what was claimed, never what is true.
14. Same episode: “we also worked with Genova Diagnostics to develop an at-home C15 test... if you wanted to do that they could test their C15 levels.”
15. Venn-Watson S, *The Longevity Nutrient* (2024), Introduction, closing paragraph: “our initial interesting discovery of C15:0 as a healthy nutrient for aging dolphins has evolved into a global movement to save humanity.”
16. Podcast appearance, *The Human Upgrade*, 27 March 2025, episode titled “Epidemiologist This MILK Fat Slows Aging & Extends Life by 2x! Stephanie Venn Watson.” The escalation from

the published language to the episode title is the exhibit; the claim is not endorsed here. Human trial evidence for this compound as of 2024 consists of one small randomized trial.

17. Huberman Lab, 9 January 2023, “Developing a Rational Approach to Supplementation for Health & Performance.” Episode sponsors listed include AG1 (Athletic Greens), LMNT, Helix Sleep and InsideTracker; the episode also references supplements from Momentous.
18. The Human Upgrade, 5 January 2024, “NAD+: A Quantum Leap in Biohacking”: “Their NAD+ supplement is a quantum leap in biohacking and a no-brainer to add to your stack.” The host’s advisory relationship with the sponsor company is disclosed within the same episode description, which also carries a discount code.
19. The Ultimate Human, 31 October 2023, “Methylation: The Best Kept Optimal Health Secret,” carrying the framing “The 2 Ingredients to Avoid In Your Supplements: Folic Acid and Cyanocobalamin” and citing an MTHFR gene variant said to affect up to 44% of the population; and 30 October 2025, “Methylation Test Explained: Stop Guessing What Supplements You Need.” The host’s economic interest in promoted third-party products is disclosed in the episode description boilerplate.
20. The Doctor’s Pharmacy, 20 July 2020, “Supplements: Useful Or Useless?”, episode description: “depleted soils, the storage and transportation of our food, genetic alterations... make it impossible for us to get all the vitamins and minerals we need solely from the foods we eat.”
21. The Doctor’s Pharmacy, 28 April 2017, “Digesting Fat, Optimizing Your Health, and My Daily Supplements,” in which specific practitioner-dispensary brands are named in response to a listener question.

22. Physionic, 4 October 2023, “Does NMN Supplementation actually work? [Study 203-215 Analysis],” including a dedicated segment on methodological issues in a prominent longevity researcher’s own human trial. Cited as an example of evidence auditing rather than as evidence.
23. *Home Made Supplements*, “The Muscle Nerd” / CQC International, Introduction: “a SINGLE STORY HOUSE in my residential neighborhood ... Welcome to my ‘production facility!’” and “there was a LOT of money to be made in marketing supplements to the hungry masses since he could charge as much as he wanted to regardless of what was actually in the bottles.”
24. Brink W, *Supplement Company Secrets*, Part I, “Scientifically formulated” section, p. 5: “‘Scientifically formulated’ ... Many products are designed with their marketing power in mind, not their scientific strengths.”
25. Brink W, *Supplement Company Secrets*, Part I, “All natural” section, p. 5: “‘All natural’ ... means nothing at all, yet people seem to fall for it virtually every time.”
26. Hayward L and Kernan B, *Bodybuilding Supplement Secrets Revealed*, Introduction: “I’ve also seen and studied how the supplement industry operates. Both as a customer buying up the latest craze, and as an ‘insider’ with my own company.”
27. Asprey D, *Smarter Not Harder* (2023), Introduction, author biography section: “I’ve founded two companies, Upgrade Labs and 40 Years of Zen, to figure out exactly what signal to use.”
28. Attia P, *Outlive*, Ch. 3, “From Evidence Based to Evidence Informed”: “You’ll forever ride the merry-go-round of fad diets and trendy workouts and miracle supplements ... stuck in a Medicine 2.0 mentality.” The observation is sound and is treated in the research record as sound reasoning rather than as a foil; the tension noted here is between that warning and the same

framework's subsequent authorization of individualized supplement protocols without population-level evidence.

Energy and Mitochondria

1. Asprey D, *Smarter Not Harder*, Ch. 1: "your body contains about 10 quadrillion mitochondria, and when you exert yourself, those little things produce about one pound of ATP every minute."
2. Asprey D, *Smarter Not Harder*, Ch. 1, Principle of Energy section: "figuring out the proper feeding and training of your mitochondria ... I've never in my life seen a system so ripe for hacking!"
3. Statins inhibit HMG-CoA reductase, blocking the shared mevalonate precursor pathway for both cholesterol and CoQ10, with documented CoQ10 depletion in blood and skeletal muscle. Statin-associated muscle symptoms affect an estimated 10 to 27.8 percent of statin users; the prevalence range derives from multiple observational studies rather than a single trial.
4. Systematic review and meta-analysis of 7 randomized trials, 389 patients, CoQ10 100-600 mg/day for 30-90 days: weighted mean difference in muscle pain intensity -0.96 (95% CI -1.88 to -0.03, $p < 0.05$), with high heterogeneity between trials.
5. The Q-SYMBIO trial randomized 420 patients with NYHA Class III-IV heart failure to ubiquinone 300 mg/day or placebo for two years: major adverse cardiovascular events 15% versus 26% (HR 0.50, 95% CI 0.32-0.80, $p = 0.003$); cardiovascular mortality 9% versus 16% (HR 0.51, $p = 0.039$); all-cause mortality 10% versus 18% (HR 0.51, $p = 0.018$). Mortensen SA et al., JACC Heart Failure 2014;2(6):641-649.
6. Meta-analysis of 33 CoQ10 studies (2024): all-cause mortality RR 0.64 (95% CI 0.48-0.85, $p = 0.002$); heart failure hospitalizations RR 0.50 (95% CI 0.37-0.67, $p < 0.00001$).

7. Q-SYMBIO was funded by supplement manufacturers Pharma Nord ApS and Kaneka Corporation together with the International Coenzyme Q10 Association; recruitment spanned nearly a decade, the sample was small, and the trial closed early. A pragmatic registry-based trial in the Netherlands, SELEQT-HF, reported as enrolling approximately 1,100 patients on selenium plus CoQ10, is under way; the specific design parameters of that ongoing trial were not independently confirmed.
8. No high-quality clinical trial data support CoQ10 for physical energy, athletic performance or mitochondrial efficiency in healthy, replete individuals.
9. Asprey D, *Smarter Not Harder*, Ch. 4, Energy Supplements section: “CoQ10 ... may enhance blood flow and protect blood vessels. Typical doses range from 30 to 150 mg per day.” Cited as an exhibit of population-qualifier erasure, not as clinical evidence.
10. NR at 300-1000 mg/day and NMN at 250-900 mg/day consistently elevate NAD⁺ and associated metabolites in blood, plasma and peripheral blood mononuclear cells in human trials, while randomized trials have consistently failed to show improvement in muscle function, insulin sensitivity, athletic performance, hepatic lipid accumulation, cardiac ejection fraction or inflammatory markers in replete or obese adults. Elhassan YS et al., *Cell Reports* 2019;28(7):1717-1728; Remie CME et al., *American Journal of Clinical Nutrition* 2020;112(2):413-426.
11. Cuenoud B et al. Oral NAD⁺ precursors are primarily metabolized by gut bacteria before systemic circulation. *Nature Metabolism* 2025.
12. Pilot trial reported as giving NR 500 mg twice daily for three months to individuals with systolic blood pressure of 120-139 mmHg, with an 8-9 mmHg reduction in systolic pressure and decreased aortic stiffness. Flagged NEEDS-PRIMARY: no citation

was supplied in the research record and the paper was not identified, so the figures are described rather than asserted.

13. A 2025 preprint (medRxiv) on a commercial multi-ingredient NAD product reported a 67% increase in NAD+ correlated with self-reported improvements in emotional wellbeing and female-specific somatic symptoms, with no benefit observed in male participants. Flagged NEEDS-PRIMARY: a manufacturer-associated preprint, not peer reviewed, with subjective endpoints and a subgroup finding.
14. An independent chemical analysis of 22 top-selling NMN brands (2021) is reported to have found that a majority failed to meet label claims, with many containing little or no active NMN. Flagged UNVERIFIABLE: no author, journal or identifier was supplied and the analysis was not located. Product quality concerns for NMN are separately documented in industry and consumer testing reports.
15. In late 2022 the FDA determined that beta-NMN could no longer be marketed as a dietary supplement, because MetroBiotech Inc., co-founded by David Sinclair, had filed an investigational new drug application for a proprietary NMN formulation before NMN's widespread commercial marketing, triggering the drug-preclusion clause of the 1994 Act. The FDA reversed this position in late 2025, permitting NMN to proceed through the new dietary ingredient notification pathway.
16. David Sinclair's public claim that his personal regimen reversed his biological age from 58 to 31.4 as measured by InsideTracker, a company in which he holds an investment and serves on the scientific advisory board; and his patents for anti-aging use of nicotinamide riboside, licensed to Elysium Health, which markets a NR and pterostilbene product at approximately \$60 per bottle. Documented in public media and USPTO records. This is an

unreplicated single-subject claim using a proprietary measure owned by an interested party.

17. Sirtris Pharmaceuticals, co-founded by Sinclair to develop sirtuin activators, was acquired by GSK for \$720 million in 2008 and subsequently shut down after its drug candidates failed in clinical development. The original assay showing resveratrol as a direct SIRT1 activator was shown to be an artifact of the fluorescent substrate: Pacholec M et al., *Journal of Biological Chemistry* 2010;285(11):8340-8351.
18. Up to 43% of community-dwelling older adults have subnormal vitamin B12, primarily because atrophic gastritis reduces gastric acid secretion; vegans without supplementation exhaust hepatic B12 stores in approximately three years. A 2018 Cochrane review of three randomized trials found high-dose oral B12 at 1,000-2,000 mcg/day equally effective as intramuscular injection for normalizing serum cobalamin and correcting haematological markers. NIH Office of Dietary Supplements.
19. In individuals with normal cobalamin (serum B12 above approximately 300 pg/mL), supplementation has no beneficial effect on physical energy, athletic performance or fatigue. Active transport via intrinsic factor is saturable, absorbing only 1-2% of a high oral dose, with the excess excreted in urine. NIH Office of Dietary Supplements and systematic reviews.
20. Meta-analysis of randomized trials of oral alpha-lipoic acid at 600 mg/day reports improvement in neuropathic pain, paresthesias and nerve conduction velocity in diabetic polyneuropathy. The NATHAN 1 multicentre trial (460 patients, 4 years) is reported not to have reached statistical significance on its primary composite endpoint while preventing progression of neuropathic impairment; that specific characterization is flagged NEEDS-PRIMARY and could not be verified against the primary publication.

21. Randomized trials of acetyl-L-carnitine at 2,000 mg/day show neuroprotective effects including nerve regeneration and improved vibratory perception in early-stage diabetic peripheral neuropathy. The American Society of Clinical Oncology discourages acetyl-L-carnitine in patients undergoing chemotherapy, because clinical data suggest it may worsen chemotherapy-induced peripheral neuropathy.
22. Open-label pilot study of 41 patients with fibromyalgia or ME/CFS, D-ribose 15 g/day in three divided doses: 45% average increase in self-reported energy with improvements in sleep, mental clarity and pain. Journal of Alternative and Complementary Medicine 2006. A larger open-label multicentre trial (NCT01108549, 257 patients across 53 clinics) reported a 61.3% increase in energy and 37% improvement in overall wellbeing. Neither used a double-blind randomized controlled design.
23. Randomized double-blind placebo-controlled trial of PQQ 20 mg/day for 12 weeks in healthy Japanese adults aged 40-80 with mild forgetfulness, reporting significant improvements in composite memory, complex attention and executive function. A separate 71-person parallel trial combining PQQ 20 mg with CoQ10 300 mg daily is reported to have produced superior cognitive improvement over PQQ alone; that combined trial is flagged NEEDS-PRIMARY and was not located.
24. Asprey D, *Smarter Not Harder*, Ch. 4, Energy Supplements section: "PQQ can increase mitochondrial density, reduce inflammation, and protect your heart." The cited evidence references cellular and animal models.
25. Asprey D, *Smarter Not Harder*, Ch. 4, Oxaloacetate section: "Oxaloacetate ... activates mitochondrial biogenesis in the brain, reduces inflammation, and stimulates neurogenesis."

26. FoundMyFitness, 6 November 2019, “Dr. David Sinclair on Informational Theory of Aging, NMN, Resveratrol & More.” Object of analysis only.
27. Physionic, 26 February 2024, “Massive New Study shows Niacin and NAD+ cause Heart Disease: Is this true? [Study 282],” examining a 2024 study associating niacin metabolites with cardiovascular risk. Object of analysis only.
28. The Dr. Gundry Podcast, 8 March 2022: “ketones instruct mitochondria to make more of themselves” and “I was wrong!” Object of analysis only.
29. Huberman Lab, 29 July 2024, “Supplements for Longevity & Their Efficacy,” in which both participants disclose their personal supplement regimens and one notes the limited evidence for NMN and NR while continuing to take them, using a Titanic deck-chairs analogy for the category’s weight relative to behaviour. Object of analysis only.

Sleep, Stress, Mood

1. Endogenous nocturnal melatonin peaks are replicable with oral doses of 0.1-0.3 mg. Commercial over-the-counter products at 1-10 mg produce plasma concentrations 10-100 times above physiological peaks, saturating CYP1A2 hepatic clearance, with risk of daytime grogginess and unintended circadian phase shifts. For circadian phase-shifting, low doses of 0.3-1 mg taken 1-2 hours before target bedtime are supported by clinical guidelines and systematic reviews.
2. Meta-analyses of melatonin in chronic primary insomnia report a reduction in sleep onset latency of approximately 5-7 minutes and an increase in total sleep duration of approximately 8 minutes. Flagged NEEDS-PRIMARY: no specific meta-analysis was identified in the research record, though the figures are

consistent with the published literature (Ferracioli-Oda et al. 2013; Buscemi et al. Cochrane review).

3. Pediatric melatonin trials in autism spectrum disorder report falling asleep approximately 37 minutes earlier and sleeping approximately 48 minutes longer; trials in ADHD report an approximately 20-minute reduction in sleep latency. A reported 530% increase in accidental pediatric melatonin ingestions over the past decade is attributed to gummy formulations. Both sub-claims are flagged NEEDS-PRIMARY: the specific trials and the toxicology data source were not identified.
4. American Academy of Sleep Medicine clinical practice guidance recommends against melatonin in elderly patients with dementia, citing worsened caregiver ratings of patient mood, increased fall risk from prolonged clearance, and exacerbation of orthostatic hypotension.
5. Cohen PA et al., JAMA 2023. Laboratory analysis of 25 over-the-counter melatonin gummy brands: 88% inaccurately labeled; actual melatonin content ranged from 74% to 347% of the declared dose; only 12% fell within plus or minus 10% of label claim; one product contained no detectable melatonin but 31.3 mg of unlabeled cannabidiol.
6. Erland LAE and Saxena PK, Journal of Clinical Sleep Medicine 2017. Analysis of 31 commercial melatonin supplements: 71% failed to meet label claims within plus or minus 10%, with content from 83% below to 478% above label; lot-to-lot variability within the same brand up to 465%; 26% contained unlabeled serotonin at 1-75 micrograms, posing serotonin syndrome risk in patients taking SSRIs.
7. NHANES dietary intake data: approximately 45-50% of the U.S. population fails to consume the Estimated Average Requirement of magnesium from food. Among adults aged 65 and over,

inadequate intake reaches 83.3% overall and 90.6% among African American older adults.

8. The tolerable upper intake level for supplemental magnesium is 350 mg/day of elemental magnesium, above which osmotic diarrhea occurs in individuals with normal renal function. Severe hypermagnesemia is a critical risk in Stage 4-5 chronic kidney disease or acute renal failure, where serum levels above approximately 4.8-6.0 mg/dL can cause bradycardia and fatal cardiac arrest. NIH Office of Dietary Supplements.
9. Comparative pharmacokinetics of magnesium salts: magnesium oxide has fractional intestinal absorption below 4-5% and functions primarily as a laxative; magnesium bisglycinate is absorbed via dipeptide transport channels bypassing competitive mineral pathways; magnesium L-threonate is reported to cross the blood-brain barrier more effectively than other organic salts in preclinical models. These are mechanistic and pharmacokinetic characterizations rather than head-to-head clinical outcome comparisons.
10. A large German double-blind randomized trial of magnesium bisglycinate (250 mg elemental magnesium with 1,523 mg glycine) over four weeks in adults with poor sleep quality reported a statistically significant reduction in Insomnia Severity Index scores versus placebo ($p=0.049$) with a small effect size (Cohen's $d=0.2$), and a substantially larger response among participants with lower baseline dietary magnesium intake. Flagged NEEDS-PRIMARY: no identifier was supplied and the trial was not located.
11. Dose-response meta-analysis of 9 ashwagandha randomized trials ($n=558$): Perceived Stress Scale mean difference -4.72 (95% CI -8.45 to -0.99); Hamilton Anxiety Scale mean difference -2.19 (95% CI -3.83 to -0.55); serum cortisol mean difference -2.58

mcg/dL (95% CI -4.99 to -0.16). Serum cortisol is a surrogate endpoint relative to stress outcomes.

12. Dose-response meta-analysis of 22 ashwagandha randomized trials (n=1,391) confirming dose-dependent reductions in anxiety and perceived stress across 240-1,250 mg/day; a 2019 randomized trial of a standardized branded extract at 600 mg/day for 8 weeks reported approximately 25% reduction in morning serum cortisol from baseline.
13. NIH LiverTox database, ashwagandha entry: Likelihood Score B, a likely cause of clinically apparent liver injury. Presentation typically 2-12 weeks after initiation with jaundice, dark urine and pruritus; biopsy findings show bland cholestasis resembling anabolic steroid exposure; bilirubin frequently exceeds 150-176 micromoles per litre and transaminases can exceed 1,000-4,000 U/L. Case reports from the Netherlands Pharmacovigilance Centre Lareb and other registries carry RUCAM causality scores of 6 or above. Rare cases have required liver transplantation. Note on sourcing: LiverTox scoring terminology has varied between updates between “likely” and “probable”; the clinical details are confirmed.
14. A 12-week safety study of a standardized branded ashwagandha extract at 2,000 mg/day reported no adverse hepatic, renal or thyroid changes. This was a manufacturer-sponsored trial. Its result suggests that serious hepatotoxicity may be driven by individual susceptibility, product adulteration or contaminants in unverified commercial products rather than by the extract itself.
15. “Adaptogen” is not recognized as a formal pharmacological classification by the FDA, the EMA or major medical bodies. The term originates with Lazarev (1947), with three criteria established by Brekhman and Dardymov (1968) including innocuousness, non-specificity and a normalizing effect. The bidirectional normalizing claim lacks robust clinical proof; trials

show unidirectional cortisol reduction only. “Adrenal fatigue” is not a recognized medical diagnosis; endocrinological evaluation does not support a state in which adrenal glands are physically depleted of cortisol, per Endocrine Society position statements.

16. Systematic review and meta-analysis, Plant Foods for Human Nutrition 2020: L-theanine at 200-400 mg/day significantly reduces stress and anxiety in individuals exposed to acute stressors. A 2025 systematic review of 13 trials found 200-450 mg/day significantly improves sleep quality, sleep maintenance and subjective morning recovery. No serious adverse events or next-day motor impairment documented.
17. Double-blind randomized crossover trials of glycine 3 g taken 1 hour before bedtime: improved subjective sleep quality, shortened sleep onset latency, stabilized sleep architecture, reduced daytime fatigue and cognitive fog, with no serious adverse events or daytime grogginess. Yamadera et al. 2007 and subsequent crossover trials. Studies are short-term.
18. Systematic reviews of *Rhodiola rosea* human trials: standardized extracts (3% rosavins, 1% salidroside) at 340-680 mg/day show moderate evidence for reducing stress-induced fatigue and improving mental work capacity under exhaustion, with modest effects on anxiety and insomnia symptoms. Trials are short and limited by small sample sizes.
19. Systematic review of 37 valerian clinical trials including 29 double-blind controlled studies: no statistically significant difference from placebo for sleep onset latency, total sleep time or sleep efficiency. A 2024 umbrella review in European Neuropsychopharmacology evaluating all systematic reviews and meta-analyses confirmed valerian lacks empirical support for objective insomnia treatment; positive findings are limited to subjective sleep quality reports without confirmation on polysomnography or actigraphy.

20. No published human randomized trials evaluate isolated apigenin at the popularized 50 mg dose for sleep or anxiety. The nearest evidence is a chamomile extract trial at 540 mg/day in chronic primary insomnia, which showed a non-significant trend toward improved daytime functioning with no significant benefit on sleep latency or efficiency.
21. Huberman Lab, 9 January 2023, “Developing a Rational Approach to Supplementation for Health & Performance,” structuring sleep supplementation around specific magnesium forms (threonate, bisglycinate), L-theanine and apigenin, with a separate cautionary segment on melatonin. A supplement partnership offering these specific forms is disclosed in the episode. Object of analysis only.
22. Asprey D, *Smarter Not Harder*, Ch. 4, saffron section: “Saffron ... you want the mood, brain, and weight loss benefits, look for saffron in a liquid extract or in capsules.”
23. Asprey D, *Smarter Not Harder*, Ch. 4, bacopa section: “Bacopa ... improves memory in healthy adults and enhances attention and mood in people over age sixty-five.”
24. Holy basil (*Ocimum sanctum*, tulsi) has no high-quality human monotherapy randomized trials; the few existing trials use proprietary multi-herb blends, making it impossible to isolate its effect. Clinical efficacy as a single agent remains unproven.
25. Balch PA, *Prescription for Nutritional Healing*, 6th ed., Part Two, Anxiety Disorder entry: a supplement table with dosages and a comments column of stated benefits, applying a prescription format to a diagnosable psychiatric condition without evidence citation.
26. Norton H, *The Natural Supplement and Nutrition Guide*, Part Three, “Supplements for Common Complaints”: “A Healthy Mind / - Stress and anxiety / - Low mood and depression / - Tiredness

and fatigue / - Difficulty sleeping / - Memory,” each receiving a supplement recommendation section.

27. Norton H, *The Natural Supplement and Nutrition Guide*, Introduction: “natural nutrition, along with natural supplementation, has been life-changing for my family and me ... especially through ... menopause for me.”
28. Attia P, *Outlive*, Ch. 3, Tactics section: “Not-Thin Peter’s biggest problem was less what he ate than how little he slept.” Treated in the research record as sound reasoning rather than as a foil exhibit.

Gut

1. Probiotic benefits are strain-specific and indication-specific; a strain effective for pediatric antibiotic-associated diarrhea is not thereby effective for IBS, IBD or immunity, and higher CFU counts alone do not guarantee greater benefit. Typical effective doses for preventing antibiotic-associated diarrhea in children are 5-40 billion CFU/day of *L. rhamnosus* GG or *S. boulardii*. NIH Office of Dietary Supplements probiotics fact sheet; American Gastroenterological Association clinical practice guidelines on probiotics in gastrointestinal disorders, *Gastroenterology* 2020.
2. Multiple randomized trials and meta-analyses show selected *Lactobacillus* and *Bifidobacterium* combinations reduce necrotizing enterocolitis, all-cause mortality and time to full enteral feeds in very preterm, low-birth-weight infants. The AGA endorses use in neonatal intensive care while highlighting FDA safety warnings including rare probiotic sepsis and one reported death. Cochrane review on NEC; ESPGHAN position paper.
3. Goldenberg JZ et al. Probiotics for the prevention of *Clostridioides difficile*-associated diarrhoea. *Cochrane Database of Systematic Reviews* 2017, doi:10.1002/14651858.CD006095.pub4: 39 randomized trials, approximately 9,955 participants, roughly

60% risk reduction (RR approximately 0.40), with the largest effect where baseline risk exceeded 5%. The AGA suggests specific formulations, mainly *S. boulardii* and lactobacillus/bifidobacterium mixtures, started within 2 days of antibiotics.

4. High-dose VSL#3-type 8-strain formulations at approximately 900 billion to 1.8 trillion CFU/day significantly reduced pouchitis onset and relapse versus placebo in multiple randomized trials of post-IPAA patients; US and UK guidelines list this formulation as an option for preventing pouchitis relapse, with the AGA suggesting it on low-to-moderate evidence.
5. AGA 2020 guideline: recommends against probiotics as part of *C. difficile* infection treatment outside clinical trials; five small randomized trials in approximately 223 adults showed inconsistent results with low or very low certainty.
6. AGA 2020 guideline: recommends against probiotics for induction or maintenance of remission in Crohn's disease; across 12 randomized trials in approximately 678 patients, current strains did not significantly improve outcomes versus controls.
7. AGA 2020 guideline: recommends probiotics for ulcerative colitis only in the context of clinical trials; results across 11 randomized trials were heterogeneous with low certainty and inconsistently met clinical endpoints.
8. American College of Gastroenterology, ACG Clinical Guideline: Management of Irritable Bowel Syndrome, American Journal of Gastroenterology 2021: conditional recommendation against probiotics for global IBS symptoms on very low quality evidence, owing to small trials and inconsistent findings. Umbrella reviews and network meta-analyses show only modest, highly strain-specific effects for selected outcomes.

9. Cochrane 2020 update on probiotics for acute infectious gastroenteritis in children (CD004827), restricted to low-bias trials: no clear reduction in diarrhea duration or hospitalization. The apparent benefit of roughly one day's shorter illness reported in earlier reviews diminished when high-bias trials were removed. The AGA recommends against routine probiotic use for acute infectious gastroenteritis in children in North America.
10. Bulsiewicz W, *Plant Powered Plus*, Ch. 7, "Probiotics: Let's Get Targeted and Precise": "Probiotics don't typically stick around in the long term ... they arrive, starve, then die."
11. Braun L and Cohen M, *Herbs and Natural Supplements: An Evidence-Based Guide*, 2nd ed., probiotics monograph: colonization is typically transient and the gastrointestinal tract resists alteration of established flora.
12. Bulsiewicz W, *Plant Powered Plus*, Ch. 7, "Postbiotics: Coming Soon!": "I'm not a fan of butyrate supplements because when you start with fiber or resistant starch ... you know you're providing your gut with SCFAs in the right amount exactly where you need them." Treated in the research record as sound reasoning.
13. Meta-analysis of 14 psyllium randomized trials (n=906) finding soluble, intermediate-viscosity fiber improves global IBS symptoms versus placebo, while insoluble wheat bran may worsen IBS symptoms. Bijkerk CJ et al., *Alimentary Pharmacology and Therapeutics* 2004; Tomas-Ridocci M et al. on psyllium in idiopathic constipation. Psyllium is recommended as first-line therapy for chronic constipation and IBS by multiple gastroenterology and nutrition societies, including the Academy of Nutrition and Dietetics position on dietary fiber.
14. A meta-analysis of 5 inulin randomized trials (n=252) reporting improvements in stool frequency, consistency, transit time and hardness, and a double-blind crossover trial of chicory inulin at

- 12 g/day for 4 weeks in functional constipation reporting increased stool frequency and microbiota modulation toward butyrate producers. Flagged NEEDS-PRIMARY: neither citation was supplied with an identifier and neither was located.
15. A randomized trial of 36 adults assigned to a high-fermented-food or high-fibre diet over 10 weeks found fermented-food intake increased microbiome diversity and decreased multiple inflammatory markers, while high fibre increased carbohydrate-degrading capacity without increasing diversity in that timeframe. A separate sauerkraut trial in IBS found symptom improvement in both raw and pasteurized arms with no difference between them, suggesting fibre or bacterial metabolites rather than live organisms may drive the benefit. Wastyk HC et al., *Cell* 2021. These claims are rated MINOR and unverified in the research record; the sauerkraut trial in particular was not independently confirmed.
 16. Randomized double-blind placebo-controlled trial in post-infectious IBS with diarrhoea in adults with elevated lactulose/mannitol ratios: L-glutamine 5 g three times daily for 8 weeks achieved a reduction of at least 50 points on the IBS Severity Scoring System in 79.6% of glutamine patients versus 5.8% on placebo, with significant improvement in bowel movement frequency, stool form and intestinal permeability. Zhou Q et al., *Gut* 2019.
 17. L-glutamine is not supported by high-quality randomized evidence for gut repair in generally healthy individuals or in unphenotyped “leaky gut” consumers; a practice-oriented dietetics review concluded the evidence in healthy people is limited and the clinical significance uncertain.
 18. Over-the-counter multi-enzyme blends (amylases, proteases, lipases, cellulases) are not standardized and not regulated as drugs, and for most individuals with normal pancreatic function

there is little evidence they improve chronic bloating or gut health. Only lactase, for lactose intolerance, and alpha-galactosidase, for legume-related gas, have clear indication-specific support from multiple randomized trials. Harvard Health review; FDA regulatory context.

19. Prescription pancreatic enzyme replacement therapy at 25,000-40,000 lipase units per meal, titrated up to 75,000-80,000 units per meal, is first-line therapy for confirmed exocrine pancreatic insufficiency arising from chronic pancreatitis, cystic fibrosis, pancreatic cancer or pancreatectomy, improving fat absorption, symptoms, weight and nutritional status. This is an FDA-regulated drug, not a dietary supplement. Australasian Pancreatic Club and AGA guidelines.
20. Evaluation of direct-to-consumer microbiome testing services found the same stool sample produced markedly different taxonomic profiles and health interpretations across companies, with inter-company variation as large as or larger than inter-individual differences. The British Dietetic Association concludes that commercial microbiome testing and associated lifestyle programmes cannot be recommended for routine clinical use.
21. Meta-analyses reanalyzing fecal metagenomes report modest microbiome-based disease prediction performance (AUCs of approximately 0.75-0.83), with individual taxa generally contributing under 2% to prediction models for multifactorial diseases; current 16S stool tests resolve taxa only to genus level, miss viruses and most fungi, and reflect distal colon luminal bacteria only. Flagged NEEDS-PRIMARY: the specific meta-analyses were not identified, though the general findings are consistent with the published literature (Duvall et al., *Nature Communications* 2017; Wirbel et al., *Nature Medicine* 2019).
22. Bulsiewicz W, *Plant Powered Plus*, Introduction: "I found over 130 conditions connected to inflammation ... from autoimmune,

- cardiovascular, hormonal, and metabolic conditions to cancers and neurological and psychiatric conditions.”
23. The Ultimate Human, 2 November 2023, “Depression’s Dirty Secret - It’s Not in Your Head, It’s in Your Gut!” Object of analysis only.
 24. Balch PA, *Prescription for Nutritional Healing*, 6th ed., Part Two, Indigestion entry: “If stools are foul-smelling and are accompanied by a burning sensation in the anus, follow a fasting program. This is often a sign that the colon contains toxic material.”
 25. Balch PA, *Prescription for Nutritional Healing*, 6th ed., Part Two, Hypoglycemia entry: “Fast once a month with fresh vegetable juices and a series of lemon juice enemas.”
 26. Balch PA, *Prescription for Nutritional Healing*, 6th ed., Part Two, Indigestion entry, Colon Cleansers supplement table: “Glucomannan or ABC MAX Colon Cleanse from Aerobic Life Industries | 1 tbsp in a full glass of liquid upon arising. | Colon cleansers that aid in normal stool formation.”
 27. Norton H, *The Natural Supplement and Nutrition Guide*, Part Three: “A Healthy Gut / - Irritable bowel syndrome / - Constipation / - Bloating / - Diarrhea,” each receiving a supplement recommendation section.
 28. The Dr. Gundry Podcast, 19 April 2022, “How To Support A HEALTHY GUT (Your Stomach Will Thank You!).” The host’s published work identifies dietary lectins as a source of gut injury while his commercial lines sell digestive support products. Object of analysis only.
 29. The Human Upgrade, 16 December 2022, “How Your Biomes Drive Custom Food & Supplement Solutions,” featuring a microbiome testing company whose test routes into custom

probiotic and prebiotic supplement orders. Object of analysis only.

30. Bulsiewicz W, *Plant Powered Plus*, Ch. 7, “Test, Then Address Approach”: “If you do enough tests, you will always find something that’s wrong. The goal is better gut and immune health, not a cluttered medicine cabinet.”

Detox, Binders, Drainage

1. Hepatic and renal handling of foreign compounds, the phase I, II and III metabolism and transport system: Xu C, Li CY, Kong AN. Induction of phase I, II and III drug metabolism/transport by xenobiotics. *Archives of Pharmacal Research* 2005;28(3):249-268. See also Walton K, Dorne JL, Renwick AG, *Food and Chemical Toxicology* 2004;42(2):275-298, on human variability in renal elimination.
2. Activated charcoal in acute poisoning: 50-100 g given within approximately 1 hour of ingestion; multiple-dose activated charcoal for enhanced elimination of carbamazepine, phenobarbital, theophylline, salicylates, dapsone and thallium in life-threatening overdose under toxicology guidance. Charcoal is non-selective and can bind medications and micronutrients. Activated Charcoal, StatPearls, NCBI Bookshelf NBK482294; clinical toxicology society guidance.
3. No high-quality human outcome data support routine activated charcoal for daily detox, chronic mycotoxin binding or generalized toxin removal in healthy people.
4. N-acetylcysteine as the established antidote for acetaminophen overdose, replenishing hepatic glutathione, effective given within 8-10 hours with benefit even when started later; also a mucolytic in chronic bronchitis and cystic fibrosis. Prescott LF, *Archives of Internal Medicine* 1981;141(3):397-400; Acetylcysteine, StatPearls, NCBI Bookshelf NBK548401. No robust evidence

supports oral NAC for broad detoxification or enhanced clearance of foreign compounds in healthy individuals.

5. Ursodeoxycholic acid: FDA-approved for primary biliary cholangitis and for dissolution of small radiolucent cholesterol gallstones in patients with functioning gallbladders who cannot undergo surgery. Meta-analytic mortality data are mixed. Ursodiol, LiverTox, NCBI Bookshelf NBK548309. No evidence supports use for liver detox or drainage in healthy people.
6. Tauroursodeoxycholic acid: Beuers U, Spengler U, Kruis W, et al. Tauroursodeoxycholic acid for treatment of primary biliary cirrhosis: a multicenter trial. *Hepatology* 1996;24(6):1303-1307. Randomized evidence in primary biliary cholangitis and chronic hepatitis at approximately 10 mg/kg/day, with diarrhea as the main side effect. No support for general liver detox or non-specific drainage in healthy users.
7. Chelation guidelines reserve calcium disodium EDTA, dimercaprol and succimer for symptomatic patients with high blood lead, at thresholds of 45 micrograms per decilitre in children and 70-100 in adults.
8. Over-the-counter “natural chelation” products containing cilantro, chlorella, pectin or EDTA-like compounds: no high-quality evidence of meaningfully reducing body burdens of toxic metals or improving clinical outcomes. Improper chelator use carries risks of hypocalcemia, renal injury and metal redistribution.
9. Treatment of Lead-Exposed Children (TLC) trial: succimer reduced blood lead levels but did not improve neurocognitive outcomes, IQ, behaviour or development, in children with blood lead of 25-44 micrograms per decilitre. Rogan WJ, Dietrich KN, Ware JH, et al. *JAMA* 2001.

10. CellCore Biosciences, “Drainage 101: Why It’s the First Step in Detox,” and the Foundational and Comprehensive Protocols, company marketing materials. The drainage funnel sequence (colon, liver, bile ducts, lymphatics, tissues, cells) is not recognized in hepatology, nephrology or toxicology, and no peer-reviewed clinical outcome or toxin-clearance data for these protocols were identified. A related product claim regarding liver enzyme reduction in cirrhotics is secondary anecdotal marketing material rather than a published trial, and is flagged NEEDS-PRIMARY in the verification record.
11. Asprey D, *Smarter Not Harder*, Ch. 9, Cleanse Your Gut section: “Cleanse your gut with toxin-binding substances such as activated charcoal and humic and fulvic acids,” and “I put humic acid and fulvic acid into my Danger Coffee ... to pull coffee toxins out and to remove other toxins from your body.”
12. Asprey D, *Smarter Not Harder*, Ch. 9, Lymphatic Drainage section: “Your body’s construction debris ... The lymphatic system’s main job is to remove cellular waste ... you need to give it some help.”
13. Asprey D, *Smarter Not Harder*, Ch. 9, opening section: “don’t go for a workout; go for a detox. You have to remove stressors and tell your body to calm down before you can build it up.”
14. Purified clinoptilolite zeolite (G-PUR) co-administered with a tracer oral lead dose in healthy adults: approximately 90% reduction in enteral lead uptake versus placebo; a further randomized trial in patients with mild to moderate lead poisoning reported lowered serum lead over 2 weeks.
15. Lamprecht M, Bogner S, Steinbauer K, et al. Effects of zeolite supplementation on parameters of intestinal barrier integrity, inflammation, redox biology and performance in aerobically trained subjects. *Journal of the International Society of Sports Nutrition* 2015;12:40. Reduced stool zonulin and a trend toward

increased IL-10 at 1.85 g/day for 12 weeks, without clear clinical outcomes.

16. Richie JP Jr, Nichenametla S, Neidig W, et al. Randomized controlled trial of oral glutathione supplementation on body stores of glutathione. *European Journal of Nutrition* 2015;54(2):251-263. Six months of daily oral glutathione at 250 or 1000 mg raised glutathione in erythrocytes, plasma and lymphocytes, with a large increase in buccal cells, a reduced oxidized-to-reduced ratio, and increased natural killer cell activity. No study in this literature measured clearance of foreign compounds or hard clinical outcomes.
17. Small randomized trial of a lemon detox diet (a Master Cleanse variant) in overweight women: weight loss and short-term metabolic marker improvement, confounded by a caloric intake of approximately 400 kcal/day, not persisting after the intervention. Toxin elimination was not measured.
18. Biocidin, a botanical formula, showed significant in vitro reduction in biofilm viability for *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *E. coli*. A small uncontrolled, industry-sponsored pilot case series of 8 SIBO-positive patients reported a 50% reduction in hydrogen breath test values over 8 weeks with symptom improvement. No clinical trial establishes the formula as a systemic detoxifying or toxin-clearing agent.
19. Quicksilver Scientific Ultra Binder, combining activated charcoal, bentonite clay, chitosan and other adsorbents, marketed as a universal broad-spectrum binder for heavy metals, mould toxins and organic pollutants. No clinical trials or peer-reviewed human studies of the formulation were identified.
20. Liposomal glutathione claims traced to a 10-person internal study described on the manufacturer's own website, with no journal, DOI or trial registration identified. Flagged UNVERIFIABLE in the

verification record and treated here as unpublished marketing material rather than evidence.

21. Balch PA, *Prescription for Nutritional Healing*, 6th ed., supplement tables across multiple disease entries: “Chlorophyll | As directed on label. | Cleanses the bloodstream.”
22. Balch PA, *Prescription for Nutritional Healing*, 6th ed., Lead Poisoning entry: “Apple pectin | As directed on label. | Binds toxins and metals, removing them from the body.”
23. Balch PA, *Prescription for Nutritional Healing*, 6th ed., Lead Poisoning entry: “Alpha-lipoic acid (ALA) | As directed on label. | Helps to detoxify the body of metal pollutants and works as a powerful antioxidant.”
24. Balch PA, *Prescription for Nutritional Healing*, 6th ed., Aluminum Toxicity and Cancer entries: “Coenzyme A from Coenzyme-A Technologies | As directed on label. | Supports the immune system’s detoxification of many dangerous substances,” with the same product and claim recurring in the Abscess and Lead Poisoning entries.
25. Klein AV, Kiat H. Detox diets for toxin elimination and weight management: a critical review of the evidence. *Journal of Human Nutrition and Dietetics* 2015;28(6):675-686. No randomized controlled trials of commercial detox diets assessing toxin elimination in healthy humans were identified, and no over-the-counter supplement has been shown to meaningfully increase renal clearance of foreign compounds in healthy people.
26. Randomized trial of a purported detoxification supplement in healthy young women, finding no benefit on body composition, gastrointestinal symptoms or blood markers versus placebo, with the product appearing safe. *Journal of Dietary Supplements* 2019;16(2):191-201. The research ledger recorded this claim

without a citation and it is flagged NEEDS-PRIMARY; the V1 endnote record supplies the journal reference given here.

27. The Doctor's Pharmacy, 3 April 2007, "How detox can help you jump-start your metabolic engine," and 26 October 2020, "How To Optimize Your Body's Detoxification System." Podcast exhibits are object of analysis throughout: they record what was claimed, never what is true.
28. The Human Upgrade, 25 October 2024, "Why Detoxes Fail: These Toxins Are STUCK In Your Body! Do THIS To Get Them Out."
29. The Human Upgrade, 30 June 2024, "How to Protect Your Detox Systems From Toxins — Mara Labs x Dave Asprey," an episode co-branded in its title with a supplement company.
30. The Ultimate Human, 15 April 2025, "Dr. Jessica Peatross: Detoxing From Environmental Mold, Lyme Disease, and Parasites." Object of analysis only.
31. The Ultimate Human, 7 December 2023, "Fasting for Detoxification and Longevity: Ancient Wisdom Meets Modern Science." Fasting induces autophagy, a cellular process clearing damaged proteins; this is distinct from removal of environmental contaminants, which the framing implies. Object of analysis only.

Immunity, Inflammation, Longevity

1. Martineau AR et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. *BMJ* 2017;356:i6583. 25 randomized trials, 10,933 participants. Overall adjusted odds ratio 0.88 (95% CI 0.81-0.96); in severely deficient participants (25-hydroxyvitamin D below 25 nmol/L) aOR 0.30, a 70% reduction with number needed to treat of 4; in replete participants aOR 0.75, number needed to treat of 20; intermittent bolus dosing aOR 0.97, no benefit.

2. FoundMyFitness, 19 May 2025, "This Supplement Could Cut Your Dementia Risk By 40%," attaching a 40% dementia risk reduction to vitamin D on the basis of a large observational study in a population largely already deficient. Object of analysis only.
3. Source conflation identified during verification: the research record described a vitamin C meta-analysis of "25 RCTs, 10,933 participants," figures which belong to the Martineau 2017 vitamin D individual-participant-data analysis. The vitamin C effect sizes are drawn from Hemila H and Chalker E, Vitamin C for preventing and treating the common cold, Cochrane Database of Systematic Reviews, doi:10.1002/14651858.CD000980.pub4, a separate review with different participant numbers.
4. Hemila H and Chalker E, Cochrane review on vitamin C and the common cold: prophylactic supplementation reduces cold duration by approximately 8% in adults and 14% in children, with an overall relative risk of 0.88 for respiratory infection; in participants under extreme physical stress, including marathon runners, skiers and soldiers in subarctic conditions, the relative risk fell to approximately 0.48. Therapeutic dosing initiated after cold onset showed consistently null results.
5. Hemila H, meta-analysis of 7 zinc lozenge randomized trials (n=575): approximately 33% reduction in cold duration with adequate dosing; zinc acetate lozenges approximately 40%, zinc gluconate approximately 28%; doses below 75 mg/day uniformly null across trials; pediatric trials consistently null; citric acid-containing formulations inactivate zinc ions in saliva. Journal of the Royal Society of Medicine Open 2011.
6. Curcumin has very poor oral bioavailability owing to rapid intestinal metabolism and hepatic conjugation. Enhanced delivery formulations report markedly greater absorption: a phospholipid complex at 29-48 times standard curcumin, a colloidal dispersion at 27 times, and a curcumin-essential oil complex at 7-27 times.

These formulation multipliers are rated MINOR and unverified in the research record.

7. An umbrella review of curcumin trials found it non-inferior to NSAIDs for osteoarthritis symptom relief; a randomized trial of a branded curcumin-essential oil complex at 500 mg twice daily showed equivalence to paracetamol at 650 mg three times daily, with superior reduction in C-reactive protein and TNF-alpha. Evidence is strongest in osteoarthritis and metabolic conditions where enhanced-bioavailability formulations were used.
8. Despite extensive preclinical data, human randomized trials of quercetin show no significant reduction in C-reactive protein, IL-6 or TNF-alpha in healthy adults; only minor subgroup benefits appear in women or in diseased cohorts at high doses.
9. A phase 2 trial of SRT501, a micronized resveratrol formulation, in relapsed multiple myeloma was halted after several patients developed acute renal failure. Popat R et al., *British Journal of Haematology* 2013. A metabolic randomized trial in older men (Kjaer et al.) found resveratrol null for metabolic outcomes and observed an increase in LDL cholesterol.
10. The National Institute on Aging Interventions Testing Program found rapamycin extends median lifespan by 10-30% in genetically heterogeneous mice, including when initiated late in life, equivalent to approximately age 60 in humans. Harrison DE et al., *Nature* 2009;460:392-395, and subsequent ITP studies. This is among the most reproducible longevity findings in mammalian aging research.
11. The PEARL rapamycin trial in healthy older adults (published 2025 in *Aging*) failed its primary efficacy endpoint of visceral adipose tissue reduction. A 2014 trial of the rapalog RAD001 improved influenza vaccine immune response by approximately 20% and reduced PD-1-positive exhausted T cells in older adults;

Mannick JD et al., Science Translational Medicine 2014. A separate trial reported approximately 20% reduction in the rate of ovarian aging with rapamycin.

12. Compounded sirolimus from compounding pharmacies can differ from the commercial product by up to 3.5-fold in bioavailability, making dose standardization critical and self-prescribed compounded use clinically unpredictable.
13. Observational data showing diabetic patients on metformin outliving non-diabetic controls has been identified as a selection-bias artifact: the non-diabetic control groups were not screened for metabolic health and likely included undiagnosed pre-diabetics. The Targeting Aging with Metformin trial had not launched as of 2026 owing to incomplete funding, and no longevity outcome data exist.
14. A 2025 trial randomized 72 older adults to metformin or placebo and reported a walking speed difference of 0.001 m/s ($P=0.96$), with hospital admission rates of 34% in the metformin group against 8% on placebo. Flagged NEEDS-PRIMARY: the trial is reported as published in Lancet Healthy Longevity but was not verified against the primary paper, so the safety signal is reported as a flag rather than asserted. Separately, the MASTERS trial found metformin blunted muscle hypertrophy compared with placebo in resistance-trained older adults.
15. A 12-month double-blind randomized trial of spermidine ($n=100$) in older adults with subjective cognitive decline failed to improve memory performance versus placebo. Schwarz C et al. Animal studies show approximately 10% lifespan extension, and the human supplement doses evaluated (0.9-3.3 mg/day) are far below those used in animal models. Observational cardiovascular data exist but are not randomized.

16. Fisetin is the most potent senolytic flavonoid in preclinical screening panels, selectively killing senescent cells and reducing senescence-associated secretory phenotype factors in animal models. No published human clinical efficacy results exist; only early-phase safety, pharmacokinetic and surrogate-biomarker trials are active. Flagged NEEDS-PRIMARY for the specific trial identifiers.
17. Bryan Johnson's publicly documented Blueprint protocol comprises over 100 daily pills including NMN or NR (500 mg, six times weekly), calcium alpha-ketoglutarate (1-2 g), CoQ10 (100 mg), low-dose aspirin (81 mg three times weekly), a testosterone patch (4 mg weekly), levothyroxine (112 mcg), spermidine (10 mg), fisetin (200 mg), acarbose (200 mg), metformin (500 mg) and curcumin (1 g), alongside caloric restriction of approximately 2,250 kcal/day in a six-hour window. Severe caloric restriction suppresses endogenous testosterone, making the testosterone patch a correction necessitated by the protocol rather than a primary intervention.
18. Stacking high-dose antioxidants with metformin, acarbose and intense caloric restriction can disrupt the reactive oxygen species signalling required for mitochondrial hormesis and muscle adaptation. Combining dozens of active compounds introduces unpredictable interactions, competing enzyme pathways and counter-regulatory blunting, and in a single-subject setting no favourable or adverse outcome can be attributed to any specific compound.
19. Venn-Watson S, *The Longevity Nutrient*, Introduction: "dismantle fifty years of dietary recommendations, and (2) challenge the entire omega-3 fish oil industry."
20. Venn-Watson S, *The Longevity Nutrient*, Ch. 2, essential fatty acids history: "only three have met the criteria for an essential fatty acid ... C15:0 [is] the first essential fatty acid to be discovered in

more than ninety years.” The criteria were applied to the compound by the author’s own research team.

21. Venn-Watson S, *The Longevity Nutrient*, Introduction: “an emerging fatty liver disease ... is likely part of a nutritional C15:0 deficiency syndrome. You know, like vitamin C deficiency and scurvy.” Related scope claim in the same section proposes declining C15:0 intake as contributing to rising rates of type 2 diabetes, heart disease and cancer.
22. Venn-Watson S, *The Longevity Nutrient*, Ch. 2: “C15:0 reverses aging at the cellular level. Of the twelve hallmarks of aging ... C15:0 targets at least six of them,” and “C15:0 directly targets inflammaging by lowering eighteen proinflammatory cytokines and chemokines, including IL-6 and MCP-1.” The cytokine results derive from a BioMAP cell-based screening panel rather than a human trial.
23. Attia P, *Outlive*, Ch. 3: “I propose that with some unorthodox but very reasonable lifestyle changes, you can minimize the most serious threats to your lifespan and healthspan and achieve your own measure of longevity alpha.”
24. The Dr. Gundry Podcast, 1 March 2022, “REVERSE AGING: What To Eat & When To Eat For LONGEVITY,” described as revealing “the molecule that can ‘turn on’ your body’s defenses against aging (and how you can get it).” Object of analysis only.
25. The Doctor’s Pharmacy, 19 September 2021, “The 7 DAILY HACKS To Reduce Inflammation & INCREASE LIFESPAN.” Object of analysis only.
26. Epigenetic aging clocks (Horvath and Hannum, first generation; PhenoAge and GrimAge, second generation trained on mortality datasets; DunedinPACE, third generation tracking rate of aging) have strong predictive power for cardiovascular morbidity, stroke and all-cause mortality in large epidemiological cohorts.

They are not validated surrogate endpoints for human longevity trials by the FDA or any regulatory authority, and individual-level noise, laboratory assay variation, cell-type heterogeneity and tissue specificity make them unreliable for personal diagnosis or therapeutic validation. Horvath S, *Genome Biology* 2013; Levine ME et al. 2018; Lu AT et al. 2019.

Performance and Physique

1. Systematic review and meta-analysis of 69 randomized trials (1,937 participants): creatine monohydrate with resistance training improved back squat strength by 5.64 kg ($p=0.001$), vertical jump height by 1.48 cm ($p=0.01$), bench or chest press by 1.43 kg ($p=0.002$), and Wingate peak power output by 47.81 W ($p=0.004$), with effects most pronounced in younger males.
2. Pooled analysis of 61 creatine trials: fat-free mass increased by a weighted mean difference of 1.39 kg (95% CI 1.07-1.70, $p<0.001$) across novice and experienced lifters; experienced lifters averaged 0.6 kg greater fat-free mass accretion than placebo.
3. ISSN Position Stand on creatine supplementation, Kreider RB et al., *Journal of the International Society of Sports Nutrition* 2017;14:18. Loading at 0.3 g/kg/day or 20 g/day in four divided doses for 5-7 days followed by 3-5 g/day maintenance; gradual saturation at 3-5 g/day over approximately 4 weeks reaches equivalent stores; co-ingestion with carbohydrate and protein maximizes uptake. Long-term prospective trials at up to 30 g/day for up to 14 years document no serious adverse events; the sole consistent side effect is a transient 1-2 kg increase in body mass from intracellular water retention.
4. Vegetarians maintain lower baseline intramuscular creatine (approximately 90-110 mmol/kg dry muscle) than omnivores at roughly 60-80% saturation, and experience 20-40% expansion of the intramuscular creatine pool on supplementation against 10-

20% in omnivores. Rated MINOR and unverified in the research record.

5. Systematic review and meta-analysis of 16 creatine trials (492 participants aged 20.8-76.4): memory improved (SMD 0.31, 95% CI 0.18-0.44) and attention time improved (SMD -0.31, 95% CI -0.58 to -0.03), with no significant improvement in executive function. GRADE certainty moderate for memory, low for processing speed and executive function. *Frontiers in Nutrition*.
6. Podcast episodes extending creatine into cognitive and aging indications, including “The Truth About Creatine & Brain Power” (14 February 2025). Object of analysis only.
7. Morton RW et al. A systematic review, meta-analysis and meta-regression of the effect of protein supplementation on resistance training-induced gains in muscle mass and strength in healthy adults. *British Journal of Sports Medicine* 2018;52(6):376-384. 49 trials, 1,863 adults: fat-free mass +0.30 kg, muscle fibre cross-sectional area +310 square micrometres, one-rep-max strength +2.49 kg; meta-regression identified a plateau at 1.62 g/kg/day (95% CI 1.03-2.20).
8. ISSN position stand on protein and exercise: during hypocaloric restriction, 2.3-3.1 g/kg/day preserves fat-free mass; during hypercaloric overfeeding, 2.4-4.4 g/kg/day minimizes surplus-induced fat accumulation; the leucine threshold for triggering muscle protein synthesis is approximately 2.5-3.0 g per meal, obtainable from 20-40 g of complete high-quality protein, with older adults requiring 30-40 g per meal owing to anabolic resistance.
9. Aragon AA and Schoenfeld BJ. Nutrient timing revisited: is there a post-exercise anabolic window? *Journal of the International Society of Sports Nutrition* 2013;10:5. Resistance training elevates muscle protein synthesis for 24-72 hours; total daily

protein intake is the primary driver of hypertrophy rather than peri-workout timing. The exception is fasted training, where immediate post-exercise protein ingestion matters.

10. FAO/WHO Digestible Indispensable Amino Acid Score framework: skim milk powder and whey protein isolate score at or above 100; soy protein isolate 87-92; pea protein concentrate 58-69, limited by methionine and cysteine; wheat protein 46-66 and white rice 42-60, limited by lysine. Rated MINOR and unverified in the research record.
11. When total daily protein intake is adequate at or above 1.6 g/kg/day, supplementing with isolated branched-chain amino acids provides no additional hypertrophic or ergogenic benefit, since muscle protein synthesis requires all nine essential amino acids; administering only the three BCAAs can competitively inhibit intestinal amino acid transporters and blunt absorption of the others. Wolfe RR, Journal of the International Society of Sports Nutrition 2017;14:30.
12. Caffeine at 3-6 mg/kg body weight ingested 30-60 minutes before exercise improves aerobic endurance (time to exhaustion by up to 16.9%), muscular strength, anaerobic power and sport-specific skill execution across multiple meta-analyses; ISSN Position Stand, Guest NS et al., Journal of the International Society of Sports Nutrition 2021;18:1. Beta-alanine at 3.2-6.4 g/day for 4-10 weeks increases muscle carnosine by up to 80%, improving performance in high-intensity efforts lasting 1-4 minutes. Citrulline malate at 6-8 g, providing 4-5.3 g of L-citrulline, improves repetitions to failure by 6.4% (SMD 0.196) without improving one-rep-max strength.
13. Dietary nitrate at 5-9 mmol/day, approximately 300-600 mg of inorganic nitrate from 70-140 mL of concentrated beetroot juice, taken 2-3 hours before exercise or as a 3-7 day loading protocol, improves exercise tolerance and submaximal oxygen efficiency in

recreationally active individuals. In highly trained endurance athletes with VO₂max at or above 65 mL/kg/min the ergogenic benefit is absent; doses above 15 mmol provide no additional benefit; antibacterial mouthwash blocks the pathway by destroying the oral bacteria that reduce nitrate to nitrite. Flagged NEEDS-PRIMARY: the supporting meta-analysis and its effect sizes (Hedges' g of 0.15 overall and 0.30 for chronic protocols) were not located, though the physiology is well established in the literature.

14. FDA labeling regulations at 21 C.F.R. 101.36 permit a “proprietary blend” to list only a total combined mass without individual ingredient doses. This allows clinically validated ingredients to be included at sub-clinical doses, for example 1 g of beta-alanine against a validated 3.2 g, or 1.5 g of citrulline malate against a validated 6-8 g, while the blend is saturated with high-dose caffeine at 300 mg or more, producing an immediate perceptible stimulant effect that implies the whole formulation is working.
15. In controlled clinical settings, thermogenic compounds produce statistically significant but clinically negligible weight loss: caffeine at 200-400 mg/day, approximately 0.5 kg over 8 weeks; green tea EGCG at 300-500 mg/day, approximately 1.3 kg over 12 weeks, with the effect severely blunted or absent in habitual caffeine users; p-synephrine at 20 mg/day or less, approximately 0.7 kg over 6 weeks. A Mayo Clinic review concluded there is little to no scientific proof supporting any dietary supplement as an effective standalone tool for long-term weight loss.
16. Synephrine (bitter orange) is structurally similar to banned ephedrine and has been shown to elevate heart rate, increase blood pressure and trigger cardiac arrhythmias, particularly combined with caffeine and exercise; use is contraindicated in hypertension, pre-existing cardiovascular disease, and with MAO inhibitors. EFSA Scientific Opinion 2012. Concentrated EGCG at

800 mg/day or above has been linked to rare but severe liver enzyme elevations and hepatotoxicity, prompting regulatory warnings from EFSA (Scientific Opinion 2018, EFSA Journal 2018;16:5239) and the FDA.

17. HMB at 3 g/day has no statistically significant effect on fat-free mass or strength in well-nourished athletes with adequate protein intake (fat-free mass change 0.30 +/- 0.13 kg, $p=0.08$). A meta-analysis of 21 randomized trials in 1,935 participants aged 50 and over found chronic oral HMB with resistance training significantly increased lean mass (WMD 0.28 kg, 95% CI 0.16-0.41), improved handgrip strength (WMD 0.54 kg) and enhanced physical functional performance.
18. A 2024 systematic review and meta-analysis of 17 betaine studies (317 participants) reported a moderate effect size of 0.47 (95% CI 0.04-0.89) for maximal strength and improved vertical jump height (SMD 0.36) after at least 7 days at 2.5-5.0 g/day, while multiple high-quality long-term randomized trials show no significant difference from placebo in strength, hypertrophy, anaerobic performance or body composition; betaine at 6 g/day decreases plasma homocysteine while increasing LDL cholesterol over 12 weeks. Flagged NEEDS-PRIMARY: neither the meta-analysis nor the null trials were identified with citations.
19. Reported magnitudes of funding bias: industry-funded sports nutrition studies described as 4-8 times more likely to conclude in favour of the sponsor's financial interests, and industry-funded clinical health research as up to 30 times more likely to report statistically significant positive findings, with null results frequently withheld from publication. Flagged NEEDS-PRIMARY: the underlying reviews were not identified, so the multipliers are described rather than asserted. The existence of funding bias in this literature is separately documented elsewhere in this book.

20. Huberman Lab Guest Series, 22 February 2023, “Dr. Andy Galpin: Optimal Nutrition & Supplementation for Fitness,” covering creatine and then rhodiola, citrulline, beetroot juice, alpha-GPC and nootropics within a single episode. Object of analysis only; the exhibit is the format’s flattening of very different evidence profiles, not any specific claim made.
21. Galpin A, 31 August 2023, “The Science of Rhodiola Rosea Supplementation - Does it Work, How Much, When, & More.” Object of analysis only.
22. Hayward L and Kernan B, *Bodybuilding Supplement Secrets Revealed*, front cover: “How to gain up to 15 lbs. of muscle in 6 weeks using potent ‘homemade’ supplement stacks and mixes.”
23. Hayward L and Kernan B, *Bodybuilding Supplement Secrets Revealed*, Ch. 1: “With supplements you can get your body to explode through the genetic barrier, and get your body to do some amazing and impossible things,” and, in the anabolic steroids section: “Can you really mimic the results of steroids with this book? ... You will experience dramatic changes in your physique of at least 5 lbs. all the way up to 25 lbs.”
24. Hayward L and Kernan B, *Bodybuilding Supplement Secrets Revealed*, Ch. 1, “The Advertisements Only Tell Part of the Story”: “the study that ‘proves’ ... the supplement works, was performed on some sickly person in the hospital who would have probably gained muscle on anything you gave them.”

The Test Funnel

1. The tripartite evaluation framework of analytical validity, clinical validity and clinical utility is the standard model in clinical laboratory medicine and is codified in the regulatory requirements for FDA-cleared diagnostic devices.
2. Commercial functional tests operate under the Clinical Laboratory Improvement Amendments (42 U.S.C. 263a; 42 C.F.R.

Part 493) as high-complexity laboratory-developed tests. CLIA certifies that a laboratory can execute its assays with technical quality; it does not establish that the measurements are biologically meaningful (clinical validity) or that acting on them improves health (clinical utility). This gap permits complex diagnostic claims to be marketed directly to consumers without FDA clearance or proof of clinical benefit.

3. Food-specific IgG and IgG4 testing is explicitly condemned for diagnosing food allergy or intolerance by the American Academy of Allergy, Asthma and Immunology, the European Academy of Allergy and Clinical Immunology, and the Canadian Society of Allergy and Clinical Immunology. Food-specific IgG4 is a normal physiological marker of immunological tolerance driven by regulatory T cells and IL-10; high levels represent active desensitization rather than inflammation or pathology. AAAAI position statement in support of the EAACI Position Paper on IgG4, *Journal of Allergy and Clinical Immunology*; CSACI position statement.
4. Acting on IgG food-sensitivity panels through exclusion diets carries documented risks including pediatric malnutrition, faltering growth and psychological food-avoidance behaviours. These panels invariably produce high numbers of positives for commonly consumed foods because IgG levels reflect dietary exposure rather than pathology.
5. The Organic Acids Test analyses 76 urinary metabolites by GC/MS and claims to identify *Candida* overgrowth, oxalate accumulation and brain neurotransmitter imbalances. Elevated arabinose and citramalic acid, interpreted as markers of intestinal *Candida*, are normal byproducts of consuming apples, grapes, pears, cranberries and mushrooms. Urinary HVA and VMA are metabolites of peripheral sympathetic nervous system activity and gastrointestinal synthesis and do not cross the blood-brain

barrier, so they cannot reflect central nervous system neurotransmitter status. The test operates under CLIA as a laboratory-developed test without FDA clearance for these indications.

6. Independent clinical evaluation of a commercial stool assay found overall sensitivity of 80% for detecting added pathogens in standardized spiked stool matrices and a clinical specificity of 26%, falsely reporting high concentrations of *H. pylori*, enterotoxigenic *E. coli* and adenovirus in negative control samples confirmed pathogen-free by gold-standard comparator assays and endoscopy.
7. American Gastroenterological Association clinical practice update: the clinical utility of commercial gut microbiome tests for guiding therapeutic or dietary decisions has not been established, and they carry no FDA clearance for diagnostic use. Metatranscriptomic sequencing platforms may be analytically sophisticated, but their proprietary machine-learning scoring and supplement recommendation engines have not undergone independent peer-reviewed clinical validation, and no randomized trials demonstrate improved health outcomes from following their recommendations.
8. Dried urine hormone testing shows high analytical validity: samples stable at room temperature for up to 84 days, with intraclass correlation above 0.90 for 14 of 17 key steroid metabolites against standard 24-hour liquid urine collection. The research record further states that nearly all published validation studies were authored or funded by the company's founder with no independent replication, and that no independent large-scale randomized trials show better outcomes from management based on these profiles. Flagged NEEDS-PRIMARY: the validation papers and their authorship were not independently verified, so the

conflict-of-interest characterization is reported rather than asserted.

9. Intracellular micronutrient testing by lymphocyte functional analysis has no published peer-reviewed studies evaluating sensitivity, specificity or reproducibility against validated reference methods. An observational study of 3,338 hypertensive patients managed with micronutrient testing lacked both control data and baseline micronutrient levels, making outcome attribution impossible. Major health insurance carriers classify the testing as investigational and medically unnecessary.
10. Clinical telomere-length testing by Flow-FISH is validated for heritable telomeropathies including dyskeratosis congenita and idiopathic bone marrow failure, with intra-assay and inter-assay coefficients of variation of 2.2% and 2.5% and R-squared of 0.94 between independent reference laboratories. Results directly alter clinical management in approximately 25% of idiopathic bone marrow failure cases by guiding transplant conditioning and donor screening. This validation does not extend to consumer wellness tests. Armanios laboratory, Johns Hopkins.
11. Consumer qPCR telomere testing carries inter-assay and inter-laboratory variability of up to 20%, sufficient to shift an individual estimate by more than 1 kilobase and therefore to change a calculated biological age by decades on analytical noise alone. qPCR T/S ratios correlate only modestly with Flow-FISH (R-squared 0.56). qPCR averages telomeric DNA across a pooled cell mixture and cannot detect the shortest telomeres, which are the biological drivers of replicative senescence.
12. Commercial at-home whole-blood NAD kits using dried blood spots or frozen samples are analytically invalid: freezing ruptures red blood cell membranes, exposing intracellular NAD to CD38, a membrane-bound NAD-consuming enzyme, producing 21-27% post-collection enzymatic degradation and a false signal of

deficiency. Accurate quantification requires immediate methanol preservation at the moment of collection, a step omitted by consumer kits. Nature Metabolism.

13. Using validated mass-spectrometry methods across seven independent human cohorts (n greater than 300), whole-blood NAD concentrations were found to be stable across the human lifespan, with no correlation to chronological age, lifestyle parameters or physical fitness; younger adults, older adults and elite athletes showed virtually identical baseline levels. Nature Metabolism.
14. Oral nicotinamide riboside raises whole-blood NAD substantially (for example from approximately 27 to 70.5 micromolar in stage 1 trials), but blood NAD does not correlate with or reflect NAD concentrations in metabolically active target tissues including skeletal muscle, liver, brain and myocardium. Whole-blood NAD measurement therefore provides no clinical utility for diagnosing localized cellular depletion or guiding dosing.
15. Perform with Dr. Andy Galpin, 7 August 2024, “How to Use & Interpret Blood Tests for High Performance,” applying clinical blood panels to performance optimization in healthy athletes. Object of analysis only.
16. The Ultimate Human, 30 October 2025, “Methylation Test Explained: Stop Guessing What Supplements You Need.” Object of analysis only.
17. The Human Upgrade, 16 December 2022, “How Your Biomes Drive Custom Food & Supplement Solutions,” featuring the founder of a company selling both the microbiome test and the supplements its results recommend. Object of analysis only.
18. Epigenetic aging clocks have high analytical validity in controlled research settings, with the pan-tissue clock correlating with chronological age at $r=0.96$, and later clocks trained on mortality

datasets or tracking rate of aging. They are not standardized for consumer use: there are no reference standards, results vary by measurement platform (array versus bisulfite sequencing), and vendor algorithms differ. Applying a blood-trained clock to saliva, a mixture of roughly 65% immune cells and 35% buccal cells, introduces major error. Steve Horvath has explicitly stated that methylation clocks are intended for population-level stratification rather than individual diagnostics. Horvath S, *Genome Biology* 2013; Levine ME et al. 2018; Lu AT et al. 2019.

19. Asprey D, *Smarter Not Harder*, Ch. 1, “Evaluate, Personalize, Repeat”: “You’ll learn about three types of tracking: real time (with a fitness tracker or continuous glucose monitor), daily ... and occasional (lab tests or imaging).”
20. Asprey D, *Smarter Not Harder*, Ch. 4, minerals overview: “As important as vitamins are, they are just the warm-up act. Minerals are the biochemical superstars ... most people are deficient in at least some of them.” Asserted without population-level epidemiological citation.
21. Asprey D, *Smarter Not Harder*, Ch. 4, iodine section: “you can even paint it on your body, where it will be absorbed through your skin. If you are low on iodine, it will be absorbed quickly.” The skin-absorption test has no clinical validation against urinary iodine standards.
22. Asprey D, *Smarter Not Harder*, Ch. 4, selenium section: “In an ideal world, it’s best to get a blood test if you’re not sure. Depending on your lab result, a level of about 100 ng/mL is good.” Reference ranges vary by laboratory and population, and no interpreting clinician is specified.
23. Attia P, *Outlive*, Ch. 3, “From Evidence Based to Evidence Informed,” on triangulating evidence and reasoning in terms of probabilities and risk, acknowledging that “living systems are

messy, and confounding, and complex.” Treated in the research record as sound reasoning.

The Short List

1. Balch PA, *Prescription for Nutritional Healing*, 6th ed., Part One: “The Elements of Health — Vitamins, Minerals, Amino Acids, Enzymes, Nutraceuticals, Herbs, Glandulars.”
2. Asprey D, *Smarter Not Harder*, Ch. 4, closing TL;DR summaries, for example: “TL;DR for Calcium: Take calcium in the forms of calcium fructoborate, calcium AEP, calcium AKG, and/or calcium-D-glucarate.”
3. Asprey D, *Smarter Not Harder*, Ch. 3, “My routine” sidebar: “My routine: ... I take 75 to 150 pills a day, but I’m an extreme case!”
4. US Preventive Services Task Force 2023 Grade A recommendation: folic acid 0.4-0.8 mg (400-800 mcg) daily for all persons planning or capable of pregnancy, beginning at least one month before conception and continuing through the first trimester, to prevent neural tube defects. Czeizel AE and Dudas I, Prevention of the first occurrence of neural-tube defects by periconceptional vitamin supplementation, *New England Journal of Medicine* 1992;327(26):1832-1835: n=4,862, 0.8 mg/day, 0% neural tube defect incidence in the intervention group against 0.25% in controls. Synthetic folic acid bioavailability is approximately 85% taken with food and near 100% on an empty stomach, against approximately 50% for food folate. NIH Office of Dietary Supplements folate fact sheet.
5. NIH Office of Dietary Supplements vitamin B12 fact sheet. Deficiency causes subacute combined degeneration of the spinal cord, progressive and irreversible, alongside megaloblastic anemia. Risk factors include atrophic gastritis in older adults, veganism, metformin and proton pump inhibitors. Deficiency is characterized by elevated serum methylmalonic acid and total

plasma homocysteine above 15 micromoles per litre.

Maintenance 1.5-2.4 mcg/day; correction of active deficiency up to 2,000 mcg/day orally, exploiting passive absorption.

6. WHO guidelines on iron supplementation in pregnancy; NIH Office of Dietary Supplements iron fact sheet. Iron deficiency anemia in pregnancy increases risk of preterm delivery, low birth weight and compromised neonatal iron stores. Diagnosis requires haemoglobin below 11 g/dL in the first and third trimesters or 10.5 g/dL in the second, with serum ferritin below 30 mcg/L. Tiered dosing: ferritin 30-70 mcg/L, 30-40 mg/day elemental iron; ferritin below 30, 60-80 mg/day; moderate to severe anemia, 100-200 mg/day. Maternal requirements rise from 0.8 mg/day absorbed in the first trimester to more than 6 mg/day in the third.
7. WHO guidelines on iodine; NIH Office of Dietary Supplements iodine fact sheet. Maternal iodine deficiency during pregnancy impairs fetal neurogenesis, causing cretinism, irreversible cognitive deficits and elevated gestational loss. Maternal thyroid hormone production must increase approximately 50% during pregnancy. Recommended intake 150 mcg/day for non-pregnant adults, rising to 220-250 mcg/day during pregnancy and lactation.
8. NIH Office of Dietary Supplements vitamin D fact sheet: deficiency threshold serum 25-hydroxyvitamin D below 30 nmol/L, causing rickets in children and osteomalacia in adults; Food and Nutrition Board recommendation of 600 IU daily to age 70 and 800 IU above. US Preventive Services Task Force 2024 draft guidance: Grade D recommendation against vitamin D supplementation, with or without calcium, for primary prevention of falls and fractures in community-dwelling, non-pregnant adults aged 60 and over. The VITAL trial found no fall or fracture benefit in replete older adults and a significant increase in nephrolithiasis;

Manson JE et al., New England Journal of Medicine 2019;380(1):33-44. Trial data indicate a U-shaped relationship, with 25-hydroxyvitamin D above approximately 40-45 ng/mL associated with increased fall risk.

9. NIH Office of Dietary Supplements magnesium fact sheet. Hypomagnesemia is serum magnesium below 0.75 mmol/L; organic salts (citrate, aspartate, lactate, chloride) have high bioavailability while inorganic forms (oxide, sulfate) are poorly absorbed and primarily laxative. In individuals with normal baseline serum magnesium, clinical trials and systematic reviews show no benefit for nocturnal leg cramps or sleep parameters. Supplemental magnesium above the 350 mg/day upper limit increases urinary excretion and gastrointestinal adverse effects.
10. Creatine monohydrate at 3-5 g/day produces a reproducible 5-15% improvement in maximal strength and power output with resistance training; ISSN Position Stand, Kreider RB et al. Brain creatine rises 3-10% with standard oral supplementation. A 2024 meta-analysis of 16 randomized trials (492 participants) found significant improvement in memory (SMD 0.31) and processing speed (SMD 0.51) in older adults and individuals with low baseline creatine stores including vegetarians and vegans, without improvement in overall or executive cognitive function in healthy, sleep-replete young adults.
11. Caffeine at 3-6 mg/kg body weight consumed 60 minutes before exercise improves physical performance by 2-4% across endurance, strength, power and sprinting; for events lasting over 2 hours, top-up doses of approximately 1 mg/kg/hour maintain concentrations, with a half-life of 3-5 hours; at approximately 2 mg/kg caffeine maintains cognitive vigilance under acute sleep deprivation. ISSN Position Stand, Guest NS et al., Journal of the International Society of Sports Nutrition 2021;18(1):1.

12. Meta-analysis of adult-only trials using zinc lozenges providing at least 75 mg/day elemental zinc as acetate or gluconate, free of chelating binders such as citric or tartaric acid: 37% reduction in common cold duration (95% CI 27-46%, $P=10$ to the minus 9), approximately 2 days. The 2024 Cochrane systematic review combining all zinc formulations including nasal sprays, syrups and tablets found the overall evidence inconclusive, illustrating that formulation specificity is critical.
13. Melatonin at 0.1-5 mg is effective for phase-shifting the sleep-wake cycle in delayed sleep-wake phase disorder and non-24-hour sleep-wake rhythm disorder in blind adults, per American Academy of Sleep Medicine guidance. At 2-5 mg it significantly improves total sleep duration and reduces sleep latency in children with autism spectrum disorder and impaired endogenous melatonin synthesis. For primary insomnia it reduces sleep onset latency by approximately 7 minutes and increases total sleep duration by approximately 8 minutes. Ferracioli-Oda E et al., *PLoS One* 2013;8(5):e63773.
14. REDUCE-IT (8,179 participants, median 4.9 years) of prescription icosapent ethyl, purified EPA, at 4 g/day in statin-treated patients with hypertriglyceridemia: 25% reduction in major cardiovascular events, 20% in cardiovascular death, 28% in stroke and 31% in myocardial infarction. Bhatt DL et al., *New England Journal of Medicine* 2019;380(1):11-22. The mineral oil comparator concern discussed in Chapter 2 applies. STRENGTH, testing combined EPA and DHA in carboxylic acid form at 4 g/day, was terminated early for low probability of benefit; Nicholls SJ et al., *JAMA* 2020;324(22):2268-2280. VITAL, at 1 g/day combined EPA and DHA in 25,871 healthy older adults, found no reduction in the composite cardiovascular endpoint but a 28% reduction in total myocardial infarction, most pronounced in African American participants and those with low baseline fish consumption.

15. Middleton P, Gomersall JC, Gould JF, et al. Omega-3 fatty acid addition during pregnancy. *Cochrane Database of Systematic Reviews*: long-chain omega-3 supplementation reduces preterm birth before 37 weeks by 11% and early preterm birth before 34 weeks by 42%.
16. Clinical synthesis: deficiency correction (folic acid at Grade A, and targeted B12, iron and iodine correction) should be prioritized as addressing fundamental biological needs and preventing irreversible pathology; pharmacological agents (omega-3, creatine, caffeine, melatonin) should be restricted to specific populations with established physiological need and clear dose-response data; community-dwelling replete adults should be counselled against beta-carotene, high-dose vitamin E, daily multivitamins, routine magnesium and routine curcumin. Supporting trial data: US Preventive Services Task Force, *JAMA* 2022;327(23):2326-2333; the ATBC trial, *New England Journal of Medicine* 1994;330(15):1029-1035; the SELECT trial, *JAMA* 2009;301(1):39-51.
17. DeKosky ST, Williamson JD, Fitzpatrick AL, et al. Ginkgo biloba for prevention of dementia: a randomized controlled trial. *JAMA* 2008;300(19):2253-2262. The Ginkgo Evaluation of Memory study enrolled 3,069 adults aged 75 and over on 240 mg/day standardized extract with median follow-up of 6.1 years, finding no effect on dementia incidence, no reduction in Alzheimer's risk and no slowing of cognitive decline in any domain. Dementia developed in 277 participants on ginkgo against 246 on placebo. Subsequent systematic reviews confirm no meaningful cognitive benefit in subjective memory complaint or mild cognitive impairment.
18. Phase III clinical trials of curcumin in Alzheimer's disease failed their primary cognitive endpoints; a trial of curcumin at 1,500 mg/day in primary sclerosing cholangitis produced no clinically

significant change in serum alkaline phosphatase, symptoms or risk scores. The clinical literature is dominated by transient surrogate biomarker changes with no evidence of disease modification or hard outcome benefit. The failures apply to standard, non-enhanced formulations with negligible systemic bioavailability.

19. Hayward L and Kernan B, *Bodybuilding Supplement Secrets Revealed*, Introduction: "I only deal in what has been proven by science and experience. Try the ones here before you move onto the latest hype. They work!"
20. Venn-Watson S, *The Longevity Nutrient*, Introduction: "our initial interesting discovery of C15:0 as a healthy nutrient for aging dolphins has evolved into a global movement to save humanity."
21. Brink W, *Supplement Company Secrets*, Part I, "Research proven" section, p. 6: "very few companies spend money on real research, preferring instead to spend money on marketing."

Be Your Own Filter

1. Brink W, *Supplement Company Secrets*, Part I, "Clinically proven" section: "'Clinically proven' ... means absolutely nothing to the average buyer."
2. Brink W, *Supplement Company Secrets*, Part I, "All natural" section: "'All natural' ... means nothing at all, yet people seem to fall for it virtually every time."
3. Martineau AR, Jolliffe DA, Hooper RL, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. *BMJ* 2017;356:i6583.
4. Mortensen SA, Rosenfeldt F, Kumar A, et al. The effect of coenzyme Q10 on morbidity and mortality in chronic heart

failure: results from Q-SYMBIO. JACC Heart Failure 2014;2(6):641-649.

5. WHO guidelines on iron supplementation in pregnancy; NIH Office of Dietary Supplements iron fact sheet, on tiered dosing by ferritin level and oxidative stress risk in replete individuals.
6. Barter PJ, Caulfield M, Eriksson M, et al. Effects of torcetrapib in patients at high risk for coronary events. New England Journal of Medicine 2007;357(21):2109-2122.
7. Multiple randomized trials of nicotinamide riboside and nicotinamide mononucleotide collectively confirm that NAD precursors raise circulating NAD levels, while no randomized trial in healthy adults has demonstrated improvement in energy, cognition, muscle function or any hard clinical outcome.
8. FDA regulations at 21 C.F.R. Part 111. “Practitioner-grade,” “pharmaceutical-grade” and “professional-grade” have no regulatory definition.
9. Practitioner supplement dispensary platforms permit practitioners to set markups above wholesale and receive a portion of each sale, including on recurring orders.
10. ConsumerLab.com 2026 multivitamin review: 32% of 22 products failed quality testing on incorrect potency or contaminants.
11. Huberman Lab, 9 January 2023, “Developing a Rational Approach to Supplementation for Health & Performance,” carrying sponsors AG1, LMNT, Helix Sleep and InsideTracker together with a Momentous supplement partnership. Object of analysis only.
12. The Ultimate Human, MTHFR gene variant series across multiple episodes, using a 44% population prevalence figure to route the audience toward methylated supplement products, with

economic interest disclosed in episode boilerplate. Object of analysis only.

13. Klein AV, Kiat H. Detox diets for toxin elimination and weight management: a critical review of the evidence. *Journal of Human Nutrition and Dietetics* 2015;28(6):675-686.
14. CellCore Biosciences “drainage funnel” protocol: the term does not appear in the hepatology, nephrology or clinical toxicology literature.
15. Seven cohort studies using properly controlled methodology demonstrate whole-blood NAD stability across the adult lifespan, contradicting the declining-NAD marketing premise. *Nature Metabolism*.
16. British Dietetic Association position statement on commercial microbiome testing for dietary guidance, concluding it lacks the clinical validity to support such recommendations.
17. Venn-Watson S, *The Longevity Nutrient*, Introduction: “Add that I’m a dolphin veterinarian who didn’t intend to find a saturated fat that would (1) dismantle fifty years of dietary recommendations ... even more scrutiny is needed.”
18. Robinson JL et al. Human randomized controlled trial of C15:0 supplementation. *Journal of Nutrition*.
19. Steffen BT et al. Mendelian randomization analysis of C15:0 and cardiovascular outcomes in the CARDIA and ARIC cohorts (n=7,085), reporting observational associations without evidence of causality.
20. Hemila H, meta-analysis of zinc lozenge trials for the common cold, comparing zinc acetate and zinc gluconate and the role of zinc dosage. *JRSM Open*. Doses below 75 mg/day of elemental zinc were null across trials, and citric-acid-containing formulations inactivate zinc ions in saliva.

21. Cochrane systematic review on zinc for the common cold, 2024 update: with all formulations pooled, the evidence is inconclusive. Formulation specificity, meaning acetate or gluconate without a citric acid binder, is critical to the finding.
22. US Preventive Services Task Force statement on vitamin D, calcium or combined supplementation for the primary prevention of fractures in community-dwelling adults.
23. REDUCE-IT used a mineral oil comparator which may have elevated biomarkers in the placebo group, potentially inflating the apparent benefit of icosapent ethyl; a Copenhagen General Population Study secondary analysis examined this question.
24. Asprey D, *Smarter Not Harder*, Ch. 4, Panax ginseng section: “In studies where individuals were not already experiencing fatigue, they did not see an increase in cognition.”
25. Attia P, *Outlive*, Ch. 3, “From Evidence Based to Evidence Informed”: “you’ll forever ride the merry-go-round of fad diets and trendy workouts and miracle supplements ... stuck in a Medicine 2.0 mentality.” Treated in the research record as sound reasoning.